STATISTICAL ANALYSIS PLAN

PROTOCOL 1002-043

A RANDOMIZED, DOUBLE-BLIND, PLACEBO-CONTROLLED STUDY TO ASSESS THE EFFECTS OF BEMPEDOIC ACID (ETC-1002) ON THE OCCURRENCE OF MAJOR CARDIOVASCULAR EVENTS IN PATIENTS WITH, OR AT HIGH RISK FOR, CARDIOVASCULAR DISEASE WHO ARE STATIN INTOLERANT

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Statistical Analysis Plan v1.0 (14Nov2022) for Protocol 1002-043 Amendment 5 (24Sep2020)

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LIST OF ABBREVIATIONS

Abbreviation/Specialist Term	Definition
ADA	American Diabetes Association
ADaM	Analysis Data Model
AE(s)	adverse event(s)
AESI(s)	adverse event(s) of special interest
ALP	alkaline phosphatase
ALT	alanine aminotransferase
ANCOVA	Analysis of Covariance
AST	aspartate aminotransferase
ATC	Anatomical Therapeutic Chemical
BLQ	below limit of quantification
BMI	body mass index
BUN	blood urea nitrogen
CAD	coronary artery disease
CeVD	cerebrovascular atherosclerotic disease
CEC	Clinical Endpoints Committee
CI	confidence interval
CK	creatine kinase
CKD	chronic kidney disease
COVID-19	coronavirus disease of 2019
CRF	Case Report Form
CV	Cardiovascular
CVD	cardiovascular disease
DALIVE	Date of Last Known Alive
DBP	diastolic blood pressure
DC	Diabetes Committee
DFDOSE	Date of First Dose
DLASMT	Date of Last Assessment (for Non-Fatal Clinical Endpoints)
DLDOSE	Date of Last Dose
DLSFU	Date of Last Survival Follow-Up
DMC	Data Monitoring Committee

Abbreviation/Specialist Term	Definition
DSC	Date of Study Completion
eGFR	estimated glomerular filtration rate
EC	Executive Committee
EOS	End-of-Study
EOT	End-of-Treatment
EU	European Union
FAS	Full Analysis Set
FDA	Food and Drug Administration
FDCP	Fixed dose combination product
HbA_{1C}	glycated hemoglobin (Hemoglobin A_{1C})
HDL-C	high-density lipoprotein cholesterol
Hgb	Hemoglobin
HR	hazard ratio
hs-CRP	high-sensitivity C-reactive protein
ICDM	Inadequately Controlled Diabetes Mellitus
ID	Identifier
IMP	investigational medicinal product
ITT	Intention-to-treat
KM	Kaplan-Meier
LDL-C	low-density lipoprotein cholesterol
LDL-M	low-density lipoprotein cholesterol - measured
LLN	lower limit of normal
LMT	lipid-modifying therapy
LSM	least squares mean
LTFU	lost to follow-up
MACE	major adverse cardiac event
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
NODM	new-onset diabetes mellitus
non-HDL-C	non-high-density lipoprotein cholesterol
PAD	peripheral arterial disease
PCSK9i	proprotein convertase subtilisin/kexin type 9 inhibitor(s)

Abbreviation/Specialist Term	Definition
PD	Protocol Deviation
PH	proportional hazard
PMM	pattern mixture model
PPS	Per-protocol Set
PT	Preferred Term
SAE(s)	serious adverse event(s)
SAS	Safety Analysis Set
SAP	Statistical Analysis Plan
SBP	systolic blood pressure
SE	standard error
SI	Système International (International System of Units)
SOC	System Organ Class
SDTM	Study Data Tabulation Model
SMQ	Standardised MedDRA Query
TB	total bilirubin
TC	total cholesterol
TE	treatment-emergent
TEAE(s)	treatment-emergent adverse event(s)
TESAE(s)	treatment-emergent serious adverse event(s)
TFL(s)	table(s), figure(s), and listing(s)
TG(s)	triglyceride(s)
TRAC	Tendon Rupture Adjudication Committee
ULN	upper limit of normal
ULQ	upper limit of quantification
US	United States
USUBJID	Unique subject identifier
WBC	white blood cell
WHO-DDE	World Health Organization – Drug Dictionary Enhanced

1. INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses for Study Protocol 1002-043 *A Randomized, Double-Blind, Placebo-Controlled Study to Assess the Effects of Bempedoic Acid (ETC-1002) on the Occurrence of Major Cardiovascular Events in Patients with, or at High Risk for, Cardiovascular Disease Who are Statin Intolerant*, Amendment 5 (24 September 2020).

2. STUDY OBJECTIVES

2.1. Primary Objective

The primary objective is to evaluate whether administration of bempedoic acid 180 mg/day versus placebo reduces the risk of major adverse cardiac event (MACE) in patients with, or at high risk for, cardiovascular disease (CVD) who are statin intolerant. This will be assessed with a composite primary efficacy endpoint that includes time to first occurrence of cardiovascular (CV) death, nonfatal myocardial infarction (MI), nonfatal stroke, or coronary revascularization.

2.2. Secondary Objectives

The secondary objectives include:

- To evaluate whether long-term treatment with bempedoic acid 180 mg/day versus placebo reduces the risk of other clinical endpoints of CV morbidity and mortality and all-cause mortality
- To evaluate the effect of long-term treatment with bempedoic acid 180 mg/day versus placebo on low-density lipoprotein cholesterol (LDL-C) and high-sensitivity C-reactive protein (hs-CRP)
- To evaluate the long-term safety and tolerability of bempedoic acid 180 mg/day compared to placebo
- To evaluate the 12-month impact of treatment with bempedoic acid 180 mg/day versus placebo on absolute change in hemoglobin A_{1C} (HbA_{1C}) in patients with inadequately controlled type 2 diabetes mellitus (HbA_{1C} of 7% or greater at baseline)
- To evaluate whether long-term treatment with bempedoic acid 180 mg/day versus placebo reduces the risk of new-onset type 2 diabetes

2.3. Tertiary Objective

- To evaluate the effect of long-term treatment with bempedoic acid 180 mg/day versus placebo on non-high-density lipoprotein cholesterol (non-HDL-C), total cholesterol (TC), high-density lipoprotein cholesterol (HDL-C), triglycerides (TG), HbA_{1C}, and fasting glucose

3. STUDY ENDPOINTS

3.1. Primary Efficacy Endpoint

- Time to first occurrence of a MACE, where MACE is defined as the composite endpoint of CV death, nonfatal MI, nonfatal stroke, or coronary revascularization (MACE-4)

3.2. Secondary Efficacy Endpoints

3.2.1. Key Secondary Efficacy Endpoints

Key secondary efficacy time-to-event endpoints include, in hierarchical order:

1. Time to first occurrence of the composite endpoint of CV death, nonfatal MI, or nonfatal stroke (MACE-3)
2. Time to first occurrence of (fatal + nonfatal) MI
3. Time to first occurrence of coronary revascularization
4. Time to first occurrence of (fatal + nonfatal) stroke
5. Time to CV death
6. Time to all-cause mortality

3.2.2. Additional Secondary Time-to-Event Endpoints

Additional secondary efficacy time-to-event include:

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

3.2.3. Secondary Efficacy Lipid and Biomarker Endpoints

- Percent change from baseline to Month 6 in LDL-C
- Percent change from baseline to Month 6 in hs-CRP
- Change from baseline to Month 12 in HbA_{1C} in patients with inadequately controlled type 2 diabetes mellitus

3.3. Tertiary Lipid and Biomarker Endpoints

- Absolute change and percent change from baseline to Months 3, 6, 12, 24, then every 6 months through the end of study in LDL-C
- Absolute change and percent change from baseline to Months 3, 6, 12, 24, then every 6 months through the end of study in non-HDL-C, TC, HDL-C, and TG
- Percent change from baseline to Month 12 and at the end-of-study (EOS) in hs-CRP
- Change from baseline to Month 3, 6, 12, then every 6 months through the end of study in HbA_{1C}
- Change from baseline to Month 3, 6, 12, then every 6 months through the end of study in fasting glucose

3.4. Safety Endpoints

- Adverse events (AEs) and adverse events of special interest (AESIs)
- Vital signs
- Clinical laboratory measures

4. STUDY DESIGN

4.1. General Description

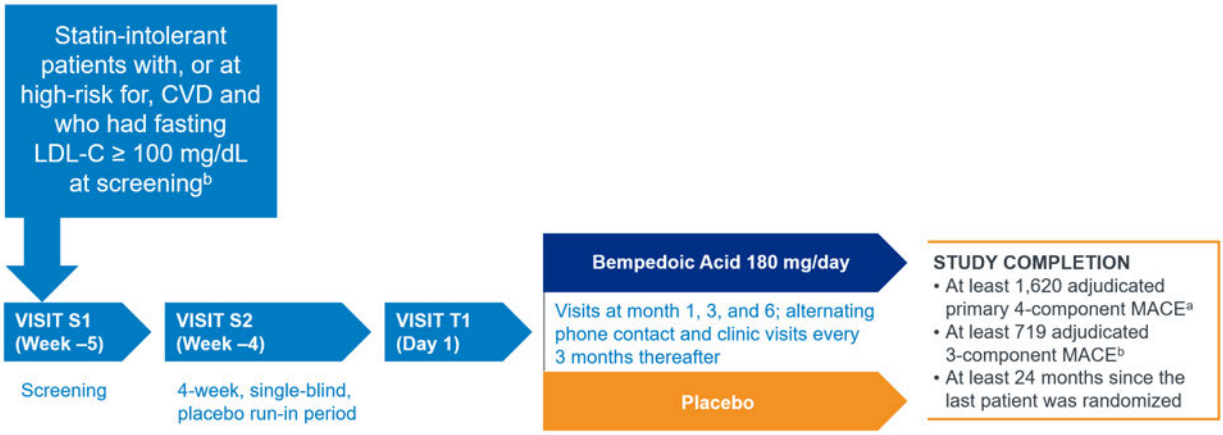
This is a Phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study assessing the occurrence of MACE in patients with, or at high risk for, CVD who are unable to tolerate statin therapy. The study is conducted at approximately 1200 clinical sites in 32 countries.

Following signing of an informed consent document prior to any study procedures, screening (Visit S1) occurred approximately 5 weeks prior to Day 1 (Visit T1) but can be extended for an additional 5 weeks if needed to adjust background medical therapy or for other reasons. All eligible patients will return at Week -4 (Visit S2, 4 weeks prior to Day 1) to initiate a 4-week Run-in Period with single-blind (blinded to patient only) placebo once daily that will include assessment of tolerability and investigational medicinal product (IMP) adherence. On Day 1 (Visit T1), approximately 14,000 eligible patients will be randomized 1:1 to receive either double-blind bempedoic acid 180 mg (n ~ 7,000) or placebo (n ~ 7,000) once daily. Randomized patients will return for clinic visits at Month 1 (Visit T2), Month 3 (Visit T3), and Month 6 (Visit

T4). Following Month 6, patients will be contacted every 3 months (alternating with a phone visit and a clinic visit) for the remainder of the study.

Patients who discontinue IMP for any reason are strongly encouraged to remain in the study to be evaluated for efficacy and safety endpoints and will be expected to continue study visits or agree to some other form of contact through the study closeout.

Figure 1: 1002-043 Study Design



4.2. Maintenance of Blinding

During the Treatment Period, Sponsor, site personnel, CRO, and patient are all unaware of patient's treatment assignment. Blinding of treatment must be maintained for all patients unless, in the opinion of the investigator, the safety of the patient may be at risk. If the blind must be broken prior to consultation with the Medical Monitor, contact must be made within 24 hours of breaking the blind.

Unblinding of IMP will NOT automatically discontinue the patient from the study. Any patient for whom the blind is broken will be permanently discontinued from IMP but should continue in the study.

Post-randomization values for individual laboratory measures for LDL-C, non-HDL-C, TC, TG, and hs-CRP are not available to blinded personnel from the clinical site, the patient, the Sponsor, or the CRO during the study.

4.3. Study Closeout

The study will continue until all the following criteria have been met:

1. at least 1,620 patients have experienced an adjudicated primary 4-component MACE (CV death, nonfatal MI, nonfatal stroke, or coronary revascularization),
2. at least 810 patients have experienced an adjudicated 3-component MACE (CV death, nonfatal MI, or nonfatal stroke) and
3. 24 months have elapsed since the last patient was randomized.

During the study closeout period (when the patients' End of Study (EOS) Visits will be scheduled), each patient still in the study will be required to complete an in-clinic visit which is

designated as the EOS Visit and perform the procedures according to Protocol Appendix 1, Schedule of Events. Patients who are still on IMP at the visit will be asked to end study treatment.

A post-treatment telephone visit will occur 30 days (± 10 days) after the EOS visit to assess AEs, SAEs and identify potential clinical endpoints.

During the study closeout period, vital status will be collected within legal and ethical boundaries (see Protocol Section 10.7.5) for all patients who did not complete the study, and only those with unknown status are considered as lost to follow-up.

4.4. Study Committees

This study includes several independent and expert committees:

- An Executive Committee (EC) oversees the design and conduct of the study and the interpretation of study results.
- An independent Data Monitoring Committee (DMC) reviews accumulating blinded and unblinded safety data from this and other ongoing studies of bempedoic acid approximately 4 times per year to ensure there is no avoidable increased risk of harm to patients. The DMC reviews safety data, reported and adjudicated MACE, and specific clinical laboratory results.
- A blinded independent Clinical Event Committee (CEC) adjudicates designated clinical endpoints, including MACE endpoints, as well as non-CV deaths.
- A blinded independent Diabetes Committee (DC) verifies diagnosis of new-onset type 2 diabetes.
- A blinded independent Tendon Rupture Adjudication Committee (TRAC) adjudicates potential events of tendon rupture.

Each of these committees has its own charter that includes additional details. Adjudicated or verified results for clinical events, diabetes and tendon rupture are maintained in a separate adjudication database.

[redacted]

4.6. Schedule of Events

The schedule of events can be found in Appendix 1.

5. PLANNED ANALYSES

The following analyses will be performed for this study:

- Safety analyses for DMC meetings
- Final Analysis

5.1. Data Monitoring Committee (DMC)

An independent DMC reviews accumulating blinded and unblinded safety in regularly scheduled intervals approximately 4 times per year to ensure there is no avoidable increased risk of harm to patients. DMC reviews safety data, reported and adjudicated MACE, and specific clinical laboratory results. The DMC is responsible for making recommendations about alteration or early termination of the study based upon their review of the blinded and unblinded data.

Analyses for the DMC are provided by an external vendor with a separate unblinded team. There are strict processes in place to ensure blinding for the study team. The details for DMC review procedures are described in the DMC Charter.

5.2. Interim Analyses

There are no interim efficacy analyses in this study.

5.3. Final Analyses

This SAP will be finalized prior to the database lock and unblinding of treatment. Additional analyses may be performed as needed but will be clearly marked as ad hoc.

6. ANALYSIS SETS

Inclusion of patients in each analysis set will be finalized prior to the unblinding of the study.

[redacted]

[redacted]

[redacted]

6.2. Full Analysis Set [FAS]

The full analysis set (FAS), used for all the efficacy analyses unless otherwise specified, is defined as all randomized patients, [redacted] The FAS is also known as the intention-to-treat (ITT) set of patients. Patients in the FAS will be included in their *assigned* treatment group.

Note that patients who participated in the study run-in period only and were not randomized will not be included in FAS.

6.3. Safety Analysis Set [SAS]

The safety analysis set (SAS), used for all the safety summaries, is defined as all patients in FAS who received at least 1 dose of double-blind IMP. Patients in the SAS will be grouped according to the *actual* treatment received, in particular:

- patients who were randomized to bempedoic acid but received placebo only will be included in the placebo group;
- patients who were randomized to placebo but received at least one dose of study IMP bempedoic acid will be included in the bempedoic acid group. Note that this does not apply to patients who received commercial bempedoic acid or commercial fixed dose combination of bempedoic acid and ezetimibe.

