REVISION HISTORY

Revision History
Previous Version (Amendment 01): V6.0
Current Version (Amendment 02): V7.0
Date of Revisions: 30 Mar 2017

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
The primary objective of conversion to Type 2 diabetes mellitus was changed to a secondary objective	The timelines to demonstrate the primary endpoint for conversion to Type 2 diabetes are not as initially projected, due to the low rate of conversion	SYNOPSIS • Primary Objectives • Secondary Objectives • Study Design • Secondary Endpoints • Primary Safety and Efficacy and Key Secondary Analyses • Primary Endpoint Analyses • Secondary Endpoint Analysis • Interim Analysis • Sample Size Rationale Section 8.1 Section 8.2 Section 9.1 Section 9.7.1.1 Section 9.7.1.6 Section 9.7.2 Section 9.7.3
Removed $HbA1_c$ from the Exploratory Objective	In order to have a broader assessment of glycemic benefit in subjects with diabetes	SYNOPSIS • Exploratory Objectives Section 8.3
Added fasting plasma glucose (FPG), fasting insulin levels, and homeostatic model	To better assess lorcaserin glycemic benefit	SYNOPSIS • Exploratory Endpoints

Revision History
Previous Version (Amendment 01): V6.0
Current Version (Amendment 02): V7.0
Date of Revisions: 30 Mar 2017

Change	Rationale	Affected Protocol Section(s)
assessment-insulin resistance (HOMA-IR)		Section 9.7.1.1
Multiple testing procedure was updated to reflect the change in the primary objective		SYNOPSIS • Primary Safety and Efficacy and Key Secondary Analyses List of Abbreviations Section 9.7.1.6
The renal objective for the overall population has been added and reorganized for clarification	To better assess the lorcaserin renal beneficial effect in the total study population	SYNOPSIS • Secondary Objectives • Secondary Endpoints • Secondary Endpoint Analyses Section 8.2 Section 9.7.1
Details of the interim analysis are outlined in the Study Integrity Charter	Clarification	SYNOPSIS • Interim Analysis Section 9.4.6 Section 9.7.3
Removed the clarification of major adverse cardiovascular events (MACE)+ events accruing after 11 months after 460 MACE events have occurred	Not needed	SYNOPSIS • Interim Analysis Section 9.7.3
Updated the timing of the interim analysis date	Update	SYNOPSIS • Study Design • Interim Analysis Section 9.1 Section 9.7.3

Revision History
Previous Version (Original Protocol): V5.0
Current Version (Amendment 01): V6.0
Date of Revisions: 06 Aug 2015

Change	Rationale	Affected Protocol Section(s)
Grammatical, typographical, and formatting changes		Throughout
Revised total number of study sites	Fewer study sites are needed for completion of the study	SYNOPSIS, Sites Section 6 Section 9.3
Reclassified the secondary objective related to glycemic control to allow for assessment in subject subpopulations as an exploratory objective.	Allow for identification of patient subpopulations in which lorcaserin may have greater efficacy	SYNOPSIS, Secondary Objectives Section 8.2
Added exploratory objective to evaluate AACE and ACE obesity-related complications	Facilitate evaluation of lorcaserin effects in relation to widely accepted endpoints	SYNOPSIS, Exploratory Objectives Section 8.3
Provided specific instructions that the 1st dose should be taken at Visit 2	To clarify instructions pertaining to initiation of study medication	SYNOPSIS, Study Design Section 9.1 Section 9.1.2.1 Section 9.4.1 Section 9.5.2.1, Table 4
Add contents related to diabetes adjudication and confirmatory test needed		SYNOPSIS, Assessments Section 9.5.1.3
Changed the designation, clinical trial safety database, to clinical trial database	To correct terminology	SYNOPSIS, Study Design Section 9.5.1.3 Section 9.5.1.5
Revised inclusion criterion pertaining to established CV disease (MI or stroke) and stable antidiabetic medication, such that randomization (not screening) is the point of reference	To minimize unnecessary exclusion of prospective subjects	SYNOPSIS, Inclusion Criterion #3 Section 9.3.1
Defined renal impairment with	To provide a more precise	SYNOPSIS, Inclusion Criterion #3

Revision History
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Change	Rationale	Affected Protocol Section(s)
reference to estimated glomerular filtration rate rather than clearance	definition of this criterion	SYNOPSIS, Exclusion Criterion #5 Section 9.3.1 Section 9.3.2
Clarified the circumstances under which subjects with high levels of hsCRP would be allowed to enter the study	To allow recruitment of subjects who have high hsCRP but are suitable for inclusion in the study.	SYNOPSIS, Inclusion Criterion #3 Section 9.3.1
Clarified that known severe valvular disease does not need to result in exclusion if corrected by valve repair or replacement	To minimize unnecessary exclusion of prospective subjects	SYNOPSIS, Exclusion Criterion #4 Section 9.3.2
Deleted moderate renal insufficiency from Exclusion Criterion #5	To allow recruitment of subjects who have moderate renal insufficiency but are nonetheless suitable for study inclusion.	SYNOPSIS, Exclusion Criterion #5 Section 9.3.2
Revised wording for exclusion criterion and prohibited therapies and drugs pertaining to serotonergic drugs	For clarity	SYNOPSIS, Exclusion Criterion #8 Section 9.3.2
Deleted cyproheptadine, amoxapine, TCAs, and mirtazapine from the list of drugs known to increase the risk for cardiac valvulopathy and/or PH	Correction	SYNOPSIS, Exclusion Criterion #9 and Concomitant Drug/Therapy Section 9.3.2 Section 9.4.7.2
Revised the list of prohibited drugs and clarified restrictions on serotonergic drugs	To provide more appropriate restrictions on concomitant drug treatment	SYNOPSIS, Exclusion Criterion #8 Section 9.3.2 Section 9.4.7.2
Clarified instances where the exclusion criterion for enrollment in other clinical trials does not apply	To minimize unnecessary exclusion of prospective subjects	SYNOPSIS, Exclusion Criterion #14 Section 9.3.2
Added exclusion for bariatric surgery performed within 1 year of screening	Study results could be confounded by significant weight loss resulting from recent bariatric surgery.	SYNOPSIS, Exclusion Criterion #15 SYNOPSIS, Concomitant Drug Therapy

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Change	Rationale	Affected Protocol Section(s)
		Section 9.3.2
Updated the exclusion criterion defining women of childbearing potential	Updated per Eisai Safety	SYNOPSIS, Exclusion Criterion #18 Section 9.3.2
Specified that valvular regurgitation ratings are to be applied to substudy echocardiograms	To clarify method for evaluating valvular regurgitation	SYNOPSIS, Safety Assessments Section 9.5.1.5
Added an analysis of proportion of subjects who have worsened valvulopathy at 1 year and yearly thereafter and had FDA-defined valvulopathy at Baseline as a secondary endpoint	Evaluate whether lorcaserin treatment worsens FDA-defined valvulopathy hypertension in subjects who have existing valvulopathy at baseline	SYNOPSIS, Secondary Endpoints & Secondary Endpoints Analyses Section 9.7.1.1 Section 9.7.1.6
Eliminated provisions for representative of subject to participate in informed consent	It is expected that all subjects will be capable of providing informed consent on their own.	Section 5.3
Deleted phrase "if applicable" from explanation of contact information	Deleted unnecessary phrase	Section 6
Changed the study population for conversion to diabetes to prediabetes population	To select a proper high diabetes risk population for the conversion to diabetes	Section 7.1
Define terminology of "Sponsor Notification of Study Completion" as announcement of study closeout.	Clarify the definition of study completion	Section 9.1 Section 9.1.2.2 Section 9.5.1.5 Section 9.5.2.1, Table 4 footnotes Section 9.5.4.1 Section 9.5.5.1
Added instruction that a confirmatory test is needed for subjects with new onset of diabetes	Further instruction of the confirmatory test was needed	Section 9.3.1
Modified dosing instructions to allow for temporarily reduced dosing for nonserious AEs likely	To enhance subject tolerability and improve study retention	Section 9.4.5.1

Revision History
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Change	Rationale	Affected Protocol Section(s)
related to drug treatment		
Changed study medication instructions to separate the 2 daily doses by at least 6 hours	To enhance compliance by eliminating unnecessary reference to mealtime	Section 9.4.5
Added guidelines for managing renal dysfunction or hepatic abnormalities	To provide specific safety guidance in the event that subjects develop severe renal dysfunction, or significant hepatic abnormalities	Section 9.4.5.1
Added instructions to allow re-initiation of study drug after discontinuation of the second of 2 serotonergic drugs (more than 1 serotonergic drug is prohibited)	To minimize unnecessary instances of failure to complete study	SYNOPSIS, Concomitant Medications Section 9.4.7.2
Added DEA-223 form as controlled substance registration certificate form	Correction	Section 9.4.9
Clarified exclusion on basis of prohibited drugs of abuse. Stated that nicotine use is not exclusionary.	For clarity	Section 9.5.1.2
AEs and Events Associated with Special Situations from AEs and Other Events of Interest	Title updated per sponsor template	Section 9.5.1.5
Deletion pertaining to duration of AE/SAE data collection	Updated per Eisai Safety Standard	Section 9.5.1.5
Deleted the statement, "Worsens (increases) to Grade 02 or higher based on the sponsor's grading for laboratory values."	Simplified reporting rules. Abnormal labs will still be reported as AE's based on the other criteria in the protocol and also will be analyzed based on the central laboratory values	Section 9.5.1.5
Deleted instructions pertaining to the requirement to categorize certain ECG findings as AEs	Simplified reporting rules. ECG abnormalities will be reported as AE's consistent with the other criteria for AE reporting within the	Section 9.5.1.5

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Change	Rationale	Affected Protocol Section(s)
	protocol and do not require a separate section.	
Hospitalization for administration of study drug or insertion of access for administration of study drug removed from list of hospitalizations that are not SAEs	Removed because not applicable for this study.	Section 9.5.1.5
Clarified that subjects who permanently discontinue study drug are to complete the EOT visit within 30 days.	Clarification	Section 9.5.1.5
Moved euphoria and suicidal ideation from study specific AEs of interest to 'SAEs and Events Associated with Special Situations'	Euphoria and suicidal ideation are listed under 'SAEs and Events Associated with Special Situations' pertaining to study-specific AEs of interest, allowing investigators to report these events correctly.	Section 9.5.4.4
Updated description of study-specific events of interest and instructions for reporting these events	To provide clearer guidance for the correct reporting of study-specific events of interest	Section 9.5.1.5 Section 9.5.4.4
Revised description of valvular heart disease to distinguish between new onset and worsened valvular heart disease	To allow for evaluation of new onset and worsened valvular heart disease	Section 9.5.4.4
Revised description of pulmonary hypertension to distinguish between new onset and worsened pulmonary hypertension	To allow for evaluation of new onset and worsened pulmonary hypertension	Section 9.5.4.4
Revised footnote b in Schedule of Procedures/Assessments pertaining to unscheduled visits to allow for assessments required by state-controlled substance requirements	Compliance with possible local regulations	Section 9.5.2.1, Table 4
Added that renal function parameters and glycemic profile	To enhance surveillance of possible renal-related	Section 9.5.2.1, Table 4, footnote f

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Change	Rationale	Affected Protocol Section(s)
should be collected at all visits	changes	
Specified that SAE collection for 30 days after the last drug dose applies only to subjects taking study drug at the time of study completion	Some subjects may have discontinued study drug before study completion, such that the 30-day interval for SAE collection may not be applicable.	Section 9.5.4.1
Deleted component of "misuse" definition pertaining to prescription drugs	This is a clinical study, therefore these statements are not applicable.	Section 9.5.4.4
Deleted instructions for reporting of significant laboratory abnormality	Simplified reporting rules. Laboratory abnormalities will be reported as AEs based on the other instructions in the protocol and also will be analyzed using the central laboratory data.	Section 9.5.4.4
Relocated language to allow for re-initiation Note that new content is provided.	To minimize unnecessary instances of failure to complete study	Section 9.5.5.1 Section 9.5.5.2

Revisions in Version 5.0 Date: 21 Oct 2013		
Change	**Rationale**	**Affected Protocol Sections**
Removed timing of evaluation from the objective for diabetes-related microvascular complications	Not needed in objective	• Synopsis -Exploratory Objectives, 2nd bullet • Section 8.3
Deleted duration of Follow-up Period	Clarification, as it may vary among subjects	• Synopsis -Study Design • Section 9.1
Qualified the EOS Visit for subjects who complete treatment	Clarification	• Synopsis -Study Design -Duration of Study Phases and Treatment • Section 9.1 • Table 4 (Notes)
Referred reviewer to the SAP for details of analyses	Clarification	• Synopsis -Analysis Sets, 1st bullet • Section 9.7.1.2
Revised window for EOS visit	Larger window is needed	• Section 9.1.2.2 • Table 4 (footnote c)
Added serum creatinine and cystatin C assessment at EOT	Correction	• Table 4
Revised last timepoint for other biomarkers sampling	Correction	• Table 4
Revised "EOS" to "the end of the study"	Clarification	• Synopsis -Exploratory Endpoints, 2nd bullet • Section 9.7.1.1, Exploratory Endpoints
Changed timing of first subject screened	Correction	• Synopsis -Study Period and Phase of Development -Study Design
Revised MACE-related objective of the study	Correction; MACE+ includes components of MACE	• Synopsis -Secondary Objectives, MACE-related; 1st bullet -Section 8.2
Qualified supportive endpoint for effects on conversion to diabetes to include its sequelae	Correction	• Synopsis -Secondary Objectives -Supportive endpoints for conversion to T2DM • Section 8.2 • Section 9.7.1.1 (Supportive endpoints for conversion to T2DM)
Estimated number of subjects who	Not needed in objectives; needs	• Synopsis

Revisions in Version 5.0 Date: 21 Oct 2013		
Change	**Rationale**	**Affected Protocol Sections**
will have ECHO assessments and revised timing of evaluation of echocardiographically determined heart valve and pulmonary artery pressure changes	to be qualified elsewhere	-Exploratory Objectives, 4th bullet -Study Design ● Section 8.3, 4th bullet ● Section 9.1 ● Section 9.5.1.5 ● Table 4 (footnote d)
Revised text regarding reduced – calorie diet and physical activity program	Clarification	● Synopsis -Study Design ● Section 9.1
Qualified definition of hypertension	Clarification	● Synopsis -Inclusion Criteria, #3 (OR scenario) "a" ● Section 9.3.1
Qualified criteria for T2DM	Clarification for the stabilization of treatment of diabetes and rescreening in enrollment.	● Synopsis -Inclusion #3 ● Section 9.3.1
Added use of lorcaserin within 6 months prior to Screening as an exclusion criterion	New restriction since it is an approved drug	● Synopsis -Exclusion #11 ● Section 9.3.2
Revised text and added FPG and additional components of the ADA diagnostic criteria to the primary efficacy/safety assessments	Clarification	● Synopsis -Primary Safety/Efficacy Assessments ● Section 9.5.1.3 (Conversion to Diabetes)
Revised timing of last hsCRP and fibrinogen assessments from EOS to EOT	EOT assessments will collect samples if a subject discontinues the treatment earlier.	● Synopsis -Biomarker Assessments ● Section 9.5.1.4 (Biomarker Assessments) ● Table 4
Redefined conversion to T2DM primary endpoint	Clarification	● Synopsis - Statistical Methods (Primary Endpoints, 2nd bullet) ● Section 9.7.1.1 Primary Endpoints, 2nd bullet)
Included an option to have other biomarkers collected for future research.	Clarification for how subjects sign the informed consent	● Section 5.3
Revised window for EOS visit	Safety requires at least 30 days follow-up.	● Section 9.1.2.2 ● Table 4

