Previous Version: V2.0 **Current Version: V3.0** **Date of Revisions: 18 May 2018**		
Change	**Rationale**	**Affected Section(s)**
Age groups: From <65, ≥ 65 yrs. To: <65, , ≥ 65 to < 75, , ≥ 75 yrs.	To evaluate safety in subjects ≥75, as per Clinical Team and TIMI	• Section 5.2.4 • Section 5.3.4, Table 2
Re wording definition of concomitant medication	For clarity	• Section 5.2.6
From: Risk Scores(0,1-2, and 3) To: Risk Scores(0,1-2, and 3 or greater)	Clarity	• Section 5.3.4, Table 3 • Section 8
Risk Score Table added weight of "1" to Prior MI	As per TIMI group	• Section 8
Deleted paragraph "All MACE or MACE+ events will be recorded in the CRF, however, only MACE or MACE+ events that are considered by the investigator to be at least possibly related to the study drug will be included in all AE summary tables, see Section 5.3.6 for more details."	As per discussions with clinical team and safety group it was decided that all AEs will presented in tables and listings.	• Section 5.6.2
Newly Developed Albuminuria definition	As per clinical needed to include Newly Developed Albuminuria definition in Table 4	• Section 8.2.1, Table 4
Censoring slides for On-Treatment – 30days	During validation it was found that for subjects who complete Study on Drug without experiencing an event with be censored on EOS visit instead of EOT visit.	• Section 13.2.1
Censoring slides for On-Treatment	During validation it was found that for subjects who premature discontinuation of Study on Drug without experiencing an event with be censored on EOT visit instead of EOS visit.	• Section 13.2.1

Previous Version: V2.0 **Current Version: V3.0** **Date of Revisions: 18 May 2018**		
Change	**Rationale**	**Affected Section(s)**
Algorithms for categorizing subjects into one of the following categories; • Subjects without Any Type of Diabetes at Baseline • Subject who are Pre-diabetic at Baseline • Subject who are Normoglycemic at Baseline • Subjects who are T2DM at Baseline • Subjects who are T1DM at Baseline • Subjects who are DM at Baseline	In order to ensure that all subjects are place into one of the categories	• Section 8
Change wording on censoring algorithm in subjects who started a weight reduction drug or had bariatric surgery.	In order to capture subjects who started a weight reduction drug or had bariatric surgery prior to randomization their censoring time is set to randomization date. In addition, for subjects who experienced an event after stopping a weight reduction drug the event will be counted.	• Section 8.5.2.4
Exploratory Endpoint: Obesity Staging analysis will not be performed • Proportions of subjects with at least a 1-stage reduction in an obesity-related complication (prediabetes, metabolic syndrome, T2DM, hypertension, and hypertriglyceridemia/dyslipidemia), incidence of other obesity-related complications will be collected	This population will show no change since Obesity Stage will be 1 for all subjects. In addition the study is not collecting all of the Obesity Staging variables to make a reliable interpretation.	• Section 7

Previous Version: V2.0 **Current Version: V3.0** **Date of Revisions: 18 May 2018**		
Change	**Rationale**	**Affected Section(s)**
through AE reports, medical history, and use of concomitant medications, will be analyzed using logistic regression including treatment as factor. Comparison between lorcaserin HCl and placebo will be made at 1 year and EOS. The odds ratio, p-value and 2-sided 95% CI will be calculated. The ITT Analysis Set will be used for this analysis.		
Exploratory Endpoint: Obesity Staging analysis will not be performed Proportion of subjects with reduction in the number of OAD medications or reduction in the dosage of OAD medications in the following subpopulations of subjects with T2DM at Baseline	It would be difficult to interpret results and data was not collected in order to answer this question	• Section 7
Included sentence "In addition, systolic and diastolic blood pressure will be summarized by clinically notable changes (see Section 8):	As per clinical	• Section 5.6.4
Definition of clinically notable changes for systolic and diastolic blood pressure was added.	As per clinical	• Section 8

Previous Version: V1.0 **Current Version: V2.0** **Date of Revisions: 31 March 2017**		
Change	**Rationale**	**Affected Section(s)**
As per protocol Amendment 02	Protocol was Amendment to remove conversion to T2DM as a co-primary endpoint and secondary endpoints were re-grouped	• Section 3.1, 3.2 • Section 4 • Section 5.1 • Section 5.3.3 • Section 5.4.1 • Section 5.4.2
Treatment compliance was change to consider subjects on BID or QD dosing as complaint	As per protocol subjects who experienced an AE are allowed to diminish dose from BID to QD dosing	• Section 5.2.7
Baseline diabetic medications categories	As per TIMI and Eisai Clinical	• Section 5.3.4, Table 2
Added Risk Scores criteria to CV risk level	As per TIMI and Eisai Clinical	• Section 5.3.4, Table 3
Added paragraph on Adjudication of Conversion to Diabetes Events	To point out that conversion to diabetes events will be adjudicated by the CEC and to reference the Conversion to diabetes CEC charter	• Section 5.3.6
Added sensitivity analyses for subjects who prematurely discontinued	FDA ask us to add multiple imputation for the MACE (Superiority) and MACE+ endpoints for subjects who discontinued the study prematurely at Study Completion.	• Section 5.4.1.1
For Subjects that start another weight reduction medication “or undergoes bariatric surgery”	As per TIMI and Eisai Clinical	• Section 5.4.1.1
For Subjects who permanently down titrate from BID dosing to QD dosing	As per TIMI and Eisai Clinical the analyses sets where change from Total Time to On-treatment and on-treatment plus 30 days	• Section 5.4.1.1
Clarification on how MACE or MACE+ events will be recorded in the CRF and reported in CSR tables	As per Eisai Saety group	• Section 5.6.2
Added the word “Central”	It was agree with clinical to only summarized Central Lab data	• Section 5.6.3

Previous Version: V1.0 **Current Version: V2.0** **Date of Revisions: 31 March 2017**		
Change	**Rationale**	**Affected Section(s)**
OAD change to "non-insulin glucose lowering or anti-diabetic agent"	As per TIMI and eisai clinical	• Section 5.8
Exploratory endpoint at least 1-stage reduction in an obesity related complication. The Safety analysis set was replace with the ITT analysis set	As per TIMI and Eisai clinical	• Section 5.8
Interim Analysis, at the end of the second paragraph, added reference to the Study Integrity Charter	More transparency	• Section 6
Interim Analysis: remove all sensitivity analyses	As requested by FDA	• Section 6.1.1
Treatment compliance was change to consider subjects on BID or QD dosing as complaint	As per protocol subjects who experienced an AE are allow to fo from BID to QD dosing	• Section 8
Added secondary prevention risk scores	As per TIMI/clinical	• Section 8
On treatment definition updated	As per discussions with TIMI and Eisai clinical	• Section 8
Subjects who completed the study on study drug definition updated	As per discussions with TIMI and Eisai clinical	• Section 8
Subjects who completed the study definition updated	As per discussions with TIMI and Eisai clinical	• Section 8
Subjects who are T2DM at Baseline definition updated	As per discussions with TIMI and Eisai clinical	• Section 8
Determination of conversion to T2DM updated	To reference the CEC charter	• Section 8.3.1
Determination of conversion to normal glucse updated	As per discussions with TIMI and Eisai clinical	• Section 8.3.2
Events that occur after database lock will not be adjudicated and will not be included in the primary analyses	As per discussions with TIMI and Eisai clinical	• Section 8.5
Events that occur after with draw of consent will be included if they are found through vital status search prior to database lock	As per discussions with TIMI and Eisai clinical	• Section 8.5

Previous Version: V1.0 **Current Version: V2.0** **Date of Revisions: 31 March 2017**		
Change	**Rationale**	**Affected Section(s)**
Interim Analysis: Censoring scheme updated to only include MACE analysis and remove sensitivity analyses	As requested by FDA	• Section 8.5.1
Table 6 Total Time on Study Censoring updated to include "Death"	As per discussions with TIMI and Eisai clinical	• Section 8.5.2.1
Inserted "first abnormal laboratory test as per the Diabetes CEC Charter , Appendix 13.81.4" in the first paragraph	As per discussions with TIMI and Eisai clinical	• Section 8.5.2.2
Table 7 updated	As per discussions with TIMI and Eisai clinical	• Section 8.5.2.3
Bariatric surgery included	As per discussions with TIMI and Eisai clinical	• Section 8.5.2.4
Deleted reference on alpha sharing MTP	Protocol was Amendment to remove conversion to T2DM as a co-primary endpoint. Therefore this procedure is not applicable.	• Section 12
Added " and Integrity Charter" to heading	Included Study Integrity charter	• Appendix 13.3.2
Made reference to Conversion to T2DM Charter	Included CEC Charter for conversion to T2DM	• Appendix 13.1.4
Added The associations between body weight or BMI change from Baseline and the presence of FDA-defined valvulopathy analysis	As per discussions with TIMI and Eisai clinical	• Section 5.4.3

STATISTICAL ANALYSIS PLAN

Study Protocol Number:	APD356-G000-401
Study Protocol Title:	A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Effect of Long-term Treatment with BELVIQ (lorcaserin HCl) on the Incidence of Major Adverse Cardiovascular Events and Conversion to Type 2 Diabetes Mellitus in Obese and Overweight Subjects with Cardiovascular Disease or Multiple Cardiovascular Risk Factors
Date:	18 May 2018
Version:	Final 3.0

SIGNATURE PAGE

Author

PPD

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Signature

Date: _____

Approval

Biostatistics Head of

PPD

[electronic signature in eDMS]
Signature

Date: _____

Study Director:

PPD

[electronic signature in eDMS]
Signature

Date: _____

1 TABLE OF CONTENTS

2 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

Abbreviation	Term
ACR	albumin-to-creatinine ratio
AE	adverse event
ANCOVA	analysis of covariance
ALT	alanine transaminase
AST	aspartate aminotransferase
ATC	anatomical therapeutic class
BELVIQ	Lorcaserin HCL
BID	twice daily
BMI	body mass index
BSA	body surface area
CAD	coronary artery disease
CI	confidence interval
CKD	chronic kidney disease
CMH	Cochran-Mantel-Haenszel
CRF	case report form
CSR	clinical study report
CV	cardiovascular
DMC	data monitoring committee
DSMB	data safety monitoring board
ECHO	echocardiography
EOS	end of study
EOT	end of Treatment
ESRD	end-stage renal disease
FDA	Food and Drug Administration
FAS	full analysis set
GFR	glomerular filtration rate
GGT	gamma-glutamyl transpeptidase
HbA1c	glycosylated hemoglobin
ITT	Intent-to-Treat
LOCF	last observation carried forward
LSM	least squares mean
LFT	liver function test
MACE	major adverse cardiac events (myocardial infarction [MI], or stroke, or CV death)
MACE+	MACE or hospitalization for unstable angina or heart failure, or any coronary revascularization
MAR	Missing at Random
MedDRA	Medical Dictionary for Regulatory Activities

Abbreviation	Term
MI	myocardial infarction
MMRM	Mixed Model with Repeated Measures
MTP	multiple testing procedure
NAFLD	Non-Alcoholic Fatty Liver Disease
NKF	National Kidney Foundation
NI	non-inferiority
OAD	Oral anti-diabetic
PD	pharmacodynamic
PH	proportional hazard
PK	pharmacokinetic
PMM	Pattern Mixture Models
ROW	Rest of World
SAE	serious adverse event
SAP	statistical analysis plan
SE	standard error
SI	Système International
TEAE	treatment-emergent adverse event
TLG	tables, listings, and graphs
T2DM	Type II Diabetes Mellitus
WHO	World Health Organization

3 INTRODUCTION

The purpose of this statistical analysis plan (SAP) is to describe the procedures and the statistical methods that will be used to analyze and report results for Eisai Protocol APD356-G000-401; A Randomized, Double-blind, Placebo-controlled, Parallel-group Study to Evaluate the Effect of Long-term Treatment with BELVIQ (lorcaserin HCl) on the Incidence of Major Adverse Cardiovascular Events and Conversion to Type 2 Diabetes Mellitus in Obese and Overweight Subjects with Cardiovascular Disease or Multiple Cardiovascular Risk Factors.

3.1 PRIMARY OBJECTIVES

When 460 adjudicated MACE (composite of cardiovascular death, myocardial infarction or stroke) events have accrued, an interim analysis will be conducted to establish whether the primary safety objective (MACE non-inferiority) has been achieved (see Section 6). This analysis will be performed by an independent statistician and governed by the independent Data Monitoring Committee (DMC) and is anticipated to occur on or before (approximately) July 2017. If the primary safety objective has been achieved, the trial will continue until 1401 MACE+ events, and 2.5 years median treatment duration. This is expected to occur on or before October 2018. The primary efficacy objectives will be assessed at Study Completion.

Safety:

- To demonstrate that, in obese and overweight subjects with CV disease and/or multiple CV risk factors, lorcaserin HCl 10 mg administered BID does not increase the incidence of MACE (myocardial infarction [MI], or stroke, or CV death) compared to placebo, with a non-inferiority margin for the hazard ratio of 1.4.

Efficacy:

(revised per Amendment 02)

- To demonstrate that, in obese and overweight subjects with CV disease and/or multiple CV risk factors, lorcaserin HCl 10 mg BID reduces the incidence of MACE+ (MACE or hospitalization for unstable angina or heart failure (HF), or any coronary revascularization) compared to placebo

3.2 SECONDARY OBJECTIVES

Key Secondary Objective:

- To confirm that, in subjects with pre-diabetes at Baseline based on 2013ADA guideline, lorcaserin HCl 10 mg BID reduces the incidence of conversion to type 2 diabetes mellitus (T2DM) compared to placebo (revised per Amendments 01 and 02)

Other Secondary Objectives (revised per Amendment 02)

MACE and MACE+ Related: (revised per Amendment 02)

- To determine whether the rates of the individual events comprising the MACE+ endpoints are different in subjects on lorcaserin compared to those on placebo

- To determine whether lorcaserin reduces all-cause mortality compared with placebo

Diabetes and Prediabetes Related: (revised per Amendment 02)

- To evaluate the effect of lorcaserin HCl 10 mg BID compared to placebo on conversion to normal glucose homeostasis at 1 year and yearly thereafter in subjects with prediabetes at Baseline (revised per Amendment 01)

- To evaluate whether in all subjects without any type of diabetes at Baseline, lorcaserin HCl 10 mg BID reduces the incidence of conversion to T2DM compared to placebo (revised per Amendment 01)

- To confirm that, in subjects with T2DM at Baseline, lorcaserin HCl 10 mg BID improves glycemic control (HbA_{1c}) compared to placebo at 6 months

Renal Related: (revised per Amendment 02)

- To evaluate the long-term effect of lorcaserin HCl compared to placebo on renal function in all subjects

- To evaluate the long-term effect of lorcaserin HCl compared to placebo on renal function in subjects with T2DM at Baseline

- To evaluate the long-term effect of lorcaserin HCl compared to placebo on renal function in subjects with prediabetes at Baseline (revised per Amendments 01 and 02)

Safety Objectives: (revised per Amendment 02)

- To evaluate echocardiographically determined cardiac valvular function and pulmonary arterial pressure changes associated with treatment with lorcaserin HCl 10 mg BID compared to placebo at 1 year

- To evaluate the long-term safety of lorcaserin HCl 10 mg BID

3.2.1 Exploratory Objectives

- To explore the effects of long-term treatment with lorcaserin HCl 10 mg BID on improving CV risk factors associated with obesity (eg, body weight, dyslipidemia, insulin

level, hypertension, inflammatory biomarkers) compared with placebo at 1 year and yearly thereafter