6.4. Per-Protocol Analysis Set [PPS]

The Per-Protocol Set (PPS) is a subset of FAS that excludes patients with selected major protocol deviations including:

The PPS has the same treatment group assignment as the FAS and is used for sensitivity analyses the primary and key secondary efficacy endpoints. The additional sensitivity analyses of on-treatment and pre-cross-in LMT analyses will also be conducted using PPS.

7. STUDY DEFINITIONS

7.1. Disposition

Study Completion: the study completion status is recorded on the *Study Completion/Early Termination* CRF. A patient is considered as having completed the study if the patient completed the designated EOS visit during the study closeout period (as determined by the site), or if the patient died during the study (i.e., had not been discontinued prior to death).

Treatment Completion: the treatment completion status is recorded on the *End of Treatment* CRF. A patient is considered as having completed study treatment if the patient is still on-

treatment (i.e., has not permanently discontinued treatment) at the EOS visit during the study closeout period or died within 30 days of last dose. Note that patients who did not complete the study will not be considered as having completed the study treatment.

7.2. Key Study Dates

7.2.1. Definition and Imputation of Key Event Dates

Date of End of Study (EOS): the study completion/early termination date recorded on the "Study Completion/Early Termination" CRF. Note that the patient may have a 30-day post EOS follow-up visit after this.

Date of Study Completion (DSC): For patients who did not complete the study, it is the later of a) the date of EOS and b) the date of the 30-day post EOS follow-up visit. For patients who completed the study, it is the latest date of a) the date of EOS, b) the date of the 30-day post EOS follow-up visit, or c) the date of death. This date is used to calculate the duration of study (follow-up) for each patient and all clinical events that happen during this period are adjudicated.

Date of First Dose of IMP (DFDOSE): for each patient, the DFDOSE is the date/time of administration recorded on the "On-Site Study Medication/ Compliance" CRF at Visit T1. If that field is missing, it is set to be next first date of administration at Visit T3.

Date of Last Dose of IMP (DLDOSE): the date of last dose is recorded on the End of Treatment CRF. In cases of missing either completely or partially, it is imputed as the earliest date of a) the last day of the month (if the month and year are present), or the last day of the year (if only the year is present); b) the Date of EOS; and c) the date of the last IMP dispense plus the number of tablets taken.

Date of Last Visit (DLVISIT): the last date recorded on either the *Visit Date* or the *Telephone Contact* CRFs. For patients who did not complete the study, this must be on or prior to the DSC.

Date of Last Known Alive (DALIVE): for patients whose vital status at the end of study is either alive or unknown, this is the last day when the patient is known to be alive. It is the latest "last known alive date" recorded on the *Survival Status* CRF. If this date is partially or completely missing, it is set to the later of last known alive date with imputation and DSC.

Date of Last Assessment for Non-Fatal Clinical Endpoints (DLASMT): Potential clinical endpoints are assessed every three months either in clinic or by telephone through the Post-EOS Phone visit. For patients who died during the study within 90 days of last visit, the DLASMT is set to the date of death. Otherwise, the DLASMT is set to be DLVISIT. Note that this definition also applies to new-onset diabetes mellitus (NODM) as an efficacy endpoint.

Date of Last Survival Follow-Up (DLSFU): For patients who completed the study, or withdrew consent, or discontinued study and were identified as dead only through survival search (death is not adjudicated), it is the DSC. For all other patients it is the Date of Last Known Alive. This is the last date for survival status follow-up.

7.2.2. Reference Start Date and Study Day

Day 1 (Reference Start Date) is defined as the Date of First Dose of IMP, or the date of randomization for patients who did not receive any dose of IMP.

Study Day will be calculated from the reference start date (Day 1) as follows:

- If the date of the event is on or after the reference date, then: Study Day = (date of event – reference start date) + 1.
- If the date of the event is prior to the reference date, then: Study Day = (date of event – reference start date).

The Study Day will be used to show start/stop day of assessments and events (including AEs, prior and concomitant medications).

7.2.3. Baseline

For safety parameters, unless otherwise specified, baseline is defined as the last non-missing measurement taken on or prior to Day 1 (including unscheduled assessments).

Baseline for fasting glucose is defined as the mean of the last two non-missing fasting values measured on or prior to Day 1. If only one value is available, then that single value will be used as baseline. Baseline HbA_{1C} is defined as the last non-missing value on or prior to Day 1.

Baseline for lipids parameters (LDL-C, non-HDL-C, TC, HDL-C, TG) is defined as the mean of the last two non-missing fasting values measured on or prior to the *date of randomization*. If only one value is available, then that single value will be used as baseline. If the patient had no fasting values available at baseline, non-fasting values will be used.

Baseline for hs-CRP is defined as the last non-missing value on or prior to the date of randomization.

7.2.4. Analysis Visit Windows

For data analysis purpose, unless otherwise specified, study assessments will be assigned to analysis visits based on the Study Day (Section 7.2.2), and analysis visit windows specified in Appendix 3.

For lipids parameters (LDL-C, non-HDL-C, TC, HDL-C, TG) and hs-CRP, the *date of randomization* will be used as the start date to determine the analysis visit windows. For hs-CRP only, the end-of-study (EOS) measurement is defined as the last measurement taken for the patient.

In cases where multiple assessments fall into the same analysis visit, and only one is used for analysis, it is selected based on the following rules.

- The assessment closest to the target (nominal visit) date will be used.
- If there are ties, the assessment after the target date will be used.
- If multiple values are available with the same date and time, the assessment with larger laboratory accession number (LBREFID) will be used.

Note that unscheduled visits are treated the same way as scheduled visits.

Nominal visits (e.g., S1, S2, T1, etc, see Appendix 1) may be used in listings as appropriate.

7.2.5. Time to Event and Date of Censoring

For time-to-event analysis of clinical endpoint events (including new-onset type 2 diabetes), the start date is the date of randomization when the FAS is used, based on the ITT principle. When the PPS is used, the start date is set to be the date of first dose. For composite endpoints, the event date is the date of the first component event.

Patients who did not have any event in question will be considered as censored for the analysis. The date of censoring is determined as the following:

- Fatal events (CV death, fatal MI, fatal stroke, all-cause mortality): censored at Date of Last Survival Follow-Up.
- Non-fatal events and composite endpoints that include both fatal and non-fatal events: censored at the Date of Last Assessment.

Please see Section 18.3 for special censoring rule as applicable to patients from Ukraine as a result of the ongoing conflict.

7.3. Prior and Concomitant Medications

Prior medications are medications which started and ended prior to Day 1.

Concomitant medications are medications that started after Day 1, or that started before Day 1 and continued through Day 1, or if the status is "ongoing" at Day 1.

7.4. Diabetes Related Definitions

7.4.1. Baseline Glycemic Status

Analyses of diabetes and related biomarkers are conducted with specific subsets of study population based on the baseline glycemic status defined in Table 1.

- For efficacy analyses of new-onset type 2 diabetes (conducted in the study population with No Diabetes at baseline), and related biomarkers HbA1c and fasting glucose, the FAS (or PPS for sensitivity analyses) is used with subpopulations defined according to the baseline glycemic status.
- For safety analyses of AESIs of *new-onset diabetes* (conducted in the study population with No Diabetes at baseline), and *worsening hyperglycemia* (Diabetes at baseline), and related safety laboratory measures including HbA1c and fasting glucose, the SAS is used with subpopulations defined according to the baseline glycemic status.

Table 1: Baseline Glycemic Status

Status	Definition
Diabetes	Meeting 1 or more of the following criteria at baseline captured by information recorded prior to Day 1: • Medical history or adverse events indicating diabetes as defined in the Diabetes Committee Charter (attached as Appendix 8) • Prior glucose-lowering medication as defined by the Diabetes Committee Charter (attached as Appendix 8) • HbA_{1C} measurement ≥6.5% • Two or more measurements of fasting glucose ≥126 mg/dL (7.0 mmol/L)
Inadequately Controlled (IC) Diabetes	With Diabetes and a HbA_{1C} of 7% or greater at baseline.
No Diabetes	Not meeting any of the criteria for Diabetes at baseline.
Prediabetes	No Diabetes at baseline, and with: • HbA_{1C} measurement of ≥5.7% and <6.5%, OR • 1 or more measurements of fasting glucose ≥100 mg/dL (5.6 mmol/L), but not more than 1 value of fasting glucose ≥126 mg/dL (7.0 mmol/L).
Normoglycemia	No Diabetes, and not meeting the criteria for Prediabetes at baseline.

7.4.2. Antidiabetic Medications

For this study, antidiabetic medications are defined based on approved medications that lower blood glucose (Appendix 8).

Baseline antidiabetic medications are defined for the FAS as those ongoing at the time of randomization.

Patients are considered to have had a *change in background antidiabetic medications* if they had any new antidiabetic medications that either started, stopped or had a dose change during the 12 weeks (84 days) prior to screening (Visit S1) to within 12 months (365 days) post randomization. These patients are excluded from a sensitivity analysis of Month 12 HbA1c response.

7.4.3. NODM as an Efficacy Endpoint

For efficacy evaluation, NODM will be assessed in the subset of patients who did not have diabetes at baseline (No Diabetes), including those patients in the subsets of "prediabetes" and "normoglycemia", but develop postbaseline new onset type 2 diabetes mellitus, defined by 1 or more of the following criteria according to the 2020 American Diabetes Association (ADA) guidelines (ADA, 2020):

1. Fasting plasma glucose ≥126 mg/dL (7.0 mmol/L). Fasting is defined as no caloric intake for at least 8 hours;* or

2. Two-hour post-prandial glucose ≥200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test as defined in the ADA guidelines;* or
3. HbA_{1C} measurement ≥6.5% (48 mmol/mol);* or
4. In a patient with classic symptoms of hyperglycemia or hyperglycemic crisis, a random plasma glucose ≥200 mg/dL (11.1 mmol/L).

*Note: In the absence of unequivocal hyperglycemia, diagnosis requires 2 abnormal test results from the same sample or in 2 separate test results.

The NODM events will be verified by the Diabetes Committee based on the [redacted] Diabetes Committee Charter.

7.5. Other Baseline Characteristics

7.5.1. Region

Study patients are grouped by the sites' location into the following regions (GHDx, 2022):

- North America: Canada and United States.
- Latin America: Argentina, Brazil, Chile, Colombia, and Mexico.
- Western Europe: Austria, Belgium, Denmark, Germany, Great Britain, Netherlands, and Spain.
- Central and Eastern Europe: Bulgaria, Croatia, Czech Republic, Estonia, Hungary, Latvia, Lithuania, Poland, Romania, Russia, Serbia, Slovakia, and Ukraine.
- Other: Australia, India, New Zealand, South Africa, and Turkey.

7.5.2. History of Hypertension

A patient is considered to have had a history of hypertension if any preferred terms of the medical history (including events recorded on the Adverse Event CRF that started prior to the Day 1) match the terms listed in Appendix 11.

7.5.3. Baseline CVD Risk Category

A patient is in the category of secondary prevention for cardiovascular diseases (CVD) if there was any documented CVD history as recorded on the *Targeted Cardiovascular History/Risk Factors* CRF, including coronary artery disease (CAD), symptomatic peripheral arterial disease (PAD), or cerebrovascular atherosclerotic disease (CeVD). Otherwise the patient is considered in the high-risk primary prevention category.

7.5.4. History of Chronic Kidney Disease

A patient is determined to have a history of chronic kidney disease (CKD) if the medical history (including events recorded on the Adverse Event CRF that started prior to Day 1) includes preferred term *chronic kidney disease*.

7.6. Lipid-Modifying Therapy (LMT)

7.6.1. Definition of LMT

For this study, lipid-modifying therapy (LMT) includes:

- Statins: all available prior history of and concomitant statin use are recorded in the "Prior and Concomitant Statin Therapy for Dyslipidemia" CRF.
- Commercial bempedoic acid:
  - Bempedoic Acid alone: preferred name is "BEMPEDOIC ACID".
  - Bempedoic Acid and Ezetimibe FDCP (fixed dose combination product): the verbatim term contains both "BEMPEDOIC ACID" and "EZETIMIBE", or the brand names "NUSTENDI" or "NEXLIZET".
- Other LMTs taken within 3 months prior to screening and concomitantly are recorded using the standard "Prior and Concomitant Medication" CRF, and a medication is classified as LMT if the coded ATC Level 2 (ATC2) term is "LIPID MODIFYING AGENTS". The non-statins LMTs are further classified based on coded terms:
  - Selected Cholesterol Absorption Inhibitors (Ezetimibe): preferred name contains "EZETIMIBE", or Bempedoic Acid and Ezetimibe FDCP as noted above.
  - PCSK-9 Inhibitors (PCSK9i): preferred name is one of "EVOLOCUMAB", "ALIROCUMAB", or if the verbatim term contains "INCLISIRAN" or "LEQVIO".
  - Bile Acid Sequestrants: ATC Level 4 (ATC4) term is "BILE ACID SEQUESTRANTS"
  - Fibrates: ATC4 term is "FIBRATES"
  - Niacin Derivatives: ATC4 term is "NICOTINIC ACID AND DERIVATIVES".
  - Other: all other LMTs. In addition, this group also includes preferred name of "MONASCUS PURPUREUS" (red yeast rice) regardless of the ATC2 term.

Note that brand names are used in some cases because the coding dictionary (Section 8.4) does not contain the appropriate preferred names.

7.6.2. Categorization of Statin Intensity

Statin intensity at any given time is categorized as high, moderate, low, or very low based on average daily dose of the statin taken at the time and the cutoffs defined in Appendix 5 , or none if not taking statin at the time. Designations of statin dose intensity were modeled after the 2018 ACC/AHA Guideline on the Management of Blood Cholesterol (ACC/AHA, 2019). The table was modified by creating a "very low dose" statin intensity category that reflected the allowed statin dosing intensities used as background therapy in the trial (Protocol Section 7.1 Inclusion Criteria #2) and recognizes the different dosing regimens that statin intolerant patients may sometimes follow (such as alternate day dosing). The average daily dose is derived from the

dose and frequency recorded on the statin therapy CRF, or if the frequency is "Other", the daily dose entered by the site is used.

7.6.3. Baseline LMT

Baseline LMT is defined as any lipid-modifying agents that were ongoing at the time of randomization.

Baseline statin intensity is derived using the baseline statin with the highest intensity.

Baseline ezetimibe use is defined as the use of ezetimibe alone or in combinations that were ongoing at the time of randomization.

7.6.4. Cross-in LMT

For patients in the FAS, cross-in LMT is defined as either initiation of new non-statin LMT or an increase in statin intensity after randomization that meets at least one of the following criteria:

1. Any statin, regardless of the specific drug, started after randomization, with increased intensity if used at baseline, and continued for 90 days or more.
2. Non-statin oral prescription LMTs (Bile Acid Sequestrants, Fibrates, Niacin Derivatives, Ezetimibe, commercial Bempedoic Acid, commercial Bempedoic Acid and Ezetimibe FDCP, as defined in Section 7.6.1) that were not used at baseline (same preferred name), started after randomization and continued for 90 days or more.
3. PCSK9i started after randomization, not used at baseline (for evolocumab), or with increased intensity if used at baseline (specifically, for alirocumab switching from 75 mg once every two weeks to 150 mg once every two weeks or 300 mg once every 4 weeks), and continued for 90 days or more if mAb (evolocumab or alirocumab); or ≥1 dose for siRNA (inclisiran) after randomization, and before the EOS visit.

Since change of dosing regimen will resulted in a new entry on the medication CRFs, to determine the treatment duration, entries for medications of the same class (any statin, either of the PCSK9i mAbs), or the same preferred name (non-statin oral LMT) will be combined if the gaps between entries are ≤ 7 days (for oral drugs), or ≤ 30 days (for PCSK9 mAb injections).

The date of starting first adjunctive cross-in LMT is defined to be the start date of the first medication that meets the cross-in criteria.

8. STATISTICAL CONSIDERATIONS

8.1. Sample Size

This event-driven study is designed to provide at least 90% power to detect an approximate 15% relative risk reduction in hazard ratio corresponding to the primary composite MACE endpoint (CV death, nonfatal MI, nonfatal stroke, or coronary revascularization) at an overall study significance level (alpha) of 0.05. There are no interim efficacy analyses.

