OBSERVATIONAL PLAN

Treatment of High and Very high riSk dyslipidemic pAtients for the PreveNTion of CardiOvasculaR Events in Europe – a MultInatioNal ObservatIonal Study (SANTORINI)

DSE-HCL-01-19

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1 SIGNATURES

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2 GLOSSARY

ADR	Adverse Drug Reaction
Apo B	Apolipoprotein B
APS	All Documented Patient Set
ASCVD	Atherosclerotic Cardiovascular Disease
BAS	Baseline Analysis Set
BUN	Blood Urea Nitrogen
CA	Competent Authority
CHD	Coronary Heart Disease
CI	Confidence Interval
CRO	Contract Research Organization
CV (D)	Cardiovascular (Disease)
DM	Data Manager
DSE	Daiichi Sankyo Europe GmbH
eCRF	electronic Case Report Form
ESC/EAS	European Society of Cardiology / European Atherosclerosis Society
ECG	Electrocardiography
EDC	Electronic Data Capturing
FAS	Full Analysis Set
FPI	First Patient In
FU	Follow Up
FQ	Feasibility questionnaire
GFR	Glomerular Filtration Rate
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HbA1c	Hemoglobin A1c
HDL-C	High Density Lipoprotein-C
He FC	Heterozygous Familial Hypercholesterolemia
HEOR	Health Economics Outcome Research
hsCRP	High Sensitive C-Reactive Protein
ICF	Informed Consent Form
ICH	International Council on Harmonization
ICJME	International Committee of Medical Journal Editors
ICU	Intensive Care Unit
IEC	Independent Ethics Committee
LDL-C	Low Density Lipoprotein-C
LFT	Liver Function Test
LMT	Lipid Modifying Therapies
Lp(a)	Lipid Protein a
LPI	Last Patient In
LPO	Last Patient Out
NIS	Non-Interventional Study
PAM	Patient Activation Measure
PCSK9	Proprotein Convertase Subtilisin/Kexin Type 9
PL	Project Lead
PRO	Patient Reported Outcome
PTCA	Percutaneous Transluminal Aoronary Angioplasty
RCT	Randomized Clinical Trials

SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TC	Total Cholesterol
TG	Triglyceride
TIA	Transient Ischemic Attack

3 RESPONSIBLE PARTIES

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3.1 Steering Committee

The Steering Committee (SC) will give scientific advice, support with setting up the study concept, and will be involved in publications.

4 SUMMARY

Study/Registry Title	Treatment of High and Very high ri**S**k dyslipidemic p**A**tients for the Preve**NT**ion of cardi**O**vascula**R** Events in Europe – a Mult**I**natio**N**al Observat**I**onal Study (SANTORINI)
Observational plan version identifier	Version 2.0
Date of last observational plan version	28 Nov 2019
Marketing Authorization Holder	NA
Main Authors	PPD, PPD, both DSE
Rationale and Background	Dyslipidemia is a major and costly health concern in Europe. Appropriate medical treatment lowers low-density lipoprotein cholesterol (LDL-C) and reduces the incidence of clinical cardiovascular events (morbidity, mortality), and their associated costs. A number of drug classes are available to decrease circulating LDL-C in Very High Risk and High Risk patients with the statins being the most widely prescribed of these. However, many patients remain inadequately treated or even untreated, and some lipid-lowering drugs may be associated with an increase in the incidence of diabetes. Furthermore, high sensitivity C-reactive protein (hsCRP), in addition to the atherogenic lipids, is of growing interest as a putative independent predictor of CV mortality. Gaining further insight into current real-life European medical practice with respect to the management of dyslipidemic patients is considered to be of interest, and may contribute to an improvement in the management of dyslipidemic patients and to an associated reduction in the clinical and economic burden associated with the management of atherosclerotic cardiovascular disease (ASCVD).
Research Question and Objectives	To assess the characteristics and management of Very High Risk and High Risk patients requiring Lipid Modifying Therapies (LMTs) and the use of healthcare resources associated with current patient management strategies, particularly with respect to the prevention of clinical cardiovascular events. Data collection methodology: As this is a non-interventional study, only data from routine clinical practice will be documented. Physicians will not be required to perform any mandatory assessment outside the routine clinical practice for this study. To facilitate accurate recording of data, patients can optionally fill in a memory aid to note important details.

	Primary objective: The primary objective is to document, in the real-world setting, the effectiveness of current treatment modalities in managing plasma levels of LDL-C in Very High Risk and High Risk patients requiring LMTs Secondary objectives: The secondary effectiveness objectives are to document: • The relationship between treatment modalities and plasma levels of other potentially ASCVD-modifying cholesterol fragments, namely, HDL-C, non-HDL-C, TC, apoB, TGs and Lp(a) • Changes in the inflammatory marker hsCRP over time • Changes in the patients´ overall CV risk assessment over time measured through CV risk score calculators The secondary safety objectives are to document: • Clinical events associated with the treatment modalities: o Laboratory abnormalities o Muscle-associated symptoms o New onset and/or worsening diabetes o Changes in the patients´ glycemic status over time o Adverse Drug Reactions associated with Bempedoic Acid and/or fixed dose combination with ezetimibe Additional secondary objectives are to document: • The characteristics of the sites and physicians caring for Very High Risk and High Risk patients • The patients' use of lipid-modifying treatment, especially with regard to a switch from one drug class to another, a dose modification of a given drug, a switch from one statin to another, any evidence of statin intolerance or insufficient responsiveness to a statin, including a maximally tolerated statin, and any use of combination drug therapy • Various HEOR parameters associated with the management of the dyslipidemic patients such as PRO outcomes, healthcare resource use and patients disease awareness.
Study Design	Multinational, multicenter, prospective observational, non-interventional study
Population	Setting: 8000 patients from different countries and care settings (primary care and secondary care and different specialties). At each study site, the patients will be enrolled consecutively. Patients will be stratified for High and Very High Risk as well as for previously and newly treated patients. Sites will be required to complete a patient screening log of eligible patients for this disease registry at their treatment centers. This log will document how patients came to be included or excluded from the study, in order to assess the representativeness of the study population. Minimal information will be recorded for all patients who are screened for

	study enrolment, but no patient-identifiable information should be recorded. Those patients who provide their informed consent will be enrolled into the study. The study population consists of Very High Risk and High Risk patients previously diagnosed and treated as well as newly treated patients receiving their first LMT. At baseline data collection point, baseline characteristics (demography, sociodemography), medical history including LDL-C and other lipid parameters, CV risk assessment and relevant CV medical history (CV events such as myocardial infarction and stroke), concomitant diseases such as diabetes, and certain HEOR variables and patient reported outcomes (EQ-5D-5L and PAM-13) will be documented. In addition, for the previously diagnosed and treated patients, details on the lipid modifying treatment during the year before enrolment will be collected. At the follow-up data collection point at 1 year (± 2 months), available information on the patients' routine management between baseline and this data collection point, and efficacy and safety variables will be collected including (LDL-C and other lipid parameters, CV risk assessment and relevant CV medical events such as myocardial infarction and stroke), changes in concomitant diseases such as diabetes, and certain HEOR variables. As an additional assessment, quality-of-life questionnaires will be completed by the patient preferably in the physician's office. Approximately 800 sites / physicians - office-based or hospital-based, general practitioners, internists, lipidologists, diabetologists, and cardiologists - in Ireland, UK, Portugal, Spain, France, Belgium, the Netherlands, Denmark, Germany, Switzerland, Italy, and Austria, as well as Norway and/or Sweden and/or Finland. It is estimated that each site will contribute 10 patients. Nonetheless, additional patients – subject to approval – may be considered.
Inclusion/exclusion criteria	Key inclusion criteria: • Very High Risk and High Risk patients requiring LMTs • ≥ 18 years of age • not simultaneously participating in any interventional study • providing written informed consent for participation in the study (ICF) • life expectancy > 1 year Patients will be stratified for High and Very High Risk as well as for previously and newly treated patients. As this is a non-interventional study, no explicit exclusion criteria are defined. The prescribing behavior will not be influenced.