- To evaluate the effect of BELVIQ (lorcaserin HCl) on other diabetes-related microvascular complications (retinopathy and neuropathy compared to placebo in subjects with prediabetes, or T2DM at Baseline at EOS. (revised per Amendment 01)
- To explore, in subjects with a diagnosis of Non-Alcoholic Fatty Liver Disease (NAFLD) at Baseline, the effects of long-term treatment with lorcaserin HCl 10 mg BID on liver function compared with placebo at 1 year and yearly thereafter
- To evaluate echocardiographically determined heart valve and pulmonary artery pressure changes associated with treatment with lorcaserin HCl 10 mg BID compared to placebo at 2 years and yearly thereafter
- To collect and store DNA samples which may be used for examination of the impact of genetic variation on weight loss, the response to lorcaserin HCl, susceptibility to diabetes, and the risk of developing CV and other end-organ disease and their associated risk factors (for participating countries/sites where ethics and regulatory approval is obtained)
- To collect and store serum and plasma biomarker samples which may be used for examination of the impact of different metabolic and CV pathologic processes on weight loss, the response to lorcaserin HCl, susceptibility to diabetes, and the risk of developing CV and other end-organ disease and their associated risk factors (for participating countries/sites where ethics and regulatory approval is obtained)
- To explore the effects of long-term treatment with lorcaserin HCl (10 mg BID) on improvement of obesity related complications, as defined by the 2014 Advanced Framework for a New Diagnosis of Obesity as a Chronic Disease (American Association of Clinical Endocrinologists [AACE] and American College of Endocrinology [ACE]) (eg, pre diabetes, metabolic syndrome, hypertriglyceridemia/dyslipidemia, and potentially others) (revised per Amendment 01)
- To demonstrate that lorcaserin HCl 10 mg BID improves glycemic control, and/or reduction in OAD medications for the subjects treated with OADs, compared to placebo at 6 months in the following subpopulations of patients with T2DM:
    - Subjects with T2DM with an HbA_{1c}>7% at Baseline
    - Subjects with T2DM who have not been treated with antidiabetic agents at Baseline
    - Subjects with T2DM who are on Monotherapy with an oral antidiabetic agent at Baseline
    - Subjects with early T2DM (duration of diagnosis of diabetes is less than 5 years) at Baseline

3.3 OVERALL STUDY DESIGN AND PLAN

This will be a multicenter, randomized, double-blind, placebo-controlled, parallel-group study in overweight and obese subjects with CV disease and/or multiple CV risk factors. Approximately 12,000 subjects will be randomized to 2 treatment groups in a ratio of 1:1, stratified by the presence of established CV disease (~80%) or CV risk factors without established CV disease

(~20%). The 80% of subjects in the established CV disease strata will consist of a group with T2DM (approximately 30% of the total number of subjects in the study) and a group without T2DM (approximately 50% of the total number of subjects in the study). The 20% of subjects in the strata with CV risk factors but without established CV disease will all have T2DM, as well as additional risk factors. Therefore, approximately 50% of the total number of subjects in the study will have T2DM (Table 1).

Table 1 Approximate Stratification of Subjects

	CV Disease	CV Disease Risk	Total
T2DM	30%	20%	50%
No T2DM	50%	0%	50%
Total	80%	20%	100%

CV = cardiovascular, T2DM = type 2 diabetes mellitus.

The study will consist of 2 phases: Prerandomization and Randomization. The Prerandomization Phase will last up to 30 days and consist of 1 visit during which subjects will be screened for eligibility. The Randomization Phase will consist of 2 periods: Treatment and Follow-up. The Treatment Period will last for approximately 5 years with approximately 18 visits. The first dose should be taken at Visit 2. (revised per Amendment 01). The Follow-up Period extends from the end of treatment (EOT) visit to the EOS visit. Sponsor Notification of Study Completion will occur once, 1401 MACE+ events, 460 MACE events, and median treatment duration of 2.5 years occur. (revised per Amendment 02). This is expected to occur on or before October 2018. Following this announcement ("Sponsor Notification of Study Completion"), sites will be instructed to bring subjects who remain on treatment for an EOT visit. An EOS visit will occur approximately 30 days later for subjects on treatment at Sponsor Notification of Study Completion. (revised per Amendment 01). Subjects who are still being followed in the study but have already discontinued study medication ≥ 30 days before will return for an EOS visit. Subjects who are still being followed in the study but who discontinued study medication within the last 30 days will return for an EOS visit approximately 30 days after their last dose of study medication.

Subjects will receive lorcaserin HCl 10 mg BID or placebo BID for approximately 5 years. Throughout the duration of the study, subjects will be provided with instructions regarding a reduced-calorie diet and increased physical activity program (see Appendix 4 of the protocol). Echocardiography will be performed on a subset of subjects at Baseline and at 6, 12, 18, and 24 months, and yearly thereafter. Acquisition of new ECHO data in all subjects will cease when at least1000 subjects have completed the Month 36 echocardiographic assessment.

All subjects will continue in the study until study completion, rather than for a prespecified number of visits. Subjects who prematurely discontinue study drug will continue in the study for all subsequent study visits until study completion and are to complete visit procedures as indicated in Table 4 in the protocol. It is preferred that these visits are in person. However, if the subject is unable to attend a visit in person, a telephone visit may be performed. The

outcome of the telephone visit must be clearly documented in the source record. At a minimum, the site should attempt to have the subject return for an in-person visit at least once per year. The study will terminate when 1401 MACE+ events have occurred and when there has been a median treatment duration of 2.5 years have accrued. (revised per Amendment 02) This is expected to occur on or before October 2018.

When 460 adjudicated MACE events have occurred, an interim analysis will be conducted on MACE events (see Section 6). It will be conducted to establish whether the primary safety objective (MACE noninferiority) has been achieved. This analysis will be performed by an independent statistician and governed by an independent Data Monitoring Committee (DMC) and is anticipated to occur on or before (approximately) July 2017. If the primary safety objective has been achieved, the trial will continue for evaluation of additional endpoints as delineated in the objectives.

An overview of the study design is presented in Figure 1.

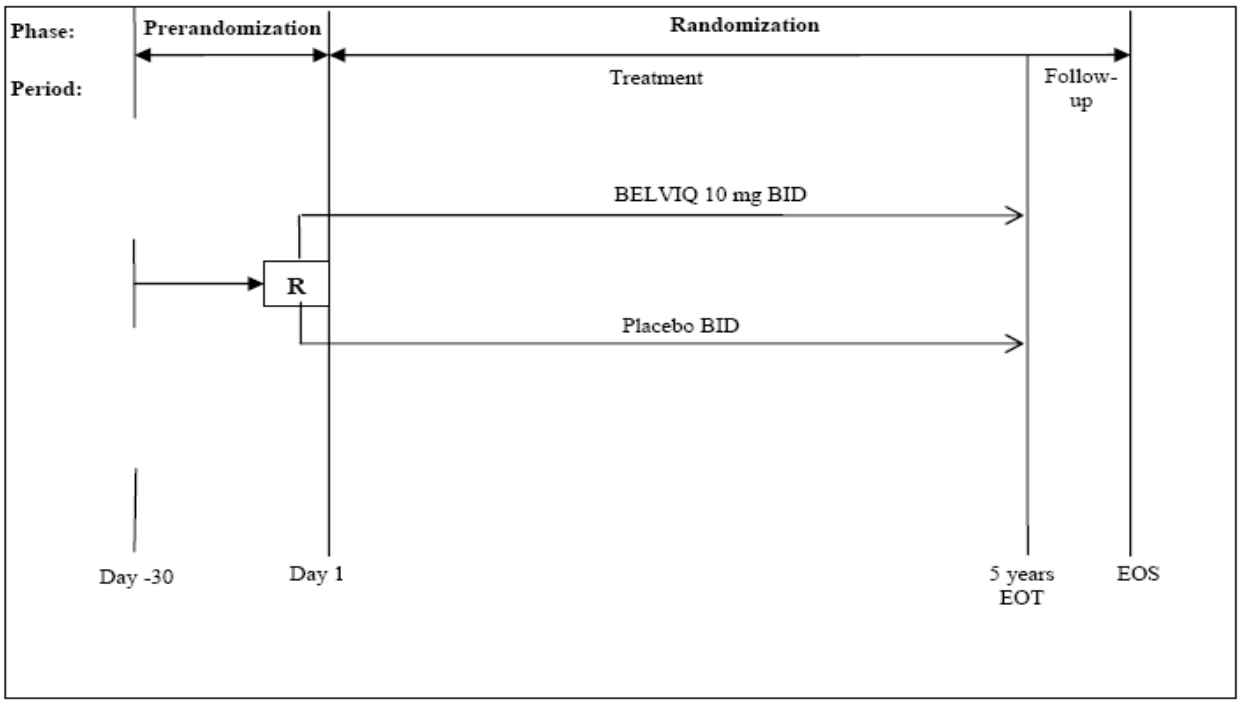


Figure 1 Study Design Schematic BID = twice daily; EOS = end of study; EOT = end of treatment; R = randomization.

3.3.1 Prerandomization Phase

The Prerandomization Phase will last up to 30 days and consist of 1 visit during which subjects will be screened for eligibility and continue until randomization or exclusion. The purpose of the Prerandomization Phase is to obtain informed consent and to establish protocol eligibility. Informed consent will be obtained after the study has been fully explained to each subject and

before the conduct of any screening procedures or assessments. Procedures to be followed when obtaining informed consent are detailed in Section 5.3 of the protocol.
Subjects must be overweight or obese with CV disease or other CV risk factors and must meet all inclusion and exclusion criteria. The Screening Disposition case report form (CRF) page must be completed to indicate whether the subject is eligible to participate in the study and to provide reasons for screen failure, if applicable.

3.3.2 Randomization Phase

The duration of the Randomization Phase will be approximately 56 months and will include 2 periods: Treatment and Follow-up. Subjects whose screening assessments and evaluations are completed and reviewed by the investigator and who continue to meet all of the inclusion/exclusion criteria will enter the Randomization Phase. Subjects will be randomized in a 1:1 ratio to receive lorcaserin HCl 10 mg BID or placebo.

3.3.2.1 Treatment Period

The Treatment Period will last for approximately 5 years with approximately 18 visits. The first dose should be taken at the Randomization visit (Visit 2). (revised per Amendment 01) During the Treatment Period, subjects will continue treatment with the dose of lorcaserin HCl 10 mg or placebo BID in blinded fashion.

3.3.2.2 Follow-up Period

For subjects who remain in the study through the Sponsor Notification of Study Completion, the Follow-up Period will begin immediately after the EOT assessments have been completed, and will consist of 1 EOS visit, occurring 30 days + 10 days after last dose of study drug for subjects who complete study treatment. (revised per Amendments 01 and 02) See Section 9.3.3 of the protocol for procedures for subjects who prematurely discontinue study drug.

The scheduled of assessments are presented in Table 4 of the protocol.

4 DETERMINATION OF SAMPLE SIZE

A sample size of 12,000 subjects should provide the required power for the primary endpoints and key secondary endpoint as follows:

Primary Endpoints (revised per Amendment 02)

- For 460 MACE events to have occurred by approximately 43 months from start of the trial, providing 95% power to exclude a noninferiority margin of 1.4, assuming an annual background rate of 1.5%, 15-month accrual period, 5% annual drop-out rate, $\alpha = 0.025$, and a 1-sided test

- For 1401 MACE+ events to have occurred by approximately 54 months from the start of the trial, providing > 85% power to detect a 15% risk reduction with lorcaserin HCl, assuming an annual background rate of 3.5%, 15-month accrual period, 5% annual drop-out rate, $\alpha = 0.05$, and a 2-sided test

Key Secondary Endpoint (revised per Amendment 02)

- For 457 events of conversion to T2DM in subjects who are prediabetic at the time of enrollment (~33%) to have occurred by approximately 54 months from the start of the study, providing 86% power to detect a 25% risk reduction with lorcaserin HCl, assuming an annual background rate of 4%, 15-month accrual period, 5% annual drop-out rate, $\alpha = 0.05$ and a 2-sided test.

5 STATISTICAL METHODS

Statistical analyses will be performed by the sponsor or designee after the study is completed and the database is locked and released for unblinding. Statistical analyses will be performed using SAS software or other validated statistical software as required.

All descriptive statistics for continuous variables will be reported using mean, standard deviation (SD), median, minimum and maximum. Categorical variables will be summarized as number (percentage) of subjects.

5.1 STUDY ENDPOINTS

Time from randomization to first occurrence of MACE will be the only endpoint to be analyzed at the Interim Analysis. All other endpoints will be analyzed at Study Completion.

5.1.1 Primary Endpoints

- Time from randomization to first occurrence of MACE (first occurrence of any of the following events: MI, stroke, or CV death) at Interim Analysis only.

- Time from randomization to first occurrence of MACE+ (first occurrence of any of the following events: MACE or hospitalization for unstable angina or HF, or any coronary revascularization)

5.1.2 Key Secondary Endpoint (revised per Amendment 02)

- Time from randomization to conversion to T2DM, defined as first occurrence of any component of the 2013 ADA diagnostic criteria[4] in subjects with prediabetes at Baseline. The diagnostic criteria are met if a subject has unequivocal hyperglycemia (random plasma glucose $\geq$ 200 mg/dL (11.1 mmol/L) with classic symptoms of hyperglycemia or hyperglycemic crisis) OR any of the following criteria are observed and subsequently confirmed on repeat laboratory testing: (revised per Amendments 01 and 02):

    - $HbA_{1c} \geq 6.5\%$
    - FPG $\geq$ 126 mg/dL (7.0 mmol/L)
    - 2-hour plasma glucose $\geq$200mg/dL (11.1 mmol/L) by an OGTT

Investigators should make every effort to obtain central lab confirmatory testing no later than 6 weeks after meeting any of the above criteria. Abnormalities of any 1 of the above 3 criteria on repeat testing constitutes diagnostic confirmation of diabetes. Subjects who have been started on anti-diabetic medications following abnormalities in preliminary testing do not require confirmatory testing. (revised per Amendments 01 and 02).

5.1.3 Other Secondary Endpoints (revised per Amendment 02)

MACE and MACE + Related: (revised per Amendment 02):

- Time from randomization to first occurrence of each of the individual components of MACE+
- Time from randomization to first occurrence of all-cause mortality

Diabetes and Prediabetes Related (revised per Amendment 02):

- Time from randomization to conversion to normal glucose homeostasis ($HbA_{1c} \leq 5.6\%$ and fasting plasma glucose <100 mg/dL without any antidiabetic treatment) in subjects with prediabetes at Baseline (revised per Amendments 01 and 02).). See Section 8.3.2 for definition.
- Time from randomization to conversion to T2DM in subjects without any type of diabetes at Baseline. (revised per Amendment 01). See Section 8.3.1 for definition
- Change from Baseline in HbA1c at 6 months in subjects with T2DM at Baseline

Renal Related (revised per Amendment 02)

- Time from randomization to first occurrence of 2 consecutive assessments within the same component of the composite endpoint or time to first occurrence of renal transplant or renal death, on scheduled or nonscheduled visits at least 30 days apart, indicative of new onset renal impairment or worsening of existing renal impairment (first occurrence of any of the following events: microalbuminuria, macroalbuminuria, worsening albuminuria, newly developed CKD or worsening of CKD, or doubling of serum creatinine, as defined above, or any of the following: ESRD, renal transplant, renal death) in all subjects. (revised per Amendment 02). See Section 8.2.1 for definitions.
- Time from randomization to first occurrence of 2 consecutive assessments within the same component of the composite endpoint or time to first occurrence of renal transplant or renal death, on scheduled or non-scheduled visits at least 30 days apart, indicative of new onset renal impairment or worsening of existing renal impairment (first occurrence of any of the following events: microalbuminuria, macroalbuminuria, worsening albuminuria, newly developed CKD or worsening of CKD, or doubling of serum creatinine, as defined above, or any of the following: ESRD, renal transplant, renal death) in subjects with prediabetes at Baseline (revised per Amendments 01 and 02). See Section 8.2.1 for definitions

- Time from randomization to first occurrence of 2 consecutive assessments within the same component of the composite endpoint or time to first occurrence of renal transplant or renal death, on scheduled or nonscheduled visits at least 30 days apart, indicative of new onset renal impairment or worsening of existing renal impairment (first occurrence of any of the following events: microalbuminuria, macroalbuminuria, worsening albuminuria, newly developed CKD or worsening of CKD, or doubling of serum creatinine, as defined above, or any of the following: ESRD, renal transplant, renal death) in subjects with T2DM at Baseline (revised per Amendment 01). (revised per Amendment 02). See Section 8.2.1 for definitions
- Time from randomization to first occurrence of 2 consecutive assessments, on scheduled or nonscheduled visits at least 30 days apart, indicative of improvement in renal function (first occurrence of regression of albuminuria or regression of CKD) in subjects with T2DM at Baseline. See Section 8.2.2 for definitions