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

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

It is expected that at least 50% of the 1620 patients experiencing an adjudicated primary 4 component MACE (810 patients) will experience an adjudicated 3 component MACE (CV death, nonfatal MI, or nonfatal stroke). Therefore, the study will not stop until at least 1620 patients have experienced an adjudicated primary MACE endpoint, with 810 patients experiencing an adjudicated 3 component MACE, and a minimum of 24 months (2 years) have elapsed since the last patient was randomized.

8.2. Multicenter Studies

This study is conducted by multiple investigators at approximately 1200 centers in 32 countries. Region (Section 7.5.1) based on the country locations of the sites is used as a covariate and for subgroup analysis. Otherwise, the study center is not considered in the analysis.

8.3. Multiplicity

There are one primary and six key secondary efficacy endpoints of interest for statistical testing in this study. A gatekeeping or hierarchical approach is used to test the primary efficacy endpoint and then key secondary efficacy endpoints sequentially to preserve the study-wise Type I error rate at 5%. For each endpoint, the null hypothesis is that of no difference between bempedoic acid and placebo groups, and the order for the hierarchical testing is:

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

5. time to first occurrence of fatal or nonfatal stroke
6. time to CV death
7. time to all-cause mortality

For the final analysis of the differences between bempedoic acid and placebo, each hypothesis in this hierarchical order will be tested at a two-sided significance level of 0.05. Statistical significance at each step is required in order to test the next hypothesis. If any of the endpoints does not reach statistical significance, p-values for subsequent endpoints will be reported for information only.

For other efficacy and safety endpoints, a nominal p-value may be reported for information only.

8.4. Coding Dictionaries

Adverse events, medical history and procedures are coded using Medical Dictionary for Regulatory Activities (MedDRA) Version 23.1 (September 2020) including system organ class (SOC), high level term (HLT) and preferred term (PT).

Prior and concomitant medications are coded using WHO Drug Dictionary (WHO-DD) version WHODrug-DDE-B2 201809 ENG (September 2018).

8.5. Missing Data Handling

For the primary analysis of the primary and key secondary endpoints, there is no imputation. All clinical endpoints, including the types and dates of events, are adjudicated by the Clinical Event Committee (CEC) with no missing types or dates. Time-to-event analyses are carried out based on the censoring rules outlined in Section 7.2.5.

For other analyses involving missing data, specific analysis methods or imputation rules are specified in the relevant sections as needed. If not specified, general rules specified in this section apply.

8.5.1. Imputation of Missing Dates

For adverse events, and for prior and concomitant medications, if the start or end dates are incomplete, the date will appear as-is (partial or missing) in the listings. When full date is needed, e.g., to compute the Study Day, imputation rules specified in Appendix 4 will be used unless otherwise specified. In essence, AEs of uncertain start date will be considered as having started after the first dose. Medications of uncertain start or end dates will be considered as having started before, or continued after the first dose, respectively.

For LMTs (Section 7.6) and antidiabetic medications (Section 7.4.2), it is important to determine whether they were being used at baseline (i.e., the time of randomization, Section 7.6.3).

- When the medication start date is partially missing, it is imputed using the default rule. If the impute start date is before the date of randomization, and the end date is either completely missing with ongoing status of no, or only contains a year that is the same as the date of randomization, the end date is imputed with the later of the medication start date and the date of informed consent. Otherwise the default rule is used to impute the end date.

- When the medication start date is completely missing, and if the end date is either completely missing with ongoing status of no, or only contains a year that is the same as the date of randomization, both start and end dates are imputed with the date of informed consent.
- Otherwise, the start/end dates are inputted using the default rule.

8.5.2. Laboratory Data Beyond the Limits of Quantification

Quantitative laboratory measurements reported as "<X", ie, below the lower limit of quantification (BLQ), or ">X", ie, above the upper limit of quantification (ULQ), will be imputed as X for the purpose of quantitative summaries, but will be presented as recorded, ie, as "<X" or ">X" in the listings.

8.6. General Principles

Descriptive statistics (n, mean, standard deviation, median, 1st quartile, 3rd quartile, minimum, and maximum) will be calculated for continuous data as appropriate.

Categorical data will be summarized using counts and percentages. Missing values may be presented as a separate category when appropriate. Counts of zero in any category will be presented without percentage. Ninety-five percent (95%) confidence intervals (CIs) of the means or percentages may be calculated for selected continuous and categorical variables.

For time-to-event endpoints, Kaplan-Meier (KM) curves will be presented graphically by treatment group. KM estimates of cumulative incidence rates at specified time intervals (e.g., month 6, year 1, year 2, and yearly after randomization) and their 95% CIs will be presented. The hazard ratio and its corresponding 95% CI will be estimated from a Cox proportional hazard (PH) model with treatment group in the model. For between-group comparison, p-values (2-sided) will be calculated using log-rank tests.

9. DISPOSITION OF STUDY PARTICIPANTS

All patients screened will be accounted for in this study. The primary reasons for screen failure are collected in the *Screen Failure* CRF and will be tabulated and listed. For screen failures due to inclusion or exclusion criteria, the unmet criterion will be presented in a listing. Patient disposition including withdrawals (both from study treatment and the study), and final survival status will be summarized for the FAS and listed. The number of patients in each analysis set will also be presented.

In addition, the disposition for patients in the FAS with baseline ezetimibe use will also be provided.

10. PROTOCOL DEVIATIONS

All protocol deviations (PDs) will be presented in a listing, including any relationship to the COVID-19 pandemic.

Major protocol deviations, and all protocol deviations related to COVID-19 will be summarized by treatment group and categories.

The protocol deviations are recorded and tracked in the Clinical Trial Monitoring System. The final protocol deviations will be determined before treatment groups are unblinded.

11. DEMOGRAPHIC AND BASELINE CHARACTERISTICS

Demographic data and other baseline characteristics will be summarized by treatment group for the FAS, SAS and PPS. These data will also be provided for patients in the SAS with baseline ezetimibe use. No statistical testing will be carried out for demographic or other baseline characteristics.

The following demographic and other baseline characteristics will be summarized and listed for this study:

- Age (years)
- Age category (<65 years, ≥65 to <75 years, or ≥75 years)
- Sex (female vs male, at birth)
- Race (American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian or Other Pacific Islander, White, and Other)
- Ethnicity (Hispanic or Latino vs Not Hispanic or Latino)
- Region (defined in Section 7.5.1)
- Weight (kg)
- Height (cm)
- Body mass index (BMI) (kg/m^2) = weight (kg)/height $(m)^2$
- BMI category (<25 kg/m^2, 25 to <30 kg/m^2, or ≥30 kg/m^2).
- Baseline vital signs (systolic blood pressure, diastolic blood pressure, and heart rate)
- Baseline key laboratory Results (LDL-C, hs-CRP, Non-HDL-C, TC, HDL-C, and TG) (LDL-C results are presented in both conventional and standardized units, the others will be in conventional units only)
- Baseline LDL-C category (<130 mg/dL, ≥130 mg/dL and <160 mg/dL, ≥160 mg/dL)
- Baseline hs-CRP category (<2 mg/L, ≥2 mg/L)
- Baseline CVD risk category (Section 7.5.3), for patients with documented CVD history (secondary prevention), the prior history of CAD, PAD or CeVD.
- History of diabetes mellitus (Yes vs No, as collected in the *Targeted Cardiovascular History/Risk Factors* CRF)
- Baseline glycemic status (Section 7.4)
- History of hypertension (Yes vs No, Section 7.5.2)
- Alcohol consumption (Non-drinker, Former Drinker, or Current drinker)
- Tobacco use (Never used, Former user, or Current user)
- Baseline background lipid-modifying therapy (LMT) (Statin use including statin only or Statin + other LMT, other LMT without statin, or none, see also Section 7.6.1)

- Baseline statin intensity (none, very low, low, moderate, and high, see Section 7.6.2 and Appendix 5)
- Baseline ezetimibe use (Yes vs No)
- Statin intolerance criteria as collected on the *Statin Intolerance Criteria Compliance* CRF [redacted]
- Baseline estimated glomerular filtration rate (eGFR) category (≥90 mL/min/1.73m^2; 60 to <90 mL/min/1.73m^2; 30 to <60 mL/min/1.73m^2; or <30 mL/min/1.73m^2)
- History of chronic kidney disease history (Yes vs No, Section 7.5.4)

12. MEDICAL AND SURGICAL HISTORY

General medical and surgical history information will be presented by Medical Dictionary for Regulatory Activities (MedDRA) SOC and PT for the FAS. Medical history conditions are those conditions that started prior to screening and collected on the *Medical History* CRF.

13. MEDICATIONS

13.1. Prior and Concomitant Medications

Prior and concomitant medications will be presented for the SAS. In general, the medications will be summarized by Anatomical Therapeutic Chemical (ATC) drug class (ATC level 4, anatomical or pharmacological groups), preferred names, and by treatment group.

According to the protocol, non-statin medications up to 3 months prior to screening are collected. *All* prior use of statins is collected on a separate *Prior and Concomitant Statin Therapy for Dyslipidemia* CRF with pre-defined terms. Therefore, prior use of statins will be presented separately from other prior medications.

13.2. Antidiabetic Medications

For patients with diabetes at baseline in the FAS, and the subset with inadequately control diabetes, baseline antidiabetic medications (see Section 7.4.2) will be summarized by preferred names and treatment group.

Patients who had a change to antidiabetic medications will be summarized by baseline glycemic status:

- within 12 weeks before screening through 12 months (365 days) post-randomization;
- within 12 weeks before screening to before randomization (only applicable for patients with diabetes at baseline);
- from randomization through 12 months (365 days) post-randomization.

13.3. Lipid-Modifying Therapy

The use of LMTs (Section 7.6.1) will be summarized separately by categories including pre-specified statins, and by treatment group for the FAS, including:

- Baseline LMT (Section 7.6.3)
- Baseline statin intensity (Section 7.6.2), shift to maximum intensity during the study, and shift to the statin intensity ongoing at the end of the study
- Cross-in LMT (Section 7.6.4), including a summary of the time to first cross-in LMT (censored at DLASMT if no cross-in).

14. STUDY MEDICATION COMPLIANCE AND EXPOSURE

The time from randomization to IMP discontinuation (last dose) will be summarized by treatment groups, and presented using a Kaplan-Meier plot for all patients in the FAS. Patients not dosed will have a time of 0.

In addition, estimated compliance with study IMP will be presented for the FAS by treatment groups. The patients will be grouped as compliant, i.e., those who have >= 80% of required tablets (taken once daily) while on treatment, versus noncompliant (<80% compliance).

The percentage compliance calculation will be based on the tablet counts using the formula:

$$\text{Total \# of tablets taken} = \sum_{\text{bottles}} (100 - (\text{\# of tablets returned}))$$

as each bottle of double-blind IMP contains 100 tablets. If a dispensed bottle is not returned, it is assumed that the patient has taken all the tablets and the number of tablets returned is set to be zero (0).

$$\%\text{compliance} = \frac{[\text{total \# of tablets taken}]}{[\text{\# of days between last and first doses}]}$$

The percentage compliance is capped as a maximum of 100% if it exceeds 100% due to the imputation above.

Note that patients who did not receive any IMP will be counted as noncompliant (0%). In addition, if a patient did not return any bottles, he/she will also be counted as noncompliant (0%).

Exposure to the study treatment is based on the duration (in years) between the last and first doses, and will be presented for the SAS by treatment groups. Exposure will also be presented for patients in the SAS with baseline ezetimibe use.

15. EFFICACY ENDPOINTS

All efficacy analyses will be performed based on the FAS if not otherwise specified. Selected sensitivity analyses will be performed based on the PPS and will be clearly specified.

15.1. Adjudicated Clinical Endpoints

Clinical events including death (CV or non-CV), nonfatal MI, nonfatal stroke, coronary revascularization, and hospitalization for unstable angina that occurred during the study are reviewed and adjudicated by the CEC in a blinded fashion as described in the Charter.

Positively adjudicated clinical events that occurred after randomization will be summarized by adjudicated event types and subtypes, and by treatment groups for the FAS. They are included in the analyses for the derivation of study endpoints (Sections 3.1, 3.2.1 and 3.2.2).

When a patient had multiple events of the same type (e.g., two coronary revascularizations) on the same day, only one event is counted in descriptive and recurrent event analyses.

All adjudicated deaths and non-fatal clinical events will be presented in listings with information from the adjudication forms.

15.2. Primary Efficacy Endpoint

15.2.1. Primary Efficacy Endpoint

The primary efficacy endpoint is the time to first occurrence of an adjudicated MACE, where MACE is defined as a composite primary efficacy endpoint that includes CV death, nonfatal MI, nonfatal stroke, and coronary revascularization (4-component MACE).

The number of patients who had experienced a primary composite endpoint will be tabulated by the type of the first event and by treatment group. When a patient had multiple events among the 4-component MACE that occurred on the same day, the events will be sorted in the order of: nonfatal MI, nonfatal stroke, coronary revascularization, and CV death.

15.2.2. Primary Analysis Method of Primary Efficacy Endpoint

The null hypothesis, H_0, is that there is no difference between bempedoic acid 180 mg/day and placebo in time to first occurrence of a confirmed (adjudicated) MACE. The alternative hypothesis, H_1, is that bempedoic acid 180 mg/day is different from placebo:

$$H_0: \beta = 0 \text{ vs. } H_1: \beta \neq 0$$

Where the hazard h(t) is modeled as: $h(t) = h_0(t)\exp(\beta x)$ and β is the log hazard ratio (HR).

The primary efficacy endpoint will be analyzed using Cox PH model with treatment as a factor. The HR and its 95% CI and p-value from log-rank test will be provided. In addition, KM curves will be provided, to present a graphical description of the time to first occurrence of confirmed adjudicated composite endpoint of CV death, nonfatal MI, or nonfatal stroke (4-component MACE).

If none of these 4-component MACE events is observed, the patient will be censored (Section 7.2.4).

The assumption of proportional hazard will be evaluated graphically for the primary efficacy endpoint by Schoenfeld residual plot and log-log plot. Ad hoc sensitivity analyses may be performed if needed.

15.2.3. Primary Efficacy Endpoint Data Censoring Pattern

For patients who were censored, i.e., did not experience MACE-4 endpoint, the pattern of censoring will be summarized by treatment, including

- censored for non-CV death
- censored on or after completion of the EOS visit during closeout
- censored prior to the study closeout period and not by non-CV death
- censored within 30 days of the last dose
- censored more than 30 days after the last dose

The total patient-year lost-to-follow-up will be calculated by treatment group as the sum of time from the date of censoring prior to study closeout and not by non-CV death, to the May 15, 2022 when the study closeout was initiated.

15.2.4. Sensitivity Analyses of Primary Efficacy Endpoint

In the primary analysis, censoring is assumed to be uninformative, i.e., patients who were censored share a common hazard function as those who were not censored in the same treatment group. However, there is a key difference between them as the censored patients also by definition stopped the treatment, while the majority of those remained on-study were still on-treatment. To evaluate the potential impact, two sensitivity analyses will be performed:

- Multiple imputation analysis: the hazard function for patients after censoring is assumed to be the same as those patients who were assigned the same treatment, had stopped treatment but remained in the study follow-up longer. The data from those patients with follow-up will be used as the model for imputation of the time to events for the censored patients.
- Tipping point (TP) analyses: The goal of this analysis is to explore the plausibility of unobserved data assumptions under which the conclusions change. Unlike the standard multiple imputation analysis, the censored patients in the active treatment group are allowed to have the same or even worse outcome than those in the placebo group. A range of assumed hazard ratios (vs placebo) will be used to evaluate when the estimated treatment effect starts to "tip", i.e., becoming in favor of the placebo.

The details of the analyses are specified in Appendix 6.

15.3. Analyses of Secondary and Other Efficacy Endpoints

15.3.1. Secondary Efficacy Time-to-Event Endpoints

Each secondary efficacy time-to-event endpoint will be analyzed in a manner analogous to that used for the primary efficacy analysis. For each endpoint, the hazard ratio estimated using Cox

PH model and its 95% CI and associated p-value from log-rank test will be provided. In addition, KM curves will be provided for each of the key secondary efficacy time-to-event endpoints. Note that for the analyses involving hemorrhagic and nonhemorrhagic stroke, any stroke for which the CEC is unable to determine the type will be included as an ischemic (nonhemorrhagic) stroke.