Variables (Observation Criteria)	Parameters to be recorded (if available) during the observation period: *To be documented at baseline (if available):* o Eligibility o Demographic and sociodemographic variables o Vital signs o Medical history, including CVD risk status-related medical history: o CV risk assessment with or without utilization of risk score o history/diagnosis and current status of dyslipidemia o heterozygous familial hypercholesterolemia (HeFH) o documented ASCVD either clinical or unequivocal on imaging o Concomitant diseases o For diabetic patients o disease type and date of diagnosis o treatment o microvascular complications o Current concomitant medication for CVD o Previous / current dietary restrictions o Previous / current use of lipid-modifying treatment Previous / current use of lipid-modifying treatment including details of dose, dose modification, switching, combination therapy, drug intolerance, insufficient responsiveness, investigators and patients assessment on compliance o Statin(s) o Bile acid sequestrant(s) o Cholesterol absorption inhibitor (Ezetimibe) o PCSK9 inhibitor(s) o Nicotinic acid o Drug combinations o Bempedoic acid and/or bempedoic acid fixed dose combination with ezetimibe o Other o Laboratory parameters (at baseline or last available measurement) o Lipid variables o LDL-C o HDL-C, non-HDL-C, TC, apoB, TG, Lp(a) o Diabetes-related parameters o fasting glucose o HbA1c o Inflammatory status o hsCRP o Renal function parameters (GFR, serum creatinine, blood urea nitrogen (BUN))

	○ Other laboratory parameters (liver function, serum chemistry, hematology) ○ HEOR parameters ○ Hospital admissions ○ Length of hospital stay ○ Number of days in ICU ○ Interventions ○ Other HEOR parameters ○ Adherence to former and current treatment ○ Patient reported outcomes (EQ-5D-5L, PAM-13) *To be documented at 1-year follow-up (if available):* ○ Vital signs ○ CVD risk status: ○ CV risk assessment with or without utilization of risk score ○ history/diagnosis and current status of dyslipidemia ○ heterozygous familial hypercholesterolemia (HeFH) ○ documented ASCVD either clinical or unequivocal on imaging ○ Concomitant diseases ○ For diabetic patients ○ disease type and date of diagnosis ○ treatment ○ microvascular complications ○ Current concomitant medication for CVD ○ Previous / current dietary restrictions ○ Previous / current use of lipid-modifying treatment Previous / current use of lipid-modifying treatment including details of dose, dose modification, switching, combination therapy, drug intolerance, insufficient responsiveness, investigators and patients assessment on compliance ○ Statin(s) ○ Bile acid sequestrant(s) ○ Cholesterol absorption inhibitor (Ezetimibe) ○ PCSK9 inhibitor(s) ○ Nicotinic acid ○ Drug combinations ○ Bempedoic acid and/or bempedoic acid fixed dose combination with ezetimibe ○ Other ○ Clinical events associated with the lipid modifying treatment modalities: ○ Insufficient lipid lowering efficacy ○ Muscle-associated symptoms ○ New-onset diabetes mellitus

	○ Reduced kidney function ○ Drug-drug interaction ○ Noncompliance ○ Neurocognitive impairment ○ Other ○ Laboratory parameters ○ Lipid variables ○ LDL-C ○ HDL-C, non-HDL-C, TC, apoB, TG, Lp(a) ○ Diabetes-related parameters ○ fasting glucose ○ HbA1c ○ Inflammatory status ○ hsCRP ○ Renal function parameters (GFR, serum creatinine, blood urea nitrogen (BUN)) ○ Other laboratory parameters (liver function, serum chemistry, hematology) ○ HEOR parameters ○ Hospital admissions ○ Length of hospital stay ○ Number of days in ICU ○ Interventions ○ Other HEOR parameters (e.g. insurance status , employment status, education) ○ Adherence to former and current treatment ○ Patient reported outcomes (EQ-5D-5L, PAM-13)
Data Sources	As this is a non-interventional study, only data on routine clinical practice will be documented. To facilitate accurate recording of data, patients can optionally fill in a memory aid (patient diary to note important details).
Study Size	Sample size considerations: As this registry is intended to collect data under real-life conditions and the statistical analysis will be performed in a purely explorative way, no primary parameter has been defined for the sample size calculation. On a pragmatic basis, data of approximately 8000 patients will be collected, whose data is to be documented both retrospectively and prospectively (over a period of 1 year). This sample size of 8000 patients will provide sufficient precision (measured by width of 95% confidence interval) for the rates of CV death, nonfatal MI, nonfatal stroke, and coronary revascularization during one year follow-up. Assuming an absolute reduction of LDL-C across all treatment modalities in a real-life setting of 0.9 mmol/L, the sample size shall provide information for an expected change in the relative risk of major vascular events with an absolute precision of ± 13% (relative precision ± 16%).
Data Analysis	Three populations will be defined: (1) The All-Documented Patient Set (APS) consists of all patients with any eCRF documentation. (2) patients with adequately completed recruitment information (Baseline Analysis Set / BAS population); (3) patients having

	completed 1-year follow-up (Full Analysis Set / FAS population). (4) The Safety Set (SAF) includes all patients who received at least one dose of bempedoic acid and/or bempedoic acid fixed dose combination according to their documentation in the eCRF. For BAS, FAS and SAF binary, categorical, and ordinal parameters will be summarized by means of absolute and percentage numbers within the various categories (including 'missing data' and 'not performed in the center' as valid category at baseline). Numerical data will be summarized by means of standard statistics (i.e. number of available data, number of missing data, mean, standard deviation, minimum, median, maximum, lower and upper quartile). At the final analysis the differences in the CV risk score for Very High Risk and for High Risk patients will be calculated. In addition, adequate graphs (e.g. bar charts, box-whisker plots) may be presented to summarize the results for some parameters. Analysis of changes in numerical parameters (as the differences in Score risk between baseline and 1-year follow up) will be done by paired Wilcoxon signed rank test and paired t-test if assumptions of parametric tests will be met. Comparison of these 1-year changes between subgroups will be done by Kruskal-Wallis test and ANOVA test if assumptions of parametric tests will be met. Also adjusted analyses for age, sex and country effects will be done. Time-to-event variables will be analyzed via a Cox proportional hazard regression model presenting hazard ratios and the corresponding 95% confidence intervals. Additionally, adjusted Cox models for age, sex and country effects will be presented. In addition, Kaplan-Meier curves will be presented for time-to-event variables. Two-sided 95%-CI will be presented for important parameters, but should be interpreted in an exploratory descriptive way. All statistical testing (including hazard ratios, relative risks etc.) will be performed in an exploratory manner only. Details regarding statistical analyses will be described in the SAP and in the statistical section of the report.
Quality Control	This study will be conducted according to the rules of 'Good Pharmacoepidemiology Practice' (GPP) and the 'Guideline on good pharmacovigilance practices' (GVP). Related quality control mechanisms (eg, data plausibility checks, monitoring of data) will be performed accordingly.
Milestones	First Patient In (FPI) / Start of Data Collection: Q1/2020 Last Patient In (LPI): Q4/2020 Last Patient Out (LPO) / End of Data Collection: Q4/2021 Final Report: Q4/2022 Timelines may be adapted in case some countries experience major delays of ethics approvals.