Secondary Endpoints Assessing Cardiac Valve Function and Pulmonary Arterial Pressure: (revised per Amendment 02)

- Proportion of subjects without FDA-defined valvulopathy at Baseline who develop FDA-defined valvulopathy at 1 year (see Section 8.4 for definition)
- Proportion of subjects with FDA-defined valvulopathy confirmed by documented objective assessments at Baseline who demonstrate worsened FDA-defined valvulopathy (see Section 8.4.1 for definition) at 1 year (revised per Amendment 01).
- Change from Baseline in estimated pulmonary artery systolic pressure at 1 year

5.1.4 Exploratory Endpoints

- Change from Baseline in CV risk factors at 1 year and yearly thereafter (e.g., body weight, dyslipidemia, insulin level, hypertension, and applicable biomarkers of CV risk and other end-organ diseases). For lipid parameters percent change from baseline will be used
- Change from Baseline in eGFR and ACR at 1 year, yearly thereafter, and at the end of the study. GFR will be estimated using creatinine, cystatin C and a combination of both (Section 8.1).
- Change from Baseline in LFTs (AST, ALT, alkaline phosphatase, GGT, total and direct bilirubin) at 1 year and yearly thereafter
- Proportion of subjects without FDA-defined valvulopathy at Baseline who develop FDA- defined valvulopathy at 2 years and yearly thereafter
- Change from Baseline in estimated pulmonary artery systolic pressure at 2 years and yearly thereafter
- Proportions of subjects with at least a 1-stage reduction in an obesity-related complication (prediabetes, metabolic syndrome, T2DM, hypertension, and hypertriglyceridemia/dyslipidemia) at 1 year and EOS; incidence of other obesity-related complications will be collected through AE reports, medical history, and use of

concomitant medications, based on 2014 Advanced Framework for a New Diagnosis of Obesity as a Chronic Disease (American Association of Clinical Endocrinologists [AACE] and American College of Endocrinology [ACE]). (revised per Amendment 01)

- Change from Baseline in HbA1c, FPG, fasting insulin levels, and homeostatic model assessment insulin resistance (HOMA-IR) at 6 months in the following subpopulations of subjects with T2DM at Baseline: (revised per Amendments 01 and 02)
    - Subjects with (HbA1c>7%) at Baseline
    - Subjects who have not been treated with antidiabetic agents at Baseline
    - Subjects who are on monotherapy with oral antidiabetic agent at Baseline
    - Subjects with early T2DM (duration of diagnosis of diabetes is less than 5 years) at Baseline

- Proportion of subjects with reduction in the number of OAD medications or reduction in the dosage of OAD medications at 6 months in the following subpopulations of subjects with T2DM at Baseline: (revised per Amendment 01)
    - Subjects with (HbA1c >7%) at Baseline
    - Subjects who are on monotherapy with oral antidiabetic agent at Baseline
    - Subjects with early T2DM (duration of diagnosis of diabetes is less than 5 years) at Baseline

- Proportions of subjects with prediabetes at Baseline who develop new diagnosis of diabetic retinopathy or new diagnosis of diabetic neuropathy by EOS (revised per Amendment 01)

- Proportions of subjects with T2DM at Baseline who develop new diagnosis of diabetic retinopathy or new diagnosis of diabetic neuropathy by EOS (revised per Amendment 01)

5.2 STUDY SUBJECTS

5.2.1 Definitions of Analysis Sets

The number (percent) of subjects included in each analysis set will be presented by analysis set, treatment group and overall. The description of the analysis data sets are:

- The Safety Analysis Set: will be the group of subjects who received at least one dose of study drug and had at least one post dose safety assessment.

- The Intent-to-Treat (ITT) Set: will be the group of all randomized subjects regardless of whether they took study drug or not. This is the same as the Full Analysis Set.

- Total Time Analysis Set: Using the ITT, events are counted that occur while subjects are on and off treatment. Subjects with no events will be censored at their last study contact or at the visit following Sponsor Notification of Study Completion, whichever

occurs first. This analysis set will be used for the primary analysis. See Section 8.5 for censoring algorithm.

- On-Treatment plus 30 Days Analysis Set: Using the ITT, events are counted that occur while subjects are "on treatment" and up to 30 days from their last dose. Subjects with no events who discontinue early or complete the study will be censored at their last dose date plus 30 days. See Section 8 for definition of "on treatment" and Section 8.5 for censoring algorithm.

- On-Treatment Analysis Set: Using the ITT, events are counted that occur while subjects are "on treatment". Subjects with no events who discontinue early or complete the study will be censored at their last dose date. See Section 8 for definition of "on treatment" and Section 8.5 for censoring algorithm.

- Prediabetes Analysis Set: This set includes all subjects in the ITT set without a history of any type of diabetes and who are prediabetic at Baseline (defined in Section 8).
- Nondiabetes Analysis Set: This set includes all subjects in the ITT set without a history of any type of diabetes at Baseline (defined in Section 8).

- T2DM Analysis Set: This set will be all subjects in the ITT who have T2DM at Baseline (defined in Section 8).

- FDA-defined Valvulopathy Analysis Set: This set will be all subjects in the ITT without FDA- defined valvulopathy at Baseline (defined in Section 8.4). The data from the ECHO sub-study will be pooled with the ECHO data from the 3 pivotal lorcaserin HCl studies (APD356-009, APD356-010, and APD356-011).

- The PD Analysis Set will be the group of subjects who have both baseline and at least one post-baseline assessment of at least one PD parameter.

Details of the censoring algorithms for time-to-event endpoints are presented in Section 8.5.

5.2.2 Subject Disposition

The number of subjects screened and the number (percent) of subjects who failed screening and the reasons for screen failure will be summarized, based on data reported on the Screening Disposition CRF. The distribution of the number of randomized subjects enrolled by each site will be summarized for each randomized treatment group. The primary reasons for screen failures; did not meet inclusion/exclusion criteria, AE, lost to follow-up, withdrawal of consent, and other, will be presented.

For study completion, the number (percent) of randomized subjects who completed the study (e.g. subject was in the study at the date of Final Sponsor Notification/Premature Study Discontinuation by Sponsor, whether subject is on or off treatment or death) and who

discontinued from the study will be summarized according to the primary reason for discontinuation based on data reported on the Final Study Disposition CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed the study, and discontinued from the study. For those who are considered to have discontinued from the study, the reasons for discontinuation from the study at Final Sponsor Notification/ Premature Study Discontinuation are captured in the Final Study Disposition CRF (Withdrawal of Consent, Lost to follow up, Study prematurely terminated by sponsor, and Other).

Completion of Study Treatment: the number (percent) of randomized and treated subjects who completed study treatment (e.g. subject was on study drug at the date of Final Sponsor Notification/Premature Study Discontinuation by Sponsor) and who discontinued from study treatment will be summarized according to the primary reason for discontinuation, based on data reported on both the Final Study Disposition CRF and Early Discontinuation from Study Drug CRF. The number (percent) will be presented by treatment group and total for subjects; randomized, not treated, treated, who completed study on treatment, off treatment, and discontinued from study treatment. The reasons for early discontinuation from study drug are: AE/SAE, Pregnancy/Breastfeeding, Subject choice unrelated to AE/SAE, Treatment Required with Prohibited Concomitant Medications, Other – study administrative reasons. Subject choice will be further summarized as per the reasons captured in the Early Discontinuation from Study Drug CRF; Inadequate Therapeutic Effect, Logistical reason, and Other.

5.2.3 Protocol Deviations

Major protocol deviations will be summarized, number (%), in addition a subject listing will be provided along with the description of the protocol deviation. Protocol deviations will be identified prior to database lock.

5.2.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics will be summarized as outlined for the Safety Analysis Set and ITT in aggregate as well as stratified by CV strata, baseline glycemic status (e.g. normal glucose homeostasis, prediabetes, nondiabetes, and T2DM at baseline as defined in Section 8).

Continuous demographic and baseline variables include age, height, weight, waist and hip circumference, duration of comorbid conditions (none, hypertension, dyslipidemia, sleep apnea, coronary artery disease (CAD)/CV disease), duration of T2DM, HbA1c, and BMI.

Categorical variables include sex, age group (<65 years, ≥65 to < 75, , ≥75 years), race, ethnicity, HbA1c (prediabetes: 5.7% to <6.5%; normal glucose homeostasis: <5.7%), BMI (<30 kg/m^2, 30 to <35 kg/m^2, ≥35 to < 40 kg/m^2 , ≥ 40 kg/m^2), baseline body weight (by quartiles), presence of comorbid conditions (none, hypertension, dyslipidemia, sleep apnea, CAD/CV disease), CV risk factors, presence of T2DM, tobacco use, albuminuria (normal: ACR

<30µg/mg; microalbuminuria: ACR 30 to 299 µg/mg; macroalbuminuria: ACR ≥300 µg/mg), GFR (mL/min per 1.73 m^2 BSA); kidney damage with normal or increased GFR ≥90; kidney damage with mildly decreased GFR 60 to 89; moderately decreased GFR 30 to 59; severely decreased GFR 15 to 29; kidney failure GFR <15 or dialysis; and type of diabetes medication used.

5.2.5 Medical History

The medical history verbatim descriptions (investigator terms from the Other Medical history and Current Medical Condition CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA). Medical history will be coded to the MedDRA (Version 16.0 or higher) lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) will also be captured in the database. The number (percent) of subjects reporting a history of any medical condition will be summarized for each treatment group and overall.

In addition, separate summary tables by treatment group and overall will be provided for; Diabetes History, Cardiovascular History, Malignancy History, Psychiatric History, and Sleep Apnea/NAFLD History.

5.2.6 Prior and Concomitant Therapy

All investigator terms for medications recorded in the CRF will be coded to an 11-digit code using the World Health Organization Drug Dictionary (WHO DD). The number (percentage) of subjects who took prior and concomitant medications will be summarized on the Safety Analysis Set by treatment group, Anatomical Therapeutic Chemical (ATC) class, and WHO DD preferred term (PT). Prior medications will be defined as medications that stopped before the first dose of study drug.

Concomitant medications will be defined as any medications taken by the subject during the 30 days before first dose administration of study drug and continued the concomitant medication during the double blind phase or started a concomitant medication during the double blind phase. All medications will be presented in subject data listing.

5.2.7 Treatment Compliance

Overall compliance rate will be determined and defined as the difference in the tablets dispensed minus the number of tables returned, divided by the expected number of tablets to be taken, multiplied by 100. Subjects will be considered compliant while they are on BID or QD dosing. Descriptive statistics (n, mean, standard deviation, median minimum, maximum) and number (%) of subjects in compliance categories (<50%, 50 to <80%, 80 to ≤120%, >120%) will be provided for the entire double-blind phase. The Safety Analysis Set will be used. See Section 8.0 for derivation of compliance.

5.3 DATA ANALYSIS GENERAL CONSIDERATIONS

5.3.1 Pooling of Centers

This study is a multicenter, international study with 476 sites. It is expected that due to the number of sites in this trial, sites will be pooled into regions, in order to have sufficient number of subjects per treatment group and CV disease strata. The countries participating in this study are Australia, Bahamas, Canada, Chile, Mexico, New Zealand, Poland, and the USA. The countries will be pooled into regions North America (USA, and Canada), and Rest of the World (Bahamas, Chile, Mexico, Poland, Australia and New Zealand). Region will be included as a covariate to explore region effects.

5.3.2 Assessment of Effect Modification

In addition, to the primary and secondary analyses, outline in Sections 5.4.1 and 5.4.2 further exploratory analyses will be performed to assess for effect modification by a number of demographic and baseline variables outlined in Section 5.3.4 including:

- Age treated as continuous and as categorical
- Gender
- Presence of T2DM
- Race
- Ethnicity
- Region
- BMI as continuous and categorical
- eGFR as continuous and categorical

A separate analysis will be performed for each covariate.

5.3.3 Multiple Comparisons/Multiplicity

This study has two primary endpoints; MACE and MACE+. The following closed sequential gatekeeping testing procedure (SGTP) will be used to control the family-wise error rate (FWER) at $\alpha = 0.05$ (two-sided) in testing the two primary endpoints (MACE and MACE+) and one key secondary endpoint, conversion to T2DM (revised per Amendment 02).

Let H_{01} be the gatekeeping null hypothesis for non-inferiority testing of the MACE endpoint using a non-inferiority margin of 1.4 for the hazard ratio.

Let $H_{02,}$ and H_{03} be the null hypotheses for superiority testing: MACE+ and conversion to T2DM, respectively.

The SGTP testing hierarchy is presented below.

- STEP1: At the interim analysis, test the non-inferiority hypothesis for MACE, H_{01} ($\alpha = 0.025$, one-sided). If H_{01} is rejected, then proceed to STEP2, otherwise stop testing and the trial will be stopped. This step will be performed as an interim analysis, see Section 6 for further details

- STEP2: At study completion, the hypothesis H_{02} ($\alpha = 0.05$, two-sided) is tested first. If the hypothesis is rejected then proceed to test H_{03} ($\alpha = 0.05$, 2-sided). If H_{02} is not rejected then testing stops at this point..

Figure 2 presents the SGTP (revised per Amendment 02)

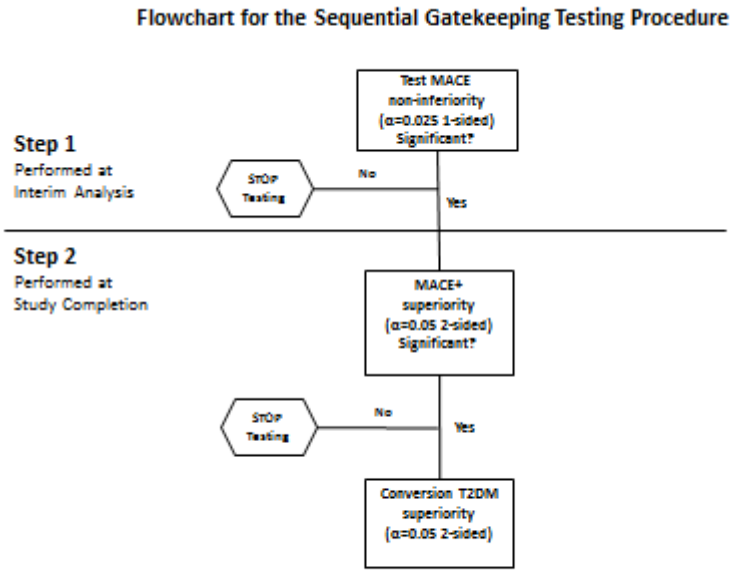


Figure 2 Flowchart for SGTP
MACE = major adverse cardiovascular events, MACE+ = MACE or hospitalization for unstable angina or heart failure, or any coronary revascularization; Step 1 will be performed when 460 adjudicated MACE events occurred, at the Interim Analysis. Step 2 will be performed upon Sponsor Notification of Study Completion which will occur once 1401 MACE+ events, and 2.5 years median treatment duration..

Analysis of other secondary endpoints will be used to support the results of primary analyses, thus no multiplicity adjustment will be performed.

5.3.4 Examination of Subgroups

The primary endpoints will be analyzed for each of the demographic and baseline characteristics subgroups listed in Tables 2, and Baseline Cardiovascular Risk Level and Risk Factors, listed in Table 3. For categorical parameters, categories with sparse number of subjects will be collapse. The final set of categories will be determined prior to database lock.