15.3.2. Secondary Efficacy Endpoint Time to NODM

All potential events of NODM are reviewed and verified by the Diabetes Committee in a blinded fashion according to the Diabetes Committee Charter. All events that were reviewed will be presented in a listing. Only verified NODMs are analyzed as efficacy endpoints.

The time to first occurrence of new onset type 2 diabetes mellitus during study will be analyzed by a Cox PH model for the patients with baseline glycemic status (Section 7.4) of no diabetes in the FAS and its subcategories of prediabetes and normoglycemia. The prediabetes subgroup is considered as the primary analysis for this endpoint. The onset date of NODM will be the earliest date of the event as verified by the Diabetes Committee.

15.3.3. Secondary Efficacy Endpoint LDL-C

For this study, the directly measured LDL-C value is used when available, otherwise the calculated LDL-C value is used. All LDL-C analyses will be presented in both the conventional unit (mg/dL) and the standardized (SI) unit (mmol/L).

Percent change from baseline in LDL-C at Month 6 will be analyzed using a linear model with percent change from baseline as response, treatment group and baseline LDL-C as covariates. Since the variances of the response are potentially different for the two treatment groups (more variable with active treatment), the model will allow different residual variances by treatment group. Specifically, PROC MIXED can be used with 'REPEATED / group = trt' statement. In addition, Kenward-Roger method is to be used for approximating the degrees of freedom ('DDFM=kenwardroger' option to MODEL statement). Fitted mean (Least Square or LS means) percent changes from baseline for each treatment group will be calculated (with 95% CI) at baseline LDL-C level of 140 mg/dL. The estimated difference in percent changes from baseline between treatment groups will be provided with 95% CI and p-value for testing of no difference.

Since patients with missing LDL-C at Month 6 may have underlying distributions depending on whether the patient was assigned to the active treatment and remained on active treatment at the time, a pattern mixture model (PMM) is used for the analysis, using a multiple imputation approach. Specifically, missing LDL-C values at Month 6 were simulated using a linear regression model with Month 6 LDL-C value as response, and covariates including baseline LDL-C value, and an indicator variable that equals 1 if and only if the patient was assigned to the active treatment and remained on treatment at Month 6 (Day 182) (this can be achieved using PROC MI with monotone regression). Simulated datasets (20 replicates) are analyzed as described previously and the resulted estimates are combined using Rubin's method (Rubin, 1987; PROC MIANALYZE).

For tertiary endpoints of LDL-C measured at all timepoints (Baseline, Month 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60), the observed values at each timepoint, changes from baseline, and percent changes from baseline will be summarized by treatment groups. Differences of the

changes from baseline, and percent changes from baseline between the treatment groups will be presented together with 95% CIs at each timepoint, as descriptive analyses with no imputation.

15.3.4. Secondary Efficacy Endpoint HbA_{1C}

All efficacy analyses of HbA1c will be carried out stratified by the baseline glycemic status in the FAS. The subgroup of patients with Inadequately Controlled Diabetes (ICDM) at baseline is of primary interest. The other subgroups include Diabetes (that includes ICDM as a subset), Prediabetes, Normoglycemic, and No Diabetes (Prediabetes and Normoglycemic combined).

Analysis for the change from baseline to Month 12 in HbA1c will be analyzed similarly as LDL-C, with change from baseline as response, treatment group and baseline HbA_{1C} as covariates. There is no need to specify variance heterogenicity (no 'REPEATED' statement) and the default method for degrees of freedom calculation can be used. Fitted mean (LS means) changes from baseline for each treatment group will be calculated (with 95% CI) at baseline HbA1c levels of 8% and 7% for ICDM and Diabetes, 6% for Pre-Diabetes and 5.5% for Normoglycemic and the combined No Diabetes groups. The estimated differences in changes from baseline between treatment groups will be provided with 95% CIs and p-values for testing of no difference.

Missing HbA1c data at Month 12 will also be handled using PMM based on whether the patient was still on treatment at Month 12 (Day 365), similar to LDL-C above.

For tertiary endpoints of HbA1c measured at all timepoints (Baseline, Month 3, 6, 12, 18, 24, 30, 36, 42, 48, 54, and 60), the observed values at each timepoint, and changes from baseline will be summarized by treatment groups. Differences of the changes from baseline between the treatment groups will be presented together with 95% CIs at each timepoint, as descriptive analyses with no imputation.

15.3.5. Secondary Efficacy Endpoint hs-CRP

Due to the highly skewed distribution of hs-CRP, a nonparametric analysis based on Wilcoxon rank sum test will be performed for percent change from baseline to Month 6. Hodges-Lehmann estimate of location shift and its 95% CI will be provided. Only observed values will be used with no imputation.

For hs-CRP measured at other timepoints (Month 12, and End-of-Study, which is defined to be the last measurement of each patient), the observed values at each timepoint, and percent changes from baseline will be summarized by treatment groups.

15.4. Sensitivity Analyses for Efficacy Endpoints

15.4.1. Per-Protocol Analyses

The primary and key secondary endpoints will be analyzed using the PPS with the same methodology.

15.4.2. On-Treatment Analysis

An on-treatment analysis will also be conducted for primary time to 4-component MACE (MACE-4) and 3-component MACE (MACE-3) endpoints in the PPS.

The sensitivity analyses will also be performed for the time to first occurrence of NODM on treatment for patients with baseline glycemic status of no diabetes, prediabetes, or normoglycemic in the PPS.

For these on-treatment analysis, events (MACE-4, MACE-3 or NODM) that occurred after DLDOSE + 30 days will be ignored. Patients who did not have events before that will be censored at the earlier of the DLDOSE + 30 days and DLASMT, the date of censoring for non-fatal events defined in Section 7.2.5.

On-treatment analyses will be performed for lipid parameters and biomarkers including LDL-C, HDL-C, non-HDL-C, total cholesterol, triglyceride, hs-CRP, HbA_{1C} and fasting glucose. For these endpoints, values measured more than 7 days after the Date of Last Dose of IMP will be excluded, and only observed values prior to that will be summarized by treatment groups, and for HbA_{1C} and fasting glucose also by baseline glycemic status.

15.4.3. Adjunctive Cross-in Lipid-Modifying Therapy

Post randomization, LDL-C results will be masked for investigators and study participants in order to maintain the blind. Beginning at Month 6 (Visit T4) and for the remaining duration of the study, the central laboratory will notify the investigator if the patient's LDL-C level is ≥25% higher than baseline LDL-C. The patients will be counseled on healthy dietary guidelines and reminded to take all lipid-regulating medications. The patient will return to the clinic for a repeat fasting blood lipid sample to confirm that the LDL-C value meets the threshold criteria. If confirmed, the patient's LDL-C-lowering treatment regimen may be adjusted, if possible, per standard of care and local practice. Any initiation and/or dose change of LDL-C-lowering medications will be documented on the electronic case report form (eCRF) and will not be provided by the Sponsor.

The use of adjunctive cross-in LMTs may obscure the difference between the treatment groups. To evaluate the treatment effects without cross-in LMTs, a sensitivity analysis will be performed for MACE-4 (primary) and MACE-3 endpoints in the PPS prior to cross-in LMT. Specifically, the patients are censored at the earlier of the date of starting the first cross-in adjunctive LMT therapy + 30 days and date of censoring for non-fatal events defined in Section 7.2.4, if there is no MACE-4 or MACE-3 event prior to that date.

For LDL-C and hs-CRP, observed values in changes and percent changes from baseline to Month 6 will be summarized by treatment group in the PPS, after excluding values measured after 7 days post the date of starting the first cross-in adjunctive LMT therapy.

15.5. Exploratory and Descriptive Analyses of Efficacy Endpoints

15.5.1. Subgroup Analyses

The primary endpoint (MACE-4) and time to 3-component MACE (MACE-3) will be analyzed within the subgroups below using FAS and the same primary analysis method previously described. The treatment and subgroup interaction will be examined by including the interaction term in the Cox PH model, and the p-values will be reported. Forest plots for the primary efficacy variable (hazard ratios) will also be presented.

- Age category (<65 years, ≥65 to <75 years, and ≥75 years)
- Race (White vs Non-white)
- Ethnicity (Hispanic or Latino vs No Hispanic or Latino)
- Sex (male vs female)
- Region (North America, South America, Western Europe, Eastern Europe, Other)
- BMI category (<25 kg/m^2, 25 to <30 kg/m^2, and ≥30 kg/ m^2)
- Baseline CVD risk category (Secondary vs Primary prevention)
- Baseline LDL-C category (<130 mg/dL, ≥130 mg/dL and <160 mg/dL, ≥160mg/dL)
- Baseline hs-CRP category (<2 mg/dL and ≥2 mg/dL)
- Baseline eGFR category (≥90; ≥60 to <90; and <60 mL/min/1.73m^2)
- Baseline CKD history (Yes vs No)
- Baseline glycemic status (normoglycemic, prediabetes, or diabetes)
- Baseline ezetimibe use (Yes vs No)
- Baseline statin use (Yes vs No)
- Statin intolerance criteria (Failed 2 or more statin, vs otherwise)

15.5.2. Covariate Analyses

Covariate analyses of the primary (MACE-4) and time to 3-component MACE (MACE-3) using Cox PH model will be performed as supportive analyses. Baseline covariates listed in Section 15.5.1 will be included in the model one at a time.

15.5.3. Total Event Analysis

Since non-fatal events (non-fatal MI, non-fatal stroke, and coronary revascularization) can happen multiple times during study follow-up, analyses of MACE-4, MACE-3, non-fatal MI, non-fatal stroke, and coronary revascularization as total (i.e., first and subsequent) events will also be performed in the FAS. When there are multiple events occurring on the same day, they will be ordered as described in Section 15.2.1, and the event times will be separated by 0.1 day so that every event time is unique. The censoring date after the last events or for patients who had no event is the DLASMT. Hazard ratio will be estimated by Andersen-Gill mean intensity

model (Andersen and Gill, 1982), with robust sandwich estimates of the covariance matrix (Lin and Wei, 1989).

15.5.4. Incidence Rates of Primary and Key Secondary Endpoints

In addition to the hazard ratio and 95% CI from Cox PH model, incidence rate (IR) as number of events per 100 person years, along with the total number of person years and difference in IR between groups with 95% CI's will be provided for primary endpoint and key secondary endpoints. For this analysis, the duration of exposure is defined to be from the date of randomization to the date of the 1st event or the date of censoring.

15.5.5. Additional Analysis of Adjudicated Events

For the adjudicated clinical events that occurred after randomization, discordance between the classification of the investigators versus that of the CEC will be tabulated by treatment in the FAS.

15.6. Tertiary and Exploratory Analyses for Lipid and Biomarkers Endpoints

15.6.1. Tertiary Lipid and Biomarker Endpoints

Tertiary lipids measurements including non-HDL-C, TC, HDL-C, and TG will be summarized for the FAS by treatment groups using observed values for each timepoint (baseline, Month 3, 6, 12, 18, 24, 30, 36, 42, 48, 54 and 60). For each parameter, the value of the parameter, change, and the percent change from baseline will be summarized by treatment group, and by analysis timepoints (Section 7.2.4). The results are presented in both conventional units and standardized units.

In addition, fasting glucose will be summarized similarly by treatment group, by analysis timepoints, and by baseline glycemic status (Section 7.4) for the FAS.

16. SAFETY OUTCOMES

The Safety Analysis Set (SAS) will be used for all safety analyses. All adverse event tables will be summarized by treatment group. There will be no statistical comparisons between the treatment groups for safety data, unless otherwise specified.

16.1. Adverse Events

16.1.1. Treatment Emergent Adverse Events

Treatment-emergent adverse events (TEAEs) are defined as AEs that begin or worsen after the first dose of double-blind IMP and through the end of the study including the Follow-up Period. For an AE that has a start date on the same day as first dose (DFDOSE) or has a (partially or completely) missing start date, it is considered as treatment-emergent if the answer to the CRF question "Did this event start prior to first dose of study medication post-randomization (double-blind)" is No.

Note that for positively adjudicated tendon rupture events, treatment-emergent is defined based on the adjudicated tendon rupture diagnosis date being on or later than the date of first dose (DFDOSE).

Severity (Protocol Section 13.1.4) is classed by the investigator as mild, moderate, or severe (increasing severity). TEAEs with missing severity will be grouped as severe in summary tables. If a patient reports a TEAE more than once within that SOC/PT, the AE with the worst-case severity will be used in the corresponding severity summaries.

Relationship to study IMP is assessed by the Investigator. For tabulation, a TEAE is considered as related, with a relationship of "possibly related", "probably related", or "definitely related" to study IMP, or if the relationship is missing.

The patient incidence of AEs will be summarized for all treatment-emergent AEs (TEAEs), serious TEAEs (SAEs), by preferred term in descending order of frequency in the active treatment group.

Patient incidence of all treatment-emergent AEs (TEAEs), serious TEAEs, treatment-related TEAEs and AEs leading to withdrawal of IMP will be tabulated by SOC and PT in descending order of frequency.

In addition, an overall summary of adverse events, incidence of serious TEAE and TEAE leading with withdrawal of IMP by SOC and PT will be provided for patients in the SAS with baseline use of ezetimibe.

16.1.2. Adverse Events of Special Interest

[redacted] AESIs will be identified by specified MedDRA PTs, or the related laboratory criteria if applicable. See Appendix 7 for the list of AESIs and their definitions. These events will be summarized by AESI category, laboratory criteria met (if applicable), and PTs.

The NODM AESI is applicable only for patients with baseline glycemic status (Section 7.4) of No Diabetes at baseline. As an AESI vs. an efficacy endpoint, NODM includes a broader definition of NODM with patients who meet one of the following conditions:

- patients with verified NODM as determined by the DC (Section 7.4.3), or
- patients who initiated a diabetes medication after first dose of IMP (Appendix 8), or
- patients meeting the laboratory criteria for NODM as in Appendix 7, or
- patients with selected AE preferred terms (see list of preferred terms for 'NODM' in Appendix 7).

Worsening Hyperglycemia AESI is applicable to patients with baseline glycemic status of Diabetes based on adverse event preferred terms as described in Appendix 7.

See Appendix 7 for the list of AESIs and their definitions. AESIs will be identified by specified MedDRA PTs, and/or the related laboratory criteria if applicable. These events will be summarized by treatment group, and by AESI category, laboratory criteria met, and PTs.

Malignancy AESI will be summarized by Standardised MedDRA Queries (SMQs) and PTs as described in Appendix 7. [redacted]

Tendon rupture will be summarized for events that are positively adjudicated according to the TRAC Charter. All potential tendon ruptures that were reviewed by the TRAC will be presented in a listing.

For AEs considered to be muscle related by the Investigator, additional information is collected on the *Muscle Related Adverse Event Complementary* CRF including the primary cause, locations, and whether the AE is unilateral or bilateral.

16.1.3. Other Adverse Events

TEAEs of *Gout* and *Gouty Arthritis* will be summarized by patients' medical history of gout and by their baseline uric acid category according to the central laboratory normal range (low/normal, versus high).

16.1.4. Exposure Adjusted Incidence Rates (EAIRs) of TEAEs

For all treatment-emergent AEs, SAEs, and AESIs, exposure-adjusted incidence rates (EAIR) will be calculated by preferred terms (PTs) and by treatment group.

For the calculation of EAIR, the duration of exposure for each patient is from the date of the first dose of IMP to the date of the first event (PT), or the DLASMT (Section 7.2.1) if the patient did not experience the event in question. For each event, the EAIR is calculated as the number of events (the first event, so each patient is counted only once) divided by the sum of duration of exposure over all patients in the SAS in the treatment group. It will be expressed as per 100 patient-years.

16.1.5. Subgroup Analyses of Adverse Events

Subgroup analyses of patient incidence and EAIR of TEAE for age group (<65, 65-75, ≥ 75 years), sex, and race (white vs non-white), baseline eGFR category (<60, 60-90, ≥90 mL/min/1.73m^2), baseline glycemic status (normoglycemic, prediabetes, and diabetes), baseline ezetimibe use (yes/no) will be presented by SOC and PT in descending order frequency.