5 AMENDMENTS TO THE OBSERVATIONAL PLAN

In case of essential changes of an existing observational plan the investigators have to be informed as well as the respective local and/or competent authorities and Independent Ethics Committees if required by local laws or regulations.

6 MILESTONES

- Start of data collection: Q1/2020
- Planned snapshots: 2 for baseline data, 2 for follow-up data
- Planned end of data collection (planned): Q4/2021
- Final report of study results (planned): Q4/2022

7 RATIONALE AND BACKGROUND

Rationale

The current understanding of real-world medical practice in the management of dyslipidemia is incomplete. Relevant and detailed treatment guidelines, based to a considerable extent on the outcomes of randomized clinical trials (RCTs), offer health care providers advice and direction with respect to the management of their dyslipidemic patients. However, there are a number of reasons – including the strictly controlled RCT environment with respect to inclusion and exclusion criteria, the provision of treatment, patient follow up and compliance with therapy and dosing – why all of these aspects are very different in the real world. The observational study (registry) is increasingly looked upon as a valid and meaningful tool for supplementing RCTs with respect to real world information[1].

A better understanding of current medical practice in the field of dyslipidemia across European countries may contribute to an improvement in patient management and to an associated reduction in the clinical and economic burden of atherosclerotic cardiovascular disease (ASCVD) in Europe.

Background

Cardiovascular disease (CVD), especially its management and associated costs, is a topic of major interest in Europe as well as globally. The economic burden of CVD is enormous. CVD has been estimated to cost the EU economy €210 billion a year. Of this amount, €111 billion is due to direct health care costs, €54 billion to productivity losses, and €45 billion to the informal care of people with CVD[2].

CVD is the leading cause of death worldwide[3], and a direct correlation between circulating levels of low-density lipoprotein cholesterol (LDL-C) and the incidence of CVD has been established beyond doubt[4]. Life-style measures such as improved diet, exercise, and loss of weight are in some cases effective in lowering LDL-C and, consequently, in reducing the risk of CVD but, ultimately, drug therapy is required in many dyslipidemia patients. While a number of classes of lipid-lowering drugs are available, statins have become the gold standard and are acknowledged as first-line therapy. They are recommended as such by the current ESC/EAS Guidelines for the Management of dyslipidemias for the reduction of circulating levels of atherogenic lipoproteins as well as for the reduction of risk of clinical cardiovascular events in both primary and secondary prevention[5,6].

Nonetheless, and in spite of the widespread availability and broad use of statins, and of the availability of other older (as well as newer) drug classes (such as bile acid sequestrants, cholesterol absorption inhibitors, Proprotein convertase subtilisin/kexin type 9 (PCSK9) inhibitors, nicotinic acid, and their various combinations), a substantial proportion of patients

with dyslipidemia remains inadequately treated. These patients are, consequently, at higher risk than they would otherwise be. The reasons for this include: insufficient efficacy of the drugs (even, in some cases, high-intensity statins at their maximally authorized doses); the caution required for their use in certain patient populations (e.g., established diabetes or risk thereof, renal insufficiency, hepatic disease and/or LFT elevations), PCSK9 inhibitor market access restrictions and poor patient compliance. In the case of statins, the latter is related to the complex phenomenon of statin intolerance and, in particular, the muscle-associated side effects of these medicines. The most common reason given for statin discontinuation is muscle pain[7, 8].

With respect to statins, poor patient compliance is a major factor in the suboptimal outcomes, but its extent and underlying causes are not fully understood. While data from RCTs suggest that the rate of statin noncompliance is quite low, e.g., in the range of 1-2%[9], data from real-life studies present a very different picture, with estimates ranging from 10-50% and even higher[10, 11, 12, 13]. Discontinuation rates after 1 year have been variously reported as being in the range of 30%[14, 15] to almost 50%[16,17].

Importantly, poor adherence to statin therapy is associated with a significantly increased risk of cardiovascular events, death and decreased survival[18, 19, 20] and, consequently, with increased healthcare costs[21 22].

A further relevant issue impacting on CV outcomes is the relatively very low percentage of patients – about 70-80%, according to a number of recent European observational trials – who reach their LDL-C target. In a study involving > 4000 Familial Hypercholesterolemia (FH) patients, most of whom were on maximally tolerated statins, it was found that only 11% reached their LDL-C goal of < 100 mg/dl[23]. In a pan-European study in almost 7000 CHD patients on all intensities of statins (or none at all), 19% achieved their target values of < 70 mg/dl at 1 year[24]. In a multi-ethnic study of close to 2000 subjects likely to have FH, statins (half of which were high-intensity statins) were prescribed to 83% and only 10% overall and 29% of those with ASCVD attained their LDL-C targets[25]. In a very recent observational study on High and Very High Risk patients in central and Eastern Europe, LDL-C success rates of 11-42% (depending on the patient characteristics) were reported[26].

High and Very High Risk CV patient journeys seems to vary from country to country, and current understanding of the process is incomplete. A real-life observational study which documents meaningful patient journey-related parameters can be expected to provide meaningful insight into the care process, country-by-country.

With the aforementioned considerations in mind, it was deemed of interest to conduct an observational study enrolling a broad range of patients at High and Very High risk in various settings: in primary and secondary care, treated by general practitioners as well as specialists, in the office and the hospital sector. It will document the current management of dyslipidemic patients in Europe, including medical outcomes and outcomes relevant to HEOR. This will contribute to an understanding the management of dyslipidemic patients and, ultimately, help to characterize the clinical and economic burden associated with the management of atherosclerotic cardiovascular disease (ASCVD) in Europe.

8 RESEARCH QUESTION AND OBJECTIVES OF THE OBSERVATION

8.1 Primary Objective

The primary objective is to document, in the real-world setting, the effectiveness of current treatment modalities in managing plasma levels of LDL-C in Very High Risk and High Risk (e.g. SMART score for Very High Risk patients and Framingham risk score for High Risk patients) patients requiring LMTs

8.2 Secondary Objectives

The secondary effectiveness objectives are to document:

- The relationship between the above-mentioned treatment modalities and plasma levels of other potentially ASCVD-modifying cholesterol fragments, namely HDL-C, non-HDL-C, TC, apoB, TGs, and Lp(a).
- Changes in the inflammatory marker hsCRP over time
  Changes in the patient´s overall CV risk assessment over time measured through CV risk score calculators

The secondary safety objectives are to document:

- Clinical events associated with the various treatment modalities:
  - Laboratory abnormalities
  - Muscle-associated symptoms
  - New onset and/or worsening diabetes
  - Changes in the patients´ glycemic status over time
  - Adverse Drug Reactions associated with bempedoic acid and/or fixed dose combination with ezetimibe

Additional secondary objectives are to document:

- The characteristics of the sites and physicians caring for Very High Risk and High Risk patients
- The patients´ use of lipid-modifying treatment, especially with regard to a switch from one drug class to another, a dose modification of a given drug, a switch from one statin to another, any evidence of statin intolerance or insufficient responsiveness to a statin, including a maximally tolerated statin, and any use of combination drug therapy
- Various HEOR parameters associated with the management of dyslipidemic patients, such as PRO and healthcare resource use.