Revisions in Version 5.0 Date: 21 Oct 2013		
Change	**Rationale**	**Affected Protocol Sections**
Deleted schedule footnote; re-lettered following footnote and revised in table	Correction	● Table 4 (footnote i)
Revised language related to withdrawal of consent to specify the appropriate CRF and point of contact for confirmation.	Clarification of the procedure	● Section 9.5.5.2
Revised language for completion of study treatment	Correction	Section 9.7.1.3
Added "approximately" symbol for EOT	Clarification	● Figure 1
Removed cross-reference to footnote e on ECHO assessment	ECHO assessments will continue after a subject discontinues study treatment	● Table 4
Delete hematology tests at EOS	They are not required	● Table 4
Add HbA_{1c}, FPG, and Fasting insulin level at EOS	To collect more data for diabetes conversion	● Table 4.
Added FPG at unscheduled visits	To collect more data for diabetes conversion	● Table 4
Revised footnote language pertaining to renal function parameters	Clarification.	Table 4 (footnote f)
Added generic name of Belviq	Correction	● Protocol Signature page ● Figure 1
Specified reporting of MACE and MACE+ to the Sponsor Pharmacovigilance Dept.	Clarification	● Synopsis -Study Design ● Section 9.5.1.3 ● Section 9.5.1.5
Revised language regarding AE reporting	Clarification	● Section 9.5.1.5
Revised timeframe for reporting pregnancy/exposure through breastfeeding	Clarification	● Section 9.5.4.3

Revisions in Version 4.0 Date: 03 Oct 2013		
Change	**Rationale**	**Affected Protocol Sections**
Ensured sampling for/measurement of creatinine at appropriate timepoints	Measurement of creatinine should be in parallel with cystatin C	● Table 4, footnote g
Revised timing from EOT to EOS for evaluating the effect of lorcaserin on microvascular complications	Correction	● Synopsis -Exploratory Objectives ● Section 8.3
Qualified biomarkers evaluated as an exploratory endpoint	Because all biomarkers are not assessed on a yearly basis; correction	● Synopsis -Exploratory Endpoints ● Section 9.7.1.1
Revised analysis of eGFR and ACR from EOT to EOS	Correction	● Synopsis -Exploratory Endpoints -Exploratory Endpoints Analyses ● Section 9.7.1.1 ● Section 9.7.1.6
Removed "percent" and "percentage" for change from Baseline	Clarification	● Synopsis -Exploratory Endpoints -Secondary Endpoints Analyses -Exploratory Endpoints Analyses ● Section 9.7.1.1 ● Section 9.7.1.6
Removed secondary reasons for discontinuation on the Subject Disposition CRF for documenting study completion	Not required	● Section 9.7.1.3
Removed reference to a 6-digit randomization number	A different number of digits may be used	● Section 9.4.3
Made participation in a reduced-calorie diet and increased physical activity program required	Clarification	● Synopsis -Study Design ● Section 9.1
Stipulated a separate ICF for other biomarker sampling/analysis	Requirement for separate ICF; correction	● Section 5.3
Revised timing of last sampling for hsCRP, fibrinogen and other biomarkers from EOT to EOS	Correction	● Synopsis -Biomarker assessments ● Section 9.5.1.4 ● Table 4 ● Appendix 5
Qualified when ECGs will be obtained	Clarification	● Section 9.5.1.5
Specified duration of the Follow-up Period	Clarification	● Synopsis -Study Design ● Section 9.1
Added text for the sensitivity analysis	To improve the sensitivity	● Synopsis

Revisions in Version 4.0 Date: 03 Oct 2013		
Change	**Rationale**	**Affected Protocol Sections**
	analysis, additional language added since the FDA-approved protocol	-Primary Endpoints Analyses ● Section 9.7.1.6
Revised protocol definition of regression of CKD	Correction	● Synopsis -PD Assessments ● Section 9.5.1.4
Separated hematology from chemistry in laboratory tests in the schedule	Because renal function tests (chemistry) will be done at some visits where hematology is not required	● Table 4
Revised existing footnote for assessments conducted via telephone contact	Clarification	● Table 4 (footnote j)
Added a footnote to stipulate the need to perform renal function tests in subjects who discontinue study drug early	Clarification, as this is a requirement	● Table 4 (footnote f)
Designate assessments not needed after end of treatment for subjects who discontinue study drug early	FDA recommendation	● Table 4 (footnote e)
Removed modified clinic visit	The information this column provides is captured instead in the footnoted assessments.	● Table 4
Added FPG as an indicator of glycemic control	Correction	● Section 9.5.1.3
Qualified use of Form FDA 1572	Non-North American sites will not use this form, so an alternative option must be added.	● Section 9.4.9 ● Section 9.6.1 ● Section 11.6
Revised molecular formula	Correction	● Section 9.4.2.1
Revised primary and secondary endpoints for conversion to T2DM	Based on discussion with the CVOT Advisory Board and consultants. It also was decided to use full 2013 ADA guidelines for definition of conversion to T2DM.	● Synopsis -Primary Endpoints -Secondary Endpoints ● Section 9.7.1.1 ● Section 10
Increased the number of sites in the study	To increase enrollment in order to meet in a timely manner, the FDA-specified number of events required to be reported in the designated timeframe.	● Synopsis -Sites ● Section 6 ● Section 9.3

Revisions in Version 4.0 Date: 03 Oct 2013		
Change	**Rationale**	**Affected Protocol Sections**
MDRD equation replaced with CKD-EPI formula for renal assessments	Based on recommendation from CVOT Advisory Board; eGFR calculated with the CKD-EPI formula is more accurate, particularly in overweight or obese populations.	• Synopsis -Inclusion Criteria, #3 (OR scenario) "c" -Exclusion Criteria #5 -PD Assessments • List of Abbreviations and Definition of Terms • Section 9.3.1 • Section 9.3.2 • Section 9.5.1.4 • Section 10
Revised and qualified definitions for albuminuria	Based on recommendation from CVOT Advisory Board; albuminuria is variable, so 2 consecutive assessments are required	• Synopsis -PD Assessments • Section 9.5.1.4 • Section 9.7.1.4
Added serum cystatin C as a PD assessment in a subset of subjects to calculate eGFR	Based on recommendation from CVOT Advisory Board; provides more accurate eGFR in the sub- population with high nephropathy risk and may provide correct reference for creatinine-based eGFR, since eGFR calculated from creatinine may not be accurate due to that muscle loss would result in decreased creatinine.	• Synopsis -PD Assessments • Section 9.5.1.4 • Table 3
Revised supportive endpoints for glycemic and end-organ benefits	Based on recommendation from CVOT Advisory Board; endpoint revision was made to align with changes made for the definition of albuminuria.	• Synopsis -Secondary Endpoints • Section 9.7.1.1
Revised language around ECHO objectives and assessments	Because ECHO assessments will stop after 460 MACE events are reached; new language since the FDA-approved protocol	• Synopsis -Study Design -Exploratory Objectives • Section 8.3 • Section 9.1 • Section 9.5.1.5 • Table 4
Added an appendix for the biomarker substudy	For completeness	• Appendix 5
Added an appendix for	For completion	• Appendix 6

Revisions in Version 4.0 Date: 03 Oct 2013		
Change	**Rationale**	**Affected Protocol Sections**
pharmacogenomic research		
Revised molecular formula	Correction	• Section 9.4.2.1

Revisions in Version 3.0 Date: 14 Jun 2013		
Change	**Rationale**	**Affected Protocol Sections**
Clarified definition of "On-Treatment plus 30 Days Analysis Set"	To address FDA comment	• Synopsis – Analysis Sets • Section 9.7.1.2

Revisions in Version 2.0 Date: 14 Jun 2013		
Change	**Rationale**	**Affected Protocol Sections**
Clarified reporting of MACE, SAEs and vital status until EOS for subjects who prematurely discontinue study drug	To address FDA comment	● Section 9.5.1.5 ● Section 9.5.5.2
Clarified actions to be taken in the case of a subject withdrawing consent	To address FDA comment	● Section 9.5.5.2
Clarified wording inclusion of subjects with established CV disease	To address FDA comment	● Synopsis, Inclusion Criteria, #3 ● Section 9.3.1
Revised the upper limit of HbA_{1c} for subjects with T2DM	To address FDA comment	● Synopsis, Inclusion Criteria, #3 ● Section 9.3.1
Added text to address the risk of hypoglycemia in subjects taking certain concomitant medications	To address FDA comment	● Section 9.4.7.2
Clarified timing of baseline ECHOs to account for subjects who may be excluded	To address FDA comment	● Table 4, footnote "e" (Schedule of Procedures/Assessments ● Section 9.5.1.5
Specified all cancers to be reported as study-specific AEs of interest	To address FDA comment	● Section 9.5.1.5 ● Section 9.5.4.3
Added ACR ≥30 as a potential CV risk factor to inclusion criteria	To address FDA comment	● Synopsis, Inclusion Criteria, #3 ● Section 9.3.1
Reduced frequency of (safety) laboratory assessments after 1 year	To address FDA comment	● Table 4
Aligned categories for albuminuria to the KDIGO 2012 guidelines	To address FDA comment	● Synopsis ● Section 9.5.1.4
Added details of adjunctive lifestyle program	To address FDA comment	● (new) Appendix 4
Added the On-Treatment plus 30 Days Analysis Set	To address FDA comment	● Synopsis ● Section 9.7.1.2 ● Section 9.7.1.6
Added all-cause mortality as a secondary endpoint	To address FDA comment	● Synopsis ● Section 9.7.1.2 ● Section 9.7.1.6
Added language for defining, reporting, and treating hypoglycemia	To address FDA comment	● Section 9.4.7.2 ● Section 9.5.4 ● Section 9.5.4.2
Described type of investigators wanted to participate in the study	Clarification	● Synopsis
Revised primary efficacy objective	Clarification	● Synopsis, Analysis Sets ● Section 8.1

Revisions in Version 2.0 Date: 14 Jun 2013		
Change	**Rationale**	**Affected Protocol Sections**
Reorganized secondary objectives to support primary objectives, with subsequent reorganization of endpoints and analyses to align with the objectives	Clarification	• Synopsis • Section 8.2 • Section 9.7.1.1 • Section 9.7.1.6
Revised concomitant medication language with regard to use of serotonergic drugs, drugs for the treatment of hypertension, dyslipidemia, and diabetes, and drugs associated with an increased risk of valvulopathy	Clarification	• Synopsis • Section 9.4.7.2
Reduced Screening Period from 42 days to 30 days	30 days is sufficient	• Synopsis • Section 9.1 • Section 9.1.1 • Figure 1 • Table 4
Revised language on reporting of MACE and MACE+	Clarification	• Synopsis • Section 9.5.1.3
Revised language regarding completion of the study, MACE/MACE+ reporting, and the interim analysis	Clarification	• Synopsis • Section 9.1
Revised date of first subject in and last subject out	Correction	• Synopsis • Section 9.1
Identified specific examples of drugs known to increase the risk of valvulopathy as exclusion criteria	Clarification	• Synopsis • Section 9.3.2
Updated contraception language in exclusion criteria	Correction	• Synopsis • Section 9.3.2
Removed the C-SSRS assessment	To address FDA comment to reduce safety assessments	• Synopsis, Exclusion Criteria #10 • Section 9.3.2, Exclusion Criteria #10 • Synopsis, Safety Assessments • Section 9.5.1.5, Safety Assessments • List of Abbreviations • Synopsis, Safety Analyses • Section 9.7.1.8, Safety Analyses • Table 4

Revisions in Version 2.0 Date: 14 Jun 2013		
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Reduced frequency of visits after 2 years to every 4 months	To address FDA comment to reduce safety assessments	● Table 4 ● Synopsis/Study Design ● Section 9.1 ● Section 9.1.2.1 ● Section 9.4.1
Reduced frequency of vital signs	To address FDA comment to reduce safety assessments	● Table 4
Removed FPG at 3 and 18 months	Not required at these visits	● Table 4
Removed Other Biomarkers sampling at Month 36	Not required	● Table 4
Added 3 additional exploratory analyses	Correction	● Synopsis ● Section 9.7.1.6
Revised one of the conditions for completion of the study	Correction	● Synopsis ● Section 9.1 ● Section 9.7.3
Revised definition for end of the study for purposes of reporting to the IRB/IEC/CA	Correction	● Section 5.1
Removed Early Discontinuation Visit; edited table note to Table 4 to identify procedures for subjects who prematurely discontinue study drug	A separately identified visit is not needed.	● Table 4, “Note”
Added Modified Clinic Visit	This visit is for subjects who prematurely discontinue study drug, but are being followed clinically.	● Table 4
Revised text regarding criteria for antidiabetic treatments at time of screening	Correction	● Synopsis, inclusion criterion 3 ● Section 9.3.1 ● Section 9.4.7
Revised definition for newly developed albuminuria	Correction	● Synopsis ● Section 9.5.1.4
Revised Classification of Causality of Adverse Events	Facilitate reporting of AEs	● Section 9.5.1.5
Revised text related to safety reporting to remove the use of forms	Alignment with use of an electronic gateway which will be used for reporting	● Section 9.5.1.5 ● Section 9.5.4.1
Revised text pertaining to analysis of ECGs	Correction	● Section 9.7.1.8
Updated clinical laboratory tests	Clarification	● Table 3

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Revised study-specific adverse events of interest	In response to discussion with FDA to appropriately assess and report AEs of interest	• Section 9.5.1.5 • Section 9.5.4.3
Added provision for Telephone Visit	For subjects who cannot attend a clinic visit in person	• Section 9.1 • Table 4 • Section 9.5.5
Removed Pharmacogenomics appendix	This plan will be provided separately.	• Appendix 3
Removed endpoint definitions for hospitalizations	These will be provided separately from the protocol for the CEC.	• (previous) Appendix 4
Updated List of Abbreviations	In response to all revisions made post-FDA review	• Section 4
Revised date and document version	Update	• Throughout protocol

1 TITLE PAGE

CLINICAL STUDY PROTOCOL

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
Sponsor:	Eisai Inc. 100 Tice Boulevard Woodcliff Lake, New Jersey 07677 USA Eisai Limited European Knowledge Centre Mosquito Way Hatfield, Hertfordshire AL10 9SN UK
Investigational Product Name:	APD356/BELVIQ® (lorcaserin hydrochloride)
Indication:	Obesity
Phase:	Phase 3b/4
Approval Date:	V1.0 04 Feb 2013 (original protocol) V2.0 14 Jun 2013 (original protocol) V3.0 14 Jun 2013 (original protocol) V4.0 03 Oct 2013 (original protocol) V5.0 21 Oct 2013 (original protocol) V6.0 06 Aug 2015 (Amendment 01) V7.0 30 Mar 2017 (Amendment 02)
IND Number:	69888
EudraCT Number:	2013-000324-34
GCP Statement:	This study is to be performed in full compliance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) and regulations. All required study documentation will be archived as required by regulatory authorities.
Confidentiality Statement:	This document is confidential. It contains proprietary information of Eisai (the sponsor). Any viewing or disclosure of such information that is not authorized in writing by the sponsor is strictly prohibited. Such information may be used solely for the purpose of reviewing or performing this study.

2 SYNOPSIS

Compound No.