16.2. Death and Major Adverse Cardiac Events

For this study deaths and positively adjudicated MACE (MI, stroke, coronary revascularization, hospitalization for unstable angina) are study endpoints and per protocol are not recorded in the Adverse Event CRF. They will be reported as adjudicated endpoints in listing and tables using the FAS.

In addition, all events leading to death as reported by the Investigator will be summarized by SOC/PT and treatment group using the SAS, and for patients in the SAS with baseline ezetimibe use.

16.3. Safety Laboratory Evaluations

The list of central laboratory assessments to be included in the outputs is included in the Table 4 of the Protocol (Section 12.1.6.1) and includes H_bA_{1c}. Urinalysis is not quantitative, and coagulation is measured at selected patients/visits only, and these will not be summarized.

In addition, eGFR will be calculated using the formula: $186 \times (\text{creatinine}/88.4)^{-1.154} \times (\text{age})^{-0.203} \times$ (0.742 if female) × (1.210 if Black), where creatinine is in µmol/L. Blood urea nitrogen (BUN)/creatinine ratio (BUN/Creatinine ratio) will also be calculated.

Summaries for all lab results will be included for the below analyses:

- Observed and change/percent change from baseline by analysis visit for hematology and blood chemistry measurements.
- Creatinine and eGFR will be summarized by treatment group and by baseline eGFR categories (<30, 30 to <60, 60 to <90, and ≥90 mL/min/1.73m^2).
- Fasting glucose and HbA1c will be summarized by baseline glycemic status, and by treatment group.

The analyses for shift tables from baseline to the worst post-baseline category or value are presented in Table 2. Note that for fasting glucose and HbA1c the analyses will be by baseline glycemic status.

Table 2: Analyses for Shift Tables of Laboratory Parameters

Parameter	Categories (From Better to Worse)
Fasting glucose (by baseline glycemic status)	<51 mg/dL ≥51 to <100 mg/dL ≥100 to <126 mg/dL ≥126 mg/dL
H_bA_{1C} (by baseline glycemic status)	<5.7% ≥5.7% and <6.5% ≥6.5 to <7% ≥7%
Alanine aminotransferase (ALT)	Normal, High (> ULN)
Aspartate aminotransferase (AST)	Normal, High (> ULN)
eGFR	≥90 mL/min/1.73m^2 ≥60 to <90 mL/min/1.73m^2 ≥30 to <60 mL/min/1.73m^2 <30 mL/min/1.73m^2
Uric acid (UA)	Low/Normal (combined) High (> 5.7 mg/dL for female, >7.0 mg/dL for male)

Lab abnormalities associated with AESIs are listed in Appendix 7 and will be summarized with the AESIs. In addition, for evaluation of potential Hy's Law cases, a pairwise scatterplot will be created with the maximum (peak) post-baseline values of ALT or AST as multiples of the ULN, against the concomitant TB (also multiples of the ULN).

Other lab abnormalities of selected parameters are presented in Table 3 and the number of patients meeting each criterion will be summarized by treatment group.

[redacted]

Patients with potentially clinically significant laboratory abnormalities (Appendix 10) will be listed. For a given parameter (or group of parameters as indicated), all values from the patient will be included in the listing if any value meets the criteria.

As a result of the pandemic, local laboratory may be used for safety labs at the investigators' discretion. The local lab data are reviewed and evaluated by the investigators for any abnormalities and adverse event reporting as applicable. Due to the diverse use of units and

variation in laboratory normal ranges, the local lab data are not used in the statistical analyses. All local laboratory measurements will be listed with the associated reference ranges if available. Abnormal laboratory results of ALT and/or AST >3 × ULN, TB >2 × ULN or CK >5 × ULN based on the non-central laboratory reference ranges (when available) will be noted in the listing.

16.4. Electrocardiogram Evaluations

The Investigator's judgment of overall assessment of electrocardiograms (Normal; Abnormal, Not Clinically Significant; or Abnormal, Clinically Significant) will be recorded, and will be summarized at baseline and at the (nominal) end-of-study visits.

16.5. Vital Signs

The following vital signs measurements will be reported for this study:

- Systolic blood pressure (SBP) (mmHg)
- Diastolic blood pressure (DBP) (mmHg)
- Heart rate (HR) (beats per minute [bpm])
- Weight (kg)
- Height (cm) (at screening only)
- BMI (kg/m^2) (calculated)

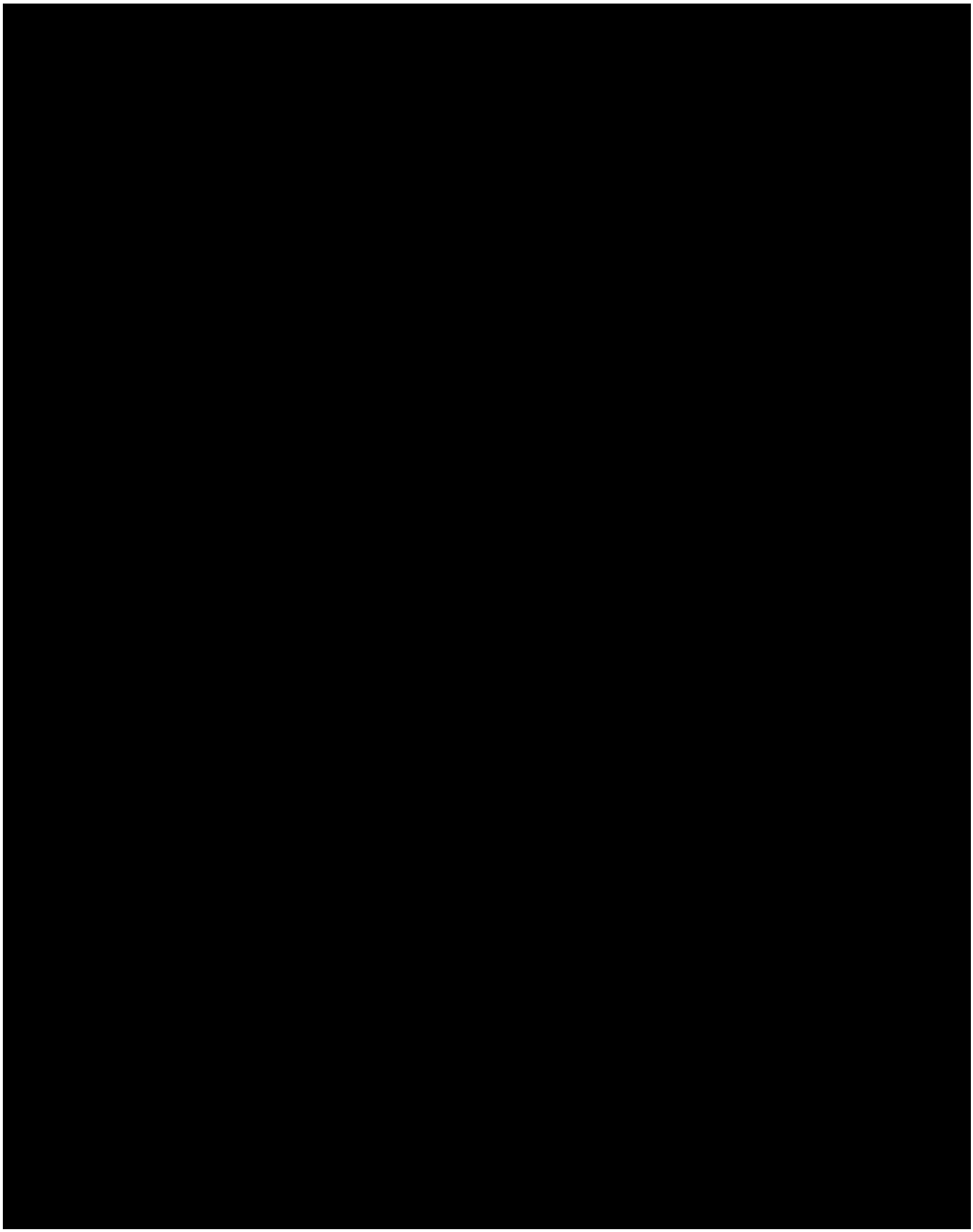
Summaries will be provided for SBP, DBP, and HR for observed values and change from baseline values by visit.

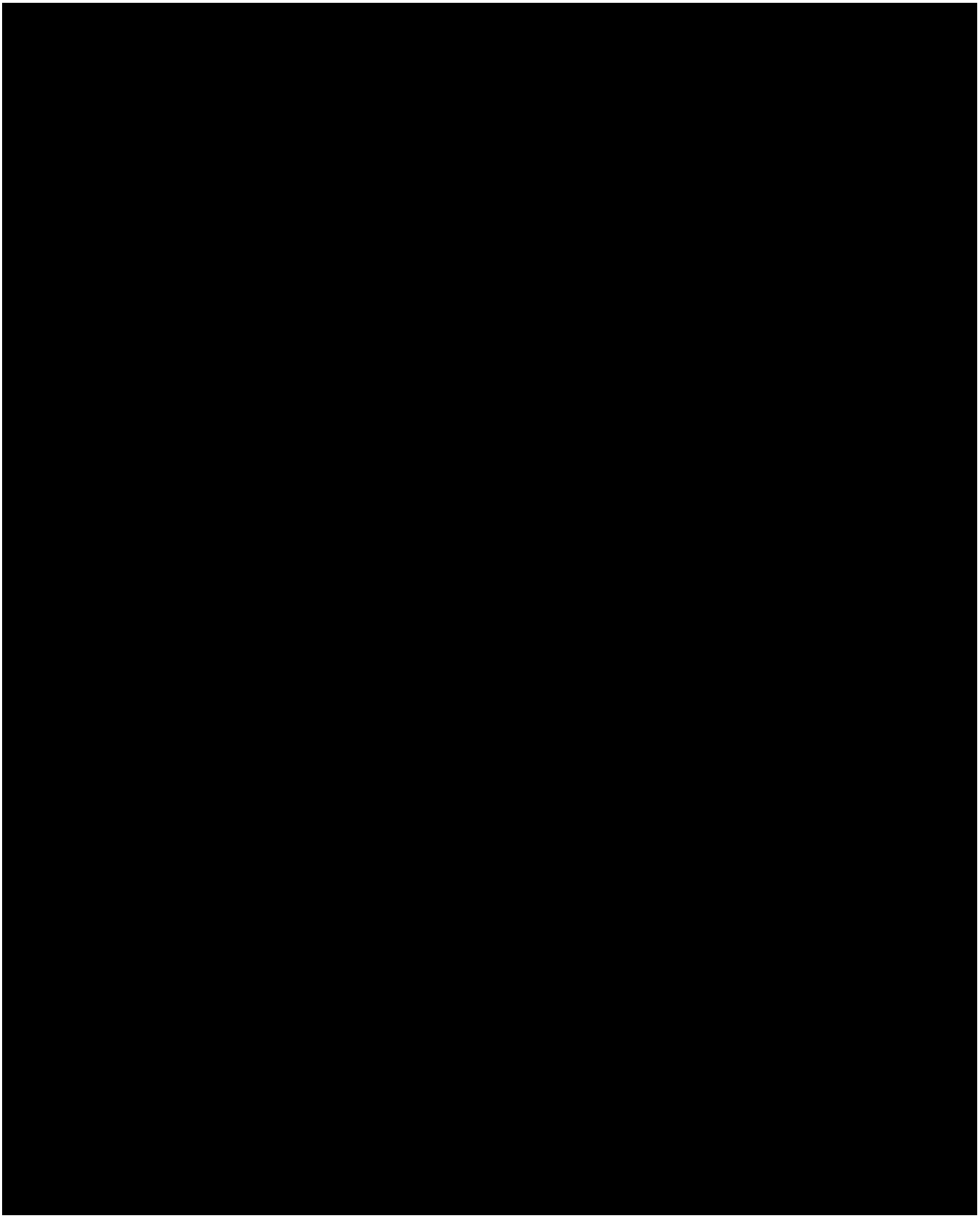
Measurement, absolute change from baseline and percent change from baseline of weight will be summarized by baseline glycemic status and by baseline BMI categories.

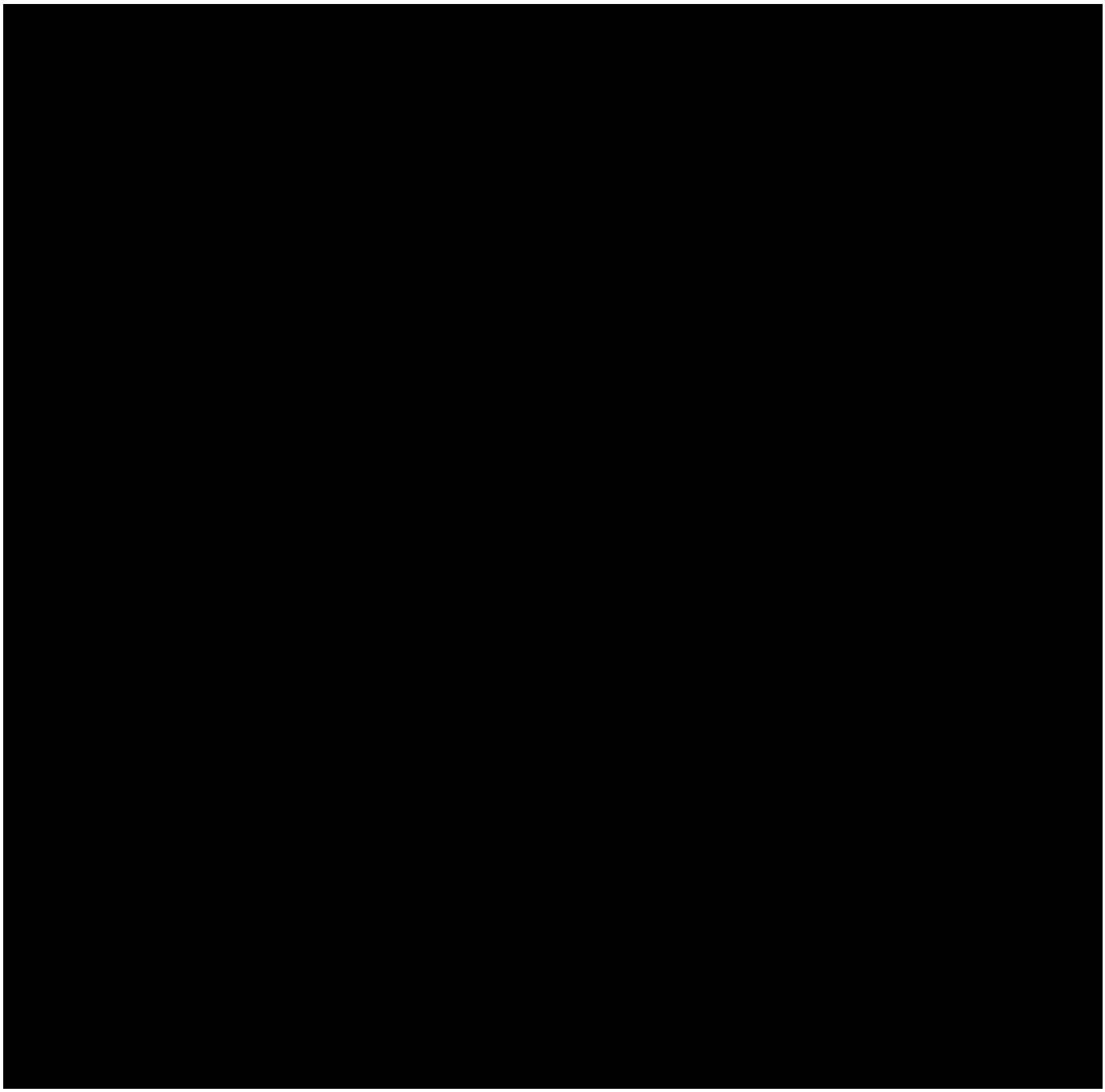
Patients with potentially clinically significant vital sign abnormalities (Appendix 10) will be listed. For a given parameter, all the patients' values will be included in the listing if any value meets the criteria.