9 RESEARCH METHODS

9.1 Study Design

Multinational, multicenter, prospective, observational, non-interventional study

9.2 Setting

Approximately 8000 patients from different care settings (primary care and secondary care, different specialties) will be enrolled consecutively at a total of approximately 800 sites. It is estimated that each site will contribute 10 patients, although additional patients - subject to approval - may be considered. At each study site, the patients will be enrolled consecutively. Patients will be stratified for High and Very High Risk (per physicians' assessment) as well as for previously and newly treated patients. Sites will be required to complete a patient screening log of eligible patients for this disease registry at their treatment centers. This log will document

how patients came to be included or excluded from the study, in order to assess the representativeness of the study population. Minimal information will be recorded for all patients who are screened for study enrolment, but no patient-identifiable information should be recorded. Those patients who provide their informed consent will be enrolled into the study.
Study population:
The study population consists of Very High Risk and High Risk dyslipidemic patients previously diagnosed and treated as well as newly treated patients receiving their first LMT.
At baseline data collection point, baseline characteristics (LDL-C and other lipid parameters, CV risk assessment, concomitant diseases such as diabetes and congestive heart failure, certain HEOR variables) and relevant medical history (CV events such as myocardial infarction and stroke) will be documented.
In addition, for the previously diagnosed and treated patients, details on the lipid modifying treatment during the year before enrolment will be collected.

This information will be collected from the patients´ chart from all dyslipidemia-related visits at which the patient has been seen by the physician, starting from date of diagnosis.
At the follow-up data collection point at 1 year (± 2 months), available information on the patients' routine management between baseline and this data collection point, and efficacy and safety variables will be collected: LDL-C and the other lipid parameters, inflammatory status, overall CV risk scores (SMART and Framingham risk scores will be calculated centrally based on collected patient information), CV events such as myocardial infarction and stroke, diabetes related parameters, renal function parameters, and the lipid-modifying therapy. As an optional assessment, PRO questionnaires will be completed by the patient preferably in the physician's office.
Electronic data capture (EDC) will be used for the recording of the information.

As this is a non-interventional study, only data that is based on routine clinical practice will be documented. Treatment pattern and treatment initiation, continuation or changes are solely at the discretion of the physician and the patient. There will be no attempt to influence the prescribing patterns of any individual treating physician. All medication will be prescribed according to usual standard of care and will not be provided by the study sponsor. Participation in the study will in no way influence payment or reimbursement for any treatment received by patients during the study.

Participating Centers
Patients will be recruited from approximately 800 sites in Ireland, UK, Portugal, Spain, France, Belgium, the Netherlands, Denmark, Germany, Switzerland, Italy, and Austria, as well as Norway and/or Sweden and/or Finland. The sites may be office-based or hospital-based, and may be involved with either primary or specialized care, the latter including cardiology, diabetes, lipidology.

Different databases are used to put a site list of potential sites together (DSE internal database, local CRO databases, external databases as available). At least 3 times the targeted number of active sites are contacted by sending a site qualification questionnaire to be completed. These contacted sites are free to accept or refuse to participate in the NIS. A stepwise process for site selection will be performed to allow for representative regional distribution of sites and site specialties. Geographic representativeness within the country is maintained as sites are selected from each province and, where applicable, language region.

The site must meet the following criteria in order to be selected for participation in this study:

- To have access to patients on LMTs or suitable for LMTs

- To be able to document the data in the English language
- To be able to complete the study in the EDC system
- To be able to conduct the study adequately, with enough time and staff to identify eligible patients, conduct the patient consent process, participate in required trainings, enter study data, and follow-up with study related activities
- To agree in following-up patients for a period of 1 year per patient according to clinical routine.

Eligibility Criteria
Very High Risk and High Risk dyslipidemic patients requiring LMT's are eligible for enrolment.
Further inclusion criteria

- ≥ 18 years of age
- not simultaneously participating in any interventional study
- providing written informed consent for participation in the study (ICF)
- life expectancy > 1 year

Patients will be stratified for High and Very High Risk as well as for previously and newly treated patients.
As this is a non-interventional study, no explicit exclusion criteria are defined.

Patient Groups
There are no formal patient groups planned. No comparator groups will be introduced.

Schedule
The total study period from FPI to LPO is 30 months. The individual start per country depends on the approval status of the protocol by the responsible Ethics Committee and Competent Authorities and will range approximately from Q3 2019 to Q4 2020. Per country, the patient recruitment period consists of 9 months, followed by a 12-month follow-up period per patient. It is expected that the last patient will complete the study in Q4/2021. The final study report is expected to be available in Q4/2022.
Patients eligible for the study at the site will be documented in a screening log to allow for judgement on representativeness of patient inclusion.

Patient data will be documented at two data collection points in time:

- Baseline at enrolment,
- FU1 approximately 12 +/- 2 months after baseline (face-to-face meeting preferred)

At baseline, the patients' medical history will be documented as well as the currently applied therapy. At the annual follow-up data collection point, changes in therapy and disease status since the last data collection point will be documented. At the baseline and the follow up data collection point the patients will be asked to complete the patient reported outcome (PRO) questionnaire EQ-5D-5L and the PAM-13 questionnaire.

9.3 Variables

Parameters recorded during the observation period:

To be documented at baseline (if available):

- Eligibility
- Demographic and sociodemographic variables
- Vital signs
- Medical history, including CVD risk status-related medical history:
  - CV risk assessment with or without utilization of risk score
  - history/diagnosis and current status of dyslipidemia
  - heterozygous familial hypercholesterolemia (HeFH)
  - documented ASCVD either clinical or unequivocal on imaging
- Concomitant diseases
- For diabetic patients
  - disease type and date of diagnosis
  - treatment
  - microvascular complications
- Current concomitant medication for CVD
- Previous / current dietary restrictions

- Previous / current use of lipid-modifying treatment
  Previous / current use of lipid-modifying treatment including details of dose, dose modification, switching, combination therapy, drug intolerance, insufficient responsiveness, investigators and patients assessment on compliance
  - Statin(s)
  - Bile acid sequestrant(s)
  - Cholesterol absorption inhibitor (Ezetimibe)
  - PCSK9 inhibitor(s)
  - Nicotinic acid
  - Drug combinations
  - Bempedoic acid and/or bempedoic acid fixed dose combination with ezetimibe
  - Other

- Laboratory parameters
  - Lipid variables
    - LDL-C
    - HDL-C, non-HDL-C, TC, apoB, TG, Lp(a)
  - Diabetes-related parameters
    - fasting glucose
    - HbA1c
  - Inflammatory status
    - hsCRP
  - Renal function parameters (GFR, serum creatinine, blood urea nitrogen (BUN))
  - Other laboratory parameters (liver function, serum chemistry, hematology)

- HEOR parameters
  - Hospital admissions
  - Length of hospital stay
  - Number of days in ICU
  - Interventions
  - Other HEOR parameters

- Adherence to former and current treatment
- Patient reported outcomes (EQ-5D-5L, PAM-13)

To be documented at 1-year follow-up (if available):