APD356

Name of Active Ingredient

BELVIQ® (lorcaserin hydrochloride)

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

Investigators

Physicians who treat patients with obesity, diabetes, or cardiovascular disease and who have experience in conducting clinical studies

Sites

Approximately 500 sites, multinationally (revised per Amendment 01)

Study Period and Phase of Development

Approximately 60 months from first subject screened (~December 2013) to last subject's last visit/last assessment (~October 2018)

Phase 3b/4

Objectives

Primary Objectives

Safety:

- To demonstrate that, in obese and overweight subjects with cardiovascular (CV) disease and/or multiple CV risk factors, lorcaserin HCl 10 mg administered twice daily (BID) does not increase the incidence of major adverse cardiovascular events (MACE = myocardial infarction [MI], or stroke, or CV death) compared to placebo, with a noninferiority 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

Secondary Objectives

Key Secondary Objective

- To confirm that, in subjects with prediabetes at Baseline based on the 2013 ADA 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 Amendments 01 and 02)
- To confirm that, in subjects with T2DM at Baseline, lorcaserin HCl 10 mg BID improves glycemic control (HbA1c) 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 (revised per Amendment 01)
- 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 Amendment 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

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 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

Study Design

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.

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. Echocardiography will be performed on a subset of approximately 3600 subjects at Baseline and at 6, 12, 18, 24 months, and yearly thereafter. Acquisition of new ECHO data in all subjects will cease when at least 1000 subjects have completed the Month 36 echocardiographic assessment. (revised per Amendment 02)

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 Randomization 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 a median treatment duration of 2.5 years have accrued. (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.

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 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 (ie, where there is evidence to suggest a causal relationship). (revised per Amendment 01)

All subjects will continue in the study until study completion rather than for a prespecified number of visits. Subjects will remain in the study even after their first nonfatal MACE event. Subjects who discontinue treatment prematurely will be followed up for safety until study completion (ie, they will attend the remaining study visits for safety assessments).

- In order to reduce intra- and inter-site variability, the CEC will centrally review each potential MACE and MACE+ 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 MACE or MACE+. The CEC will remain blinded to treatment allocation and its activities and the criteria for classification of MACE/MACE+ events will be documented in the CEC Charter.

When 460 adjudicated MACE events have occurred, an interim analysis will be conducted on MACE events. 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. (revised per Amendment 02) If the primary safety objective has been achieved, the trial will continue for evaluation of additional endpoints as delineated in the objectives.

As required by some regulatory agencies, the following estimates are provided:

- The study will begin in December 2013.
- 460 MACE events are expected to occur on or before December 2017; the interim analysis is anticipated to occur on or before (approximately) July 2017. (revised per Amendment 02).
- 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
- The estimated period for each subject on study is anticipated to be approximately 60 months.

Number of Subjects

Approximately 18,000 subjects will be screened to provide 12,000 randomized subjects.

Inclusion Criteria

1. Body mass index (BMI) $\geq 27 kg/m^2$
2. Subjects able and willing to comply with a reduced-calorie diet and an increased physical activity program
3. Age ≥40 years with established CV disease as defined by 1 of the following:
    a. History of documented MI or ischemic stroke >1 month before Randomization (revised per Amendment 01)
    b. History of peripheral artery disease as manifested by symptomatic claudication with an ankle-brachial pressure index of <0.85
    c. History of revascularization (coronary, carotid, or peripheral artery)
    d. Significant unrevascularized coronary arterial stenosis defined as ≥50% in 2 or more coronary arteries

    OR

    Age ≥55 years for women or ≥50 years for men who have T2DM without established CV disease plus at least 1 of the following CV risk factors:

    a. Hypertension, defined as systolic blood pressure (SBP) >140 or diastolic blood pressure (DBP)

>90, or currently receiving therapy for documented hypertension

b. Dyslipidemia, defined as low density lipoprotein-cholesterol (LDL-C) >130 mg/dL, or high density lipoprotein-cholesterol (HDL-C) <40 mg/dL, or currently taking prescription lipid-lowering therapy for documented dyslipidemia

c. Estimated glomerular filtration rate (eGFR) ≥30 to ≤60 mL/min/1.73 m^2 per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation (revised per Amendment 01)

d. High sensitivity C-reactive protein (hsCRP) > 3 mg/L detected by the central laboratory in the absence of known acute or chronic inflammatory conditions (eg, infection, rheumatologic disease) (revised per Amendment 01)

e. Urinary albumin-to-creatinine ratio (ACR) ≥30 µg/mg in spot urine

Subjects with T2DM may have a pre-existing or new diagnosis of T2DM. Subjects with pre-existing T2DM should have prior documentation consistent with the diagnosis and/or be on active pharmacotherapy for T2DM. A new diagnosis of T2DM (ie, discovered at Screening) should be based on the 2013 American Diabetes Association (ADA) guidelines. The diagnostic criteria are met if a subject has unequivocal hyperglycemia (random plasma glucose ≥200 mg/dL (11.1 mmol/L) with classic symptoms of hyperglycemia or hyperglycemic crisis) OR any of the following criteria are observed and then confirmed:

- HbA_{1c} ≥6.5%
- fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)
- 2-hour plasma glucose ≥200 mg/dL (11.1mmol/L) by an oral glucose tolerance test (OGTT)

All T2DM subjects must have an HbA_{1c} <10% at Screening. If subjects are being treated, or upon diagnosis need to be treated with antidiabetic agents, the T2DM treatment regimen must be stable for at least 3 months before randomization. A single rescreen is allowed following stabilization. Stable control refers to minimal dose changes to existing medications for glycemic control and no medications being initiated for glycemic control in the 3 months before Randomization. (revised per Amendment 01) Minimal changes are defined as a change in insulin dose <10% of daily dose, without any change in dose frequency, no add-on or discontinuation of other antidiabetic agents, and the subject has not been hospitalized due to hypo- or hyperglycemic events. (revised per Amendment 01)

4. Provide written informed consent
5. Willing and able to comply with all aspects of the protocol

Exclusion Criteria

1. Current moderate or greater symptoms of congestive cardiac failure (New York Heart Association [NYHA] class III or IV)
2. Known left ventricular (LV) ejection fraction <20%
3. Current moderate or greater symptoms of pulmonary hypertension (PH) **(**World Health Organization [WHO] functional Class III and IV)
4. Known severe valvular disease defined by clinical diagnosis and/or most recent echocardiography. History of severe valvular disease is allowed if it has been corrected by valve replacement or repair. (revised per Amendment 01)
5. Severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m^2 per the CKD-EPI equation based on ideal body weight), or end-stage renal disease (ESRD) (revised per Amendment 01)
6. Severe hepatic impairment (Child-Pugh score 10 to 15)
7. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs,

and herbal preparations within 1 month prior to Screening

8. Use of more than 1 serotonergic drug within 1 month before Screening or during the screening window, including, but not limited to: (revised per Amendment 01)
    a. selective serotonin reuptake inhibitors (SSRIs)
    b. serotonin norepinephrine reuptake inhibitors (SNRIs)
    c. tricyclic antidepressants (TCAs)
    d. bupropion
    e. triptans
    f. St. John's Wort and tryptophan
    g. Monoamine oxidase inhibitors [MAOIs]
    h. linezolid
    i. dextromethorphan
    j. lithium
    k. tramadol
    l. antipsychotics or other dopamine antagonists
9. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months prior to Screening including, but not limited to: pergolide, ergotamine, methysergide, or cabergoline (revised per Amendment 01)
10. History or evidence of clinically significant disease (eg, malignancy, cardiac, respiratory, gastrointestinal, renal, or psychiatric disease) that in the opinion of the investigator(s) could affect the subject's safety, interfere with the study assessments, or result in a life expectancy of less than 1 year
11. Use of lorcaserin HCl within 6 months prior to Screening or hypersensitivity to lorcaserin HCl or any of the excipients
12. History of alcohol dependence or abuse within 2 years prior to Visit 1 (Screening)
13. Recreational drug use within the 2 years prior to Visit 1 (Screening)
14. Currently enrolled in another clinical trial or used any investigational drug or device within 30 days preceding informed consent (the exclusion criterion will not apply if the subjects are no longer in follow-up and have discontinued use of an investigational drug or device for at least 30 days. It will not apply if subjects are enrolled in registries or observational studies). (revised per Amendment 01)
15. Planned bariatric surgery or bariatric surgery performed within 1 year before screening (revised per Amendment 01)
16. Subjects considered by the investigator to have insufficient motivation to remain in a long-term clinical trial or who are considered likely to drop out for nonmedical reasons, (eg, social issues)
17. Females must not be breastfeeding or pregnant at Visit 1 (Screening) or Visit 2 (Baseline) (as documented by a negative beta-human chorionic gonadotropin [β-hCG]). A separate Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.
18. All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy or bilateral oophorectomy, all with surgery at least 1 month before dosing). Females of childbearing potential are defined as those who: (revised per Amendment 01)
    - Had unprotected sexual intercourse within 30 days before study entry
    - Do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine

device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation.

- Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation.
- Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation.

Study Treatment

Test drug

Lorcaserin HCl will be provided as blue, round, film-coated biconvex tablets, one 10-mg tablet to be administered orally, BID

Comparator Drug

Lorcaserin HCl-matching placebo, 1 tablet to be administered orally, BID

Duration of Study Phases and Treatment

Prerandomization Phase: approximately 30 days

Randomization Phase:

- Treatment Period: approximately 5 years
- Follow-up Period: 30 days +10 days after last dose of study drug for subjects who complete study treatment (revised per Amendment 02)

Concomitant Drug/Therapy

The following are prohibited as concomitant medications:

- Other products intended for weight loss including prescription drugs, OTC drugs, and herbal preparations are prohibited as concomitant medications. Any drug that has a risk for serotonin syndrome in its label, or that has been associated with a risk of serotonin syndrome including OTC drugs, should be used only when clearly indicated and within approved dose ranges and durations, as specified in the appropriate labeling. More than 1 additional serotonergic agent is prohibited in combination with lorcaserin HCl (eg, an SSRI, antipsychotic, and lorcaserin). (revised per Amendment 01)

  Serotonergic drugs include, but are not limited to: (revised per Amendment 01)

  a. selective serotonin reuptake inhibitors (SSRIs)
  b. serotonin norepinephrine reuptake inhibitors (SNRIs)
  c. tricyclic antidepressants (TCAs)
  d. bupropion
  e. triptans
  f. St. John's Wort and tryptophan
  g. Monoamine oxidase inhibitors [MAOIs]
  h. Linezolid
  i. dextromethorphan
  j. lithium
  k. tramadol
  l. antipsychotics or other dopamine antagonists
- If a second nonstudy serotonergic agent is required by the subject during the study, temporarily discontinue study drug and, if possible, wait 3 days after study drug has been discontinued before starting the second serotonergic agent.

- If the subject discontinues treatment with the 2nd, nonstudy serotonergic agent, lorcaserin HCl may be restarted when the 2nd serotonergic agent has been discontinued for at least 15 days, with the following exceptions, which must be discontinued for longer periods of time before restarting study drug.
    - -30 days: fluoxetine, phenelzine, and isocarboxazid;
    - -90 days: the injectable formulation of fluphenazine, haloperidone, paliperidone, and zuclopenthixol.
- If a subject requires treatment with an agent that has a documented correlation with increased incidence of cardiac valvulopathy and/or PH (eg, pergolide, ergotamine, methysergide, or cabergoline), lorcaserin HCl should be stopped. (revised per Amendment 01) If the subject discontinues treatment with the other agent, lorcaserin HCl may be restarted as long as the other agent has been discontinued for at least 1 month. (revised per Amendment 01)

The following concomitant medication guidelines/restrictions will apply:

- Medications for the treatment of hypertension, dyslipidemia, or diabetes may be started, discontinued, or adjusted during the study according to local standards of care if, in the judgment of the investigator or the subject's physician, such a change is medically indicated.

Assessments

Safety/Efficacy Assessments (revised per Amendment 02)

Potential MACE will be recorded throughout the study and assessed by the CEC for the primary safety endpoint.

Blood samples for measurement of HbA_{1c} and FPG will be collected at Screening, Baseline, and specified timepoints throughout the study. HbA_{1c}, FPG, and when available, additional components of the ADA diagnostic criteria will be assessed. All potential cases of conversion to diabetes will undergo central review of relevant supporting data. (revised per Amendment 01)

Potential MACE+ events will be recorded throughout the study and assessed by the CEC for a primary efficacy endpoint.

Pharmacokinetic Assessments
Not applicable

Pharmacodynamic Assessments
The following will be measured for assessment of CV risk factors:

1. Body weight, BMI, waist and hip circumference
2. SBP, DBP, heart rate (HR)
3. Triglycerides, total cholesterol, HDL-C, LDL-C
4. FPG, fasting insulin

The following parameters related to renal function will be assessed:

- Urinary ACR:
    - ACR will be measured in spot urine
    - The following are the definitions of newly developed, worsening, and regression of albuminuria which need to be documented in 2 consecutive scheduled or non-scheduled assessments at least 30 days apart:
        - Newly developed albuminuria, defined as first evidence of microalbuminuria (ACR ≥30 μg/mg in spot urine) **or** macroalbuminuria (ACR ≥300 μg/mg), and ACR value increases ≥30% from

previous assessment during treatment

- Worsening albuminuria, defined as when subjects with microalbuminuria at Baseline develop macroalbuminuria, and ACR value increases ≥30% from previous assessment during treatment
- Regression of albuminuria, defined as when subjects with macroalbuminuria at Baseline develop microalbuminuria or non-albuminuria, or subjects with microalbuminuria at Baseline become non-albuminuric, and ACR value decreases ≥30% from previous assessment during treatment

- Estimated glomerular filtration rate (eGFR):
  - eGFR will be calculated by the CKD-EPI equation based on creatinine measurement in the total population and/or cystatin C measurement in a selected population. The full criteria for determining whether creatinine, cystatin C, or an algorithm incorporating both will be used to estimate GFR will be detailed in the statistical analysis plan (SAP).
  - Definitions for newly developed, worsening, and regression of chronic kidney disease (CKD) in the absence of acute, transient, kidney injury
    - Newly developed CKD, defined as when a subject with 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, defined as when a subject with 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
    - 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, 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
- Serum creatinine:
  - Doubling of serum creatinine concentration, defined as when a subject's creatinine value is at least 2 times the Baseline value and ≥1.5mg/dL during treatment
- Serum cystatin C:
  - Serum cystatin C will be measured to estimate eGFR in the population of subjects who are in CKD Stage 1 or 2 at Baseline. CKD Stage 1 or 2 is defined as albuminuria and eGFR >60 mL/min per 1.73 BSA.

Additional diabetes-related microvascular complications will be assessed by monitoring AEs associated with retinopathy and neuropathy. (revised per Amendment 01)

The following parameters related to non-alcoholic fatty liver disease (NAFLD) will be measured: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma glutamyl transpeptidase (GGT), total and direct bilirubin.

Obesity-related complications that are not assessed by any of the objective measures listed in this protocol may be evaluated using data from AE reporting, changes in concomitant medications, or reports of changes in medical history. (revised per Amendment 01)

Biomarker Assessments

The following inflammatory biomarkers will be assessed to further define the CV risk study population and to investigate potential correlation with changes in CV risk factors, MACE, and MACE+, as well as weight loss and susceptibility to diabetes:

- hsCRP will be measured at the time of Screening and will be followed up yearly through EOT.
- Fibrinogen will be measured at the time of randomization and will be followed up yearly through EOT.
- Other biomarkers related to obesity, diabetes, CV disease, and associated risk factors may be evaluated in serum and plasma samples in selected countries, where applicable.

Pharmacogenomic Assessments

A blood sample for potential investigation of genetic variability associated with genotypes relating to response to lorcaserin HCl, weight loss, susceptibility to diabetes, and CV and other end-organ disease and their associated risk factors will be taken at the time of randomization in the study, where applicable.

Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; laboratory evaluation for hematology, blood chemistry, and urinalysis; periodic measurement of vital signs and electrocardiograms (ECGs); and the performance of physical examinations.

In addition, echocardiography will be performed in a subset of subjects at predefined visits. Valvular regurgitation as assessed in the echocardiogram substudy will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; the rating will be absent or present for the pulmonic valve. (revised per Amendment 01) The evaluations will be based on guidelines from the American Society of Echocardiography. Pulmonary artery pressure will be estimated from the tricuspid regurgitant jet velocity.

Other Assessments

None

Bioanalytical Methods

Not applicable

Statistical Methods

Study Endpoints

Primary Endpoints

- Time from randomization to first occurrence of MACE (first occurrence of any of the following events: MI, stroke, or CV death)
- 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) (revised per Amendment 02)

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 in subjects with prediabetes at Baseline. The diagnostic criteria are met if a subject has unequivocal hyperglycemia (random plasma glucose ≥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} ≥6.5%
    - FPG≥126 mg/dL (7.0 mmol/L)
    - 2-hour plasma glucose ≥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)

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} ≤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)
- Time from randomization to conversion to T2DM in subjects without any type of diabetes at Baseline (revised per Amendment 01)
- Change from Baseline in HbA_{1c} 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)
- 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 prediabetes at Baseline (revised per Amendments 01 and 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 subjects with T2DM at Baseline (revised per Amendment 02)
- 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

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

- Proportion of subjects without Food and Drug Administration (FDA)-defined valvulopathy at Baseline who develop FDA-defined valvulopathy at 1 year
- Proportion of subjects with FDA-defined valvulopathy confirmed by documented objective assessments at Baseline who demonstrate worsened FDA-defined valvulopathy at 1 year (revised per Amendment 01)
- Change from Baseline in estimated pulmonary artery systolic pressure at 1 year

Exploratory Endpoints:

- Change from Baseline in CV risk factors at 1 year and yearly thereafter (eg, body weight, dyslipidemia, insulin level, hypertension, and applicable biomarkers of CV risk and other end-organ diseases)
- Change from Baseline in eGFR and ACR at 1 year, yearly thereafter, and at the end of the study
- 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 $HbA_{1c,}$ 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 (HbA_{1c} >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 (HbA_{1c} >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)

Analysis Sets

The Safety Analysis Set will be the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.

The Intent-to-Treat set (ITT) will be the group of all randomized subjects regardless of whether they took study drug or not.

- Total Time Analysis Set: Using the ITT, events are counted that occur while subjects are on and off treatment. Subjects with no events who discontinue early or complete the study will be censored at their last study contact (see details in the SAP). This will be used for the primary analysis.

- 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 day plus 30 days.

- 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 day.

- 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. Definition of prediabetes will be found in the SAP. (revised per Amendment 01)

- Nondiabetes Analysis Set: This set includes all subjects in the ITT set without a history of any type of diabetes at Baseline. Definition of nondiabetes will be found in the SAP. (revised per Amendment 01)

T2DM Analysis Set: This set will be all subjects in the ITT who have T2DM at Baseline.

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

The Pharmacodynamic (PD) Analysis Set will be the group of subjects who have both baseline and at least 1 postbaseline assessment of at least 1 PD parameter.

Primary Safety and Efficacy and Key Secondary Analyses (revised per Amendment 02)

The primary endpoints, MACE, and MACE+, 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). (revised per Amendment 02) For secondary and exploratory endpoints a 2-sided $\alpha = 0.05$ significance level will be used. The MACE analysis ("interim" analysis) will be conducted when

460 adjudicated MACE events have been recorded; the other analyses will be conducted when 1401 adjudicated MACE+ events have been recorded, and the study has completed. (revised per Amendment 02)

Sequential Gatekeeping Testing Procedure

The following closed sequential gatekeeping testing procedure (SGTP) will be used to control the family-wise error rate (FWER) at $\alpha = 0.05$ (2-sided) in testing the 2 primary endpoints (MACE and MACE+) and 1 key secondary endpoint, conversion to T2DM. (revised per Amendment 02)

Let H_{01} be the gatekeeping null hypothesis for noninferiority testing of the MACE endpoint using a noninferiority margin of 1.4.

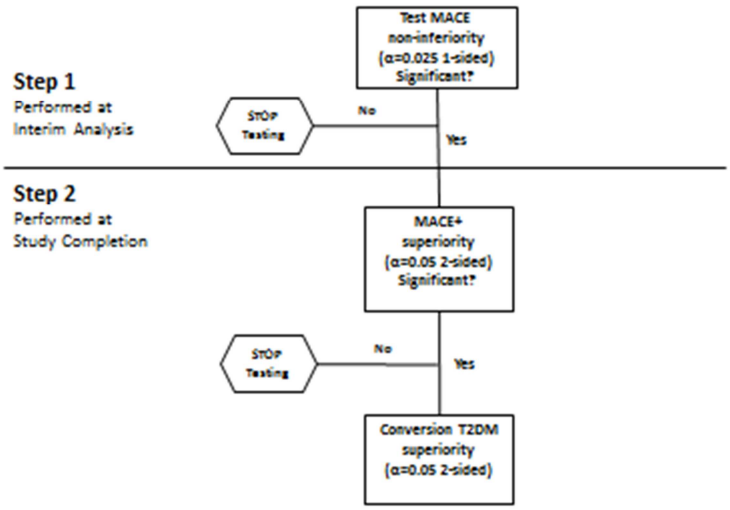
Let H_{02} and H_{03} be the null hypotheses for superiority testing: MACE+ and conversion to T2DM, respectively. (revised per Amendment 02)

The SGTP testing hierarchy is presented below. (revised per Amendment 02)

- STEP1: At the interim analysis, test the noninferiority hypothesis for MACE, H_{01} ($\alpha = 0.025$, 1-sided). If H_{01} is rejected, then proceed to STEP2, otherwise stop testing and the trial will be stopped.
- STEP2: At study completion the hypothesis H_{02} ($\alpha = 0.05$, 2-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.

The flowchart below presents the SGTP:

Flowchart for the Sequential Gatekeeping Testing Procedure



Primary Endpoint Analyses

- **Time to MACE:** The estimate of the hazard ratio of lorcaserin HCl to placebo and the corresponding 1-sided 97.5% confidence interval (CI) will be calculated. Noninferiority of lorcaserin HCl to placebo will be declared if the upper limit of the 97.5% CI is less than the noninferiority margin of 1.4. The Total Time Analysis Set will be used as the primary analysis at 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 sensitivity analyses at study completion. (revised per Amendment 02)

- **Time to MACE+:** The estimate of the hazard ratio of lorcaserin HCl to placebo and the corresponding 2-sided 95% CI will be calculated. The Total Time Analysis Set will be used as the primary analysis. (revised per Amendment 02) The On-Treatment Analysis and the On-Treatment plus 30 Days Analysis Set will be used as sensitivity analyses.

The incidence rate difference and the incidence rate ratio between lorcaserin HCl and placebo will also be analyzed as supportive analysis for the primary endpoints above, at study completion. (revised per Amendment 02)

Sensitivity analyses will be performed at study completion for the MACE and MACE+ endpoints using the Total Time Analysis Set. (revised per Amendment 02) This sensitivity analysis will not count a MACE or MACE+ event that occurs after the subject starts another weight reduction medication or undergoes bariatric surgery. (revised per Amendment 02)

Key Secondary Endpoint Analysis (revised per Amendment 02)

- **Time to conversion to T2DM:** The estimate of the hazard ratio of lorcaserin HCl to placebo and the corresponding 2-sided 95% CI will be calculated. The Prediabetes and Total Time Analyses Sets will be used as the primary for this 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)

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.

  - 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 ≤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)

- 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 at 1 year 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. The ITT will be used for this analysis. (revised per Amendment 01)

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 and stratification variable (presence of established CV disease or CV risk factors without established CV disease) as factors. Comparison between lorcaserin HCl and placebo will be made at 1 year. The ITT will be used for this analysis.
- For subjects with NAFLD at Baseline, the change from Baseline in LFTs (AST, ALT, alkaline phosphatase, GGT, total and direct bilirubin) will be analyzed using a mixed-effects model with repeated measures with treatment and stratification variable (presence of established CV disease or CV risk factors without established CV disease) as factors. Comparison between lorcaserin HCl and placebo will be made at 1 year. The ITT will be used for this analysis.
- 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 2 years and yearly thereafter. 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 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 ITT will be used for this analysis.
- 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 2 years and yearly thereafter. The ITT will be used for this analysis.
- Change from Baseline in HbA_{1c}, FPG, fasting insulin levels, and 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 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, in the following subpopulations. (revised per Amendments 01 and 02)

- Subjects with (HbA_{1c}>7%) at Baseline
- Subjects who have not been treated with antidiabetic agents at Baseline
- Subjects who are on monotherapy with oral antidiabetic agents 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 T2DM Analysis Set will be used for this analysis, in the following subpopulations: (revised per Amendment 01)
  - Subjects with (HbA_{1c} >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 Safety Analysis Set will be used for this analysis. (revised per Amendment 01)

Logistic regression including treatment as factor will be used for the following endpoints. Comparison between lorcaserin HCl and placebo will be made at EOS. (revised per Amendment 01)

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

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

Pharmacokinetic Analyses
Not applicable

Pharmacodynamic Analyses
A PD analysis plan may be defined and reported separately.

Biomarker Analyses
A biomarker analysis plan may be defined and reported separately.

Pharmacogenomic Analyses
A pharmacogenomic analysis plan may be defined and reported separately.

Safety Analyses

Evaluations of safety 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, suicidality and vital sign measurements will be summarized yearly by treatment group using descriptive statistics.

The incidence of AEs of interest will be summarized separately. In addition, for each AE of interest, Kaplan-Meier curves and median time and 95%CI will be presented. The Safety Analysis Set will be used for this analysis.

Other Analyses

- Not applicable

Interim Analysis

There will be 1 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. The study will continue to accrue events until the required number of MACE+ have occurred. (revised per Amendment 02) Sensitivity analysis for MACE endpoint will be performed after all the MACE+ events have accrued. (revised per Amendment 02) At the time of MACE+ analyses, there will be approximately 600 MACE events.

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) Jul 2017. (revised per Amendment 02) The interim analysis will be conducted 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 (as outlined in the Study Integrity Charter), 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. (revised per Amendment 02)

At the interim analysis for MACE, the estimate of the hazard ratio of lorcaserin HCl to placebo and the corresponding 97.5% CI will be calculated. Noninferiority between lorcaserin HCl and placebo will be declared if the upper limit of the 97.5% CI is less than or equal to the noninferiority margin of 1.4. If the upper limit of the 97.5% CI is greater than 1.4, then lorcaserin HCl will be declared as not noninferior to placebo and the trial will stop.

If noninferiority 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 MACE+ events at approximately 54 months from the start of the study, and a minimum median treatment duration of 2.5 years have accrued. (revised per Amendment 02) The events for MACE+ and T2DM will be tested according to the SGTP described previously, upon study completion. (revised per Amendment 02)

Sample Size Rationale

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 study, 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 study, 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.

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4 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

(revised per Amendments 01 and 02)

Abbreviation	Term
AACE	American Association of Clinical Endocrinologists
ACE	American College of Endocrinology
ACR	albumin-to-creatinine ratio
ADA	American Diabetes Association
AE	adverse event
ALT	alanine aminotransferase
AST	aspartate aminotransferase
BID	twice daily
BMI	body mass index
BNP	B-type natriuretic peptide
BP	blood pressure
BSA	body surface area
CA	Competent Authority
CAD	coronary artery disease
CEC	Clinical Endpoint Committee
CFR	Code of Federal Regulations
CI	confidence interval
CKD	chronic kidney disease
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CRA	clinical research associate
CRF	case report form
CRO	contract research organization
CV	cardiovascular
CVD	cardiovascular disease
CVOT	cardiovascular outcomes trial
DEA	Drug Enforcement Administration
DMC	Data Monitoring Committee
DPP	Diabetes Prevention Program
eGFR	estimated glomerular filtration rate
ECG	electrocardiogram
EER	Estimated Energy Requirement
EOS	end of study
EOT	end of treatment
ESRD	end-stage renal disease
EU	European Union

Abbreviation	Term
FDA	Food and Drug Administration
FPG	fasting plasma glucose
FWER	family-wise error rate
GCP	Good Clinical Practice
GGT	gamma glutamyl transpeptidase
HbA_{1c}	glycosylated hemoglobin
HDL-C	high density lipoprotein-cholesterol
HF	heart failure
HR	heart rate
hsCRP	high sensitivity C-reactive protein
ICF	informed consent form
ICH	International Conference on Harmonisation
IEC	Independent Ethics Committee
IL	interleukin
IND	Investigational New Drug
IRB	Institutional Review Board
ITT	Intent-to-Treat
IxRS	interactive voice and/or web response system
LDL-C	low density lipoprotein-cholesterol
LFTs	liver function tests
LNH	low/normal/high
LV	left ventricular
MACE	major adverse cardiovascular events
MACE+	MACE or hospitalization for unstable angina or heart failure, or any coronary revascularization
MAOI	monoamine oxidase inhibitor
MedDRA	Medical Dictionary for Regulatory Activities
MI	myocardial infarction
MRI	magnetic resonance imaging
SGTP	sequential gatekeeping testing procedure
NAFLD	Non-Alcoholic Fatty Liver Disease
NKF	National Kidney Foundation
OGTT	oral glucose tolerance test
OTC	over-the-counter
PD	pharmacodynamic
PGx	pharmacogenomics
PH	pulmonary hypertension
PI	principal investigator
PK	pharmacokinetic

Abbreviation	Term
PT	preferred term
QTc	corrected QT interval
RBC	red blood cell
SAE	serious adverse event
SAP	statistical analysis plan
SNRI	serotonin norepinephrine reuptake inhibitor
SOC	system organ class
SOP	standard operating procedure
SSRI	selective serotonin reuptake inhibitor
SUSAR	Suspected, Unexpected, Serious Adverse Reaction
T2DM	type 2 diabetes mellitus
TCA	tricyclic antidepressant
TEAE	treatment-emergent adverse event
TEMAV	treatment-emergent markedly abnormal laboratory values
TIMI	Thrombolysis in Myocardial Infarction
TNF-α	tumor necrosis factor-alpha
ULN	upper limit of normal
US	United States
WBC	white blood cell
WHO DD	World Health Organization Drug Dictionary

5 ETHICS

5.1 INSTITUTIONAL REVIEW BOARDS/INDEPENDENT ETHICS COMMITTEES

The protocol, informed consent form (ICF), and appropriate related documents must be reviewed and approved by an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) constituted and functioning in accordance with International Conference on Harmonisation (ICH) E6 (Good Clinical Practice [GCP]), Section 3, and any local regulations. Any protocol amendment or revision to the ICF will be resubmitted to the IRB/IEC for review and approval, except for changes involving only logistical or administrative aspects of the study (eg, change in clinical research associates [CRAs], change of telephone numbers). Documentation of IRB/IEC compliance with the ICH E6 and any local regulations regarding constitution and review conduct will be provided to the sponsor.

A signed letter of study approval from the IRB/IEC must be sent to the Principal Investigator (PI) (or if regionally required, the head of the medical institution) with a copy to the sponsor before study start and the release of any study drug to the site by the sponsor or its designee (ICH E6, Section 4.4). If the IRB/IEC decides to suspend or terminate the study, the investigator (or if regionally required, the head of the medical institution) will immediately send the notice of study suspension or termination by the IRB/IEC to the sponsor.