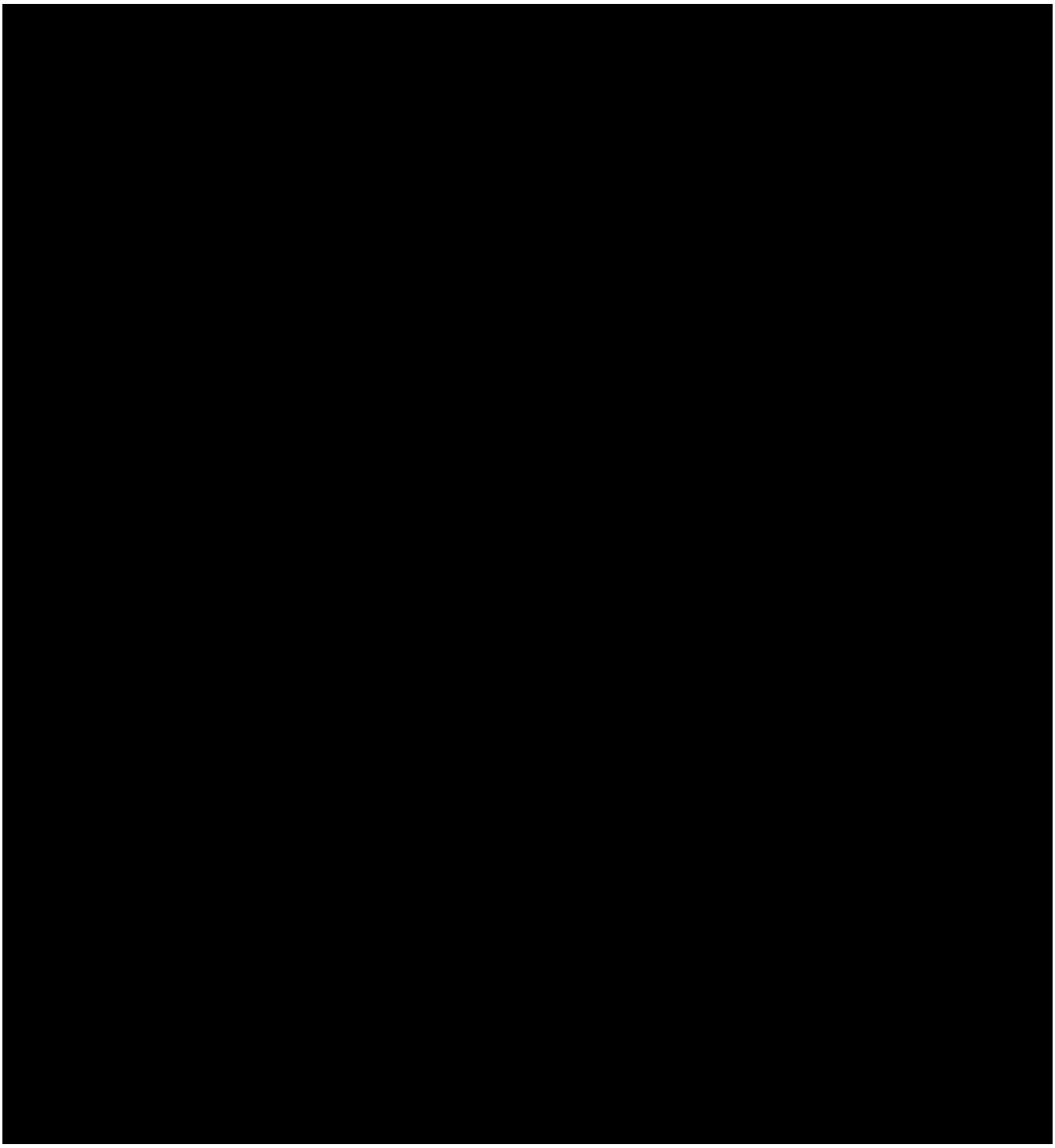
16.6. Physical Examination

Abnormalities in physical examinations will be presented in a listing.









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APPENDIX 1. SCHEDULE OF EVENTS

	Screen and Run-In		Treatment														
							PV		PV		PV		PV		PV		PV
Visit	**S1[1]**	**S2**	**T1**	**T2**	**T3**	**T4[8]**	**T5[8]**	**T6[8]**	**T7[8]**	**T8[8]**	**T9[8]**	**T10[8]**	**T11[8]**	**T12[8]**	**T13[8]**	**EOS[9,10]**	**PT1**
Week/ Month	**Wk -5**	**Wk -4**	**Day 1/ Wk 0**	**Mth 1**	**Mth 3**	**Mth 6**	**Mth 9**	**Mth 12**	**Mth 15**	**Mth 18**	**Mth 21**	**Mth 24**	**Mth 27**	**Mth 30**	**Mth 33**		**30 days ±10 after EOS**
Procedure	**Day -35**	**Day -31 to -25**		**±3 Days**	**±5 Days**	**±5 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**		
Informed Consent	X																
Enrollment Criteria	X	X	X														
Demographics	X																
Medical History	X																
Concomitant Medications	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Diet and Exercise Counseling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Adverse Event Recording	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X
Physical Exam		X														X	
Weight[2]	X		X	X	X	X		X		X		X		X		X	

	Screen and Run-In		**Treatment**														
							PV		**PV**		**PV**		**PV**		**PV**		**PV**
Visit	**S1[1]**	**S2**	**T1**	**T2**	**T3**	**T4[8]**	**T5[8]**	**T6[8]**	**T7[8]**	**T8[8]**	**T9[8]**	**T10[8]**	**T11[8]**	**T12[8]**	**T13[8]**	**EOS[9,10]**	**PT1**
Week/ Month	**Wk -5**	**Wk -4**	**Day 1/ Wk 0**	**Mth 1**	**Mth 3**	**Mth 6**	**Mth 9**	**Mth 12**	**Mth 15**	**Mth 18**	**Mth 21**	**Mth 24**	**Mth 27**	**Mth 30**	**Mth 33**		**30 days ±10 after EOS**
Procedure	**Day -35**	**Day -31 to -25**		**±3 Days**	**±5 Days**	**±5 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**		
Height	X																
12-Lead ECG		X														X	
Vital Signs[3]	X		X	X	X	X		X		X		X		X		X	
Serology[4]		X															
Serum or Urine Pregnancy/ FSH[5]	X		X														
TSH	X																
Clinical Safety Labs[6]	X		X	X	X	X		X		X		X		X		X	
Basic Fasting Lipids[7]	X	X	X		X	X		X		X		X		X		X	
HbA_{1C}	X				X	X		X		X		X		X		X	
hs-CRP			X			X		X								X	
Randomization			X														
Single-Blind Drug Dispensing		X															

	Screen and Run-In		Treatment														
							PV		PV		PV		PV		PV		PV
Visit	**S1[1]**	**S2**	**T1**	**T2**	**T3**	**T4[8]**	**T5[8]**	**T6[8]**	**T7[8]**	**T8[8]**	**T9[8]**	**T10[8]**	**T11[8]**	**T12[8]**	**T13[8]**	**EOS[9,10]**	**PT1**
Week/ Month	**Wk -5**	**Wk -4**	**Day 1/ Wk 0**	**Mth 1**	**Mth 3**	**Mth 6**	**Mth 9**	**Mth 12**	**Mth 15**	**Mth 18**	**Mth 21**	**Mth 24**	**Mth 27**	**Mth 30**	**Mth 33**		**30 days ±10 after EOS**
Procedure	**Day -35**	**Day -31 to -25**		**±3 Days**	**±5 Days**	**±5 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**		
Single-Blind Drug Return			X														
Double-blind Drug Dispensing			X		X	X		X		X		X		X			
Double-Blind Drug Return					X	X		X		X		X		X		X	

ALT = alanine aminotransferase; AST = aspartate aminotransferase; CK = creatine kinase; DBP = diastolic blood pressure; ECG = electrocardiogram; eGFR = estimated glomerular filtration rate; EOS = End of Study; FSH = follicle-stimulating hormone; HbA_{1C} = glycated hemoglobin; HBsAg = hepatitis B surface antigen; HCV-Ab = hepatitis C antibody; HDL-C = high-density lipoprotein cholesterol; HR = heart rate; hs-CRP = high-sensitivity C-reactive protein; Labs = laboratory tests; LDL-C = low-density lipoprotein cholesterol; MACE = major adverse cardiovascular event; SBP = systolic blood pressure; TC = total cholesterol; TG(s) = triglyceride(s); TSH = thyroid-stimulating hormone; PV=phone visit; wk=weeks; mth=month.

[1] An additional visit approximately 1 week after Visit S1 and prior to Visit S2 MAY be completed if patient's LDL-C and/or TG level fails to meet entry criteria. Also, an additional visit and/or assessment between Visits S1 and T1 MAY be completed if the patient's DBP, SBP, TSH, eGFR, ALT, AST, and/or CK fails to meet entry criteria. If this optional visit/assessment is completed, the value from the repeat visit/assessment will be used to determine eligibility. Also, at Visit S1 an optional hs-CRP may be measured only if needed for Reynolds Risk Score and a local hs-CRP value is not available. Finally, the number of days between Week -5 (Visit S1) and Week -4 (Visit S2) may be less than 7, and the number of days between Week -5 (Visit S1) and randomization may be less than 35 as long as eligibility can be determined.

[2] Body weight will be measured in the morning while fasting, using consistent scales, after voiding, and without shoes and outerwear (eg, coats).

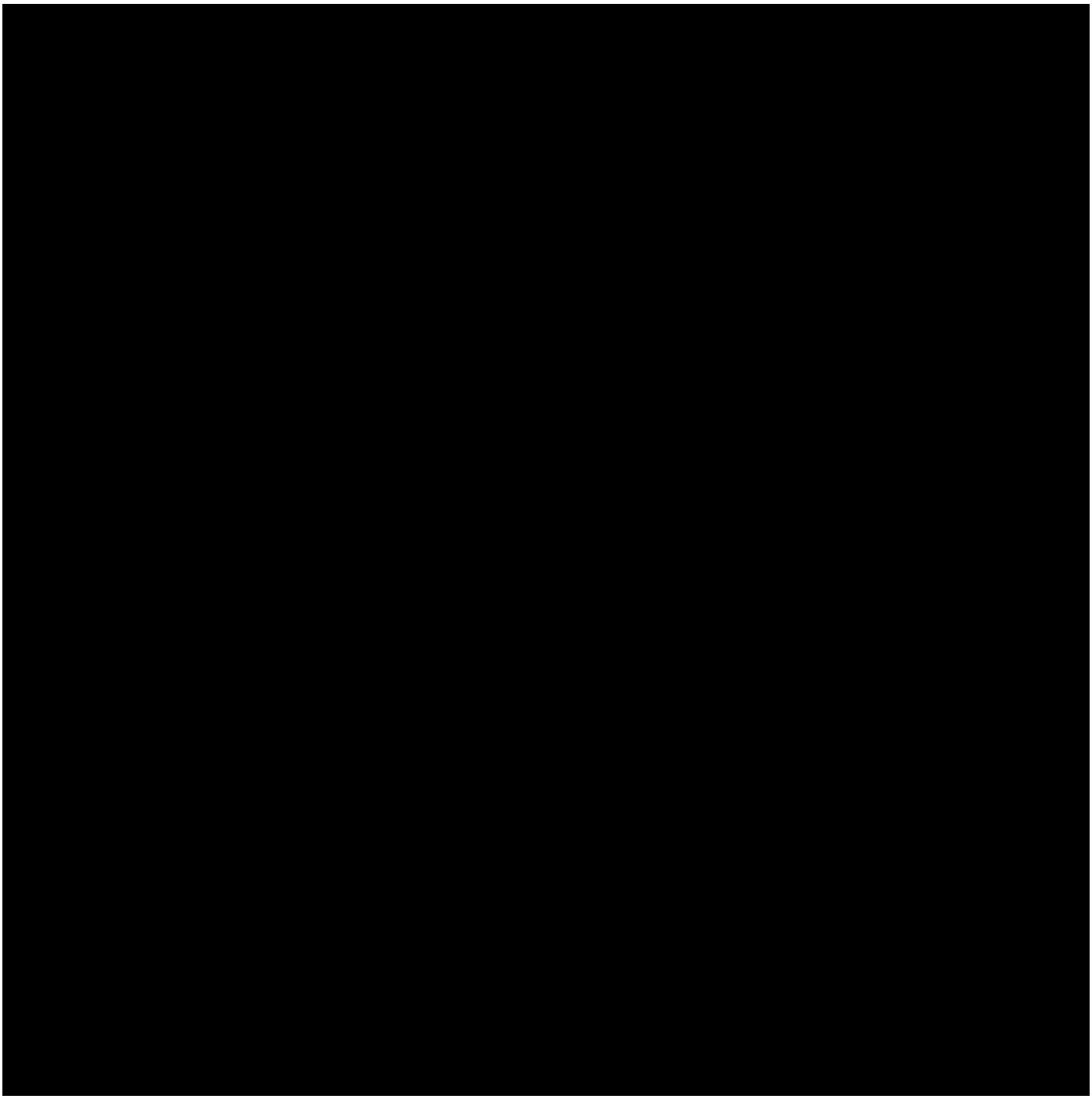
[3] Vital signs will include DBP, SBP, HR and will be collected prior to any blood sample collection. The patient will rest for several minutes prior to assessments.

[4] Serology for HBsAg and HCV-Ab.

[5] Pregnancy tests completed in premenopausal women only, serum test at Week -5 (Visit S1) and urine test at Day 1 (Visit T1); FSH completed on postmenopausal women <55 years of age.

	Screen and Run-In		Treatment														
							PV		PV		PV		PV		PV		PV
Visit	**S1[1]**	**S2**	**T1**	**T2**	**T3**	**T4[8]**	**T5[8]**	**T6[8]**	**T7[8]**	**T8[8]**	**T9[8]**	**T10[8]**	**T11[8]**	**T12[8]**	**T13[8]**	**EOS[9,10]**	**PT1**
Week/ Month	**Wk -5**	**Wk -4**	**Day 1/ Wk 0**	**Mth 1**	**Mth 3**	**Mth 6**	**Mth 9**	**Mth 12**	**Mth 15**	**Mth 18**	**Mth 21**	**Mth 24**	**Mth 27**	**Mth 30**	**Mth 33**		**30 days ±10 after EOS**
Procedure	**Day -35**	**Day -31 to -25**		**±3 Days**	**±5 Days**	**±5 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**	**±10 Days**		

[6] Clinical safety laboratory tests include hematology, blood chemistry, and urinalysis. Urinalysis includes dipstick measured at the clinic and microscopic, if abnormal, completed by the central lab. A limited safety laboratory assessment (ALT, AST, TB, and CK) will be completed at Visit T2 only. A coagulation panel will be completed only if needed for patients on anticoagulant therapy at Day 1 (Visit T1) and 3 to 5 days later.
[7] Basic fasting lipids include TC, calculated LDL-C, HDL-C, non-HDL-C, and TGs.
[8] After Visit T4 (Month 6), telephone and clinic visits (alternating every 3 months) will continue until the study is completed.
[9] All procedures will be completed at the EOS or Early Termination Visit.
[10] Duration of treatment for each patient will vary and is dependent on accumulation of MACE in the entire study. For individual patients, treatment duration will be a minimum of 24 months and may continue for up to approximately 57.5 months.



APPENDIX 3. ANALYSIS VISIT WINDOWS

Analysis Visit	Nominal Visit	Target Visit Day (Study Day)	Fasting Lipids, Glucose and HbA1c (Study Day)	Safety Lab, Vital Signs and Physical Exams (Study Day)	hs-CRP (Study Day)
Baseline	T1	1	Day 1/before 1st dose		
Month 1	T2	30	-	2 – 60	-
Month 3	T3	91	2 – 136	61 – 136	-
Month 6	T4	182	137 – 273		2 – 273
Month 12	T6	365	274 – 456		
Month 18	T8	547	457 – 638		
Month 24	T10	730	639 – 821		
Month 30	T12	912	822 – 1003		
Month 36	T14	1095	1004 – 1186		
Month 42	T16	1277	1187 – 1368		
Month 48	T18	1460	1369 – 1551		
Month 54	T20	1642	1552 – 1733		
Month 60	T22	1825	1734 –1916		
Month 66	T24	2007	1917 – 2098		

APPENDIX 4. IMPUTATION OF DATES

The following rules will be used to impute partial missing dates. Note that imputed dates may be used to calculate 'study day' but will NOT be presented in the listings.