- Vital signs
- CVD risk status:
  - CV risk assessment with or without utilization of risk score
  - history/diagnosis and current status of dyslipidemia
  - heterozygous familial hypercholesterolemia (HeFH)
  - documented ASCVD either clinical or unequivocal on imaging
- Concomitant diseases
- For diabetic patients
  - disease type and date of diagnosis
  - treatment
  - microvascular complications
- Current concomitant medication for CVD
- Previous / current dietary restrictions

- Previous / current use of lipid-modifying treatment
  Previous / current use of lipid-modifying treatment including details of dose, dose modification, switching, combination therapy, drug intolerance, insufficient responsiveness, investigators and patients assessment on compliance
  - Statin(s)
  - Bile acid sequestrant(s)
  - Cholesterol absorption inhibitor (Ezetimibe)
  - PCSK9 inhibitor(s)
  - Nicotinic acid
  - Drug combinations
  - Bempedoic acid and/or bempedoic acid fixed dose combination with ezetimibe
  - Other

- Clinical events associated with the lipid modifying treatment modalities:
  - Insufficient lipid lowering efficacy
  - Muscle-associated symptoms
  - New-onset diabetes mellitus
  - Reduced kidney function
  - Drug-drug interaction
  - Noncompliance
  - Neurocognitive impairment
  - Laboratory abnormalities
  - Other

- Adverse drug reactions associated with the use of bempedoic acid and/or bempedoic acid fixed dose combination with ezetimibe

- Laboratory parameters
  - Lipid variables
    - LDL-C
    - HDL-C, non-HDL-C, TC, apoB, TG, Lp(a)
  - Diabetes-related parameters
    - fasting glucose

    - HbA1c
  - Inflammatory status
    - hsCRP
  - Renal function parameters (GFR, serum creatinine, blood urea nitrogen (BUN))
  - Other laboratory parameters (liver function, serum chemistry, hematology)

- HEOR parameters
  - Hospital admissions
  - Length of hospital stay
  - Number of days in ICU
  - Interventions
  - Other HEOR parameters (e.g. insurance status , employment status, education)
  - Adherence to former and current treatment
  - Patient reported outcomes (EQ-5D-5L, PAM-13)*

*For documenting PRO (Patient Reported Outcomes) two validated questionnaires/assessments will be used as explained below.

EQ-5D-5L. The EuroQol (EQ-5D-5L), developed by the EuroQoL group, is a generic utility measure rating the current overall health states. It consists of five domains (mobility, self-care, usual activities, pain or discomfort, and anxiety or depression) and a visual analogue scale (VAS). The scores range from 0 to 100 based on the level of health for each domain given by participants. A score of 100 indicates that the current health is equivalent to full health; a score of 0 indicates that the current health is equivalent to death. According to the scores of the five domains, a sum utility score is calculated ranging from 0 to 1. A score of 1 represents a perfect state. In addition, patients have to rate their current health on a 20-centimeter vertical visual analogue scale scored from 0 to 100 reflecting the continuum from a best imaginable to the worst imaginable health state. The EQ-5D is proved to be a reliable, valid, self-reported measure. It is used most widely for general healthcare evaluation, including cost-utility evaluation.

PAM-13. PAM assesses patient knowledge, skills, and confidence for self-management based on 13 items.
It segments individuals into one of four activation levels along an empirically derived 100-point scale.
Each level provides insight into an extensive array of health-related characteristics, including attitudes, motivators, and behaviors. Individuals in the lowest activation level do not yet understand the importance of their role in managing their own health, and have significant knowledge gaps and limited self-management skills. Individuals in the highest activation level are proactive with their health, have developed strong self-management skills, and are resilient in times of stress or change.

9.4 Data Sources

As this is a non-interventional study, only data on clinical routine practice will be documented. To facilitate accurate recording of data, patients can optionally fill in a memory aid (patient diary) to note important details.

For this disease registry, safety reporting for drugs will be covered outside the scope of this study through the local processes of spontaneous reporting.
Scheduled assessments for the study are presented in the Data Collection Flow Chart provided below (Table 1). All data elements will be collected from information routinely recorded in the

patient files/medical records. No visits or examinations, laboratory tests or procedures are mandated as part of this study.
The EQ-5D-5Land PAM-13 questionnaires need to be filled out by the patients at the physician's office.

The completed forms will be collected at the site and sent on a regular basis to the responsible CRO for data transfer. The relevant information out of the PRO questionnaire and the assessment will be manually entered into the eCRF.

Table 1: Data Collection Flow Chart

Variable	Baseline	Follow-up
Eligibility criteria	x	
Baseline Characteristics	x	
Vital signs	x	x
Medical History	x	
Hypercholesterolemia risk factors and predisposing comorbidities	x	x
Use pattern of previous/current lipid modifying treatment	x	x
Previous and current dietary restrictions	x	x
Concomitant medications for cardiovascular disease	x	x
Concomitant diseases For diabetic patients: Disease type and date of diagnosis, detailed treatment information, microvascular complications	x	x
Laboratory examinations (as available in medical records*) **physicians will not be required to perform any mandatory laboratory assessment for this study*	x	x
Clinical events and hospitalizations		x
Management of hypercholesterolemia and physician contacts	x	x
PRO	x	x
Resource consumption/Health care utilization	x	x
ADRs related to bempedoic acid and/or bempedoic acid fixed-dose combination with ezetimibe**		x

** Only applicable for Patients with bempedoic acid and/or bempedoic acid fixed dose combination with ezetimibe treatment:

9.5 Sample Size Calculation

As this registry is intended to collect data under real-life conditions and the statistical analysis will be performed in a purely explorative way, no primary parameter has been defined for the sample size calculation. On a pragmatic basis, data of approximately 8000 patients will be collected, whose data is to be documented both retrospectively and prospectively (over a period of 1 year). This sample size of 8000 patients will provide sufficient precision (measured by width of 95% confidence interval) for the rates of CV death, nonfatal MTI, nonfatal stroke, and coronary revascularization during one year follow up.
Assuming an absolute reduction of LDL-C across all treatment modalities in a real-life setting of 0.9 mmol/L, the sample size shall provide information for an expected change in the relative risk of major vascular events with an absolute precision of ± 13% (relative precision ± 16%).

9.6 Data Management

The CRO's EDC system will be used for data capture. Data will be collected in standardized English eCRFs.

A data management plan will be created in the study start phase and will describe all functions, processes, and specifications for data collection, cleaning and validation. The eCRFs will include automated plausibility checks (e.g. range checks, conditional checks, etc.) at data entry to obtain immediate feedback if data are missing, out of range, illogical or potentially erroneous and allow for correction or confirmation by the site. Concurrent manual data review will be performed based on parameters defined in the data management plan. If necessary, queries will be manually generated within the EDC system and followed up for resolution.

Critical data variables will be defined that need to be filled in by the site to be able to complete and sign the eCRF module.

Data from the project specific EDC database will be exported into SAS data sets (as per CDISC SDTM definition) for further validation and analysis.

Data Entry/Electronic Data Capture

All data will be collected and entered directly into the CRO EDC system. Each participating site will have access to its enrolled patient data only. All sites will be fully trained on using the on-line data capture system, and on the eCRF completion guidelines and other help files. Sites will be responsible for entering patient data into the secure internet-based EDC database via the eCRF. Investigators and site personnel will be able to access their account with a unique personalized username and password. All eCRFs should be completed by designated, trained personnel as appropriate. Each eCRF is to be reviewed, electronically signed, and dated by the investigator. All changes or corrections to eCRFs will be documented in an audit trail and an adequate explanation is required.