Study progress is to be reported to IRB/IECs annually (or as required) by the investigator or sponsor, depending on local regulatory obligations. If the investigator is required to report to the IRB/IEC, he/she will forward a copy to the sponsor at the time of each periodic report. The investigator(s) or the sponsor will submit, depending on local regulations, periodic reports and inform the IRB/IEC (or if regionally required, the investigator and the relevant IRB via the head of the medical institution) of any reportable adverse events (AEs) per ICH guidelines and local IRB/IEC standards of practice. Upon completion of the study, the investigator will provide the IRB/IEC with a brief report of the outcome of the study, if required.

At the end of the study, the sponsor should notify the IRB/IEC and Competent Authority (CA) within 90 days. The end of the study will be the date of database lock. The sponsor should also provide the IRB/IEC with a summary of the study's outcome.

In the case of early termination/temporary halt of the study, the investigator should notify the IRB/IEC and CA within 15 calendar days, and a detailed written explanation of the reasons for the termination/halt should be given.

5.2 ETHICAL CONDUCT OF THE STUDY

This study will be conducted in accordance with standard operating procedures (SOPs) of the sponsor (or designee), which are designed to ensure adherence to GCP guidelines as required by the following:

- Principles of the World Medical Association Declaration of Helsinki 2008
- ICH E6 Guideline for GCP (CPMP/ICH/135/95) of the European Agency for the Evaluation of Medicinal Products, Committee for Proprietary Medicinal Products, International Conference on Harmonisation of Pharmaceuticals for Human Use
- Title 21 of the United States (US) Code of Federal Regulations (US 21 CFR) regarding clinical studies, including Part 50 and Part 56 concerning informed subject consent and IRB regulations and applicable sections of US 21 CFR Part 312
- A waiver from the IRBs/IECs will be obtained before study initiation for non-US studies conducted under an Investigational New Drug (IND) application.
- European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC for studies conducted within any European Union (EU) country. All Suspected, Unexpected, Serious Adverse Reactions (SUSARs) will be reported, as required, to the Competent Authorities of all involved EU member states, if applicable.
- Other applicable regulatory authorities' requirements or directives

This study will be conducted in accordance with national and local laws (eg, Drug and Narcotics laws of the countries where study sites are located).

5.3 SUBJECT INFORMATION AND INFORMED CONSENT

As part of administering the informed consent document, the investigator must explain to each subject the nature of the study, its purpose, the procedures involved, the expected duration, the potential risks and benefits involved, any potential discomfort, potential alternative procedures or courses of treatment available to the subject, and the extent of maintaining confidentiality of the subject's records. (revised per Amendment 01) Each subject must be informed that participation in the study is voluntary, that he/she may withdraw from the study at any time, and that withdrawal of consent will not affect his/her subsequent medical treatment or relationship with the treating physician.

This informed consent should be given by means of a standard written statement, written in nontechnical language. The subject should understand the statement before signing and dating it and will be given a copy of the signed document. If a subject is unable to read, an impartial witness should be present during the entire informed consent discussion. (revised per Amendment 01) After the ICF and any other written information to be provided to subjects is read and explained to the subject, and after the subject has orally consented to participate in the study and, if capable of doing so, has signed and personally dated the ICF, the witness should sign and personally date the consent form. (revised per Amendment 01) The subject will be asked to sign an ICF before any study-specific procedures are performed. No subject can enter the study before his/her informed consent has been obtained.

An unsigned copy of an IRB/IEC-approved ICF must be prepared in accordance with ICH E6, Section 4, and all applicable local regulations. Each subject must sign an approved ICF before study participation, including an option to have other biomarkers collected for future research. The form must be signed and dated by the appropriate parties. The original, signed ICF for each subject will be verified by the sponsor and kept on file according to local procedures at the site. Subjects will be asked to sign a separate ICF for the collection of pharmacogenomic samples.

6 INVESTIGATORS AND STUDY PERSONNEL

This study will be conducted by qualified investigators under the sponsorship of Eisai (the sponsor) at approximately 500 multinational investigational sites. (revised per Amendment 01)

The name and telephone and fax numbers of the medical monitor and other contact personnel at the sponsor and of the contract research organizations (CROs) will be listed in the Investigator Study File provided to each site. (revised per Amendment 01)

7 INTRODUCTION

Obesity has reached global epidemic proportions as the prevalence has nearly doubled from 20 years ago. According to the World Health Organization (WHO), more than 1 billion adults worldwide are overweight, and at least 300 million are obese.[1] In the US, more than one-third of adults (35.7%) and almost 17% of children and adolescents are obese.[2] Obesity is a major risk factor for life threatening diseases such as type 2 diabetes mellitus (T2DM), heart attack, stroke, and some forms of cancer. For example, the age-adjusted relative risk of developing T2DM is approximately 10-fold higher for men with a body mass index (BMI) of 30 kg/m^2 relative to men with a BMI <23 kg/m^2 and the risk is even higher for women, where a BMI of 30 kg/m^2 is associated with an approximately 30-fold higher risk.[3,4] Obesity is a major cause of morbidity and mortality, and it is estimated that there are 300,000 obesity-related deaths annually in the US alone.[5]

It is well established that modest weight reductions of 5% to 10% of body weight can decrease blood pressure (BP) and total blood cholesterol, improve glucose tolerance in diabetic patients and those with impaired glucose tolerance prone to develop diabetes, and reduce the severity of obstructive sleep apnea. Given the rise in the prevalence of obesity, even modest weight loss can be important to the overall health.

Current approaches to weight management include life style modification, pharmacotherapy and invasive bariatric procedures. Lifestyle modification involving a combination of diet, exercise, and behavioral change is the preferred and essential strategy for weight management in obese and overweight individuals. Although behavior modification can be very efficacious in some patients, adherence to the prescribed regimens is often poor. As such, lifestyle modification alone is often not adequate and the weight loss is often transient. On the other hand, bariatric surgery and various other invasive procedures are generally reserved for the severely obese population.

Pharmacotherapy can play a significant role in weight management programs and is often combined with behavioral changes to enhance weight loss beyond that which is normally achieved with diet and exercise alone. Current pharmacotherapies offer the potential to significantly augment weight loss when combined with diet and exercise. The beneficial effects of many available agents are in part offset by side effects that can include increased BP (agents with sympathomimetic activity) or unpleasant gastrointestinal events (orlistat).

Over the past 2 decades there have been numerous attempts to develop safe and effective drugs for weight management. However, most have failed to gain approval or have been withdrawn from the market due to serious safety concerns. Furthermore, no agent has demonstrated long-term cardiovascular (CV) benefit.

APD356/BELVIQ® (lorcaserin hydrochloride) is a selective serotonin 2c receptor agonist which was approved by the US Food and Drug Administration (FDA) on 27 June 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adult patients with a BMI greater than or equal to 30 kg/m^2 (obese), or adult patients with a BMI

greater than or equal to 27 kg/m^2 (overweight) in the presence of at least 1 weight-related comorbid condition.

The Phase 3 clinical evaluation of lorcaserin HCl in clinical trials of more than 7700 patients, including 604 patients with T2DM, demonstrated clinically meaningful efficacy and a safety profile that includes minimal and easily managed risks. In each of the individual studies and in the pooled efficacy analyses, the lorcaserin HCl 10 mg twice daily (BID) dose met prespecified primary endpoints for weight loss:

- A significantly greater proportion of patients taking lorcaserin HCl lost ≥5% of baseline body weight at 1 year as compared to placebo
- The mean weight loss at 1 year in patients taking lorcaserin HCl was significantly greater than that in patients taking placebo
- A significantly greater proportion of patients taking lorcaserin HCl lost ≥10% of baseline body weight at 1 year as compared to placebo
- The weight loss efficacy was supported in each trial by favorable trends in multiple other measures of CV risk, glycemic control and quality of life.
- Glycosylated hemoglobin (HbA_{1c}) was statistically significantly reduced by 0.5% among patients with T2DM compared to placebo.

Based on the results of the Phase 3 data, BELVIQ (lorcaserin HCl) has a favorable benefit-risk profile as a pharmacological agent for weight management in obese and overweight patients.

The overall efficacy and safety profile of BELVIQ (lorcaserin HCl) makes it an ideal pharmacological agent for weight management, potentially leading to a long term CV benefit.

7.1 STUDY RATIONALE

The sample size and duration of this cardiovascular outcomes trial (CVOT) allows us to design the study not only to meet FDA's requirements but, in addition, to evaluate additional indications. In the previously pooled Phase 3 dataset from Studies APD356-009 and APD356-011 (the 2 nondiabetic studies, total n=7190), BELVIQ (lorcaserin HCl) significantly improved BMI, waist circumference, serum lipid profiles, BP, glycemic parameters, and other markers of CV risk (high sensitivity C-reactive protein [hsCRP], fibrinogen). These findings suggest that rather than there being a risk of an increase in CV events, it is possible that through improvement in risk parameters, BELVIQ (lorcaserin HCl) may have a favorable impact on CV risk, and therefore a reduction in major adverse cardiovascular events (MACE)+ is included in the study as a coprimary endpoint.

By selecting a large diabetes subpopulation within a population of otherwise high CV risk subjects, this study will be able to evaluate the safety of BELVIQ (lorcaserin HCl) in patients with type 2 diabetes and additional CV risk, contributing to satisfying the requirement of establishing CV safety for a potential future diabetes indication.

In a historic clinical trial, Diabetes Prevention Program (DPP)[6], a 5% weight loss translated to a significant decrease in the incidence of new diabetes. In the pooled Phase 3 dataset from studies APD356-009 and APD356-011 (the 2 nondiabetic studies, total n=7190), weight loss was significantly greater than 5% in the BELVIQ-treated group. In the prediabetes subpopulation (25% of the total combined population) of the aforementioned studies, BELVIQ (lorcaserin HCl) statistically significantly decreased the incidence of newly developed T2DM (HbA_{1c} ≥6.5). In addition, the 2 studies demonstrated that BELVIQ (lorcaserin HCl) improves fasting glucose, HbA_{1c}, and insulin resistance in these insulin-resistant nondiabetic populations. In the current proposed study, there is a significant prediabetic obese population (approximately 25% to 35% of the total population), which allows confirmation of the Phase 3 trial findings. (revised per Amendment 01) In addition, the large sample size and long follow-up duration in this subpopulation provides the opportunity to demonstrate BELVIQ (lorcaserin HCl) not only can delay conversion to T2DM, but also delay the progression of renal impairment due to diabetes, which will confirm that the effect is indeed due to glycemic benefit, not due to improvement of other risk factors.

In the APD356-010 trial (n=508), BELVIQ (lorcaserin HCl) significant improved glycemic control across all BMI categories on top of standard diabetes treatment. The proposed substudy in T2DM subjects at Baseline treated with oral anti-diabetics (OADs) allow confirmation of the Phase 3 trial finding that BELVIQ (lorcaserin HCl) improves glycemic control in this diabetic subpopulation. The large sample size (the diabetes population at Baseline is about 50% of the total population) allows further demonstration of the independent effect of glycemic benefit from other improvement in weight reduction-related risk factors.

8 STUDY OBJECTIVES

8.1 PRIMARY OBJECTIVES

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 noninferiority 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

8.2 SECONDARY OBJECTIVES

Key Secondary Objective

- To confirm that, in subjects with prediabetes at Baseline based on the 2013 ADA guideline, lorcaserin HCl 10 mg BID reduces the incidence of conversion to 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 (revised per Amendment 01)
- 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 Amendment 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

8.3 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, prediabetes, 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: (revised per Amendments 01 and 02)
    - 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 treated with mono oral antidiabetic agent at Baseline
    - Subjects with early T2DM (duration of diagnosis of diabetes is less than 5 years) at Baseline.

9 INVESTIGATIONAL PLAN

9.1 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 (revised per Amendment 02)

	CV Disease	**CV Disease Risk Factors**	**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 have accrued. 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). 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 least 1000 subjects have completed the Month 36 echocardiographic assessment. (revised per Amendment 02)

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. 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 9.7.3). 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. (revised per Amendment 02). 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.

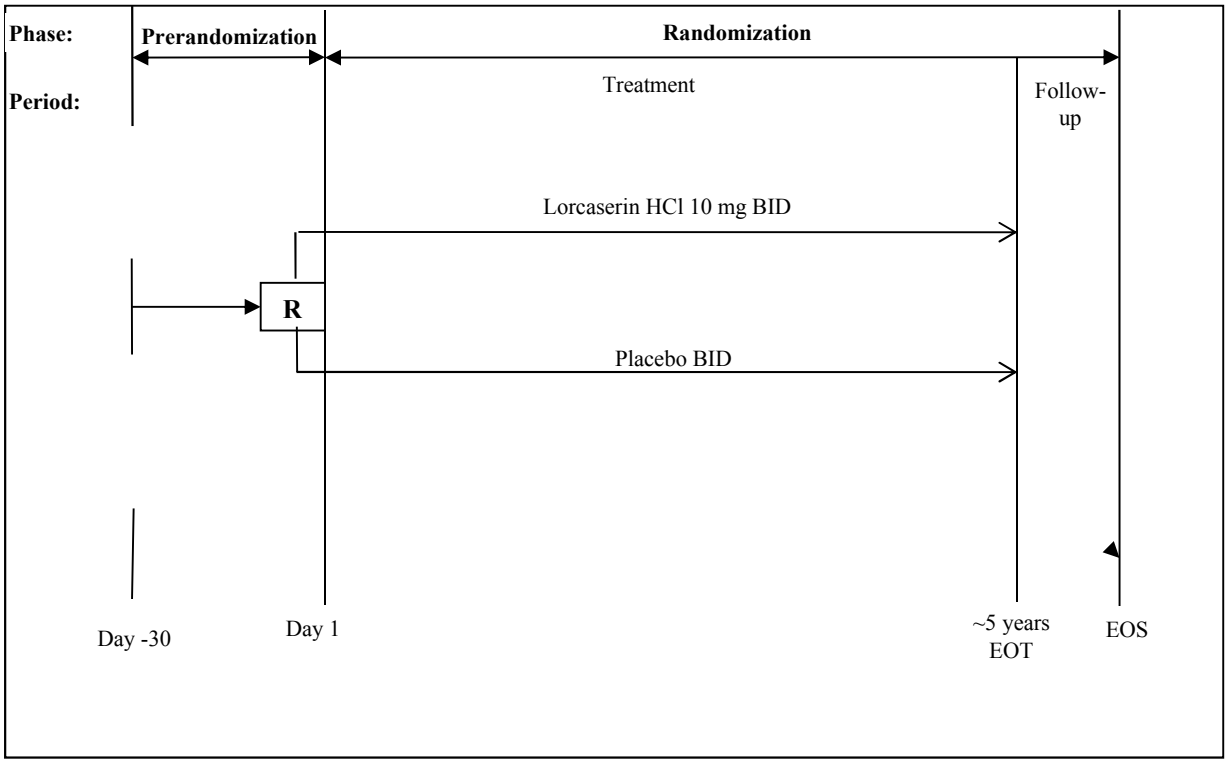


Figure 1 Study Design Schematic

BID = twice daily; EOS = end of study; EOT = end of treatment; R = randomization.

9.1.1 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.

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.

9.1.2 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.

9.1.2.1 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.

9.1.2.2 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 for procedures for subjects who prematurely discontinue study drug.