Table 2 Subgroups of Demographic and Baseline Characteristics

Characteristic	Categories
Age	≤65, ≥65 to < 75, ≥75 years
Gender	Female, Male
Race	White Black or African American Other Asian American Indian or Alaska Native Native Hawaiian or Other Pacific Islander Other
BMI	< 30 kg/m^2 ≥ 30 to < 35 kg/m^2 ≥ 35 to < 40 kg/m^2 ≥ 40 kg/m^2
Waist circumference	Women <35 Inches (88cm) ≥35 Inches (88cm) Men <40 Inches (102cm) ≥40 Inches (102cm)
Weight	≤ 1st Quartile >1st Quartile to ≤ 2nd Quartile >2nd Quartile to ≤ 3rd Quartile > 3rd Quartile
Duration of Type 2 Diabetes (years)	< 5 years ≥ 5 to < 10 years ≥ 10 to < 20 years ≥ 20 years
HbA1C	Non-diabetics (see Section 8) Normal (< 5.7%) Pre-diabetes (≥ 5.7% to < 6.5%) Diabetics (see Section 8) < 6.5% ≥ 6.5% to <7% ≥ 7 to < 8% ≥ 8 to < 9% ≥ 9%

Table 2 Subgroups of Demographic and Baseline Characteristics

Characteristic	Categories
FPG	< 100 mg/dL ≥ 100 to < 126 mg/dL ≥ 126 to < 150 mg/dL [≥ 7.0 mmol/L to < 8.3 mmol/L] ≥ 150 to < 220 mg/dL [≥ 8.3 mmol/L to < 12.2 mmol/L] ≥ 220 to < 300 mg/dL [≥ 12.2 mmol/L to < 16.7 mmol/L] ≥ 300 mg/dL [≥ 16.7 mmol/L]
Blood Pressure	Systolic BP (mmHg) <140 ≥140 Diastolic BP (mmHg) <90 ≥90
Renal Function (eGFR)	> 60 mL/min ≥ 30 to ≤ 60 mL/min < 30 mL/min
Albumin/creatinine ratio	< 30 mg/g [< 3.4mg/mmol] ≥ 30 to < 300 mg/g [≥ 3.4 mg/mmol - < 33.9 mg/mmol] ≥ 300 mg/g [≥ 33.9 mg/mmol]
Region and Country	North America (US/Canada) Rest of World (ROW) Europe Central and South America Australia/NZ
Baseline Diabetic Medication use	No medications/any insulin/oral meds without insulin GLP1 agonist/no GLP1 agonist SGLT2 inhibitor/no SGLT2 inhibitor SFU/no SF Metformin/no metformin SFU and Metformin/others Insulin/no insulin Insulin and SFU/others

Table 2 Subgroups of Demographic and Baseline Characteristics

Characteristic	Categories
Baseline Cardiovascular Medication Use	ASA Dual antiplatelet (ASA and P2Y12 receptor antagonist) Lipid Lowering Therapy Beta blocker ACEi/ARB/Aldosterone antagonist

Table 3 Subgroups of Baseline Cardiovascular Risk Level and Risk Factors

Characteristic	Categories
CV Risk Level	Primary prevention - Patients with multiple risk factors for CV events, but without established CV disease Secondary prevention - Patients with established CV disease
Primary Prevention (Risk Factors as defined in protocol inclusion criteria)	**By risk factor:** - Dyslipidemia - Hypertension - Renal impairment with either Calculated creatinine clearance ≥30 to ≤60 mL/min per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation or ACR≥30 µg/mg in spot urine - hsCRP > 3 mg/L **By number of risk factors in addition to T2DM:** 1 additional risk factor (Dyslipidemia, hypertension, renal dysfunction or elevated hsCRP) 2 additional risk factors 3 additional risk factors 4 additional risk factors
Secondary Prevention (Established CV Disease as defined in the protocol inclusion)	Coronary artery disease Peripheral vascular disease Cerebrovascular disease Risk Scores(0,1-2, and 3 or greater) See Section 8 for definition

5.3.5 Handling of Missing Data, Drop-outs, and Outliers

Data will be monitored during the trial in order to minimize missing data. A detail retention plan in order to prevent missing data is found in Appendix 13.1. The primary endpoints are time to event endpoints for MACE/MACE+. Every effort will be made to find subjects who are lost to follow-up using patient finder services. Once these subjects are found the sites will contact the

subject and will try to obtained vital status information on the subject. Primary consideration is to establish if the subject is dead or alive.

5.3.6 Other Considerations

Potential MACE/MACE+ events will be recorded throughout the study. During this study, the endpoints of MACE and MACE+ will need to be reported in an expedited fashion by investigators to the Clinical Endpoint Committee (CEC) and to the Eisai Product Safety Department. MACE/MACE+ events will be recorded on the Adverse Event (AE) case report form, but these events will not be considered as AEs, nor will they be recorded as serious adverse events (SAEs) in the clinical trial safety database or be required to be reported to regulatory authorities in an expedited timeframe, with the exception of MACE or MACE+ events that are considered by the investigator to be at least possibly related to the study drug (i.e., where there is evidence to suggest a causal relationship).

Details of which events to report, how to report, and the required supporting documentation will be detailed in a separate manual provided to the sites.

Adjudication of Component Events for MACE/MACE+

The component events of MACE; MI, or stroke, or CV death and the component events of MACE+; MI, or stroke, or CV death, or hospitalization for unstable angina or HF, or any coronary revascularization, will be adjudicated by the CEC, in order to reduce intra- and inter-site variability. The CEC will centrally review each potential component event of MACE and MACE+ to ensure standardization of data collection and interpretation of such events reported throughout the study. The CEC will determine whether each potential component event meets criteria for MACE or MACE+. The CEC will remain blinded to treatment allocation and its activities and the criteria for classification of each component event of MACE/MACE+ will be documented in the CEC Charter, see Appendix 13.1.1.

Adjudication of Conversion to Diabetes Events

The conversion to diabetes events will be adjudicated by the CEC Diabetes Adjudication Charter, in order to reduce intra- and inter-site variability. The CEC will centrally review each potential event to ensure standardization of data collection and interpretation of such events reported throughout the study. The CEC will determine whether each potential event meets criteria for conversion to diabetes. The CEC will remain blinded to treatment allocation and its activities and the criteria for classification of each event will be documented in the charter, see Appendix 13.1.4.

5.4 EFFICACY ANALYSES

The primary and key secondary endpoints, MACE, MACE+, and conversion to T2DM, will be analyzed using a Cox proportional hazards model that includes factors for treatment and stratification variable (presence of established CV disease or CV risk factors without established CV disease). For other secondary and exploratory endpoints a two-sided $\alpha = 0.05$ significance level will be used. The primary safety analysis for MACE will be conducted when 460

adjudicated MACE events have been recorded at the interim analysis; the other analyses will be conducted when 1401 adjudicated MACE+ events have been recorded, and the study has completed. See Section 6 for Interim Analysis Plan.

Secondary and exploratory time-to-event endpoints will be analyzed using a Cox proportional hazards model that includes factors for treatment and stratification variable (presence of established CV disease or CV risk factors without established CV disease), except for those endpoints that used the population with no T2DM at Baseline, the CV stratification variable will not be included in the model.

For all time-to-event endpoints, plots of the Kaplan-Meier estimate of the survival function, cumulative hazard function, kernel-smoothed estimate of the hazard function, and median time estimates along with 100(1-α) % CI will be presented. In addition, parameter estimates, standard errors, hazard ratio and 100(1-α) % CI will presented. In addition, event rates will be presented per 100 patient years where appropriate.

Details of the censoring algorithms for time-to-event endpoints are presented in Section 8.5.

5.4.1 Primary Endpoint Analyses

The primary safety analysis (Time to MACE using the Total Time Analysis Set) will be the only analysis performed at the interim analysis as outlined in Section 6. All other analyses will be performed at Study Completion, see Section 8 for definition of Study Completion.

Primary Safety Analyses

- **Time to MACE(Non-inferiority):** The estimate of the hazard ratio of lorcaserin HCl to placebo and the corresponding one-sided 97.5% confidence interval (CI) will be calculated. Non-inferiority of lorcaserin HCl to placebo will be declared if the upper limit of the 97.5% CI is less than the non-inferiority margin of 1.4. The Total Time Analysis Population will be used as the primary analysis at the time of the Interim Analysis. (revised per Amendment 02) The On-Treatment Analysis Set and the On-Treatment plus 30 Days Analysis Set will be used as a sensitivity analysis at Study Completion. (revised per Amendment 02)

Primary Efficacy Analyses

- **Time to MACE+ (Superiority):** The estimate of the hazard ratio of lorcaserin HCl to placebo and the corresponding two-sided 95% CI will be calculated. The Total Time Analysis Population will be used as the primary analysis. (revised per Amendment 02) The On-Treatment Analysis Set and On-Treatment plus 30 Days Analysis Set will be used as a sensitivity analysis at Study Completion. (revised per Amendment 02)

5.4.1.1 Additional Sensitivity Analyses at Study Completion

- **Time to MACE (Non-inferiority):** The primary safety analysis above, which will be conducted at the interim analysis, will be repeated at study completion as a sensitivity analysis.

- **Time to MACE (Superiority):** The estimate of the hazard ratio of lorcaserin HCl to placebo and the corresponding one-sided 97.5% confidence interval (CI) will be calculated. Superiority lorcaserin HCl to placebo will be declared if the upper limit of the 97.5% CI is less than 1. The Total Time Analysis Set, the On-Treatment Analysis Set, and the On-Treatment plus 30 Days Analysis Sets will be used.

- The incidence rate difference and the incidence rate ratio between lorcaserin and placebo will also be analyzed as supportive analysis for each of the primary endpoints above. The adjusted risk difference (incidence rate difference) and relative risk (incidence rate ratio) along with their respective 95% CI will be estimated using a Poisson regression model (using PROC GENMOD in SAS) with a robust error variance (sandwich error estimator)[1,2]. The model will include factors for treatment and stratification variable (presence of established CV disease or CV risk factors without established CV disease). The Total Time Analysis Set, the On-Treatment Analysis Set, and the On-Treatment plus 30 Days Analysis Sets will be used.

- **Subjects that start another weight reduction medication or had bariatric procedure:** For MACE and MACE+ endpoints using the Total Time Analysis Set. In this sensitivity analysis subjects will be censored when the subject starts another weight reduction medication or undergoes a bariatric procedure.
- **Subjects who permanently down titrate from BID dosing to QD dosing:** For MACE and MACE+ endpoints using the On-treatment and On-treatment plus 30 days Analyses Sets. In this sensitivity analysis events will be not counted when the subject is on QD dosing.
- **Subjects who prematurely discontinued:** For the MACE (Superiority) and MACE+ endpoints, multiple imputation will be used to impute censored data for those subjects who are lost to follow-up. The Total Time Analysis Set will be used.

5.4.2 Key Secondary Analysis (revised per Amendment 02)

- **Time to conversion to T2DM (Superiority)**. The estimate of the hazard ratio of lorcaserin HCl to placebo and the corresponding two-sided 95% CI will be calculated. The Prediabetes and Total Time Analyses Sets will be used as the primary analysis. The Prediabetes along with the On-Treatment Analysis Set and the On-Treatment plus 30 Days Analysis Set will be used as a sensitivity analysis at Study Completion (revised per Amendment 02).

5.4.3 Secondary Endpoint Analyses

For the following endpoints, a Cox proportional hazards model with factors for treatment and stratification variable (presence of established CV disease or CV risk factors without established CV disease) will be used. The estimate of the hazard ratio of lorcaserin HCl to placebo and the corresponding 2-sided 95% CI will be calculated. See Section 8.5 for details on censoring algorithms for the time-to-event endpoints.

The secondary endpoints are considered as supportive analysis to the primary endpoints and key secondary endpoint, therefore no correction for Type I error rate will be performed.

- The time-to-event of each component of MACE+. The Total Time Analysis Set will be used as the primary analysis. The On-Treatment Analysis Set and the On-Treatment plus 30 Days Analysis Set will be used as sensitivity analyses.
- Time-to-event of all-cause mortality. The Total Time Analysis Set will be used as the primary analysis. The On-Treatment Analysis Set and the On-Treatment plus 30 Days Analysis Set will be used as sensitivity analyses.
- Time-to-event of new onset renal impairment or worsening existing renal impairment in all subjects. The ITT Analysis Set will be used for this analysis. (revised per Amendment 02)
- Time-to-event of new onset renal impairment or worsening existing renal impairment in subjects with T2DM at Baseline. The T2DM Analysis Set will be used for this analysis.
- Time-to-event of new onset renal impairment or worsening existing renal impairment in subjects with prediabetes at Baseline. The Prediabetes Analysis Set will be used for this analysis. (revised per Amendment 01)
- Time-to-event of improvement in renal function. The T2DM Analysis Set will be used for this analysis.
- Time-to conversion to T2DM in subjects without any type of diabetes at Baseline. The Nondiabetes Analysis Set will be used for this analysis. (revised per Amendment 01)
- Time to conversion to normal glucose homeostasis (HbA1c $\leq$5.6% and fasting plasma glucose <100 mg/dL without any antidiabetic treatment). The Prediabetes Analysis Set will be used for this analysis. (revised per Amendments 01 and 02)

- Change from Baseline in HbA_{1c} at 6 months in subjects with T2DM at Baseline will be analyzed using an analysis of covariance (ANCOVA) model with treatment and stratification variable (presence of established CV disease or CV risk factors without established CV disease) as factors, and baseline HbA_{1c}, as a covariate. Comparison between lorcaserin HCl and placebo will be made at 6 months. The estimated treatment difference between lorcaserin HCl and placebo and the 2-sided 95% CI will be calculated. The T2DM Analysis Set will be used for this analysis. (revised per Amendment 01)

In addition to the analysis of the ECHO data from this study, the following analyses will be repeated by pooling the ECHO data from this study with the data from the 3 pivotal lorcaserin

HCl studies (APD356-009, -010, and -011) with terms added for study and treatment by study interaction term in the model in order to account for the variability of the different studies.

- The proportion of subjects who meet FDA-defined valvulopathy in echocardiographically determined heart valve changes will be analyzed using logistic regression including treatment as a factor and baseline BMI as a covariate. Comparison between lorcaserin HCl and placebo will be made at 1 year. The FDA-defined Valvulopathy Analysis Set will be used for this analysis.
- The proportion of subjects with FDA-defined valvulopathy at Baseline who demonstrate worsened FDA-defined valvulopathy will be analyzed using logistic regression including treatment as a factor and baseline BMI as a covariate. A comparison between lorcaserin HCl and placebo will be made at 1 year. The ITT analysis set in subjects with FDA-defined valvulopathy at Baseline will be used for this analysis. (revised per Amendment 01)
- The change from Baseline in echocardiographically-determined pulmonary arterial systolic pressure will be analyzed using a mixed-effects model with repeated measures with treatment as a factor and baseline BMI as a covariate. Comparison between lorcaserin HCl and placebo will be made at 1 year and the corresponding 2-sided 95% CI will be calculated. (revised per Amendment 01) The ITT will be used for this analysis.

5.4.4 Other Efficacy Analyses

The associations between the presence of FDA-defined valvulopathy and Change from Baseline in body weight or BMI, at 1 year, will be analyzed using logistic regression including stratification variable (presence of established CV disease or CV risk factors without established CV disease), baseline weight (or BMI), age, and Week 52 weight change (or BMI change) as independent variables in the model. The model will be run for each treatment group separately and for all patients (with their treatment group not included in the model). The odds ratio, p-value and 2-sided 95% CI will be calculated, along with the regression coefficients, standard errors and 95%CIs. The ITT analysis set in subjects with FDA-defined Valvulopathy at Baseline will be used for this analysis.

5.5 PHARMACOKINETIC, PHARMACODYNAMIC AND PHARMACOGENOMIC / PHARMACOGENETIC

5.5.1 Pharmacokinetic Analyses

Not applicable.

5.5.2 Pharmacodynamic Analyses

A PD analysis plan will be defined and reported separately.

5.5.3 Biomarker Analyses

A biomarker analysis plan will be defined and reported separately

5.5.4 Pharmacogenomic/Pharmacogenetic Analyses

A pharmacogenomic analysis plan will be defined and reported separately.

5.6 SAFETY ANALYSES

All safety analyses will be performed on the Safety Analysis Set. The incidence of AEs (including changes from baseline in physical examination), out-of-normal-range laboratory safety test variables, abnormal ECG findings, along with change from Baseline in laboratory safety test variables, ECGs, and vital sign measurements summarized yearly by treatment group using descriptive statistics.