Source Documents

In most cases, the source documents are contained in the patients' medical record and data collected on the eCRFs must be traceable to these source documents in the patients' medical records. In some cases, the eCRF, or part of the eCRF, may also serve as source documents. In these cases, a document should be available at the investigator's site and clearly identify those data that will be recorded directly in the eCRF, and for which the eCRF will be regarded as the source document. All original source documentation is expected to be stored at the site for the longest possible time required by local applicable regulations. The site will be instructed to notify the sponsor before any destruction of medical records of study participants.

File Retention and Archiving

To enable evaluations and/or audits from regulatory authorities or the sponsor, the investigator agrees to keep records, including the identity of all participating patients, all original signed informed consent forms and source documents. The records should be retained by the investigator according to local regulations, or as specified in the study contract, whichever is longer.

Each site will receive a study site file at study initiation which contains all documents necessary for the conduct of the study and is updated throughout the study. This file must be available for review in the event the site is selected for monitoring, audits, or inspections and must be safely archived for at least 10 years or according to local legislation respectively after completing the participation in the study. Documents to be archived include the patient screening log, copy of eCRF burned on a CD and the signed informed consent forms (ICF).

9.7 Data Analysis

This section describes the most relevant parts of the statistical analyses planned for a NIS/registry. All statistical methodology will be described in detail in the Statistical Analysis Plan (SAP) which will be finalized at the latest prior to database lock. All variables collected in the CRFs and/or other recordings (if applicable) and all derived parameters will be used in the statistical analysis.
A report including descriptive statistics of all documented parameters will be generated also if required for each participating country. Details on the selection criteria used will be given in the SAP and in the statistical section of the report.
Referring to the primary objective, the statistical analysis will be performed in a purely explorative descriptive way according to DSE SOP R-440.

Data will be collected at the following data collection points

- baseline ,
- 1-year prospective follow-up

Following analysis sets will be used for analysis

- The All-Documented Patient Set (APS) consists of all patients with any eCRF documentation.
- The Baseline Analysis Set (BAS) consists of all eligible patients of the APS who provide adequate baseline information.
- The Full Analysis Set (FAS) consists of all patients from the BAS with available 1-year follow-up data.
- The Safety Set (SAF) includes all patients who received at least one dose of bempedoic acid and/or bempedoic acid fixed dose combination according to their documentation in the eCRF.

No primary endpoint was defined in this study. No formal statistical tests will be performed within the statistical analysis.
All statistical analyses will be performed in a purely exploratory descriptive way.

Binary, categorical, and ordinal parameters will be summarized by means of absolute and percentage numbers within the various categories (including ‘missing data’ as valid category at baseline).

Numerical data will be summarised by means of standard statistics (i.e. number of available data, number of missing data, mean, standard deviation, minimum, median, maximum, lower and upper quartile). In addition, adequate graphs (e.g. bar charts, box-whisker plots) may be presented to summarize the results for some parameters. Analysis of changes in numerical parameters (as the differences in Score risk between baseline and 1-year follow up) will be done by paired Wilcoxon signed rank test and paired t-test if assumptions of parametric tests will be met. Comparison of these 1-year changes between subgroups will be done by Kruskal-Wallis test and ANOVA test if assumptions of parametric tests will be met. Also adjusted analyses for age, sex and country effects will be done. Time-to-event variables will be analyzed via a Cox proportional hazard regression model presenting hazard ratios and the corresponding 95% confidence intervals. Additionally, adjusted Cox model for age, sex and country effects will be presented. In addition, Kaplan-Meier curves will be presented for time-to-event variables. Two-sided 95% confidence intervals will be presented for important parameters, but should be interpreted in an exploratory descriptive way.
Depending on the variable(s) of interest, additional selection criteria for patients (e.g. subgroup analyses) considered in specific analyses may be used, if considered useful during the statistical

analysis. Details on the selection criteria used will be given in the Statitical Analysis Plan (SAP) and in the statistical section of the report.

The statistical analysis will be performed using SAS version 9.4 or higher

9.8 Quality Control/Monitoring

Data quality checks will be performed on an ongoing regular basis. Queries will be raised by the responsible CRO and shall be answered by the site in due course. The purpose is to ensure that the rights of the patients are protected, that the reported data are accurate and complete, and that the conduct of the study is in compliance with the observational plan and applicable regulatory requirements.

Particular attention will be paid during monitoring activities to the completeness and correctness of safety data.

The physician will comply with the confidentiality policy as described in the site contract. The physician will comply with the observational plan and the requirements described in the contract. The physician is ultimately responsible for the conduct of all aspects of the NIS at the site and verifies by signature the integrity of all data transmitted to the sponsor.
On-site monitoring will be performed in 20% randomly selected sites. During on-site monitoring the monitor will verify 100% of informed consent documentation and perform source data verification against the patients' medical records in randomly selected patients (3 per site).
This study will be conducted according to the rules of 'Good Pharmacoepidemiology Practice' (GPP) and the 'Guideline on Good Pharmacovigilance Practices' (GVP). Related quality control mechanisms (e.g., data plausibility checks, monitoring of data) will be performed accordingly.

9.9 Limitations of the Research Methods

Although sites will be selected to guarantee representativeness for the respective country or region as much as possible, sites also need to have sufficient capabilities, interest and capacities to participate in the NIS. This may influence the sites' representativeness in some smaller regions.

Eligible patients not giving their informed consent to participate in the NIS cannot be enrolled. Therefore this may impact the consecutive enrolment at a site. To be able to assess the consecutiveness of enrolment, eligible patients will be listed in the patient screening log. Patients participating in competing interventional trials are not eligible and will not be entered in the screening list.

At the annual documentation time point all relevant changes/events since the last documentation time point need to be entered. Due to the long time between Baseline and the Follow-up data collection point an underreporting of data might occur that are not considered essential or that are difficult to remember. The patient memory aid and the patients' medical records at the site shall support the precise documentation of the time between two annual data documentation time points. The utility of both records is however influenced by the precision and accuracy with which the memory aid and the medical records have been completed in the meantime. It is expected that possible underreporting will not appear in case of severe events and hospitalizations and that this data is considered to be representative for the whole study population.

In addition to the above mentioned underreporting of events, the time between two documentation points might cause an incorrect documentation of treatment changes. This could lead to a misclassification with respect to the exposure. However, this risk is considered to be low as relevant treatment changes are usually documented in the medical records and can furthermore be entered into the eCRF at any time (log-file approach). In addition, the patient memory aid again supports a precise documentation.

Also differences between the countries/regions might occur, especially when rating compliance. Therefore, especially for the compliance the analysis by country/region will be carefully looked at. In case that there will be mentionable differences, the interpretation has to be very careful and should consider regional differences.

As the study is non-interventional, only data from the clinical routine treatment can be obtained. Therefore some information may be missing or unavailable. This needs to be taken into account when data are analyzed and reported.

No explicit non-eligibility criteria are defined to avoid selection of patients and thus violation of the 'real-life' principle.

10 PROTECTION OF HUMAN SUBJECTS

10.1 Review by Ethics Committees/Competent Authorities

Notification to or approval by independent Ethics Committees (IECs) and competent authorities (CAs) or other organizations will be performed as required by national regulations in the participating countries before commencement of enrolment at a study center.