AE start date	If only Day is missing:	If the AE start year and month are the same as that for the first dose (Day 1) date, then the AE start day will be imputed as the day of first dose date; otherwise, the AE start day will be imputed as the first day of the month.
	If both Day and Month are missing:	If AE start year is the same first dose year, then the AE start Month and Day will be imputed as the Month and Day of first dose date; otherwise, the AE start date will be imputed as 01 January.
	If Year of AE start date is missing or AE start date is complete missing:	The AE start date will be imputed as the first dose date.
AE stop date	If only Day is missing:	If only Day is missing and AE stop month and year are the same as the month and year of the EOS date, use the EOS date; otherwise the last day of the month will be imputed.
	If both Day and Month are missing:	If both Day and Month are missing and AE stop year is the same as the year of the EOS date, the EOS date will be used to impute. If the year of the AE end date precedes the year of the EOS date, AE end month and day will be set to 31 December.
	If the Year of AE stop date is missing or AE stop date is completely missing:	If the AE stop date is completely missing, 1) if the "Ongoing" status is "Yes", the EOS Date will be assigned to the stop date; 2) if the "Ongoing" status is "No" or missing, the stop date will be assigned as the Date of Informed Consent, or the start date if present (partially imputed if necessary) and later. If only Year is missing, the EOS year will be assigned to the stop date.

AE = adverse event; EOS = End-of-Study

Medication start date	If only Day is missing:	If only Day is missing, the first day of the month will be assumed.
	If only Day and Month are missing:	If both Day and Month are missing, the first day of the year will be assumed.
	If only Year is missing or date is completely missing:	If medication start date is completely missing, the informed consent signature date or medication end date whichever is earlier, will be used to impute.

AE start date	If only Day is missing:	If the AE start year and month are the same as that for the first dose (Day 1) date, then the AE start day will be imputed as the day of first dose date; otherwise, the AE start day will be imputed as the first day of the month.
	If both Day and Month are missing:	If AE start year is the same first dose year, then the AE start Month and Day will be imputed as the Month and Day of first dose date; otherwise, the AE start date will be imputed as 01 January.
	If Year of AE start date is missing or AE start date is complete missing:	The AE start date will be imputed as the first dose date.
		If only Year is missing, then informed consent signature year will be used to impute.
Medication stop date	If only Day is missing	If only Day is missing, the last day of the month will be assumed.
	If both Day and Month are missing	If both Day and Month are missing, the medication stop month and day will be set to 31 December.
	If Only Year is missing or medication end date is completely missing	If medication end date is completely missing, 1) if the "Ongoing" status is "Yes", the EOS Date will be assigned to the stop date; 2) if the "Ongoing" status is "No" or missing, the end date will be assigned as the Date of Informed Consent, or the start date if present (partially imputed if necessary) and later. If only Year is missing, the EOS year will be assigned.
Other dates	If only Day is missing	If only Day is missing, the last day of the month will be assumed.
	If only Day and Month are missing:	If both Day and Month are missing, the first day of the year will be assumed.
	If the year is missing, or the date is completely missing.	Will not be imputed.

AE = adverse event; EOS = End-of-Study

APPENDIX 6. MULTIPLE IMPUTATION AND TIPPING POINT ANALYSIS

For the primary 4-component MACE endpoint (MACE-4), the multiple imputation and tipping point (TP) analyses are comprised of the following steps:

Step1. Model for Unobserved Events

A parametric exponential survival model (e.g., PROC LIFEREG in SAS) is used for the events after stopping the assigned treatment. Specifically, when fitting the model, the start time of each patient is the date of the last dose. The event or censoring time remains the same as in the primary analysis. Patients who had events prior to the last dose will not be included in the analysis. Treatment assignment is included as a covariate and the parameters are intercept α, and β which is the log hazard ratio between active treatment and placebo groups after they have stopped the assigned treatment.

Step 2: Simulation of Unobserved Events

For patients who were censored (i.e., did not experience a MACE-4), a time to event is simulated from the fitted model in Step 1, and it is added to the date of last dose for each patient. Afterwards, all patients are censored at the calendar date of [redacted] or their date of non-CV death.

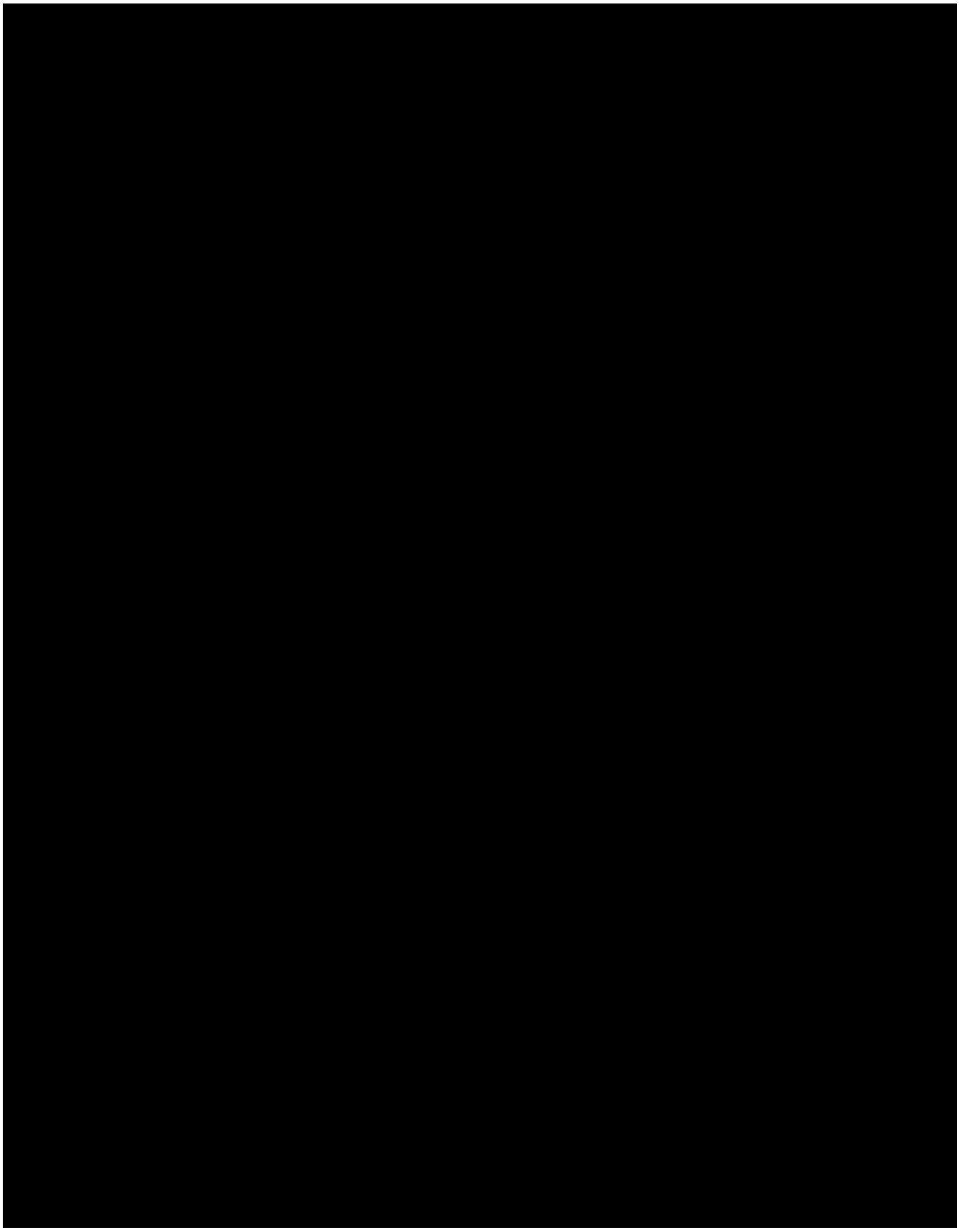
- For multiple imputation, the parameters $(\tilde{\alpha}, \tilde{\beta})$ will be drawn from a bivariate normal distribution centered around the MLEs $(\hat{\alpha}, \hat{\beta})$ with the model-based variance-covariance matrix. This is an approximate to the posterior distribution of the parameters when a flat non-informative prior is used.
- For TP, $\hat{\alpha}$ is used. However, instead of the observed treatment effect $\hat{\beta}$, a range of values (from hazard ratios of 1.00 to 1.10 in 0.01 increment) will be used to allow the patients assigned to the active treatment to have the same or event worse outcome than those assigned to the placebo group after dropping out and stopping the treatment.

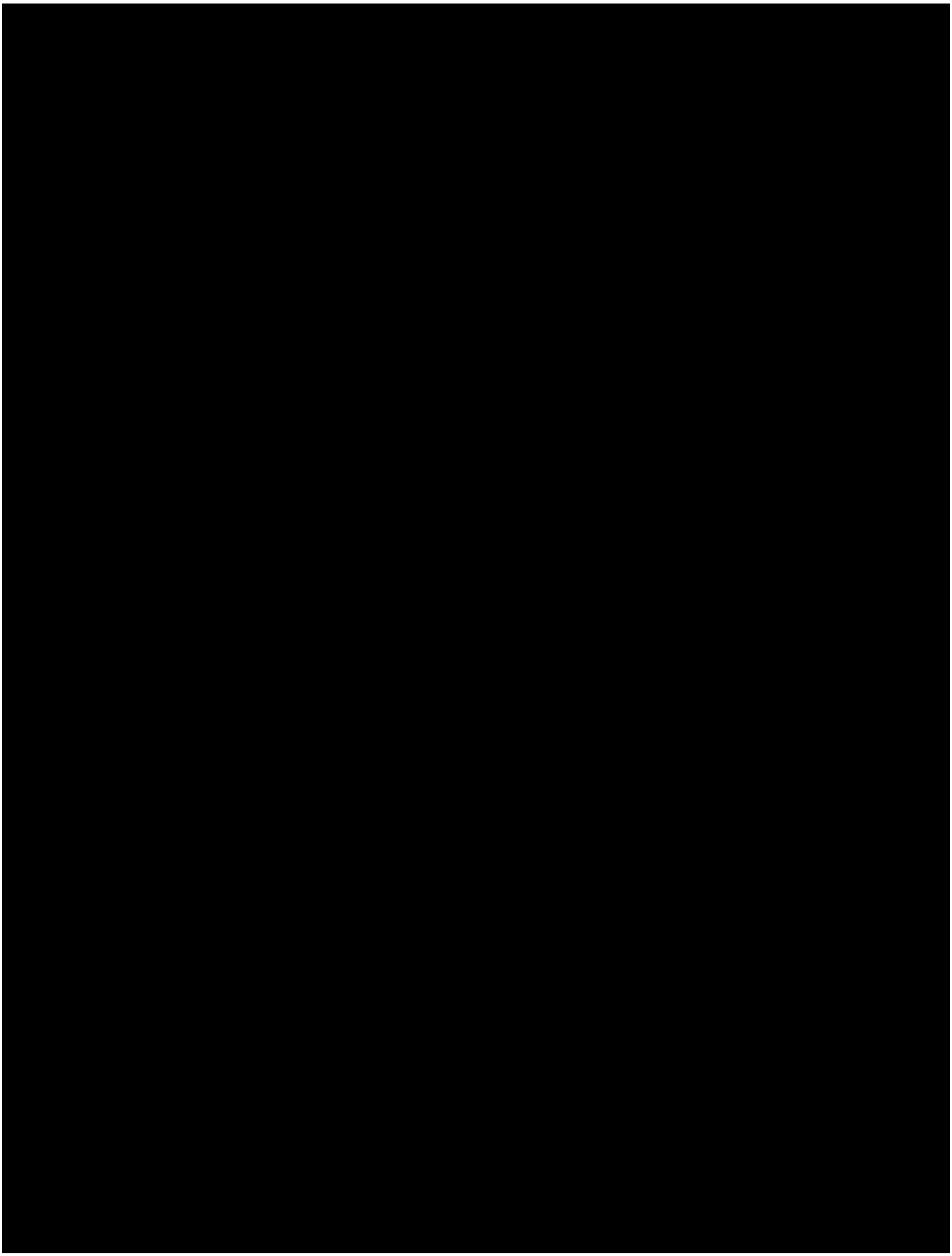
A total of 100 datasets will be simulated for each scenario.

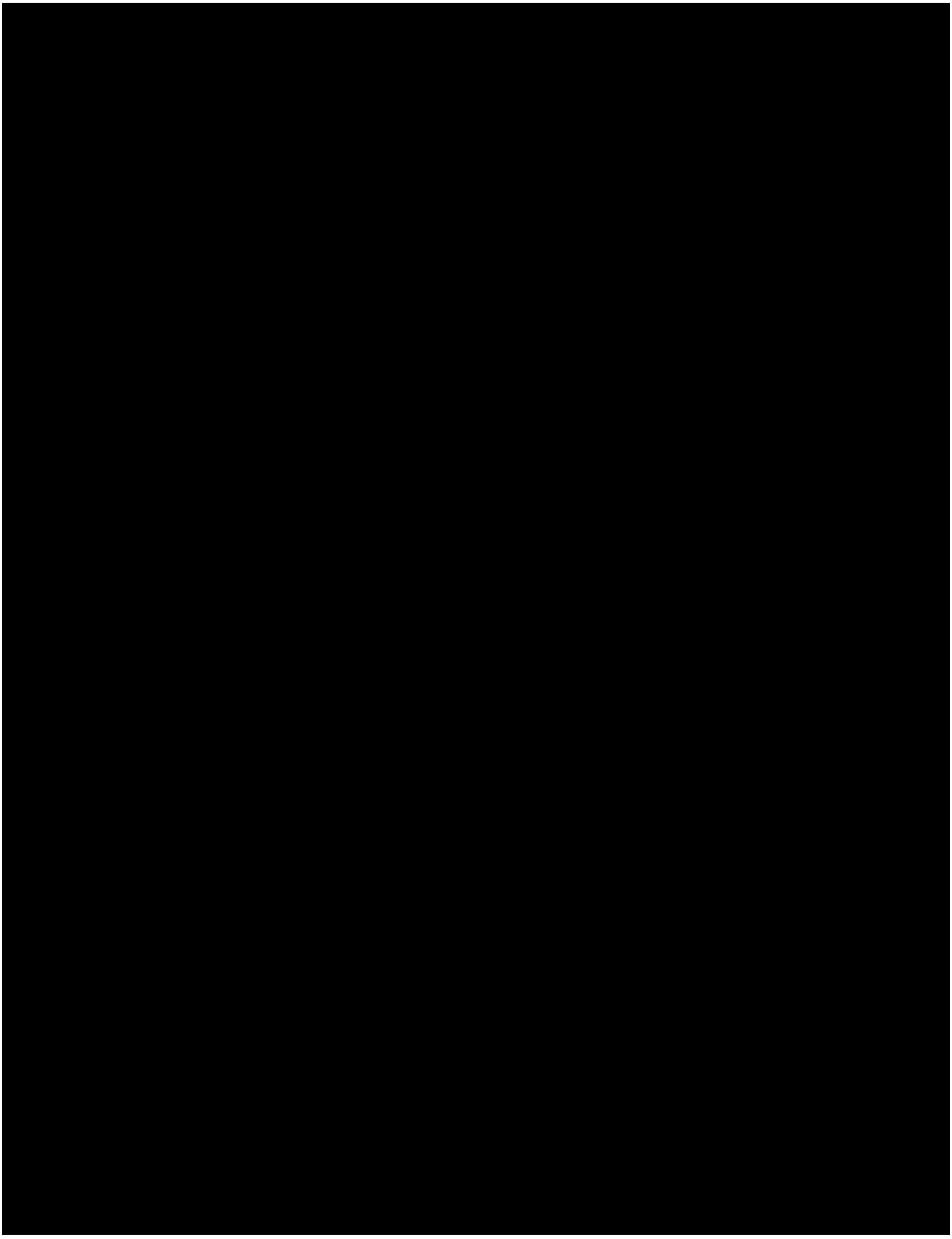
Step 3: Fitting Cox PH Model using Simulated Data and Final Inference