5.6.1 Extent of Exposure

Cumulative exposure to study drug will be summarized by the number and percentage of subjects (remaining in study) exposed to study drug in days or other time units by treatment group. In addition, the number of days or other time units of exposure will be summarized descriptively as a continuous variable. The average dose and relative dose intensity (actual dose administered divided by planned dose) will be summarized by month and overall study and by treatment group.

5.6.2 Adverse Events

The AE verbatim descriptions (investigator terms from the CRF) will be classified into standardized medical terminology using the Medical Dictionary for Regulatory Activities (MedDRA - Version 16.0 or higher). AEs will be coded to the MedDRA lower level term (LLT) closest to the verbatim term. The linked MedDRA preferred term (PT) and primary system organ class (SOC) are also captured in the database.

All AEs observed during the study will be reported on the CRF. All AEs, regardless of relationship to study drug or procedure, should be collected beginning from the time the subject signs the study ICF through the end of the study and for a minimum of 30 days after the last dose. Serious AEs will be collected through the end of study, and for a minimum of 30 days after the last dose.

A treatment-emergent AE (TEAE) is defined as an AE that emerges during treatment, having been absent at pretreatment (Baseline) or

- Reemerges during treatment, having been present at pretreatment (Baseline) but stopped before treatment, or
- Worsens in severity during treatment relative to the pretreatment state, when the AE is continuous.

Only those AEs that were treatment emergent (including CEC adjudicated events) will be included in summary tables. All AEs, treatment emergent or otherwise, will be presented in subject data listings.

TEAEs will be summarized by treatment group on the Safety Analysis Set. The incidence of TEAEs will be reported as the number (percentage) of subjects with TEAEs by SOC and PT (these summaries will be done with and without CEC adjudicated events). A subject will be counted only once within a SOC and PT, even if the subject experienced more than one TEAE within a specific SOC and PT. The number (percentage) of subjects with TEAEs will also be summarized by maximum severity (mild, moderate, or severe). The number (percentage) of subjects with TEAEs will also be summarized by relationship to study drug (Yes = related, and No = Not related).

AEs will be summarized by the following subgroups: age (< 65 years, ≥ 65 years to <75years, ≥75 years), sex (male, female), race (white, black, other), presence of established CV disease or CV risk factors without established CV disease, pre-diabetes at Baseline, and T2DM at Baseline (with and without).

- The number (percentage) of subjects with TEAEs leading to death will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to death will be provided.

- The number (percentage) of subjects with treatment-emergent SAEs will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all SAEs will be provided.

- The number (percentage) of subjects with TEAEs leading to discontinuation from study drug will be summarized by MedDRA SOC and PT for each treatment group. A subject data listing of all AEs leading to discontinuation from study drug will be provided.

- The incidence of AEs of interest (Study Specific Events, see Section 9.5.4.4 of the protocol) will be summarized separately. In addition, for each AE of interest, Kaplan-Meier curves and median time to first event and 95% CI will be presented. The Safety Analysis Set will be used for this analysis.

5.6.3 Laboratory Values

Central Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in protocol Section 9.5.1.5 Safety Assessments (Laboratory Measurements), the actual value and the change from baseline to each postbaseline visit and to the EOT (defined as the last on-treatment value) will be summarized by visit and treatment group using descriptive statistics. Qualitative parameters listed in protocol Section 9.5.1.5 will be summarized using frequencies (number and percentage of subjects), and changes from baseline to each postbaseline visit and to EOT will be reported using shift tables. Percentages will be based on the number of subjects with both nonmissing baseline and relevant postbaseline results.

Laboratory test results will be assigned a low/normal/high (LNH) classification according to whether the value was below (L), within (N), or above (H) the laboratory parameter's reference

range. Within-treatment comparisons for each laboratory parameter will be based on 3-by-3 tables (shift tables) that compare the baseline LNH classification to the LNH classification at each postbaseline visit and at the EOT. Similar shift tables will also compare the baseline LNH classification to the LNH classification for the highest and lowest value during the treatment period.

Appendix 13.1 (Sponsor's Grading for Laboratory Values) presents the criteria that will be used to identify subjects with treatment-emergent markedly abnormal laboratory values (TEMAV). Except for phosphate, a TEMAV is defined as a postbaseline value with an increase from baseline to a grade of 2 or higher. For phosphate, a TEMAV was defined as a postbaseline value with an increase from baseline to a grade of 3 or higher. When displaying the incidence of TEMAVs, each subject may be counted once in the laboratory parameter high and in the laboratory parameter low categories, as applicable.

5.6.4 Vital Signs

Descriptive statistics for vital signs parameters (i.e., diastolic and systolic BP, pulse, weight) and changes from Baseline will be presented by visit and treatment group. Descriptive statistics and changes from Baseline will also be presented by visit and treatment group for waist and hip circumference. In addition, systolic and diastolic blood pressure will be summarized by clinically notable changes (see Section 8).

5.6.5 Electrocardiograms

Abnormal ECG findings will be presented as shifts from baseline (normal/abnormal clinically significant/abnormal not clinically significant) to post baseline (normal/abnormal clinically significant/abnormal not clinically significant) visits. The number and percent of subjects will be presented.

5.7 Other Analyses

No other analyses are planned.

5.8 Exploratory Endpoint Analyses

- The change from Baseline in CV risk factors (body weight, BMI, waist and hip circumference, dyslipidemia, insulin level, hypertension, inflammatory biomarkers) will be analyzed using a mixed-effects model with repeated measures with treatment, month, month by treatment interaction and stratification variable (presence of established CV disease or CV risk factors without established CV disease) as factors and Baseline value as a covariate. Comparison between lorcaserin HCl and placebo will be made at 1year. The estimated treatment difference in the LSM between lorcaserin HCl and placebo, p-value, and the two-sided 95% CI will be calculated. The ITT will be used for this analysis. SAS PROC MIXED will be used using an unstructured covariance matrix (TYPE=UN). If the model fails to converge then other covariance structures such as; Heterogeneous Toeplitz covariance structure (TYPE= TOEPH), heterogeneous Autoregressive (TYPE=ARH(1)) or compound symmetry (TYP=CS) will be used.

- For subjects with NAFLD at Baseline, the change from Baseline in liver function tests (AST, ALT, alkaline phosphatase, GGT, total and direct bilirubin) will be analyzed using a mixed-effects model with repeated measures with treatment, month, month by treatment interaction and stratification variable (presence of established CV disease or CV risk factors without established CV disease) as factors and Baseline value as a covariate. Comparison between lorcaserin HCl and placebo will be made at 1 year. The estimated treatment difference in the LSM between lorcaserin HCl and placebo, p-value, and the two-sided 95% CI will be calculated. The ITT will be used for this analysis. SAS PROC MIXED will be used using an unstructured covariance matrix (TYPE=UN). If the model fails to converge then a Heterogeneous Toeplitz covariance structure (TYPE= TOEPH) will be used.

- The proportion of subjects who meet FDA-defined valvulopathy in echocardiographically determined heart valve changes will be analyzed using a logistic GLMM for repeated measures including treatment, month, month by treatment interaction as factors and baseline BMI as a covariate. Comparison between lorcaserin HCl and placebo will be made at 2 years and yearly thereafter. The odds ratio, p-value and 2-sided 95% CI will be calculated. The FDA-defined Valvulopathy Analysis Set will be used for this analysis.

- The change from baseline in eGFR and ACR will be analyzed using a mixed-effects model with repeated measures with treatment, month and month by treatment interaction as a factor and baseline value as a covariate. Comparison of the trajectories for lorcaserin HCl and placebo will be made at 1 year, yearly thereafter, and at EOS. The estimated treatment difference in the LSM between lorcaserin HCl and placebo, p-value, and the two-sided 95% CI will be calculated. The ITT will be used for this analysis. SAS PROC MIXED will be used using an unstructured covariance matrix (TYPE=UN). If the model fails to converge then a Heterogeneous Toeplitz covariance structure (TYPE= TOEPH) will be used.

- The change from Baseline in echocardiographically-determined pulmonary arterial systolic pressure will be analyzed using a mixed-effects model with repeated measures with treatment, month, month by treatment interaction as factors and baseline pulmonary arterial systolic pressure and baseline BMI as covariates. Comparison between lorcaserin HCl and placebo will be made at 2 years and yearly thereafter. The estimated treatment difference in the LSM between lorcaserin HCl and placebo, p-value, and the two-sided 95% CI will be calculated. The ITT will be used for this analysis. SAS PROC MIXED will be used using an unstructured covariance matrix (TYPE=UN). If the model fails to converge then a Heterogeneous Toeplitz covariance structure (TYPE= TOEPH) will be used.

- Change from Baseline in HbA1c, FPG, fasting insulin levels, and homeostatic model assessment insulin resistance (HOMA-IR), at 6 months in subjects with T2DM at Baseline will be analyzed using an ANCOVA model with treatment and stratification variable (presence of established CV disease or CV risk factors without established CV

disease) as factors, and baseline HbA1c, as a covariate. Comparison between lorcaserin HCl and placebo will be made at 6 months. The estimated treatment difference in the LSM between lorcaserin HCl and placebo, p-value, and the two-sided 95% CI will be calculated. The T2DM Analysis Set will be used for this analysis, in the following subpopulations.

  - Subjects with (HbA1c>7%) at Baseline
  - Subjects who have not been treated with antidiabetic agents at Baseline
  - Subjects who are on monotherapy with oral antidiabetic agent at Baseline
  - Subjects with early T2DM (duration of diagnosis of diabetes is less than 5 years) at Baseline.

- Proportion of subjects with reduction in the number of OAD medications or reduction in the dosage of OAD medications in the following subpopulations of subjects with T2DM at Baseline will be analyzed using logistic regression including treatment as factor. Comparison between lorcaserin HCl and placebo will be made at 6 months. The odds ratio, p-value and 2-sided 95% CI will be calculated. The T2DM Analysis Set will be used for this analysis, in the following subpopulations:

  - Subjects with (HbA1c >7%) at Baseline
  - Subjects who are on monotherapy with oral antidiabetic agent at Baseline
  - Subjects with early T2DM (duration of diagnosis of diabetes is less than 5 years) at Baseline.

- Proportions of subjects with at least a 1-stage reduction in an obesity-related complication (prediabetes, metabolic syndrome, T2DM, hypertension, and hypertriglyceridemia/dyslipidemia), incidence of other obesity-related complications will be collected through AE reports, medical history, and use of concomitant medications, will be analyzed using logistic regression including treatment as factor. Comparison between lorcaserin HCl and placebo will be made at 1 year and EOS. The odds ratio, p-value and 2-sided 95% CI will be calculated. The ITT Analysis Set will be used for this analysis.

Logistic regression including treatment as factor will be used for the following endpoints. Comparison between lorcaserin HCl and placebo will be made at EOS. The odds ratio, p-value and 2-sided 95% CI will be calculated.

The Prediabetes Analysis Set will be used for the following analyses: (revised per Amendment 01)

- Proportions of subjects with prediabetes at Baseline who develop new diagnosis of diabetic retinopathy at EOS.

- Proportions of subjects with prediabetes at Baseline who develop new diagnosis of diabetic neuropathy at EOS.

The T2DM Analysis Set will be used for the following analyses: (revised per Amendment 01)

- Proportions of subjects with T2DM at Baseline who develop new diagnosis of diabetic retinopathy at EOS.

- Proportions of subjects with T2DM at Baseline who develop new diagnosis of diabetic neuropathy at EOS.

6 INTERIM ANALYSES

There will be one interim analysis; when 460 adjudicated MACE events have occurred, the primary analysis for MACE will be conducted. This will be the analysis to rule out a hazard ratio of 1.4. If the non-inferiority margin is met, the study will continue to accrue events until the required number of MACE+ and diabetes conversion events have occurred.

The interim analysis for MACE endpoint will be performed by an independent statistician and governed by an independent DMC and is anticipated to occur on or before (approximately) July 2017. The interim analysis will be conducted according to a DMC Charter to establish whether the MACE primary objective has been achieved.

To maintain the integrity and credibility of the trial, procedures will be implemented to ensure the DMC and independent statistician have sole access to evolving information from the clinical trial regarding comparative efficacy and safety data aggregated by treatment group. Full details of the DMC procedures including primary responsibilities of the DMC, its relationship with other trial components, its membership, and the purpose and timing of its meetings will be documented in the DMC Charter. These details will also include procedures to ensure confidentiality and proper communication, the safety and statistical monitoring guidelines to be implemented by the DMC, and an outline of the content of the closed reports and open reports that will be provided to the DMC. See Appendix 13.1.2 for the DMC charter. In addition, the Study Integrity Charter in Appendix 13.1.2, describes the membership, responsibilities, data access, and firewalls, when 460 adjudicated MACE events are achieved and the IA is conducted.

At the interim analysis for MACE, the estimate of the hazard ratio of lorcaserin HCl to placebo and the corresponding one-sided 97.5% CI will be calculated. Non-inferiority between lorcaserin HCl and placebo will be declared if the upper limit of the 97.5% CI is less than the non-inferiority margin of 1.4. Otherwise, lorcaserin HCl will be declared as not noninferior to placebo and the trial will stop.

If non-inferiority between lorcaserin HCl and placebo is confirmed when 460 adjudicated MACE events are observed at approximately 43 months from the start of the study, then the study will be continued to observe 1401 adjudicated MACE+ events at approximately 54 months from the start of the study, and 2.5 years median treatment duration.

6.1 INTERIM ANALYSIS STATISTICAL ANALYSIS PLAN

At the interim analysis; when 460 adjudicated MACE events have occurred, the following analysis will be performed using a Cox proportional hazards model that includes factors for treatment and stratification variable (presence of established CV disease or CV risk factors without established CV disease).

Details of the censoring algorithm for the MACE endpoint is presented in Section 8.5.1.

6.1.1 Primary Endpoint Analysis for time to MACE

Primary endpoint analysis for time to MACE for Non-inferiority: The estimate of the hazard ratio of lorcaserin HCl to placebo and the corresponding one-sided 97.5% CI will be calculated. Non-inferiority of lorcaserin HCl to placebo will be declared if the upper limit of the 97.5% CI is less than the non-inferiority margin of 1.4. The Total Time Analysis Population will be used.

7 CHANGES IN THE PLANNED ANALYSES

The following exploratory endpoints were not analyzed.

- Proportion of subjects with reduction in the number of OAD medications or reduction in the dosage of OAD medications in the following subpopulations of subjects with T2DM at Baseline will be analyzed using logistic regression including treatment as factor. Comparison between lorcaserin HCl and placebo will be made at 6 months. The odds ratio, p-value and 2-sided 95% CI will be calculated. The T2DM Analysis Set will be used for this analysis, in the following subpopulations:
    - Subjects with (HbA1c >7%) at Baseline
    - Subjects who are on monotherapy with oral antidiabetic agent at Baseline
    - Subjects with early T2DM (duration of diagnosis of diabetes is less than 5 years) at Baseline.

Reason: Difficulty in defining reduction or change in dosage OAD medications and interpretation of results.

- Proportions of subjects with at least a 1-stage reduction in an obesity-related complication (prediabetes, metabolic syndrome, T2DM, hypertension, and hypertriglyceridemia/dyslipidemia), incidence of other obesity-related complications will be collected through AE reports, medical history, and use of concomitant medications, will be analyzed using logistic regression including treatment as factor. Comparison between lorcaserin HCl and placebo will be made at 1 year and EOS. The odds ratio, p-value and 2-sided 95% CI will be calculated. The ITT Analysis Set will be used for this analysis.

Reason: It was determined that this population will show no change in Obesity Staging

8 DEFINITIONS AND CONVENTIONS FOR DATA HANDLING

The baseline value for efficacy and safety will be defined as the most recent value reported prior to or at randomization. Adverse events with missing severity will be assigned the highest severity. Adverse events with missing relationship will be assigned as related, as part of a sensitivity analysis. Adverse events and Concomitant Medications with partial dates will be imputed according the algorithm defined in the SDTM specifications, also included in Appendix 13.6.