9.2 DISCUSSION OF STUDY DESIGN

Randomization will be used in this study to avoid bias in the assignment of subjects to treatment, to increase the likelihood that known and unknown subject attributes (eg, demographics and baseline characteristics) are balanced across treatment groups, and to ensure the validity of statistical comparisons across treatment groups. Blinding to treatment will be used to reduce potential bias during data collection and evaluation of endpoints. A placebo control is considered appropriate because study drug treatment will be adjunctive to all standard-of-care therapies for background CV risk factors.

The population selected for the study targets high CV risk obese patients in order to demonstrate that BELVIQ (lorcaserin HCl) does not cause an increase in MACE events and may even reduce MACE+ events within the study period. There is significant linkage between obesity and diabetes and most T2DM subjects are obese. T2DM with CV risk factors confers greater CV risk. Inclusion of 50% of subjects with diabetes with additional CV risk factors in the total study population will ensure that the population is representative of patients with more advanced diabetes, and may also help to establish the CV safety profile for BELVIQ (lorcaserin HCl) if a diabetes indication is pursued in the future. In addition, the sample size of this population allows the evaluation of BELVIQ's short term effects on glycemic control.

The sample size of nondiabetic subjects (50% of the total study population) allows further confirmation of BELVIQ's benefit in delaying conversion from nondiabetes to diabetes and further explores BELVIQ's benefit in delaying diabetes progression in the long follow-up study duration. In addition, it may also help to establish the clinical significance of reduction of conversion to diabetes by the assessment of T2DM-specific induced renal impairment and its progression.

9.3 SELECTION OF STUDY POPULATION

Approximately 18,000 subjects will be screened to provide 12,000 randomized subjects at approximately 500 sites in regions that include North America, South America, Europe, and the Asia-Pacific. (revised per Amendment 01)

9.3.1 Inclusion Criteria

1. BMI ≥27 kg/m^2
2. Subjects able and willing to comply with a reduced-calorie diet and an increased physical activity program
3. Age ≥40 years with established CV disease as defined by 1 of the following:

    a. History of documented MI or ischemic stroke >1 month before Randomization (revised per Amendment 01)

    b. History of peripheral artery disease as manifested by symptomatic claudication with an ankle-brachial pressure index of <0.85

    c. History of revascularization (coronary, carotid, or peripheral artery)

    d. Significant unrevascularized coronary arterial stenosis defined as ≥50% in 2 or more coronary arteries

OR

Age ≥55 years for women or ≥50 years for men who have T2DM without established CV disease plus at least 1 of the following CV risk factors:

a. Hypertension, defined as systolic blood pressure (SBP) >140 or diastolic blood pressure (DBP) >90, or currently receiving therapy for documented hypertension
b. Dyslipidemia, defined as low density lipoprotein-cholesterol (LDL-C) >130 mg/dL, or high density lipoprotein-cholesterol (HDL-C) <40 mg/dL[7] or currently taking prescription lipid-lowering therapy for documented dyslipidemia
c. Estimated glomerular filtration rate (eGFR) ≥30 to ≤60 mL/min/1.73 m^2 per the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation[8] (revised per Amendment 01)
d. hsCRP >3 mg/L[9] detected by the central laboratory in the absence of known acute or chronic inflammatory conditions (eg, infection, rheumatologic disease) (revised per Amendment 01)
e. Urinary albumin-to-creatinine ratio (ACR) ≥30 µg/mg in spot urine

Subjects with T2DM may have a pre-existing or new diagnosis of T2DM. Subjects with pre-existing T2DM should have prior documentation consistent with the diagnosis and/or be on active pharmacotherapy for T2DM. A new diagnosis of T2DM (ie, discovered at Screening) should be based on the 2013 American Diabetes Association (ADA) guidelines. The diagnostic criteria are met if a subject has unequivocal hyperglycemia (random plasma glucose ≥200 mg/dL (11.1 mmol/L) with classic symptoms of hyperglycemia or hyperglycemic crisis) OR any of the following criteria are observed and then confirmed: (revised per Amendments 01 and 02)

- HbA_{1c} ≥6.5%
- fasting plasma glucose (FPG) ≥126 mg/dL (7.0 mmol/L)
- 2-hour plasma glucose ≥200 mg/dL (11.1mmol/L) by an oral glucose tolerance test (OGTT)

All T2DM subjects must have an HbA_{1c} <10% at Screening. If subjects are being treated, or upon diagnosis need to be treated with antidiabetic agents, the T2DM treatment regimen must be stable for at least 3 months prior to randomization. A single rescreen is allowed following stabilization. Stable control refers to minimal dose changes to existing medications for glycemic control and no medications being initiated for glycemic control in the 3 months before Randomization. (revised per amendment 01) Minimal changes are defined as a change in insulin dose <10% of daily dose, without any change in dose frequency, no add-on or discontinuation of other antidiabetic agents, and the subject has not been hospitalized due to hypo- or hyperglycemic events. (revised per Amendment 01)

4. Provide written informed consent
5. Willing and able to comply with all aspects of the protocol

9.3.2 Exclusion Criteria

1. Current moderate or greater symptoms of congestive cardiac failure (New York Heart Association [NYHA] class III or IV)
2. Known left ventricular (LV) ejection fraction <20%
3. Current moderate or greater symptoms of pulmonary hypertension (PH) **(**WHO functional Class III and IV)[10] (see Appendix 1)
4. Known severe valvular disease defined by clinical diagnosis and/or most recent echocardiography. History of severe valvular disease is allowed if it has been corrected by valve replacement or repair. (revised per Amendment 01)
5. Severe renal impairment (estimated glomerular filtration rate <30 mL/min/1.73 m2 per the CKD-EPI equation based on ideal body weight), or end-stage renal disease (ESRD) (revised per Amendment 01)
6. Severe hepatic impairment (Child-Pugh score 10 to 15)
7. Use of other products intended for weight loss including prescription drugs, over-the-counter (OTC) drugs, and herbal preparations within 1 month prior to Screening

8. Use of more than 1 serotonergic drug within 1 month before Screening, or during the screening window, including but not limited to: (revised per Amendment 01)
    a. selective serotonin reuptake inhibitors (SSRIs)
    b. serotonin norepinephrine reuptake inhibitors (SNRIs)
    c. tricyclic antidepressants (TCAs)
    d. bupropion
    e. triptans
    f. St. John's Wort and tryptophan
    g. Monoamine oxidase inhibitors (MAOIs)
    h. linezolid
    i. dextromethorphan
    j. lithium
    k. tramadol
    l. antipsychotics or other dopamine antagonists
9. Use of drugs known to increase the risk for cardiac valvulopathy within 6 months prior to Screening including, but not limited to: pergolide, ergotamine, methysergide, or cabergoline (revised per Amendment 01)
10. History or evidence of clinically significant disease (eg, malignancy, cardiac, respiratory, gastrointestinal, renal or psychiatric disease) that in the opinion of the investigator(s) could affect the subject's safety, interfere with the study assessments, or result in a life expectancy of less than 1 year
11. Use of lorcaserin HCl within 6 months prior to Screening or hypersensitivity to lorcaserin HCl or any of the excipients
12. History of alcohol dependence or abuse within 2 years prior to Visit 1 (Screening)
13. Recreational drug use within the 2 years prior to Visit 1 (Screening)
14. Currently enrolled in another clinical trial or used any investigational drug or device within 30 days preceding informed consent (the exclusion criterion will not apply if the subjects are no longer in follow-up and have discontinued use of an investigational drug or device for at least 30 days. It will not apply if subjects are enrolled in registries or observational studies.) (revised per Amendment 01)
15. Planned bariatric surgery or bariatric surgery performed within 1 year before screening (revised per Amendment 01)
16. Subjects considered by the investigator to have insufficient motivation to remain in a long-term clinical trial or who are considered likely to drop out for nonmedical reasons (eg, social issues)
17. Females must not be breastfeeding or pregnant at Visit 1 (Screening) or Visit 2 (Baseline) (as documented by a negative beta-human chorionic gonadotropin [ß-hCG]). A separate

Baseline assessment is required if a negative screening pregnancy test was obtained more than 72 hours before the first dose of study drug.

18. All females will be considered to be of childbearing potential unless they are postmenopausal (amenorrheic for at least 12 consecutive months, in the appropriate age group and without other known or suspected cause) or have been sterilized surgically (ie, bilateral tubal ligation, total hysterectomy or bilateral oophorectomy, all with surgery at least 1 month before dosing). Females of childbearing potential are defined as those who: (revised per Amendment 01)
    - Had unprotected sexual intercourse within 30 days before study entry
    - Do not agree to use a highly effective method of contraception (eg, total abstinence, an intrauterine device, a double-barrier method [such as condom plus diaphragm with spermicide], a contraceptive implant, an oral contraceptive, or have a vasectomized partner with confirmed azoospermia) throughout the entire study period and for 28 days after study drug discontinuation.
    - Are currently abstinent, and do not agree to use a double-barrier method (as described above) or refrain from sexual activity during the study period and for 28 days after study drug discontinuation.
    - Are using hormonal contraceptives but are not on a stable dose of the same hormonal contraceptive product for at least 4 weeks before dosing and who do not agree to use the same contraceptive during the study and for 28 days after study drug discontinuation.

9.3.3 Removal of Subjects From Therapy or Assessment

Refer to Section 9.5.5 (Completion/Discontinuation of Subjects).

9.4 TREATMENTS

9.4.1 Treatments Administered

The following treatments will be administered to subjects in this study (Table 2). Study drug will be dispensed at each study visit starting at the Randomization Visit (Visit 2, at which time the first dose should be taken; see Table 4). (revised per Amendment 01)

Table 2 Treatments Administered

Drug Name	Strength	Oral Dose Form	Number Dispensed and Frequency	Duration
lorcaserin HCl	10 mg	Tablet	1 × 10 mg tablet, BID, orally	≈ 5 years
Placebo (to match lorcaserin HCl 10 mg)	N/A	lorcaserin HCl-matched tablet	1 tablet, BID, orally	≈ 5 years

BID = twice daily, N/A = not applicable.

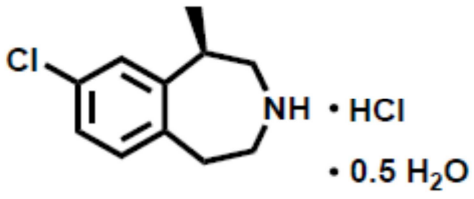
9.4.2 Identity of Investigational Product

BELVIQ (lorcaserin hydrochloride) is a (US) Drug Enforcement Administration (DEA) Scheduled IV Drug Product (C – IV).

Test drug and placebo will be supplied by the sponsor in labeled containers. The sponsor will provide the study drugs packaged in a double-blind configuration. Lorcaserin HCl tablets will be supplied as blue, round, film-coated, biconvex tablets containing 10 mg of drug substance and excipients (silicified microcrystalline cellulose, hydroxypropyl cellulose, croscarmellose sodium, magnesium stearate, Opadry II blue). Identical matching tablets will be provided for placebo.

9.4.2.1 Chemical Name, Structural Formula of BELVIQ

- Test drug code: APD356
- Generic name: lorcaserin hydrochloride
- Chemical name: (R)-8-chloro-1-methyl-2,3,4,5-tetrahydro-1H-3-benzazepine hydrochloride hemihydrate
- Molecular formula: $C_{11}H_{15}Cl_2N \cdot 0.5H_2O$
- Molecular weight: 241.16 g/mol
- Structural formula:



9.4.2.2 Comparator Drug

Placebo matched to lorcaserin HCl 10-mg tablets will be the comparator drug in the study.

9.4.2.3 Labeling for Study Drug

Lorcaserin HCl will be labeled in accordance with text that is in full regulatory compliance with each participating country and will be translated into the required language(s) for each of those countries.

The clinical study labels will contain, but are not limited to:

1. Name, address and telephone number of the Sponsor
2. Pharmaceutical dosage form, route of administration, quantity of dosage units, identifier, and potency
3. Lot number

4. Protocol number
5. Directions of use (if applicable)
6. Storage conditions
7. Storage restrictions (if applicable)
8. Expiration date (if applicable, and not required for US)
9. The appropriate controlled drug symbol (where required per local regulation)
10. CAUTION: Federal law prohibits the transfer of this drug to any person other than the patient for whom it was prescribed (US sites)

All packaging and labeling will be performed according to Good Manufacturing Practice (GMP) and GCP guidelines. A separate manual, detailing clinical supplies responsibilities, including the dispensing procedure, will be signed between an approved contract packaging and labeling vendor and the Sponsor.

Study drug must be stored as instructed on the study drug label and in accordance with the DEA Regulations for Scheduled III - V Drugs (US sites). All relevant site-specific guidelines and country-specific labeling requirements must be followed. Study drug must be kept in a secure location and carefully stored at the study site within its original container.

The investigator (or pharmacist, as appropriate) must maintain records of the delivery of the study drug to the study site, the inventory at the site, use for each subject, and return of the study drug to a delegate of the Sponsor. Total study site accountability will be conducted at the end of the study and the investigator must explain all discrepancies.

A Drug Dispensing Log must be kept current and should contain the following information:

- Identification (subject ID number and initials) of subject to whom the study drug was dispensed
- The dates and lot numbers for dispensed study drug
- Initial inventory on receipt of drug at the site
- Final inventory on completion of the study

All records and inventory must be available for inspection by the clinical study monitor.

9.4.2.4 Storage Conditions

Where applicable, investigational product will be stored in accordance with the DEA Regulations for Scheduled III-V Drugs and labeled storage conditions. Temperature monitoring is required at the storage location to ensure that the study drug is maintained within an established temperature range. The investigator or designee (or if regionally required, the head

of the medical institution) is responsible for ensuring that the temperature is monitored throughout the total duration of the study and that records are maintained.

9.4.3 Method of Assigning Subjects to Treatment Groups

Subjects will be assigned to treatments based on a computer-generated randomization scheme that will be reviewed and approved by an independent statistician. The randomization scheme and identification for each subject will be included in the final clinical study report for this study.

After the Prerandomization Phase, subjects will be randomized to 1 of 2 treatment groups in a ratio of 1:1, stratified by the presence of established CV disease (roughly 80%) or CV risk factors without established CV disease (approximately 20%). Each treatment group will receive either lorcaserin HCl or placebo BID. Randomization will be performed centrally by an interactive voice and/or web response system (IxRS). The IxRS or clinical supply vendor will generate the randomized identification numbers to be included on study packaging. Upon signature of the ICF, the investigator or designee will access the IxRS to register the subject information. At Randomization (Visit 2), the IxRS will assign each subject a unique randomization number. At each subsequent visit during the Treatment Period and Follow-up Period, the investigator or designee will access IxRS to obtain dispensing information and to register the subject's visit.

9.4.4 Selection of Doses in the Study

The dose selected for this study is 10 mg BID, which is the FDA-approved dose for BELVIQ (lorcaserin HCl).

9.4.5 Timing of Dose for Each Subject

Subjects should take the study medication twice daily at least 6 hours apart (revised per Amendment 01) and be encouraged to take the study medication with an adequate amount of water (8 oz or 240 mL).

9.4.5.1 Dose Reduction, Interruption, and Restarting of Study Drug (revised per Amendment 01)

Dose Reduction to 10 mg QD

- Subjects who experience intolerable nonserious AEs believed to be related to study drug, in the opinion of the investigator, may be dosed at 10 mg QD.
- Subjects should take 1 tablet (lorcaserin 10 mg or placebo) QD for up to 7 days.
- After 7 days of 10 mg QD dose, subjects will resume to twice daily dosing. Subjects should be encouraged to remain on 10 mg BID for 7 days following QD dosing before dose reduction may be considered again.
- The temporary reduced dosing option may be implemented for the subject up to 3 times.
- Subjects who have attempted the temporary 10 mg QD dose reduction and escalation to the standard 10 mg BID dose regimen 3 times and confirmed that they can tolerate the 10 mg QD dose but cannot tolerate the 10 mg BID dose are allowed to stay on prolonged

10 mg QD dose regimen for the remainder of their participation in the study. Please contact the Thrombolysis in Myocardial Infarction (TIMI) Hotline before initiation of prolonged once daily dosing.