10.2 Insurance and Liability

All treatments of patients included in this NIS are local standard of care and occur as part of the clinical routine practice. The NIS is non-interventional and does not foresee any change of treatment nor additional examinations apart from the standard of care. Claims of the patient upon his/her physician resulting from an inappropriate use of the prescribed medication will not be covered by Daiichi Sankyo. A specific patient insurance for NIS is not necessary (if not in contradiction with specific legal requirements in the country of conduct).

10.3 Patient Information, Informed Consent (if applicable)

Written Informed Consent (ICF) will be obtained from all patients.
It is the responsibility of the investigator to inform the patient about his/her disease, possibilities for diagnostic and therapeutic measures, independent of a possible participation in any survey and therefore this information will not be part of the ICF.
The written ICF will be provided to the sites in the local language(s) of the planned patient population. The ICF and any revision(s) will be approved by the Independent Ethics Committee (IEC) prior to being provided to potential patients, or submitted to IEC where no approval is required.
The patients' written informed consent will be documented in the patients' medical records of the investigator. Two ICF forms should be signed and personally dated both by the patient and by the investigator who conducted the informed consent discussion. One original signed ICF should be retained at the study center (preferably in the patients' medical records). The second original of the signed consent form should be provided to the patient. The date informed consent was given will also be recorded in the Case Record Forms (eCRF).

10.4 Data Protection

The patients' privacy will be kept according to the requirements of the Regulation (EU) 2016/679 (General Data Protection Regulation). Data will be collected in a pseudonymous way. An identification number assigned to each patient will be used in lieu of the patient's name to protect the patient's identity when reporting study-related data.
Only authorized personnel as hospital staff at the site has access to the identification list or original source documents (medical records). Representatives of the sponsor, the contract research organization (CRO) and authorities are allowed to get access in case of audit or inspection or for monitoring purposes. The patient will agree to this by signing a respective statement on the ICF.
The database will be maintained under the CRO domain by the service provider with all safety instalments for a physically and logically secure computer system. The system is fully validated and in line with industry and regulatory standards. The system also meets the standards of the International Council on Harmonization (ICH) guideline E6R2 regarding electronic study data handling and is available for audit upon request. Patient confidentiality will be strictly maintained.

10.5 Numbering and Identification of Patients

A unique identification number (patient ID) will be assigned to each patient when reporting data in the eCRF.
At each study center a patient identification list will be kept linking the identification number to the patient's identity.

10.6 Assessments (according to the study type)

The investigators will be instructed about the correct documentation of the required variables for each patient in the eCRF. These data are available as part of the routine treatment. All examinations performed depend on the discretion and clinical routine of the physician. No diagnostic or monitoring procedures are applied to the patients in the study other than those performed as standard of care.

11 COLLECTION AND REPORTING OF ADVERSE DRUG REACTIONS/ADVERSE EVENTS (IF APPLICABLE)

In this disease registry, the physician has to report any ADR in his/her routine ways as regular spontaneous reports in accordance with the Guideline on Good Pharmacovigilance Practices (GVP) as well as in accordance with local laws for all medication except bempedoic acid and/or bempedoic acid fixed dose combination with ezetimibe treatment.

For patients treated with bempedoic acid and/or bempedoic acid fixed dose combination with ezetimibe treatment the following process needs to be followed in case of an Adverse Drug Reaction (ADR):

11.1 Definitions

Adverse Drug Reaction (ADR)

A response to a medicinal product which is noxious and unintended and which occurs at doses normally used in man for the prophylaxis, diagnosis or therapy of disease or for the restoration, correction or modification of physiological function.

Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility.

Adverse reaction also includes adverse clinical consequences associated with use of the product outside the terms of the Summary of Product Characteristics or other conditions laid down for the marketing and use of the product (including prescribed doses higher than those recommended, overdoses or abuse).

Serious Adverse Drug Reaction (SADR)

Serious adverse reaction means an adverse reaction which

- Results in death,
- Is life-threatening,
- Requires inpatient hospitalization or prolongation of existing hospitalization,
- Results in persistent or significant disability or incapacity, or
- Is a congenital anomaly/birth defect.

Life threatening in this context refers to a reaction in which the patient was at risk of death at the time of the reaction; it does not refer to a reaction that hypothetically might have caused death if more severe.

Medical and scientific judgement should be exercised in deciding whether other situations should be considered serious reactions, such as important medical events that might not be immediately life threatening or result in death or hospitalization but might jeopardize the patient or might require intervention to prevent one of the other outcomes listed above. Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasia or convulsions that do not result in hospitalization or development of dependency or abuse.

Note:

Procedures are not ADRs or SADRs, but the reason for the procedure may be an ADR or SADR. Pre-planned (prior to signing the Informed Consent Form) procedures or treatments requiring hospitalizations for pre-existing conditions that do not worsen in severity are not ADRs.

11.2 Reporting of Suspected ADRs by the Investigator

All bempedoic acid or fixed dose combination related adverse drug reactions need to be reported within 24 hours, and will be documented by the site in the respective section of the eCRF as soon as the site becomes aware of it. The pharmacovigilance department of the sponsor (Daiichi Sankyo Europe GmbH, Clinical Safety & Pharmacovigilance Department, Zielstattstrasse 48, 81379 Munich, Germany) and the local safety officers (LSO) at the responsible Daiichi Sankyo affiliate will receive an automated notification email. All ADR details will be obtained from the eCRF and will be processed further in line with the requirements for spontaneous reporting and in accordance with the Guideline on Good Pharmacovigilance Practices (GVP).

If a patient completed the SANTORINI study, and an ADR occurs, the site will proceed further in line with spontaneous reporting as described above; if the outcome is not clear at the end of the SANTORINI study, then the site will fup until it is solved.

11.3 Pregnancy

Daiichi Sankyo must be notified of those patients only who become pregnant while receiving or within 30 days of discontinuing bempedoic acid and/or fixed dose combination with ezetimibe. The patient should discontinue bempedoic acid and/or fixed dose combination with ezetimibe upon confirmation of pregnancy.

Although pregnancy is technically not an adverse reaction, pregnancies for patients treated with Bempedoic acid and/ or fixed dose with ezetimibe must be followed to conclusion to determine their outcome. This information is important for both drug safety and public health concerns. It is the responsibility of the Investigator, or designee, to report any pregnancy in a female patient using the Exposure In Utero (EIU) Reporting form.

Please contact your study monitor to receive the EIU Reporting Form upon learning of a pregnancy. The Investigator should make every effort to follow the patient until completion of the pregnancy and complete the EIU Reporting Form with complete pregnancy outcome information, including normal delivery and induced abortion.

The adverse pregnancy outcome, either serious or non-serious, should be reported in accordance with study procedures. If the outcome of the pregnancy meets any criteria for immediate classification as a SADR (e.g., post-partum complications, spontaneous or induced abortion, stillbirth, neonatal death, or congenital anomaly, including that in an aborted fetus), the Investigator should follow the procedures for reporting ADRs outlined in Section 11.2.

12 DOCUMENTATION AND ARCHIVING

The sponsor is responsible for archiving study specific documentation (Observational plan, potential amendments, Final Report and Database) for at least ten years. Archived data may be held on electronic record, provided that a back-up exists and that hard copies can be obtained, if required.
The investigator is responsible for archiving the patient identification list, all signed ICFs and his contract for at least ten years and in accordance with local legislation, if applicable.
Physicians are obliged to keep patient files according to national requirements.