DEFINITIONS

- Clinically Notable Changes in Blood Pressure:

  Systolic blood pressure

  Increase from baseline of ≥ 20 mm Hg
  Post-baseline value > 160mm Hg
  Post-baseline value > 160mm and Increase ≥ 20 mm Hg
  Decrease from Baseline of ≥ 20 mm Hg
  Post-baseline value <60 mm Hg
  Post-baseline value < 60mm and Decrease ≥ 20 mm Hg

  Diastolic blood pressure

  Increase from baseline of ≥ 20mm Hg
  Post-baseline value > 100mm Hg
  Post-baseline value > 100mm Hg and Increase ≥ 20mm Hg
  Decrease from Baseline of ≥ 10 mm Hg
  Post-baseline value < 50 mm Hg
  Post-baseline value < 50 mm Hg and Decrease ≥ 10 mm Hg

- Treatment Compliance: Treatment compliance will be determined for the entire double blind phase. Subjects taking BID or QD dosing will be considered as been compliant. The total tablets taken = total tablets dispensed – total tablets returned.

  Compliance = 100 x Total tablets taken / Total tablets Expect

- Secondary Prevention Risk Scores

  The Risk score is calculated by totaling the number of risk factors a subject has at baseline and categorizing the total score into 0, 1-2, or ≥3. See table below.

Risk Factor	Points
Congestive heart failure	1
Hypertension	1
Age ≥ 75 years	1
Diabetes mellitus	1
Prior stroke	1
Prior CABG	1
Peripheral arterial disease	1
Renal dysfunction (eGFR <60 mL/min 1.73 m^{-2}	1
Current smoker	1
Prior MI	1

- On treatment: This definition applies to the "On-Treatment" and "On-Treatment plus 30 Days" Analyses Sets described in Section 5.2.1. A subject is considered to be "on treatment" while the subject is on study drug. If a subject permanently discontinues study drug, the subject is considered to be "off treatment". If a subject is taking BID dosing or QD dosing, or stops and restart study drug then the subject is still considered to be "on treatment"

- Subject who Completed the Study on Study Drug : A subject is considered to have completed the study on study drug, if the last dose date for the subject falls 1 day prior or on/after the date of Sponsor notification of Study Completion and "Subject Status at Final Sponsor Notification Visit/Premature Study Discontinuation or "Subject Status at Final 30-Day Follow-up Visit" = "Completed", "Death".

- Subject who Completed the Study : A subject is considered to have completed the study , if in the Final Study Disposition CRF, "Subject Status at Final Sponsor Notification Visit/Premature Study Discontinuation Visit" = "Completed" , "Death", or "Subject Status at Final 30 Day Follow-up Visit" = "Completed" or "Death". For these subjects the EOT is the same as the EOS visit.

- Study Completion: Sponsor Notification of Study Completion will occurred once 1401 MACE+ adjudicated events, and 2.5 years median treatment duration.

- Subjects without Any Type of Diabetes at Baseline: Subject must meet the following conditions;

    - On the Diabetes History Form "Clinical diagnosis of diabetes?" = "No" and

    - Not initiated any diabetes treatment prior to or at Baseline and
    - None of the following where available

        - HbA1c ≥ 6.5% in all central or local labs assessments prior to or at Baseline and
        - FPG ≥ 126 mg/dL (7.0 mmol/L) in all central or local labs assessments prior to or at Baseline and
        - 2-hour plasma glucose ≥ 200 mg/dL(11.1mmol/L) by an OGTT test prior to or at Baseline and
        - random plasma glucose > or = 200 with associated symptoms of hyperglycemia prior to or at Baseline

- Subject who are Pre-diabetic at Baseline: Subject must meet all the following conditions;

    - On the Diabetes History Form "Clinical diagnosis of diabetes?" = "No" and

    - Not initiated any diabetes treatment prior to or at Baseline and
    - At least one of the following:

        - HbA1c 5.7% to <6.5% or
        - FPG 100 to 125 mg/dL (5.55 to 6.94 mmol/L) between Screen and Baseline and
    - None of the following where available
        - HbA1c ≥ 6.5% in all central or local labs assessments prior to or at Baseline and
        - FPG ≥ 126 mg/dL (7.0 mmol/L) in all central or local labs assessments prior to or at Baseline and
        - random plasma glucose > or = 200 with associated symptom of hyperglycemia prior to or at Baseline and
        - 2-hour plasma glucose ≥ 200 mg/dL(11.1mmol/L) by an OGTT test prior to or at Baseline and

- Subject who are Normoglycemic at Baseline: Subject must meet the following conditions;

    - On the Diabetes History Form "Clinical diagnosis of diabetes?" = "No" AND
    - Not initiated any diabetes treatment prior to or at Baseline AND
    - None of the following where available:
        - HbA1c ≥ 5.7% in all central or local labs assessments prior to or at Baseline

  - FPG ≥ 100 mg/dL (5.55 mmol/L) in all central or local labs assessments prior to or at Baseline
  - 2-hour plasma glucose ≥ 200 mg/dL(11.1mmol/L) by an OGTT test prior to or at Baseline
  - Random glucose > or = 200 with associated symptoms of hyperglycemia prior to or at Baseline
- Subject is not otherwise defined as 'pre-diabetic' at baseline

- Subjects who are T2DM at Baseline: Subject must meet at least one of the following conditions.
  - On the Diabetes History Form "Clinical diagnosis of diabetes?" = "Yes" and Type of Diabetes = 2 on Diabetic History CRF or
  - HbA1c ≥ 6.5% prior to or at Baseline in either central or local labs or
  - FPG ≥ 126 mg/dL (7.0 mmol/L) prior to or at Baseline in either central or local labs or
  - 2-hour plasma glucose ≥ 200 mg/dL(11.1mmol/L) by an OGTT test or
  - Random plasma glucose > or = 200 with associated symptoms of hyperglycemia prior to or at Baseline
  - Any diabetes treatment prior to or at Baseline
- Subjects who are T1DM at Baseline: Subject must meet the following conditions.
  - On the Diabetes History Form "Clinical diagnosis of diabetes?" = "Yes" and Type of Diabetes = 1 on Diabetic History CRF
- Subjects who are DM at Baseline:
  - Subjects who meet criteria for T1DM or T2DM above

8.1 CALCULATION OF GFR

The following equations[5] will be used to estimate GFR.

Cystatin C Equation

$GFR = 133 \times \min(scys/0.8, 1)^{-0.499} \times \max(scys/0.8, 1)^{-1.328} \times 0.966^{age} \times [0.932 \text{ (if female)}]$

Creatinine-Cystatin C Equation

$$GFR = 135 \times \min(scr/k, 1)^{\alpha} \times \max(scr/k, 1)^{-0.601} \times \min(scys/0.8, 1)^{-0.375} \times \max(scys/0.8, 1)^{-0.711} \times 0.995^{age} \times [0.969x (\text{if female})] \times [1.08(\text{if black})]$$

Where, k and α are defined by gender below, scr = serum creatinine, scys = serum cystatin, min (a, 1) = indicates the minimum of a or 1, max (a, 1) = indicates the maximum of a or 1, and (if *condition*) = 1 if true or 0 if false.

	Female	Male
k	0.7	0.9
α	-0.248	-0.207

8.2 DETERMINATION OF RENAL IMPAIRMENT OR IMPROVEMENT

8.2.1 Determination of new onset or worsening of Renal Impairment

Time from randomization to first occurrence of 2 consecutive assessments within the same component of the composite endpoint or time to first occurrence of renal transplant or renal death, on scheduled or nonscheduled visits at least 30 days apart, indicative of new onset renal impairment or worsening of existing renal impairment (first occurrence of any of the following events: microalbuminuria, macroalbuminuria, worsening albuminuria, newly developed CKD or worsening of CKD, or doubling of serum creatinine, or any of the following: ESRD, renal transplant, renal death). Table 4 presents the definitions for each of these events and Appendix 13.2 presents the definition of Chronic Kidney Disease (CKD) stages.

Table 4 Definitions of newly develop or worsening of renal impairment events

Renal Impairment Event	Definition
Newly Developed Albuminuria	For subjects without any microalbuminuria (ACR ≥ 30 µg/mg in spot urine), or macroalbuminuria(ACR ≥ 300 µg/mg in spot urine) at baseline or subject shows first evidence of; • microalbuminuria (ACR ≥ 30 µg/mg in spot urine) with an ACR value increased ≥ 30% from Baseline or • macroalbuminuria(ACR ≥ 300 µg/mg in spot urine) with an ACR value increased ≥ 30% from Baseline
Worsening albuminuria	microalbuminuria present at Baseline and develops macroalbuminuria, and ACR value increases ≥30% from baseline assessment during treatment
Newly develop CKD	eGFR ≥ 90 mL/min per 1.73 body surface area (BSA) and without kidney damage at Baseline changes to CKD Stage 1 or higher classified by the 2002 National Kidney Foundation (NKF) guidelines, where kidney damage referred to in the guideline is defined as the emergence of microalbuminuria as defined above, during treatment
Worsening of CKD	CKD Stage 1 or higher defined by NKF guidelines worsens to higher CKD stages (eGFR ≥ 90 with albuminuria at Baseline decreases to < 90, or eGFR 60 to 89 at Baseline becomes <60, or eGFR 30 to 59 at Baseline becomes < 30 mL/min per 1.73 BSA) during treatment
Doubling of serum creatinine	creatinine value is at least 2 times the Baseline value and ≥ 1.5mg/dL during treatment
ESRD	eGFR < 15 mL/min per 1.73 body surface area (BSA) or renal dialysis (captured as an SAE)
renal transplant	Captured as an SAE
renal death	Adjudicated death event by SAE

8.2.2 Determination of Improvement of Renal function

Time from randomization to first occurrence of 2 consecutive assessments, on scheduled or nonscheduled visits at least 30 days apart, indicative of improvement in renal function (first occurrence of regression of albuminuria or regression of CKD), see Appendix 13.2 for definitions CKD stages. The renal improvement events are defined as;

Regression of albuminuria: defined as when subjects with macroalbuminuria at Baseline develop microalbuminuria or non-albuminuria (ACR < 30 µg/mg in spot urine), or subjects with microalbuminuria at Baseline become non-albuminuric, and ACR value decreases ≥ 30% from previous assessment during treatment.

Regression of CKD: defined as when a subject with CKD Stage 1 or higher at Baseline improves to normal or lower stages by NKF guideline (eGFR ≥ 90 with albuminuria at

Baseline improves to eGFR ≥ 90 without albuminuria (ACR < 30 µg/mg in spot urine), or eGFR 60 to 89 at Baseline becomes eGFR ≥ 90 with or without albuminuria, or eGFR between 30 to 59 at Baseline improves to > 60 mL/min per 1.73 BSA) during treatment.

8.3 DETERMINATION OF CONVERSION TO T2DM OR TO NORMAL GLUCOSE HOMEOSTASIS

8.3.1 Determination of conversion to T2DM

For the following 2 cohorts, subjects without any type diabetes at Baseline and subjects who are prediabetic at Baseline, as per the definitions in Section 8 above, the time from randomization to conversion to T2DM will be adjudicated as per the CEC Diabetes Adjudication Charter, see Appendix 13.1.4.

For subjects who did not experienced any event, the censoring algorithm is described in Section 8.5.2.2.

8.3.2 Determination of conversion to normal glucose homeostasis

For subjects with prediabetes at Baseline the time from randomization to conversion to normal glucose homeostasis (HbA_{1c} ≤5.6% and fasting plasma glucose <100 mg/dL without any antidiabetic treatment . The primary analysis will be based on conversion to normal glucose homeostasis that is achieved and maintained through the duration of the study. Sensitivity analyses will include an assessment of 1) any conversion to normal glucose homeostasis at one or more time points during the study and 2) sustained for 2 consecutive measurements separated by 30 days. For subjects who did not experienced any event, the censoring algorithm is described is in Table 7.

8.4 FDA DEFINED VALVULOPATHY AND PULMONARY ARTERIAL PRESSURE

The aortic and mitral valve regurgitation will be categorized as absent, trace, mild, moderate or severe. FDA-defined valvulopathy, or simply "FDA valvulopathy," stipulate that significant valvular regurgitation comprises **mild or greater aortic valve regurgitation and/or moderate or greater mitral valve regurgitation**. The ECHO sub-study data presents the mitral and aortic valve severity as 5 categories; ABSENT, TRACE, MILD, MODERATE, and SEVERE.

For each subject and visit a dichotomous variable will be created, where;

1 = mild or greater aortic valve regurgitation and/or moderate or greater mitral valve regurgitation

0 = aortic valve regurgitation is absent or trace and mitral valve regurgitation is mild or less.

For the secondary endpoints assessing cardiac valve function and pulmonary arterial pressure listed in Section 5.1.2 the ECHO sub-study data from this study will be pooled with studies ADP356-009, -010, and -011.

8.4.1 Worsened FDA-defined valvulopathy

For subjects with FDA-defined valvulopathy at Baseline, worsened FDA-defined valvulopathy is define as any increase in valvular regurgitation from Baseline in either the aortic or mitral valve.

8.5 CENSORING

The individual EOS date will be defined as the time of the last visit or study contact for each individual patient. If no event occurs for an endpoint, the earlier of the last study contact, the visit following Sponsor Notification of Study Completion or death will be treated as the censoring date.

MACE, MACE+ and conversion to T2DM events will be handled in the following manner according to their timing with respect to study milestones:

- Events that are recorded as beginning prior to the date of randomization will not be counted in the event analyses. The subject will be included in the analysis as not experienced the event. These events that are recorded as beginning prior to the date of randomization they will be included in a listing.
- Events that occur at any time after randomization and up to and including the first of the last visit/contact or visit following Sponsor Notification of Study Completion and reported *before* database lock will be adjudicated and included in all efficacy and safety analyses.
- Events that occur at any time after randomization and up to and including the last visit/contact and reported *after* database lock will be not be adjudicated and will not be included in the primary efficacy and safety analysis. They will be recorded in a tabular fashion as part of the final study report and may be included in sensitivity analyses.
- Events that occur after last visit/contact will not be included in the primary efficacy and safety analyses but may be included in the safety database if they fulfill safety reporting criteria.

Events in subjects who withdraw consent for clinical follow-up:

- All events that occur before withdraw of consent are included in analyses.
- Events that occur after withdraw of consent will be included in the primary analyses if they were found through vital status search prior to database lock.

Events in subjects who stop and re-start study medication.

- For the Total Time Analysis Set all events are counted regardless of whether the subject is on or off treatment.

- For the On-treatment Analysis Set events are counted only when the subject in "on-treatment". See Section 8, for definition of "on-treatment".

- For the On-treatment plus 30 days Analysis Set events are counted when the subject is "on-treatment" and up to 30 days from their last dose. See Section 8, for definition of "on-treatment".

For ITT subjects who were not treated the censoring time will be determined from the randomization date to the date of final disposition.

8.5.1 Censoring at Interim Analysis for MACE

There will be one interim analysis; when 460 adjudicated MACE events have occurred, the primary analysis for MACE will be conducted. The censoring algorithm is found in the Table 5 and see Appendix 13.2 for diagrams of censoring algorithms. See Section 6 for details on interim analysis.

For subjects who experienced an event, their time-to-event will be determined from the randomization date to the date of the event, for the Total Time Analysis. The censoring variable will be, CENSORED=0. For subjects who do not experienced an event, the censoring time will be determined from the randomization date to the date of the data extraction for those continuing in the study or according to the details below for subjects who are not continuing in the study at the time of the interim analysis. For these subjects, the censoring variable will be, CENSORED=1.