- Subjects on prolonged 10 mg QD dose regimen may resume 10 mg BID at any time if it is safe to do so in investigators' opinion. Subjects who had previously discontinued study drug due to a nonserious AE considered to be related to study drug can also be re-initiated on study drug starting with a temporary 10 mg QD dose regimen. Subjects are encouraged to try 10 mg BID, but if that cannot be tolerated, then the prolonged 10 mg QD dose regimen can be considered.
- Utilization of dose reduction will be recorded in the applicable subject's chart for source documentation purposes and captured in the eCRF.

Dose Interruption for Renal and Hepatic Abnormalities

Severe Renal Dysfunction (revised per Amendment 01)

- If eGFR <30 mL/min/1.73 m^2, continue study drug but repeat eGFR within 1 week.
- If eGFR still <30 mL/min/1.73 m^2 on repeat measurement, temporarily discontinue study drug.

- Follow-up after study drug discontinuation due to severe renal dysfunction:
  - Recheck eGFR per clinical practice
  - Consider re-initiation of study drug with resolution of reversible cause of acute kidney injury and when eGFR ≥30ml/min/1.73 m^2 on at least 2 consecutive measurements spaced at least 1 week apart.

Significant Hepatic Abnormalities

- Temporarily discontinue study drug if there is any evidence for hepatic dysfunction defined as either:
  - Clinical evidence for severe acute hepatitis associated with either ALT elevation >5x upper limit of normal (ULN) or total bilirubin level >3xULN.
  - Known chronic hepatic disease with an increase in the Child-Pugh Score to ≥10. http://www.mdcalc.com/child-pugh-score-for-cirrhosis-mortality/
- Confirm the new or worsening hepatic dysfunction with repeat liver function tests (LFTs) and determine its cause. Repeat LFTs weekly until the clinical picture resolves and laboratory values are stable for at least 2 weeks, or until it is determined that the hepatic dysfunction is chronic.

Consider re-initiation of study drug with resolution of a reversible cause of liver injury and improvement of lab abnormalities to values below thresholds listed above.

Restarting of Study Drug

Study drug should be restarted at the standard BID dosing unless study drug was discontinued due to an AE considered related to the study drug. Those individuals can be started on QD dosing as per the instructions above. Subjects discontinued from study drug due to a serious or severe AE considered to be related to study drug by the investigator should not be restarted on study drug. Prior to restarting study drug for subjects who have been discontinued, consideration should be given as to whether the subject has developed any conditions (eg, change in medical status, use of concomitant medications, lack of contraception) exclusionary to taking study drug. (see Section 9.4.7.2 for specific instructions concerning restart of study drug for individuals requiring a second nonstudy drug serotonergic agent).

9.4.6 Blinding

During the Randomization Phase, subjects and all personnel involved with the conduct and interpretation of the study, including investigators, site personnel, and sponsor staff will be blinded to the treatment codes. Randomization data will be kept strictly confidential, filed securely by an appropriate group with the sponsor or CRO and accessible only to authorized persons (eg, Eisai Global Safety) until the time of unblinding, per SOP.

A master list of all treatments and the subject numbers associated with them will be maintained in a sealed envelope by the clinical supply vendor, the IxRS vendor, and the sponsor. In the event that emergency conditions require knowledge of the study treatment given, the blind may be broken via the code breaker facility within the IxRS. Emergency procedures for revealing drug codes are given in Section 9.5.4.6. If possible, before breaking the blind, the investigator should consult with the sponsor or designee to ascertain the necessity of breaking the code.

An interim analysis will be conducted during the trial when 460 adjudicated MACE events have been reported. 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 (as outlined in the Study Integrity Charter), 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. (revised per Amendment 02)

9.4.7 Prior and Concomitant Therapy

Any medication (including OTC medications) or therapy administered to the subject during the study (starting at the date of informed consent), any medications for T2DM, CV risk factors, or

established CV disease taken by the subject during the 90 days before first dose/administration of study drug, and any other medications taken by the subject during the 30 days before first dose/administration of study drug will be recorded on the Prior and Concomitant Medication CRF or Non-Pharmacological Procedures CRF. Exact doses of these medications and duration of treatment prior to the study must be recorded, as well as any changes in dosing during the study. The investigator will record on the Adverse Event CRF any AE for which the concomitant medication/therapy was administered. If the concomitant medication/therapy is being administered for a medical condition present at the time of entry into the study, the investigator will record the medical condition on the Medical History and Current Medical Condition CRF.

Any antidiabetic agents taken by diabetic subjects prior to randomization must be stabilized for 3 months with minimal changes. Minimal changes are defined as no change in insulin dose >10% of daily dose, no change in dose frequency, no add-on or reduction of anti-diabetic agents, and the subject has not been hospitalized due to hypo-, or hyperglycemic events.

See Section 9.4.7.2 for specific restrictions on the use of concomitant therapies.

9.4.7.1 Drug-Drug Interactions

Not applicable

9.4.7.2 Prohibited Concomitant Therapies and Drugs

- The following are prohibited as concomitant medications: Other products intended for weight loss including prescription drugs, OTC drugs, and herbal preparations are prohibited as concomitant medications. Any drug that has a risk for serotonin syndrome in its label, or that has been associated with a risk of serotonin syndrome including OTC drugs, should be used only when clearly indicated and within approved dose ranges and durations, as specified in the appropriate labeling. More than 1 additional serotonergic agent is prohibited in combination with lorcaserin HCl (eg an SSRI, antipsychotic and lorcaserin). (revised per Amendment 01)

  Serotonergic drugs include, but are not limited to: (revised per Amendment 01)

  a. selective serotonin reuptake inhibitors (SSRIs)
  b. serotonin norepinephrine reuptake inhibitors (SNRIs)
  c. tricyclic antidepressants (TCAs)
  d. bupropion
  e. triptans
  f. St. John's Wort and tryptophan
  g. Monoamine oxidase inhibitors [MAOIs]
  h. linezolid
  i. dextromethorphan

j. lithium
k. tramadol
l. antipsychotics or other dopamine antagonists

- If a second nonstudy serotonergic agent is required by the subject during the study, temporarily discontinue study drug and, if possible, wait 3 days after study drug has been discontinued before starting the second serotonergic agent.
- If the subject discontinues treatment with the 2nd nonstudy serotonergic agent, lorcaserin HCl may be restarted when the 2nd serotonergic agent has been discontinued for at least 15 days, with the following exceptions, which must be discontinued for longer periods of time before restarting study drug.
    - -30 days: fluoxetine, phenelzine, and isocarboxazid;
    - -90 days: the injectable formulation of fluphenazine, haloperidone, paliperidone, and zuclopenthixol.
    - If a subject requires treatment with an agent that has a documented correlation with increased incidence of cardiac valvulopathy and/or PH (eg, pergolide, ergotamine, methysergide, or cabergoline) lorcaserin HCl should be stopped. (revised per Amendment 01) If the subject discontinues treatment with the other agent, lorcaserin HCl may be restarted as long as the other agent has been discontinued for at least 1 month. (revised per Amendment 01)

The following concomitant medication guidelines/restrictions will apply:

- Medications for the treatment of hypertension, dyslipidemia, or diabetes may be started, discontinued, or adjusted during the study according to local standards of care if, in the judgment of the investigator or the subject's physician, such a change is medically indicated.
- For diabetic subjects treated with sulfonylureas, insulin, or other antidiabetic agents with hypoglycemic risk, the risk of hypoglycemic events may be higher if the subjects experience rapid and significant weight loss (more than 10% weight reduction than at the previous visit). It is recommended that the physician advise the subject to monitor their blood glucose more frequently and adjust their antidiabetic medications and diet accordingly.
- The antihyperglycemic medication dose would be considered for reduction in the event of 1 documented and otherwise unexplained hypoglycemic event (blood glucose concentration <65 mg/dL) or 2 undocumented and otherwise unexplained suspected hypoglycemic events between any 2 scheduled visits. (revised per Amendment 01) For subjects on more than 1 antihyperglycemic medication, it is recommended to reduce insulin first (if applicable), then the oral and/or other injectable antidiabetic agents. If the previous criteria are met again following dose reduction, further dose reductions or

cessation of 1 or more anti-hyperglycemic agents, are suggested. See Section 9.5.4.2 for the definition and reporting of hypoglycemic events.

- To minimize the risk of cardiac valve toxicity:
  - Subjects must not initiate use of agents that have documented correlation with increased incidence of valvulopathy and/or PH (eg, pergolide, ergotamine, methysergide, or cabergoline) during the study. (revised per Amendment 01) If any of the above agents are clinically warranted, and subjects initiate any of these agents, lorcaserin HCl should be discontinued but can be restarted on lorcaserin HCl after being off the medications above for 1 month. Otherwise, the study medication should not be restarted, but the subject should continue all study visits.
- Use of serotonergic drugs:
  - The US Prescribing Information for BELVIQ (lorcaserin HCl) allows for concomitant use of serotonergic drugs with extreme caution, noting that if concomitant administration of lorcaserin HCl with an agent that affects the serotonergic neurotransmitter system is clinically warranted, extreme caution and careful observation of the patient is advised, particularly during treatment initiation and dose increases.

For the purposes of this clinical study, any drug that has a risk for serotonin syndrome in its label, or that has been associated with a risk of serotonin syndrome in the medical literature, including OTC drugs, should be used only when clearly indicated and within approved dose ranges and durations as specified in the appropriate labeling. More than 1 additional serotonergic agent is prohibited in combination with lorcaserin HCl. See Section 9.4.8 for instructions related to study drug discontinuation and restart if a subject requires treatment with a second nonstudy drug serotonergic agent. (revised per Amendment 01)

9.4.8 Treatment Compliance

Records of treatment compliance for each subject will be kept during the study. CRAs will review treatment compliance during site visits and at the completion of the study.

9.4.9 Drug Supplies and Accountability

In compliance with local regulatory requirements, drug supplies will not be sent to the investigator until the following documentation has been received by the sponsor:

- A signed and dated confidentiality agreement
- A copy of the final protocol signature page, signed and dated by both the sponsor and investigator
- Written proof of approval of the protocol, the ICFs, and any other information provided to the subjects by the IRB/IEC for the institution where the study is to be conducted
- A copy of the IRB/IEC-approved ICF and any other documentation provided to the subjects to be used in this study

- The IRB/IEC membership list and statutes or Health and Human Services Assurance number
- A copy of the certification and a table of the normal laboratory ranges for the reference laboratory conducting the clinical laboratory tests required by this protocol
- An investigator-signed and dated FDA Form 1572 or equivalent
- Financial Disclosure form(s) for the PI and all subinvestigators listed on Form FDA 1572 or equivalent
- A signed and dated curriculum vitae of the PI including a copy of the PI's current medical license or medical registration number on the curriculum vitae
- A signed and dated clinical trials agreement
- Where required, a copy of the regulatory authority approval for the country in which the study is being conducted, and the Import License
- A Controlled Substance Registration Certificate, form DEA-223 (US sites only) (revised per Amendment 01)

The investigator and the study staff will be responsible for the accountability of all study drugs (dispensing, inventory, and record keeping) following the sponsor's instructions and adherence to GCP guidelines as well as local or regional requirements.

Under no circumstances will the investigator allow the study drugs to be used other than as directed by this protocol. Study drugs will not be dispensed to any individual who is not enrolled in the study.

The site must maintain an accurate and timely record of the following: receipt of all study drugs, dispensing of study drugs to the subject, collection and reconciliation of unused study drugs that are either returned by the subjects or shipped to site but not dispensed to subjects, and return of reconciled study drugs to the sponsor or (where applicable) destruction of reconciled study drugs at the site. This includes, but may not be limited to: (a) documentation of receipt of study drugs, (b) study drugs dispensing/return reconciliation log, (c) study drugs accountability log, (d) all shipping service receipts, (e) documentation of returns to the sponsor, and (f) certificates of destruction for any destruction of study drugs/study supplies that occurs at the site. All forms will be provided by the sponsor. Any comparable forms that the site wishes to use must be approved by the sponsor.

The study drugs and inventory records must be made available, upon request, for inspection by a designated representative of the sponsor or a representative of a health authority (eg, FDA, Medicines and Healthcare Products Regulatory Agency [MHRA]). As applicable, all unused study drugs and empty and partially empty containers from used study drugs are to be returned to the investigator by the subject and together with unused study drugs that were shipped to the site but not dispensed to subjects are to be returned to the sponsor's designated central or local depots during the study or at the conclusion of the study, unless provision is made by the sponsor for

destruction of study drugs and containers at the site. Destruction at the site will only occur under circumstances where regulation or supply type prohibits the return of study drugs to the central or local depots. Approval for destruction to occur at the site must be provided by the sponsor in advance. Upon completion of drug accountability and reconciliation procedures by the site's personnel and documentation procedures by the sponsor's personnel, study drugs that are to be returned to the sponsor's designated central or local depots must be boxed and sealed and shipped back to the central or local depots following all local regulatory requirements. In some regions, study drugs may be removed from the site and hand delivered to the central or local depot by sponsor representatives. Where study drugs are approved for destruction at the site, destruction will occur following the site's standard procedures and certificates of destruction will be provided to the sponsor.

Drug accountability will be reviewed during site visits and at the completion of the study.

9.5 STUDY ASSESSMENTS

9.5.1 Assessments

9.5.1.1 Demography

Subject demography information will be collected at the Screening Visit. Demography information includes date of birth (or age), sex, and race/ethnicity.

9.5.1.2 Baseline Assessments

MEDICAL, CARDIOVASCULAR, AND DIABETES HISTORY

Pertinent medical and surgical history and current medical conditions will be recorded at the Screening Visit. All pertinent medical and surgical history must be noted in the Medical History and Current Medical Conditions CRF.

Specifically, CV and diabetes history must be recorded at Screening. For subjects with T2DM at Screening, duration of disease and treatment history since becoming diabetic must be recorded (see Section 9.4.7).

URINE DRUG SCREENING

A urine sample will be collected for testing for common drugs of use/abuse: (eg, cocaine, cannabinoids, phencyclidine, nicotine/cotinine, opioids [as a group], benzodiazepines, barbiturates, and amphetamines). Nicotine use (ie, cotinine positive on urine screen) is not exclusionary. In the absence of prescription use without concern for abuse, positive testing for other common drugs of use/abuse is exclusionary on the basis of Exclusion Criterion No. 12 (Section 9.3.2) and should result in screen failure. (revised per Amendment 01)

9.5.1.3 Primary Safety/Efficacy Assessments

MACE/MACE+ EVENTS

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 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 (ie, where there is evidence to suggest a causal relationship). (revised per Amendment 01)

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.

In order to reduce intra- and intersite variability, the CEC will centrally review each potential MACE and MACE+ 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 MACE or MACE+. The CEC will remain blinded to treatment allocation and its activities and the criteria for classification of MACE/MACE+ events will be documented in the CEC Charter.

CONVERSION TO DIABETES

HbA_{1c} and FPG will be measured in blood samples collected at Screening, Baseline, and specified timepoints throughout the study.