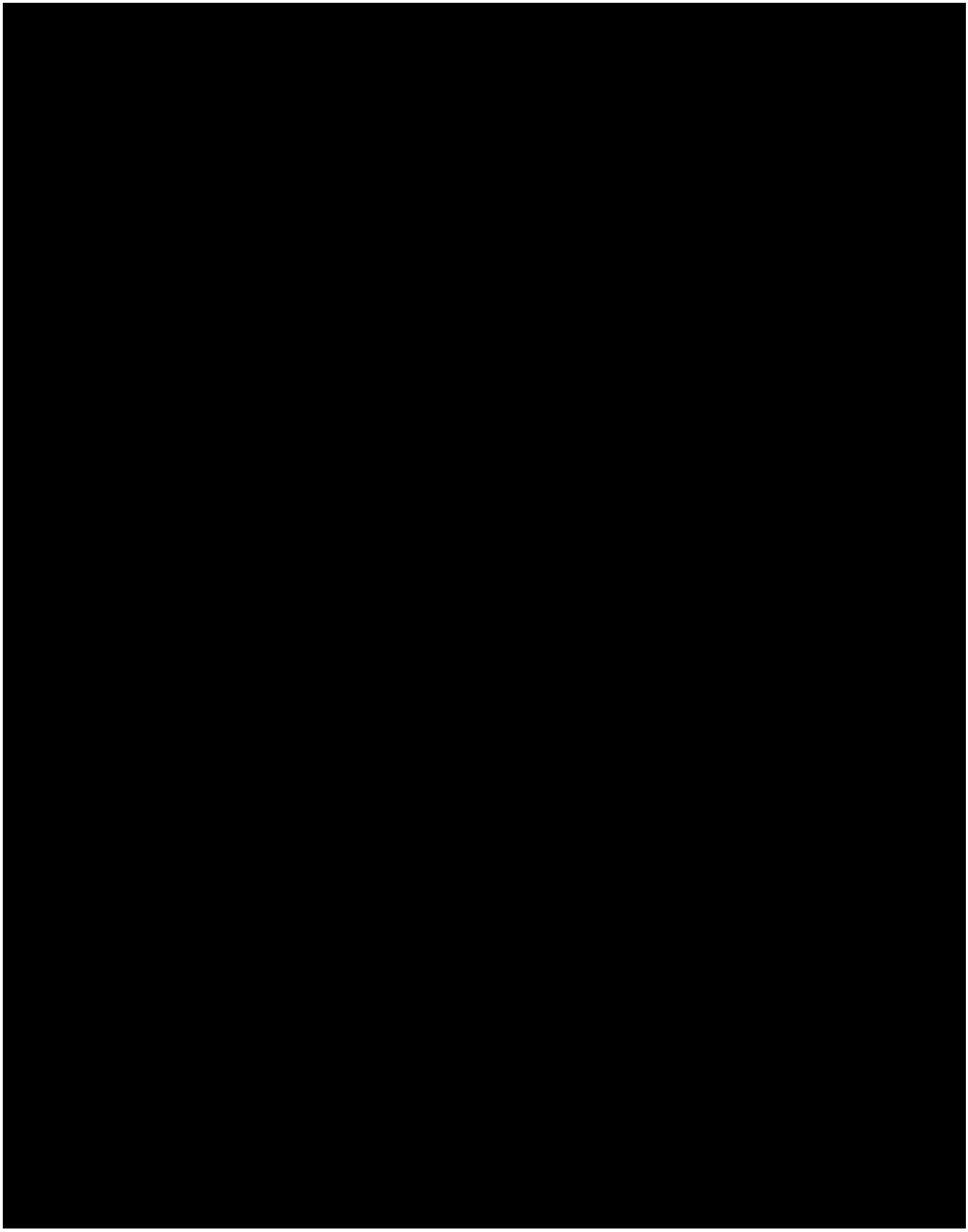
For each simulated dataset, a Cox PH model is used to estimate the difference (log hazard ratio) between the active treatment and placebo groups.

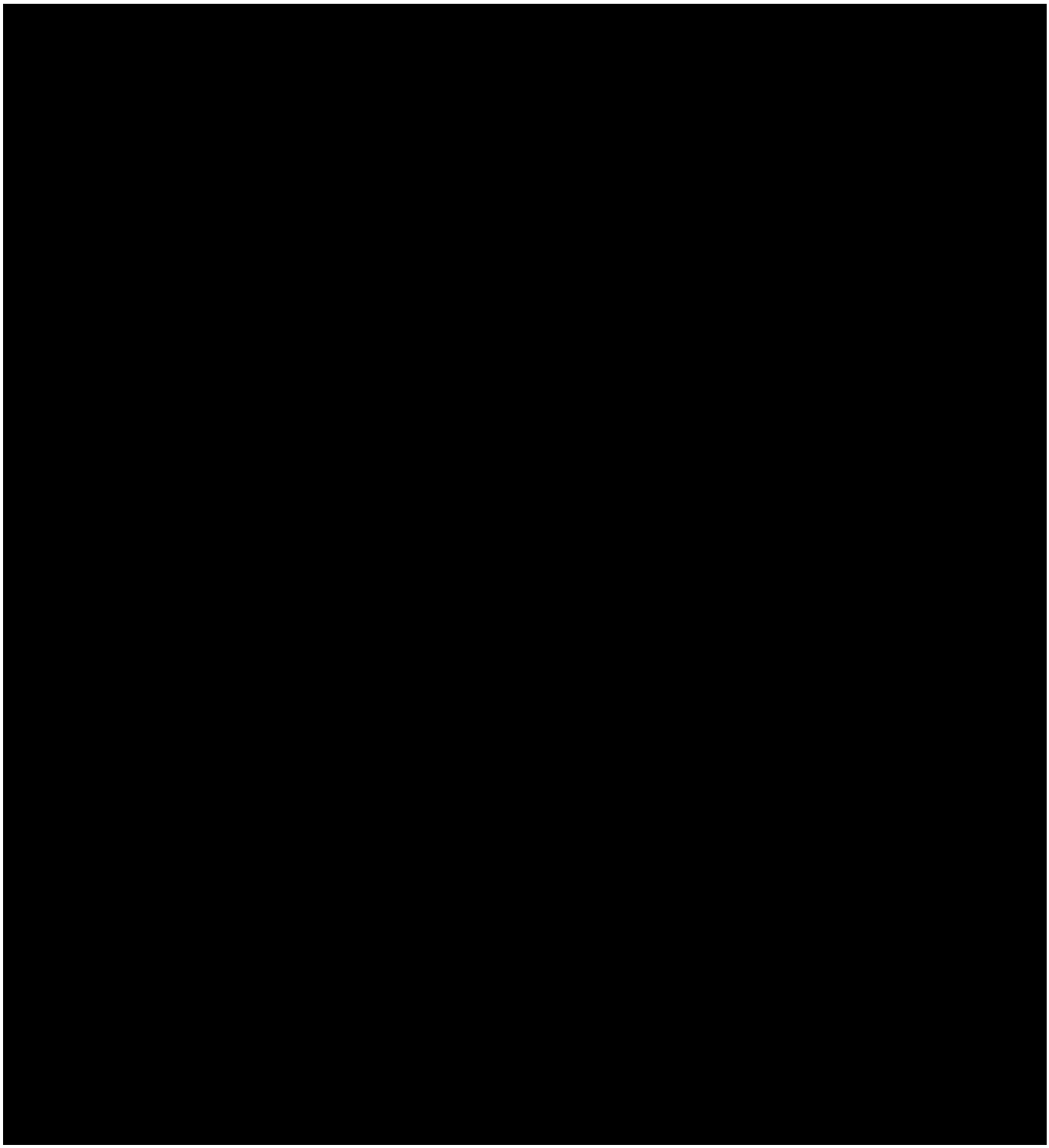
The resulted estimates are combined using Rubin's method (Rubin, 1987), e.g., using PROC MIANALYZE in SAS.







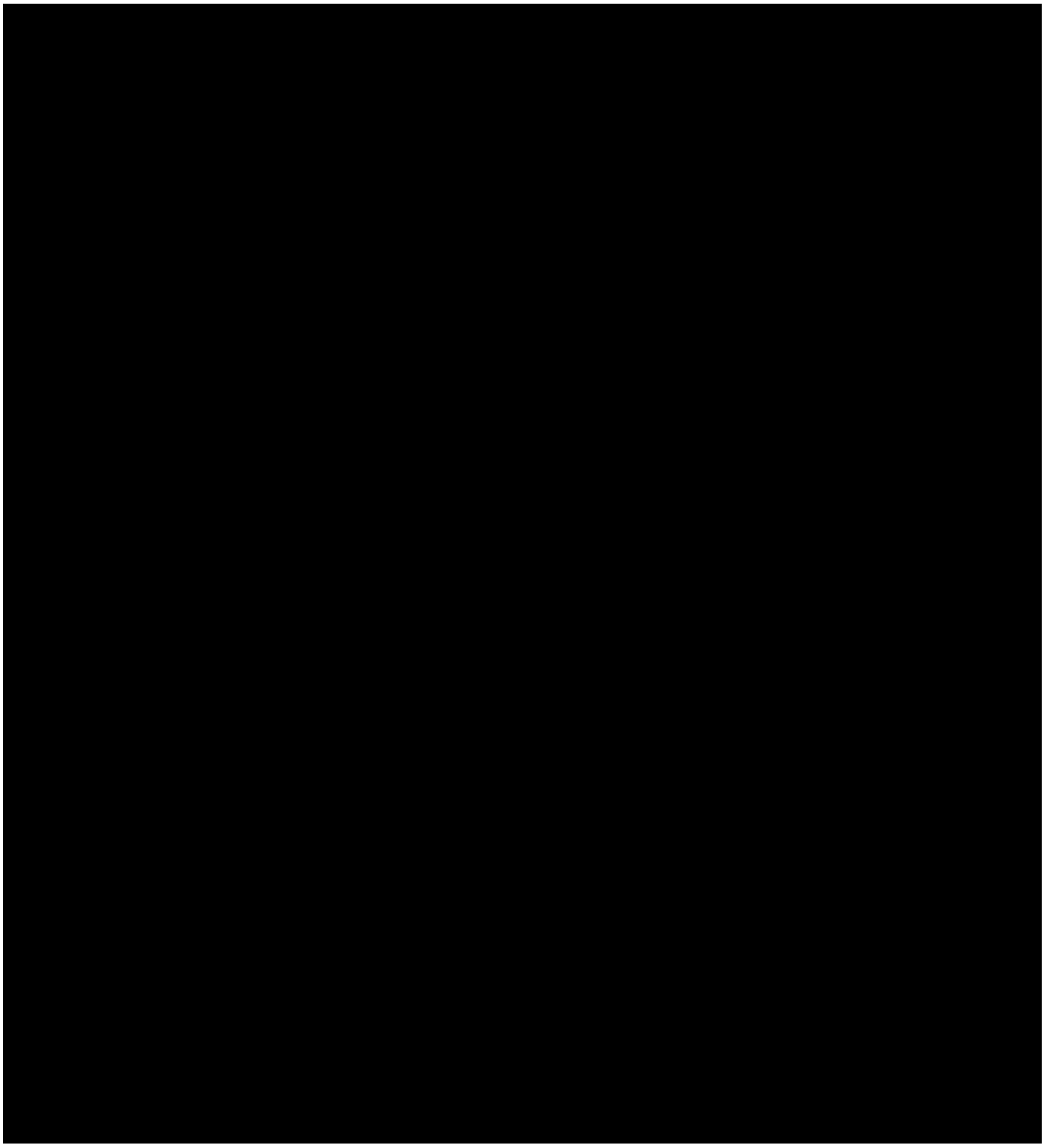




APPENDIX 8. TYPE 2 DIABETES MEDICAL HISTORY AND PRIOR MEDICATION

MedDRA Preferred Terms for Type 2 Diabetes	
	Acquired lipoatrophic diabetes
	Diabetes complicating pregnancy
	Diabetes mellitus
	Diabetes mellitus inadequate control
	Diabetes mellitus malnutrition-related
	Diabetes with hyperosmolarity
	Diabetic arteritis
	Diabetic coma
	Diabetic complication
	Diabetic dyslipidaemia
	Diabetic endorgan damage
	Diabetic coronary microangiopathy
	Diabetic hepatopathy
	Diabetic hyperglycaemic coma
	Diabetic hyperosmolar coma
	Diabetic ketoacidosis
	Diabetic ketoacidotic hyperglycaemic coma
	Diabetic ketosis
	Diabetic wound
	Diabetic metabolic decompensation
	Euglycaemic diabetic ketoacidosis
	Fulminant type 1 diabetes mellitus
	Insulin resistant diabetes
	Insulin-requiring type 2 diabetes mellitus
	Ketosis-prone diabetes mellitus
	Latent autoimmune diabetes in adults
	Monogenic diabetes
	New onset diabetes after transplantation
	Pancreatogenous diabetes
	Steroid diabetes
	Type 1 diabetes mellitus
	Type 2 diabetes mellitus
	Type 3 diabetes mellitus

Medication (WHODrug ATC4) for Type 2 Diabetes	
A10AB	Insulins and Analogues for Injection, Fast-Acting
A10AC	Insulins and Analogues for Injection, Intermediate-Acting
A10AD	Insulins and Analogues for Injection, Intermediate- or Long-Acting Combined with Fast-Acting
A10AE	Insulins and Analogues for Injection, Long-Acting
A10AF	Insulins and Analogues for Inhalation
A10BA	Biguanides
A10BB	Sulfonylureas
A10BC	Sulfonamides (Heterocyclic)
A10BD	Combinations of Oral Blood Glucose Lowering Drugs
A10BF	Alpha-Glucosidase Inhibitors
A10BG	Thiazolidinediones
A10BH	Dipeptidyl Peptidase-4 (DPP-4) Inhibitors
A10BJ	Glucagon-Like Peptide-1 (GLP-1) Analogues
A10BK	Sodium-Glucose Co-Transporter 2 (SGLT2) Inhibitors
A10BX	Other Blood Glucose Lowering Drugs, Excl. Insulins



APPENDIX 10. POTENTIALLY CLINICALLY SIGNIFICANT LABORATORY AND VITAL SIGN ABNORMALITIES

Parameter	Criteria
ALT, AST, and Total Bilirubin [a]	ALT >3× ULN AST >3× ULN TB >2× ULN
ALP	ALP >1.5× ULN
CK	>5× ULN
eGFR	<30 mL/min/1.73m2
Creatinine , BUN [a]	Creatinine >0.5 mg/dL increase from baseline Creatinine >30% increase from baseline BUN >2× baseline BUN/Creatinine >30% increase from baseline
Glucose	>126 mg/dL (fasting) >200 mg/dL (non-fasting) <70 mg/dL (fasting or non-fasting)
HbA1c	>10%
hs-CRP	>10 mg/L
Albumin	<LLN
Hemoglobin	≥2 g/dL decrease from baseline and < LLN
LDL-C	≥25% increase from baseline
TG	≥1000 mg/dL
Other safety chemistry and hematology parameters [b]	<LLN or >ULN
Heart Rate	≤50 bpm and decrease from baseline ≥20 bpm ≥120 bpm and increase from baseline≥20 bpm
SBP	≤95 mmHg and decrease from baseline ≥20mmHg ≥160 mmHg and increase from baseline ≥20 mmHg
DBP	≤45 mmHg and decrease from baseline ≥10 mmHg ≥110 mmHg and increase from baseline ≥10 mmHg
Weight	≥10% increase or decrease from baseline

LLN: Lower Limit of Normal; ULN: Upper Limit of Normal.
Note: list all the values of the parameter from the patient if any criteria are met.
[a] For these groups of parameters, include all parameters in the listing, by timepoint first.
[b] Parameters not explicitly mentioned in this table, excluding lipids.