Table 5 Censoring Date For subjects who did not experienced an event at the Interim Analysis

Analysis Set[a]	Ongoing	Withdrawal From Study Follow-up
Total Time on Study	Date of the adjudicated CEC database lock will be used for all ongoing subjects	In the Final Study Disposition Form use the date from, Date of Final Sponsor Notification/Premature Study Discontinuation and status for discontinuation equals any of the following; • Withdrew Consent • Non- CV Death • Other
[a] See Section 5.2.1 for definitions of Analysis Sets and Appendix 13.5.1 for diagrams of censoring algorithms		

8.5.2 Censoring at Study Completion

8.5.2.1 Censoring for MACE, MACE+, each Component of MACE, and All-Cause Mortality

If non-inferiority between lorcaserin HCl and placebo is confirmed at the interim analysis, then the study will be continued to observe; 1401MACE+ events at approximately 54 months from the start of the study and 2.5 years median treatment duration.

MACE non-inferiority and superiority, each component of MACE, and All-cause mortality will analyzed at study completion as part of additional sensitivity analyses. The censoring algorithm is the same for these endpoints but differs by Analysis Set as described in the Table 6, and see Appendix 13.2 for diagrams of censoring algorithms.

For subjects who experienced an event, their time-to-event will be determined from the randomization date (for the Total Time Analysis) and the start date of study drug (for the On-Treatment and On-Treatment + 30-Days Analyses), to the date of the event. The censoring variable will be, CENSORED=0. For subjects who do not experienced an event, the censoring time will be determined from the randomization date (for the Total Time Analysis) and the start date of study drug (for the On-Treatment and On-Treatment + 30-Days Analyses), to the date described in Table 6, along with a matching censoring variable, CENSORED=1.

Table 6 Censoring Date For subjects who did not experienced an event at Study Completion

Analysis Set[a]	Completed the Study	Withdrawal From Study Follow-up
Total Time on Study	In the Final Study Disposition Form use the date from , Date of Final Sponsor Notification/Premature Study Discontinuation and status is equal to completed	In the Final Study Disposition Form use the date from , Date of Final Sponsor Notification/Premature Study Discontinuation and status for discontinuation equals any of the following; • Withdrew Consent • Lost to Follow up • Study Terminated by Sponsor • death (except for All Cause-mortality) • Other
On-Treatment + 30 Days	Date of last dose from Study Medication Form + 30 Days	Date of last dose from Study Medication Form + 30 Days
On-Treatment	Date of last dose from Study Medication Form	Date of last dose from Study Medication Form
[a] See Section 5.2.1 for definitions of Analysis Sets and Appendix 13.5.2 for diagrams of censoring algorithms		

8.5.2.2 Censoring for Conversion to T2DM

For subjects who experienced an event, their time-to-event will be determined from the randomization date to the date of first abnormal laboratory test as per the Diabetes CEC Diabetes Adjudication Charter, Appendix 13.1.4. The censoring variable will be, CENSORED=0. For subjects who do not experienced an event, the censoring time will be determined from the randomization date to the date described in the Table 6, using the Total Time on Study Analysis Set, along with a matching censoring variable, CENSORED=1. The above censoring algorithm

will be applied to both cohorts 1) subjects without any type diabetes at Baseline and 2) subjects with prediabetis at Baseline.

8.5.2.3 Censoring for Secondary Time-to-Event Endpoints

The censoring algorithm is the same for all secondary time-to-event endpoints and across the different Analysis Sets. Since all the Analyses Sets used the ITT population for these secondary endpoints, then for subjects who experienced an event, their time-to-event will be determined from the randomization date to the date of the event. The censoring variable will be, CENSORED=0. For subjects who do not experienced an event, the censoring time will be determined from the randomization date to the date described in Table7, along with a matching censoring variable, CENSORED=1.

Table 7 Censoring Date for Subjects who did not Experience an Event at Study Completion for Secondary Renal and Glucose Homeostasis Endpoints

Time-to-Event Endpoint	Analysis Set[a]	Completed the Study	Withdrawal From Study Follow-up
New onset of renal impairment or worsening of existing renal impairment in subjects with T2DM at Baseline	T2DM	In the Final Study Disposition Form use the date from ; Date of Final Sponsor Notification/Premature Study Discontinuation and status is equal to completed	In the Final Study Disposition Form use the date from, Date of Final Sponsor Notification/Premature Study Discontinuation and status for discontinuation equals any of the following; • Withdrew Consent • Lost to Follow up • Study Terminated by Sponsor • Death • Other
New onset of renal impairment or worsening of existing renal impairment in all subjects enrolled in the study	Total Time		
Improvement in renal function	T2DM		
New onset of renal impairment or worsening of existing renal impairment in subjects with prediabetes at Baseline	Prediabetes		
Conversion to normal glucose homeostasis	Prediabetes		

[a] See Section 5.2.1 for definitions of Analysis Sets

8.5.2.4 Censoring for Sensitivity Analysis Time-to-Event Endpoints

Subjects that start another weight reduction medication or has a bariatric procedure: MACE and MACE+ endpoints will be analyzed using the Total Time Analysis Set.

For subjects who experienced an event and did not start on another weight reduction medication or did not have bariatric surgery, their time-to-event will be determined from the randomization date to the date of the event. The censoring variable will be, CENSORED=0.

For subjects who experienced an event and started on another weight reduction medication or undergoes bariatric surgery, the censoring variable will be , CENSORED=0, if date of event is either prior to date of starting a weight reduction medication or having bariatric surgery or the event occurred after having stopped taking a weight reduction medication. Their time-to-event time will be determined from randomization date to date of the event. The censoring variable will be, CENSORED=1, if the date of event is equal to or greater than date of having bariatric surgery or the event date occurred while on a weight reduction medication. The censoring time will be determined from the randomization date to the earliest date of starting another weight reduction medication and/or having bariatric surgery. If date of starting another weight reduction medication or having bariatric surgery is prior to the randomization date, then censoring time will be set to the randomization date.

For subjects who do not experience an event and did not start on another weight reduction medication or did not have bariatric surgery, the censoring time will be determined from the randomization date to the date described in the Table 6 using the Total Time on Study Analysis Set, along with a matching censoring variable, CENSORED=1.

For subjects who do not experience an event and start on another weight reduction medication or undergoes bariatric surgery, the censoring time will be determined from the randomization date to the date of starting a weight reduction medication or the date of the bariatric surgery, along with a matching censoring variable, CENSORED=1. If date of starting another weight reduction medication or having bariatric surgery is prior to the randomization date, then censoring time will be set to the randomization date.

8.6 DEFINITION OF VISIT WINDOWS

Table 4 of the protocol presents the schedule of procedures/Assessments. Some procedures/assessments are performed at 3 months, 6 months or yearly intervals. Table 8 presents the protocol specified visits/months and corresponding time windows used for visit-wise analyses are presented in terms of days relative to the first dose. For subjects that are randomized, the last available assessment on or before the randomization date will be used as the Baseline-Day 1. If more than one measurement is included in a visit window, the measurement collected closest to the scheduled date will be used in the analysis. In the case where two measurements were collected an equal number of days before and after the Scheduled Day the later of the two measurements will be used for analysis.

For ECHO and PAH assessments when assessing a new or worsened event then the most severe assessment will be selected if 2 or more assessments fall within a visit window.

Table 8 Visit Windows Measurements

Scheduled Visit	Scheduled Month	Scheduled Day	Time Window (Days)		Time Window (Days) For 6 Month Interval Assessments		Time Window (Days) For Yearly Interval Assessments	
1	Screening		-30	-1				
2	Baseline/ Randomization	1	1		1		1	
3	3	90	2	135				
4	6	180	136	225	2	270		
5	9	270	226	315				
6	12	360	316	405	271	450	2	540
7	15	450	406	495				
8	18	540	496	585	451	630		
9	21	630	586	675				
10	24	720	676	780	631	810	541	900
11	28	840	781	900				
12	32	960	901	1020				
13	36	1080	1021	1140			901	1260
14	40	1200	1141	1260				
15	44	1320	1261	1380				
16	48	1440	1381	1500			1261	1620
17	52	1560	1501	1620				
EOT	56	1680	1621	1710				
EOS	58	1740	1711	Open				

8.7 PROTOCOL DEVIATIONS

Protocol Deviations will be collected in the eCRF and included in the database. These protocol deviations will be review and monitored during the course of the study by the study team. Protocol deviations will rated as “Major” or “Minor” and finalized prior to data base lock.

9 PROGRAMMING SPECIFICATIONS

The rules for programming derivations and dataset specifications are provided in separate documents.

10 STATISTICAL SOFTWARE

All statistical analyses will be performed by Eisai Inc. or designee, using SAS Version 9.2 or later.

11 MOCK TABLES, LISTINGS AND GRAPHS (TLGS)

The study TLG shells will be provided in a separate document, which will show the content and format of all tables, listings, and graphs in detail.

12 REFERENCES

1. Zou, G. A Modified Poisson Regression Approach to Prospective Studies with Binary Data. Am. J. Epidemiol., 2004; 159:702-706.
2. Spiegelman, D. and Hertzmark, Easy Calculations for Risk or Prevalence Ratios and Differences. Am. J. Epidemiol., 2005; 162:199-200.
3. American Diabetes Association Position Statement: Standards of Medical Care – 2013. Diabetes Care, Volume 36, Supplement 1, January 2013.
4. Inker, L.A. et. al. Estimating Glomerular Filtration Rate from Serum Creatinine and Cystatin C. N Engl. J. Med., 2012;367:20-29.

13 APPENDICES

13.1 Sponsor's Grading for Determining Markedly Abnormal Laboratory Results

The following table of Sponsor's Grading for Laboratory Values is copied from the protocol, Appendix 5.**Sponsor's Grading for Laboratory Values**

	Grade 1	Grade 2	Grade 3	Grade 4
BLOOD/BONE MARROW				
Hemoglobin	< LLN – 10.0 g/dL < LLN – 100 g/L < LLN – 6.2 mmol/L	< 10.0 – 8.0 g/dL < 100 – 80 g/L < 6.2 – 4.9 mmol/L	< 8.0 g/dL < 80 g/L < 4.9 mmol/L; transfusion indicated	life-threatening consequences; urgent intervention indicated
Leukocytes (total WBC)	< LLN – 3.0 x 10^9/L < LLN – 3000/mm^3	< 3.0 – 2.0 x 10^9/L < 3000 – 2000/mm^3	< 2.0 – 1.0 x 10^9/L < 2000 – 1000/mm^3	< 1.0 x 10^9/L < 1000/mm^3
Lymphocytes	< LLN – 800/mm^3 < LLN – 0.8 x 10^9/L	< 800 – 500/mm^3 < 0.8 – 0.5 x 10^9/L	< 500 – 200/mm^3 < 0.5 – 0.2 x 10^9/L	< 200/mm^3 < 0.2 x 10^9/L
Neutrophils	< LLN – 1.5 x 10^9/L < LLN – 1500/mm^3	< 1.5 – 1.0 x 10^9/L < 1500 – 1000/mm^3	< 1.0 – 0.5 x 10^9/L < 1000 – 500/mm^3	< 0.5 x 10^9/L < 500/mm^3
Platelets	< LLN – 75.0 x 10^9/L < LLN – 75,000/mm^3	< 75.0 – 50.0 x 10^9/L < 75,000 – 50,000/mm^3	< 50.0 – 25.0 x 10^9/L < 50,000 – 25,000/mm^3	< 25.0 x 10^9/L < 25,000/mm^3
METABOLIC/ LABORATORY				
Albumin, serum- low (hypoalbuminemia)	< LLN – 3 g/dL < LLN – 30 g/L	< 3 – 2 g/dL < 30 – 20 g/L	< 2 g/dL < 20 g/L	life-threatening consequences; urgent intervention indicated
Alkaline phosphatase	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
ALT	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
AST	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
Bicarbonate, serum-low	< LLN – 16 mmol/L	< 16 – 11 mmol/L	<11 – 8 mmol/L	< 8 mmol/L
Bilirubin (hyperbilirubinemia)	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 10.0 x ULN	> 10.0 x ULN
Calcium, serum-low (hypocalcemia)	< LLN – 8.0 mg/dL < LLN – 2.0 mmol/L	< 8.0 – 7.0 mg/dL < 2.0 – 1.75 mmol/L	< 7.0 – 6.0 mg/dL < 1.75 – 1.5 mmol/L	< 6.0 mg/dL < 1.5 mmol/L
Calcium, serum-high (hypercalcemia)	> ULN – 11.5 mg/dL > ULN – 2.9 mmol/L	> 11.5 – 12.5 mg/dL > 2.9 – 3.1 mmol/L	> 12.5 – 13.5 mg/dL > 3.1 – 3.4 mmol/L	> 13.5 mg/dL > 3.4 mmol/L
Cholesterol, serum-high (hypercholesterolemia)	> ULN – 300 mg/dL > ULN – 7.75 mmol/L	> 300 – 400 mg/dL > 7.75 – 10.34 mmol/L	> 400 – 500 mg/dL > 10.34 – 12.92 mmol/L	> 500 mg/dL > 12.92 mmol/L
Creatinine	> ULN – 1.5 x ULN	> 1.5 – 3.0 x ULN	> 3.0 – 6.0 x ULN	> 6.0 x ULN
GGT (γ-Glutamyl transpeptidase)	> ULN – 3.0 x ULN	> 3.0 – 5.0 x ULN	> 5.0 – 20.0 x ULN	> 20.0 x ULN
Glucose, serum-high (hyperglycemia)	Fasting glucose value: > ULN – 160 mg/dL > ULN – 8.9 mmol/L	Fasting glucose value: > 160 – 250 mg/dL > 8.9 – 13.9 mmol/L	> 250 – 500 mg/dL; > 13.9 – 27.8 mmol/L; hospitalization indicated	> 500 mg/dL; > 27.8 mmol/L; life-threatening consequences
Glucose, serum-low (hypoglycemia)	< LLN – 55 mg/dL < LLN – 3.0 mmol/L	< 55 – 40 mg/dL < 3.0 – 2.2 mmol/L	< 40 – 30 mg/dL < 2.2 – 1.7 mmol/L	< 30 mg/dL < 1.7 mmol/L life-threatening consequences; seizures
Phosphate, serum-low (hypophosphatemia)	< LLN – 2.5 mg/dL < LLN – 0.8 mmol/L	< 2.5 – 2.0 mg/dL < 0.8 – 0.6 mmol/L	< 2.0 – 1.0 mg/dL < 0.6 – 0.3 mmol/L	< 1.0 mg/dL < 0.3 mmol/L

The following table of Sponsor's Grading for Laboratory Values is copied from the protocol, Appendix 5.**Sponsor's Grading for Laboratory Values**

	Grade 1	Grade 2	Grade 3	Grade 4
				life-threatening consequences
Potassium, serum-high (hyperkalemia)	> ULN – 5.5 mmol/L	> 5.5 – 6.0 mmol/L	> 6.0 – 7.0 mmol/L hospitalization indicated	> 7.0 mmol/L life-threatening consequences
Potassium, serum-low (hypokalemia)	< LLN – 3.0 mmol/L	< LLN – 3.0 mmol/L; symptomatic; intervention indicated	< 3.0 – 2.5 mmol/L hospitalization indicated	< 2.5 mmol/L life-threatening consequences
Sodium, serum-high (hypernatremia)	> ULN – 150 mmol/L	> 150 – 155 mmol/L	> 155 – 160 mmol/L hospitalization indicated	> 160 mmol/L life-threatening consequences
Sodium, serum-low (hyponatremia)	< LLN – 130 mmol/L	N/A	< 130 – 120 mmol/L	< 120 mmol/L life-threatening consequences
Triglyceride, serum-high (hypertriglyceridemia)	150 – 300 mg/dL 1.71 – 3.42 mmol/L	> 300 – 500 mg/dL > 3.42 – 5.7 mmol/L	> 500 – 1000 mg/dL >5.7 – 11.4 mmol/L	> 1000 mg/dL > 11.4 mmol/L life-threatening consequences
Uric acid, serum-high (hyperuricemia)	> ULN – 10 mg/dL ≤ 0.59 mmol/L without physiologic consequences	N/A	> ULN – 10 mg/dL ≤ 0.59 mmol/L with physiologic consequences	> 10 mg/dL > 0.59 mmol/L life-threatening consequences

ALT = alanine aminotransferase (serum glutamic pyruvic transaminase), AST = aspartate aminotransferase (serum glutamic oxaloacetic transaminase), GGT = γ-glutamyl transpeptidase, LLN = lower limit of normal, N/A = not applicable, ULN = upper limit of normal, WBC = white blood cell.
Based on Common Terminology Criteria for Adverse events (CTCAE) Version 4.0. Published: May 28, 2009 (v4.03: June 14, 2010).