13 LEGAL REQUIREMENTS

This NIS fulfils the requirements of the Directive 2001/83 EC, Guidelines on Good Pharmacovigilance Practices (GVP), Directive 95/46 EC, the Declaration of Helsinki and will be conducted in accordance with the respective SOPs of DSE.

13.1 Reimbursement

Compensation according to local regulations and to the time spent to inform patients and to document patient data will be paid. This compensation also includes the honorarium for responding to queries and for monitoring if applicable.

13.2 Registration

This registry will be listed in a public registry which meets International Committee of Medical Journal Editors (ICJME) requirements, before the onset of patient enrolment.

14 FINAL REPORT

A final NIS report will be presented latest one year after data base lock, if not required earlier by local legislation.

15 PUBLICATION

In order to protect confidential information and/or the interests of DSE, all publications (manuscripts and congress presentations) or announcements originating from this research are governed jointly by the SC and the Sponsor.

Aside from the main publication, participating investigators in the study can propose subgroup analysis and related second level publications to the SC and the Sponsor. Such publications may be produced by a dedicated team of authors other than the SC in common agreement with and governed jointly by the SC and the Sponsor.

16 PREMATURE TERMINATION OF THE NIS/REGISTRY

The physician may withdraw his/her participation in this registry at any time. In the case of a premature termination of the entire NIS/registry by the sponsor, the project leader has to inform all participating sites, Ethics Committees, and authorities.

17 REFERENCES

1. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-World Evidence - What Is It and What Can It Tell Us? N Engl J Med. 2016 Dec 8;375(23):2293-2297.

2. Wilkins E, Wilson L, Wickramasinghe K, et al. European Cardiovascular Disease Statistics 2017. European Heart Network, Brussels.

3. Nichols M, Townsend N, Scarborough P, Rayner M. Cardiovascular disease in Europe 2014: epidemiological update. Eur Heart J. 2014 Nov 7;35(42):2950-2959.

4. Mihaylova B, Emberson J, Blackwell L, et al. (Cholesterol Treatment Trialists' (CTT) Collaborators). The effects of lowering LDL cholesterol with statin therapy in people at low risk of vascular disease: meta-analysis of individual data from 27 randomised trials. Lancet. 2012 Aug 11;380(9841):581-590.

5. Law MR, Wald NJ, Rudnicka AR. Quantifying effect of statins on low density lipoprotein cholesterol, ischaemic heart disease, and stroke: systematic review and meta-analysis. BMJ. 2003 Jun 28;326(7404):1423.

6. Mach F, Baigent C, Catapano AL, et al. 2019 ESC/EAS Guidelines for the management of dyslipidaemias: lipid modification to reduce cardiovascular risk. Eur Heart J. 2019 Aug 31. doi: 10.1093/eurheartj/ehz455.

7. Vrablik M, Catapano AL, Wiklund O, et al. Understanding the Patient Perception of Statin Experience: A Qualitative Study. Adv Ther. 2019 Oct;36(10):2723-2743.

8. Krähenbühl S, Pavik-Mezzour I, von Eckardstein A. Unmet Needs in LDL-C Lowering: When Statins Won't Do! Drugs. 2016 Aug;76(12):1175-1190.

9. Vonbank A, Drexel H, Agewall S, et al. Reasons for disparity in statin adherence rates between clinical trials and real-world observations: a review. Eur Heart J Cardiovasc Pharmacother. 2018 Oct 1;4(4):230-236.

10. Lansberg P, Lee A, Lee ZV, Subramaniam K, Setia S. Nonadherence to statins: individualized intervention strategies outside the pill box. Vasc Health Risk Manag. 2018 May 24;14:91-102.

11. Vonbank A, Agewall S, Kjeldsen KP, et al. Comprehensive efforts to increase adherence to statin therapy. Eur Heart J. 2017 Aug 21;38(32):2473-2479.

12. Deshpande S, Quek RG, Forbes CA, et al. A systematic review to assess adherence and persistence with statins. Curr Med Res Opin. 2017 Apr;33(4):769-778.

13. Pedro-Botet J, Climent E, Benaiges D. Muscle and statins: from toxicity to the nocebo effect. Expert Opin Drug Saf. 2019 Jul;18(7):573-579.

14. Kamal-Bahl SJ, Burke T, Watson D, Wentworth C. Discontinuation of lipid modifying drugs among commercially insured United States patients in recent clinical practice. Am J Cardiol. 2007 Feb 15;99(4):530-534.

15. Zhang H, Plutzky J, Skentzos S, Morrison F, et al. Discontinuation of statins in routine care settings: a cohort study. Ann Intern Med. 2013 Apr 2;158(7):526-534.

16. McGinnis B, Olson KL, Magid D, et al. Factors related to adherence to statin therapy. Ann Pharmacother. 2007 Nov;41(11):1805-1811.

17. Wei MY, Ito MK, Cohen JD, Brinton EA, Jacobson TA. Predictors of statin adherence, switching, and discontinuation in the USAGE survey: understanding the use of statins in America and gaps in patient education. J Clin Lipidol. 2013 Sep-Oct;7(5):472-483.

18. Cohen JD, Brinton EA, Ito MK, Jacobson TA. Understanding Statin Use in America and Gaps in Patient Education (USAGE): an internet-based survey of 10,138 current and former statin users. J Clin Lipidol. 2012 May-Jun;6(3):208-215.

19. Mampuya WM, Frid D, Rocco M, et al. Treatment strategies in patients with statin intolerance: the Cleveland Clinic experience. Am Heart J. 2013 Sep;166(3):597-603.

20. Serban MC, Colantonio LD, Manthripragada AD, et al. Statin Intolerance and Risk of Coronary Heart Events and All-Cause Mortality Following Myocardial Infarction. J Am Coll Cardiol. 2017 Mar 21;69(11):1386-1395.

21. Graham JH, Sanchez RJ, Saseen JJ, et al. Clinical and economic consequences of statin intolerance in the United States: Results from an integrated health system. J Clin Lipidol. 2017 Jan - Feb;11(1):70-79.

22. Rodriguez F, Maron DJ, Knowles JW, et al. Association of Statin Adherence With Mortality in Patients With Atherosclerotic Cardiovascular Disease. JAMA Cardiol. 2019 Mar 1;4(3):206-213.

23. Perez de Isla L, Alonso R, Watts GF, et al. (SAFEHEART Investigators). Attainment of LDL-Cholesterol Treatment Goals in Patients With Familial Hypercholesterolemia: 5-Year SAFEHEART Registry Follow-Up. J Am Coll Cardiol. 2016 Mar 22;67(11):1278-1285.

24. Reiner Ž, De Backer G, Fras Z, et al. (EUROASPIRE Investigators). Lipid lowering drug therapy in patients with coronary heart disease from 24 European countries--Findings from the EUROASPIRE IV survey. Atherosclerosis. 2016 Mar;246:243-250.

25. Zafrir B, Jubran A, Lavie G, et al. Clinical determinants and treatment gaps in familial hypercholesterolemia: Data from a multi-ethnic regional health service. Eur J Prev Cardiol. 2017 May;24(8):867-875.

26. Petrov I, Dumitrescu A, Snejdrlova M, et al. Clinical Management of High and Very High Risk Patients with Hyperlipidaemia in Central and Eastern Europe: An Observational Study. Adv Ther. 2019 Mar;36(3):608-620.