13.2 Classification of Chronic Kidney Disease

Chronic Kidney Disease: A Clinical Action Plan			
Stage	**Description**	**GFR (mL/min/1.73m2)**	**Action***
	At increased risk	≥90 (with CKD risk factors)	Screening CKD risk reduction
1	Kidney damage with normal or GFR	≥90	Diagnosis and treatment: Treatment of comorbid conditions, slowing progression, CVD risk reduction
2	Kidney damage with mild GFR	60-89	Estimating progression
3	Moderate GFR	30-59	Evaluating and treating complications
4	Severe GFR	15-29	Preparation for kidney replacement therapy
5	Kidney Failure	<15 (or dialysis)	Replacement (if uremia present)

Shaded area identifies patients who have chronic kidney disease; unshaded area designates individuals who are at increased risk for developing chronic kidney disease. Chronic kidney disease is defined as either kidney damage or GFR <60 mL/min/1.73 m_2 for 3 months. Kidney damage is defined as pathologic abnormalities or markers of damage, including abnormalities in blood or urine tests or imaging studies.
* Includes actions from preceding stages.
Abbreviations: GFR, glomerular filtration rate; CKD, chronic kidney disease; CVD, cardiovascular disease.

13.1 CHARTERS AND RETENTION PLAN TO PREVENT MISSING DATA

13.1.1 CEC Charter

Final CEC Charter

13.1.2 DMC Charter and Integrity Charter

Final DMC Charter and Integrity Charter

13.1.3 Retention Plan to prevent missing data

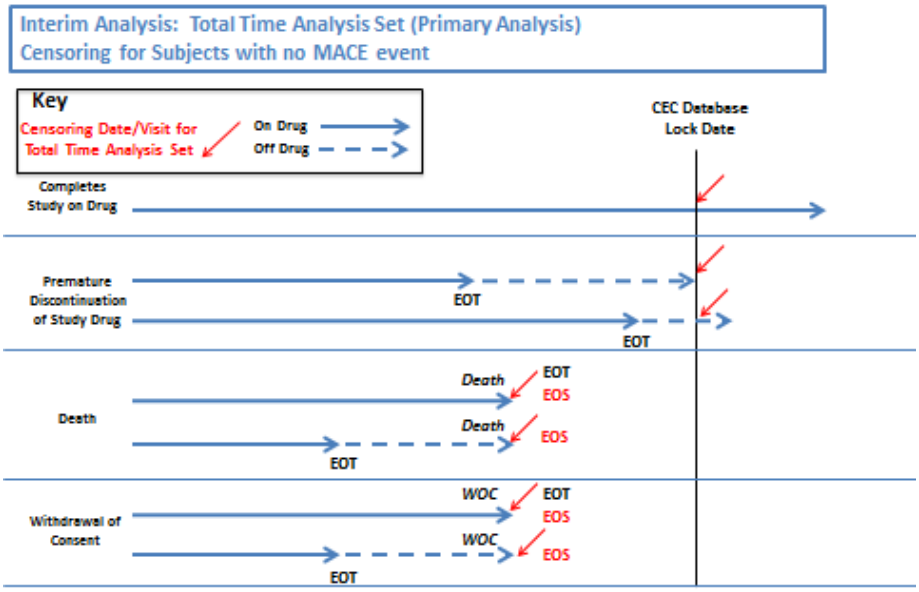
Final Retention Plan to Prevent Missing Data

13.1.4 Conversion to Type II Diabetes Adjudication Charter

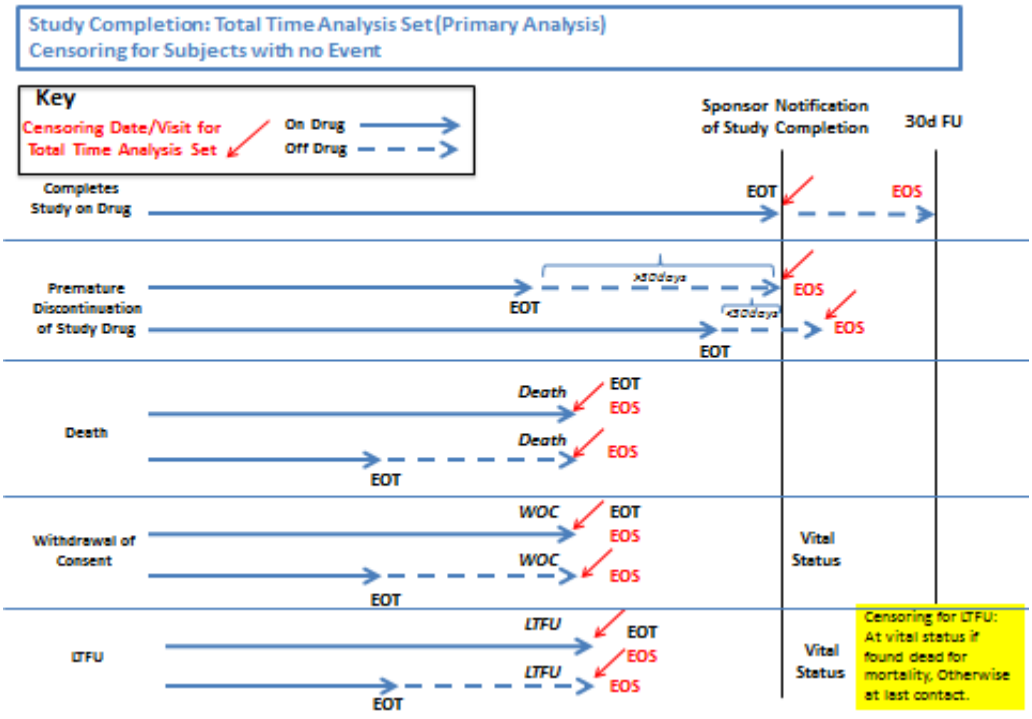
Final Clinical Events Committee Diabetes Adjudication Charter

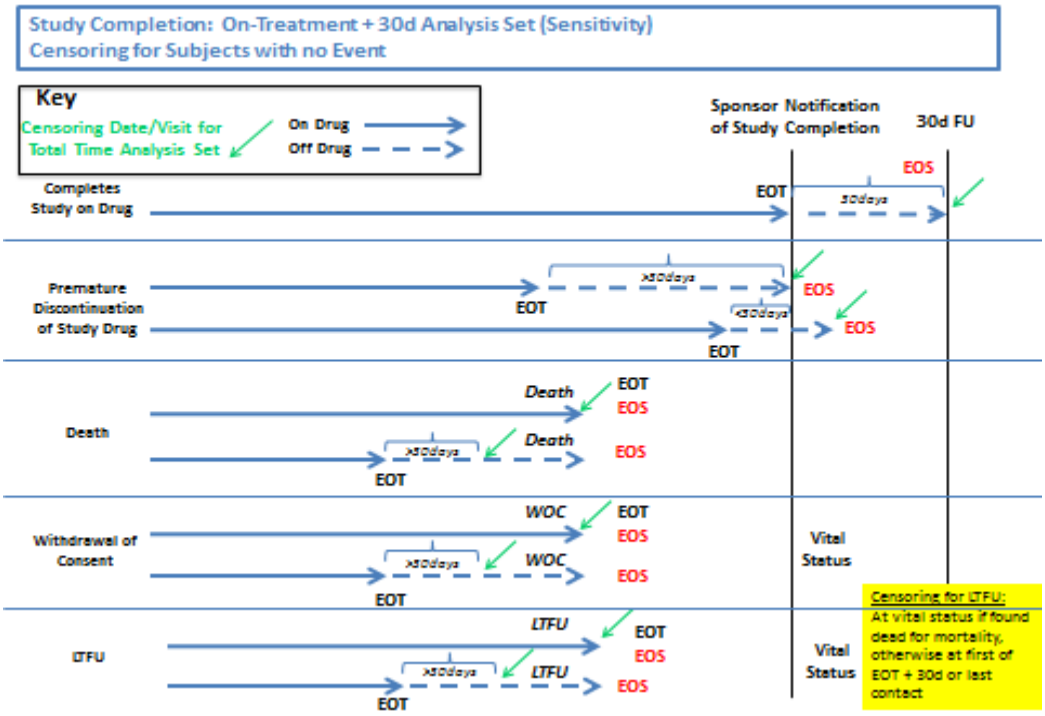
13.2 DIAGRAMS OF CENSORING ALGORITHMS

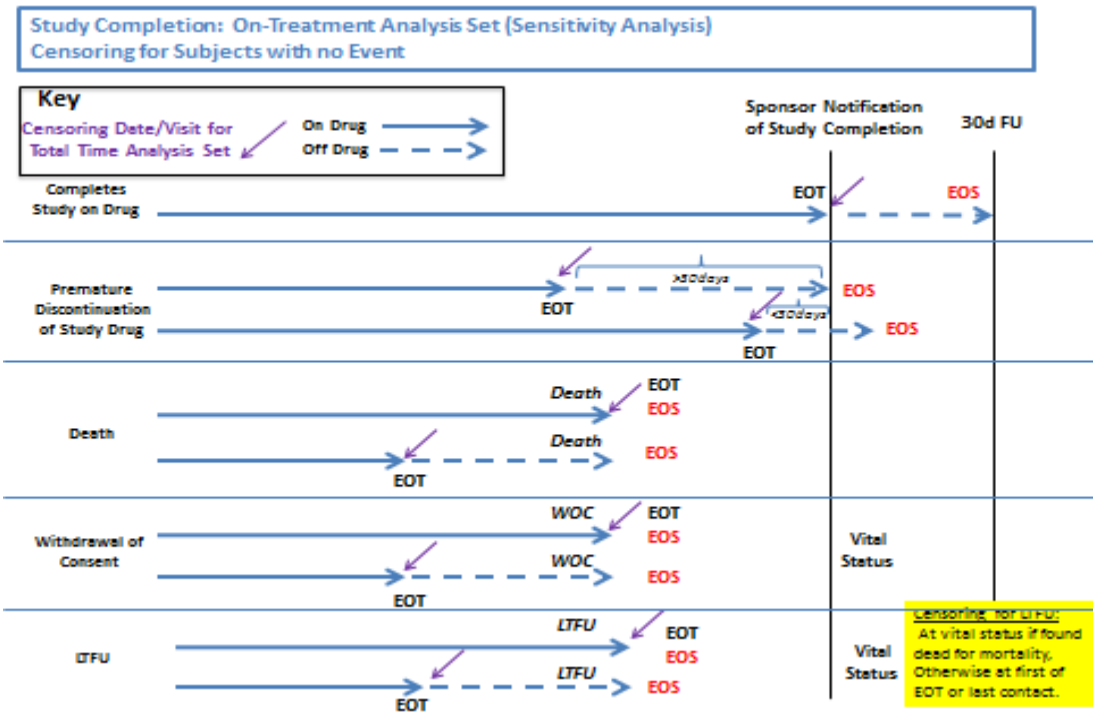
13.2.1 Censoring at Interim Analysis



13.2.2 Censoring at Study Completion




Study Completion: On-Treatment + 30d Analysis Set (Sensitivity)
Censoring for Subjects with no Event
Key
Censoring Date/Visit for Total Time Analysis Set
On Drug
Off Drug
Sponsor Notification of Study Completion
30d FU
Completes Study on Drug
EOT
EOS
30days
Premature Discontinuation of Study Drug
>30days
<30days
Death
WOC
Withdrawal of Consent
LTFU
Vital Status
Censoring for LTFU:
At vital status if found dead for mortality, otherwise at first of EOT + 30d or last contact


Study Completion: On-Treatment Analysis Set (Sensitivity Analysis)
Censoring for Subjects with no Event
Key
Censoring Date/Visit for Total Time Analysis Set
On Drug
Off Drug
Sponsor Notification of Study Completion
30d FU
Completes Study on Drug
EOT
EOS
Premature Discontinuation of Study Drug
>30days
<30days
Death
WOC
Withdrawal of Consent
LTFU
Vital Status
Censoring for LTFU:
At vital status if found dead for mortality, Otherwise at first of EOT or last contact.

13.3 ADVERSE EVENT START AND END DATE IMPUTATION ALGORITHM

Description of Incomplete End Date		Imputed date
Day missing (YearMonth only) and Date of Death is not missing		
YearMonth earlier than YearMonth of Date of Death	→	Impute to the last day of the month
YearMonth equals YearMonth of Date of Death	→	Date of Death
Month missing (Year) and Date of Death is not missing		
Year earlier than Year of Date of Death	→	Impute to the last day of the year
Year equals Year of Date of Death	→	Date of Death
ALL is missing and Date of Death is not missing		
	→	Date of Death
Day missing (YearMonth) and Date of Death is missing		
YearMonth		Impute to the last day of the month
Month missing (Year) and Date of Death is missing		
Year	→	Impute to the last day of the year
ALL is missing and Date of Death is missing		
	→	No imputation

Description of Incomplete Start Date		Imputed date
Day missing (YearMonth Only)		
YearMonth earlier than YearMonth of First Dose Date	→	Impute to first of the month
YearMonth equal YearMonth of First Dose Date	→	Impute to First Dose Date or AE End Date, whichever is earlier
YearMonth greater than YearMonth of First Dose Date	→	Impute to first of the month
Month missing (Year)		
Year earlier than Year of First Dose Date	→	Impute to first of the year
Year equal Year of First Dose Date	→	Impute to First Dose Date or AE End Date, whichever is earlier
Year greater than Year of First	→	Impute to first of the year

Dose Date	
ALL is missing →	Impute to First Dose Date (or randomization date for subjects who did take study treatment) or AE End Date, whichever is earlier

13.4 CONCOMITANT MEDICATION START AND END DATE IMPUTATION ALGORITHM

There is clear evidence the drug was STOPPED **BEFORE** the Screening Visit (from Prior Meds page)

Description of Incomplete End Date		Imputed date
Day missing (YearMonth) and Date of Screening is not missing		
YearMonth earlier than YearMonth of Date of Screening	→	Impute to the last day of the month
YearMonth equals YearMonth of Date of Screening	→	Date of Screening
Month missing (Year) and Date of Screeningis not missing		
Year earlier than Year of Date of Screening	→	Impute to the last day of the year
Year equals Year of Date of Screening	→	Date of Screening
ALL is missing and Date of Screening is not missing		
	→	Date of Screening

There is NO clear evidence the drug was STOPPED **BEFORE** the Screening Visit

Description of Incomplete End Date		Imputed date
Day missing (YearMonth only) and Date of Death is not missing		
YearMonth earlier than YearMonth of Date of Death	→	Impute to the last day of the month
YearMonth equals YearMonth of Date of Death	→	Date of Death
Month missing (Year) and Date of Death is not missing		
Year earlier than Year of Date of Death	→	Impute to the last day of the year
Year equals Year of Date of Death	→	Date of Death
ALL is missing and Date of Death is not missing		
	→	Date of Death
Day missing (YearMonth) and Date of Death is missing		
YearMonth		Impute to the last day of the month
Month missing (Year) and Date of Death is missing		
Year	→	Impute to the last day of the year
ALL is missing and Date of Death is missing		
	→	No imputation

Description of Incomplete Start Date		**Imputed date**
Day missing (YearMonth Only)		
YearMonth earlier than YearMonth of First Dose Date	→	Impute to first of the month
YearMonth equal YearMonth of First Dose Date	→	Impute to First Dose Date or Med End Date, whichever is earlier
YearMonth greater than YearMonth of First Dose Date	→	Impute to first of the month
Month missing (Year)		
Year earlier than Year of First Dose Date	→	Impute to first of the year
Year equal Year of First Dose Date	→	Impute to First Dose Date(or randomization date for subjects who did take study treatment) or Med End Date, whichever is earlier
Year greater than Year of First Dose Date	→	Impute to first of the year
ALL is missing		
	→	Impute to First Dose Date or Med End Date, whichever is earlier