HbA_{1c}, FPG and when available, additional components of the ADA diagnostic criteria will be assessed. All potential cases of conversion to diabetes will undergo central review of relevant supporting data. (revised per Amendment 01)

9.5.1.4 Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic/Pharmacogenetic Assessments

PHARMACOKINETIC ASSESSMENTS

Not applicable

PHARMACODYNAMIC ASSESSMENTS

The following will be measured for assessment of CV risk factors:

1. SBP, DBP, heart rate (HR)
2. Triglycerides, total cholesterol, HDL-C, LDL-C
3. FPG, fasting insulin

The following parameters related to renal function will be assessed.

- Urinary ACR

- ACR will be measured in spot urine.
- The following are the definitions of newly developed, worsening, and regression of albuminuria which need to be documented in 2 consecutive scheduled or nonscheduled assessments at least 30 days apart:
  - Newly developed albuminuria, defined as first evidence of microalbuminuria (ACR ≥30 μg/mg in spot urine) **or** macroalbuminuria (ACR ≥300 μg/mg),[11] and ACR value increases ≥30% from previous assessment during treatment
  - Worsening albuminuria, defined as when subjects with microalbuminuria at Baseline develop macroalbuminuria, and ACR value increases ≥30% from previous assessment during treatment
  - Regression of albuminuria, defined as when subjects with macroalbuminuria at Baseline develop microalbuminuria or non-albuminuria, or subjects with microalbuminuria at Baseline become non-albuminuric, and ACR value decreases ≥30% from previous assessment during treatment

- Estimated glomerular filtration rate (eGFR):
  - eGFR will be calculated by the CKD-EPI equation based on creatinine measurement in the total population and/or cystatin C measurement in a selected population. The full criteria for determining whether creatinine, cystatin C, or an algorithm incorporating both will be used to estimate GFR will be detailed in the statistical analysis plan (SAP).
  - Definitions for newly developed, worsening, and regression of chronic kidney disease (CKD)[12] (see Appendix 2) in the absence of acute, transient, kidney injury
    - Newly developed CKD, defined as when a subject with 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, defined as when a subject with 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
    - 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, 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
- Serum creatinine:
  - Doubling of serum creatinine concentration, defined as when a subject's creatinine value is at least 2 times the Baseline value and ≥1.5mg/dL during treatment
- Serum cystatin C:
  - Serum cystatin C will be measured to estimate eGFR in the population of subjects who are in CKD Stage 1 or 2 at Baseline. CKD Stage 1 or 2 is defined as albuminuria and eGFR >60 mL/min per 1.73 BSA

Additional diabetes-related microvascular complications will be assessed by monitoring AEs associated with retinopathy and neuropathy . (revised per Amendment 01)

The following parameters related to NAFLD will be measured: aspartate aminotransferase (AST), alanine aminotransferase (ALT), alkaline phosphatase, gamma glutamyl transpeptidase (GGT), total and direct bilirubin

Obesity-related complications that are not assessed by any of the objective measures listed in this protocol may be evaluated using data from AE reporting, changes in concomitant medications, or reports of changes in medical history. (revised per Amendment 01)

BIOMARKER ASSESSMENTS

The following inflammatory biomarkers will be assessed to further define the CV risk study population and to investigate potential correlation with changes in CV risk factors, MACE, and MACE+, as well as weight loss and susceptibility to diabetes:

- hsCRP will be measured at the time of Screening and will be followed up yearly through EOT.
- Fibrinogen will be measured at the time of randomization and will be followed up yearly through EOT.
- For subjects who provide consent, other biomarkers related to obesity, diabetes, CV disease, and associated risk factors will be evaluated in serum and plasma samples in selected countries, where applicable (see Appendix 5).

PHARMACOGENOMIC ASSESSMENTS

A blood sample for potential investigation of genetic variability associated with genotypes relating to response to lorcaserin HCl, weight loss, susceptibility to diabetes, and CV and other end-organ disease and their associated risk factors will be taken at the time of randomization in the study, where applicable. DNA samples may be used to examine the role of genetic variability in subject's absorption, distribution, metabolism, and excretion, or the development of AEs (see Appendix 6).

Variation in lorcaserin HCl exposure or AEs may be evaluated by correlation of single-nucleotide polymorphisms with pharmacokinetic (PK), safety or pharmacodynamic (PD) data.

A pharmacogenomics plan will be provided separately.

Subjects who decline to give informed consent for pharmacogenomic/genetic analysis can participate in the study.

9.5.1.5 Safety Assessments

Safety assessments will consist of monitoring and recording all AEs and SAEs; regular monitoring of hematology, blood chemistry, and urinalysis; periodic measurement of vital signs and electrocardiograms (ECGs); and performance of physical examinations. Additional safety assessments specific to this study will include echocardiography.

AEs and Events Associated with Special Situations
(revised per Amendment 01)

An adverse event (AE) is any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product. An AE does not necessarily have a causal relationship with the medicinal product. For this study, the study drug is lorcaserin HCl.

The criteria for identifying AEs are:

- Any unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of an investigational product, whether or not considered related to the investigational product
- Any new disease or exacerbation of an existing disease
- Any deterioration in nonprotocol-required measurements of a laboratory value or other clinical test (eg, ECG or x-ray) that results in symptoms, a change in treatment, or discontinuation of study drug
- Recurrence of an intermittent medical condition (eg, headache) not present pretreatment (Baseline)
- An abnormal laboratory test result should be considered an AE if the identified laboratory abnormality leads to any type of intervention, whether prescribed in the protocol or not.

A laboratory result should be considered by the investigator to be an AE if it:

- Results in the withdrawal of study drug
- Results in withholding of study drug pending some investigational outcome
- Results in an intervention, based on medical evaluation (eg, potassium supplement for hypokalemia)
- Results in any out-of-range laboratory value (Sponsor's Grading for Laboratory Value provided as reference in Appendix 3) that in the investigator's judgment fulfills the definitions of an AE with regard to the subject's medical profile (revised per Amendment 01)

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. –(revised per Amendment 01)

MACE and MACE+ events and other study-specific AEs of interest will be followed until EOS. (revised per Amendment 01)

Abnormal laboratory values should not be listed as separate AEs if they are considered to be part of the clinical syndrome that is being reported as an AE. Any laboratory abnormality considered to constitute an AE should be reported on the Adverse Event CRF.

It is the responsibility of the investigator to review all laboratory findings in all subjects and determine if they constitute an AE. Medical and scientific judgment should be exercised in deciding whether an isolated laboratory abnormality should be classified as an AE.

(revised per Amendment 01)

All AEs must be followed for at least 30 days after Sponsor Notification of Study Completion, or until resolution, whichever comes first. (revised per Amendment 01)

Every effort must be made by the investigator to categorize each AE according to its severity and its relationship to the study treatment.

ASSESSING SEVERITY OF AEs

AEs will be graded on a 3-point scale (mild, moderate, severe) and reported in the detail indicated on the CRF. The definitions are as follows:

Mild	Discomfort noticed, but no disruption of normal daily activity
Moderate	Discomfort sufficient to reduce or affect normal daily activity
Severe	Incapacitating, with inability to work or to perform normal daily activity

The criteria for assessing severity are different than those used for seriousness (see SAEs and Other Events of Interest, Section 9.5.1.5 for the definition of an SAE).

ASSESSING RELATIONSHIP TO STUDY TREATMENT

Items to be considered when assessing the relationship of an AE to the study treatment are:

- Temporal relationship of the onset of the event to the initiation of the study treatment
- The course of the event, especially the effect of discontinuation of study treatment or reintroduction of study treatment, as applicable
- Whether the event is known to be associated with the study treatment or with other similar treatments
- The presence of risk factors in the study subject known to increase the occurrence of the event
- The presence of nonstudy, treatment-related factors that are known to be associated with the occurrence of the event

CLASSIFICATION OF CAUSALITY

Causality will be based on the response to the following question:

Was there a reasonable possibility that the drug caused the adverse event? Yes/No

Where Yes = related and No = Not related

SAEs AND EVENTS ASSOCIATED WITH SPECIAL SITUATIONS

(revised per Amendment 01)

A serious adverse event (SAE) is any untoward medical occurrence that at any dose:

- Results in death
- Is life-threatening (ie, the subject was at immediate risk of death from the AE as it occurred; this does not include an event that, had it occurred in a more severe form or was allowed to continue, might have caused death)
- Requires inpatient hospitalization or prolongation of existing hospitalization
- Results in persistent or significant disability/incapacity
- Is a congenital anomaly/birth defect (in the child of a subject who was exposed to the study drug)

Other important medical events that may not be immediately life-threatening or result in death or hospitalization but, when based on appropriate medical judgment, may jeopardize the subject or may require intervention to prevent 1 of the outcomes in the definition of SAE listed above should also be considered SAEs. Medical and scientific judgment should be exercised in deciding whether expedited reporting is appropriate in such situations.

The study-specific events that are listed on the Reporting of Events Associated with Special Situations (Section 9.5.4.4) should always be considered as SAEs and be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1). If the event does not meet other serious criteria, it should be reported under the serious criterion of Important Medical Event. (revised per Amendment 01)

Study-specific AEs of interest which are always to be reported as SAEs are included in the list on the Reporting of Events Associated with Special Situations (Section 9.5.4.4). (revised per Amendment 01)

In addition to the list on the Reporting of Events Associated with Special Situations (Section 9.5.4.4), other events associated with special situations include pregnancy or exposure to study drug through breastfeeding; AEs associated with study drug overdose, misuse, abuse, or medication error. These events, associated with special situations, are to be captured using the SAE procedures but are to be considered as SAEs only if they meet 1 of the above criteria. All AEs associated with special situations are to be reported on the CRF whether or not they meet the criteria for SAEs; and any treatment-emergent significant laboratory abnormality (revised per Amendment 01)

During this study, the endpoints of MACE and MACE+ will need to be reported in an expedited fashion by investigators to the CEC and to the Eisai Product Safety Department, but will not be

recorded as SAEs in the clinical trial 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 (ie, where there is evidence to suggest a causal relationship). (revised per Amendment 01)

All MACE and MACE+ events are to be reported on the AE CRF and the MACE/MACE+ section of the CRF, but will not be considered as AEs.

The following hospitalizations are not considered to be SAEs because there is no "AE" (ie, there is no untoward medical occurrence) associated with the hospitalization:

- Planned hospitalizations required by the protocol
- Hospitalization planned before informed consent (where the condition requiring the hospitalization has not changed post study drug administration)
- (revised per Amendment 01)
- Hospitalization for routine maintenance of a device (eg, battery replacement) that was in place before study entry

LABORATORY MEASUREMENTS

Clinical laboratory tests to be performed, including hematology, chemistry, and urinalysis, are summarized in Table 3. Subjects should be in a seated or supine position during blood collection. The Schedule of Procedures/Assessments (Table 4) shows the visits and timepoints at which blood for clinical laboratory tests and urine for urinalysis will be collected in the study.

Table 3 Clinical Laboratory Tests

Category	Parameters
Hematology	hematocrit, hemoglobin, platelets, RBC count, and WBC count with differential (bands, basophils, eosinophils, lymphocytes, monocytes, neutrophils)
Chemistry	
Electrolytes	bicarbonate, chloride, potassium, sodium
Liver function tests	ALT, alkaline phosphatase, AST, direct bilirubin, total bilirubin, GGT
Renal function parameters	blood urea/blood urea nitrogen, creatinine
Other	albumin, calcium, globulin, glucose, lactate dehydrogenase, LDL-C, HDL-C, phosphorus, total cholesterol, total protein, triglycerides, uric acid,
Urinalysis	glucose, ketones, protein, RBCs, WBCs, albumin and creatinine for ACR
Other	HbA_{1c}, serum cystatin C, fasting insulin, FPG, hsCRP, fibrinogen, serum pregnancy, urine drug screen

ACR = albumin-to-creatinine ratio; ALT = alanine aminotransferase, AST = aspartate aminotransferase, FPG = fasting plasma glucose; GGT = gamma glutamyl transpeptidase, HbA_{1c} = glycosylated hemoglobin, HDL-C = high density lipoprotein-cholesterol, hsCRP = high sensitivity C-reactive protein, LDL-C = low density lipoprotein-cholesterol, RBC = red blood cell, WBC = white blood cell.

Clinical laboratory tests during the study will be performed by a central laboratory. All blood and urine samples will be collected and sent to the central laboratory on the day of collection unless otherwise instructed. In cases of a safety concern, blood samples will be split (or 2 samples drawn) to allow a local laboratory analysis in addition to the central laboratory.

A laboratory abnormality may meet the criteria to qualify as an AE as described in this protocol (see AEs and Other Events of Interest [Section 9.5.1.5]) and the CRF Completion Guidelines. In these instances, the AE corresponding to the laboratory abnormality will be recorded on the Adverse Event CRF.

Laboratory abnormalities meeting the criteria of SAEs (see SAEs and Other Events of Interest [Section 9.5.1.5]), must be reported to the sponsor in the same manner as SAEs (see Reporting of SAEs [Section 9.5.4.1]). In addition, the laboratory report must be provided to the sponsor, as regionally required.

VITAL SIGNS AND HEIGHT/WEIGHT MEASUREMENTS

Vital sign measurements (ie, systolic and diastolic BP [mmHg], pulse [beats per minute], and weight (kg) will be obtained at the visits designated on the Schedule of Procedures/Assessments (Table 4) by a validated method. BP and pulse will be measured after the subject has been sitting for 15 minutes. All BP measurements should be performed on the same arm, preferably by the same person.

Height will be measured at Screening for calculation of BMI. Additionally, waist and hip circumference will be measured at the visits designated on the Schedule of Procedures/Assessments (Table 4).

The waist and hip circumferences will be measured to the nearest integer. For a given subject and as much as is possible, the same site personnel should measure the waist and hip throughout the study to avoid variability in the method of measurement. All measurements will be reported in centimeters (cm). Each measurement will be made and recorded 3 times at each scheduled assessment; the average of the 3 values will be reported. In order to standardize the method used, measurements should be obtained as follows:

Waist Measurement: waist measurement will be done according to the National Heart, Lung, and Blood Institute (NHLBI) Guideline in the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults.[13] To define the level at which the waist circumference is measured, a bony landmark is first located and marked. The subject stands and the examiner, positioned at the right of the subject, palpates the upper hip bone to locate the right iliac crest. Just above the uppermost lateral border of the right iliac crest, a horizontal mark is drawn, and then crossed with a vertical mark on the midaxillary line. The measuring tape is placed in a horizontal plane around the abdomen at the level of this marked point on the right side of the trunk. The plane of the tape is parallel to the floor and the tape is snug, but does not compress the skin. The measurement is made at a normal minimal respiration (Figure 2).

Hip Measurement: With a tape measure, measure the distance around the largest extension of the buttocks.

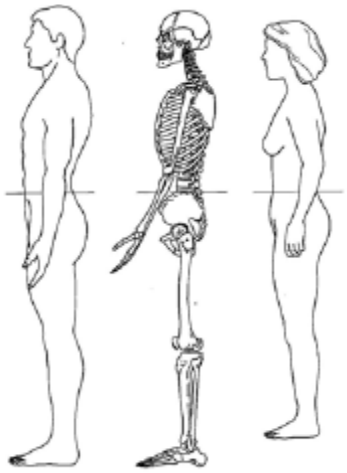


Figure 2 Measuring Tape Position for Waist Circumference

PHYSICAL EXAMINATIONS

Physical examinations (targeted or symptom directed) will be performed as designated on the Schedule of Procedures/Assessments (Table 4). A targeted physical examination will include evaluations of the heart and lungs, abdomen, and limbs. Examinations of other systems will only be required in the presence of clinical symptoms related to this region. Documentation of the physical examination will be included in the source documentation at the site. Significant findings at the Screening Visit will be recorded on the Medical History and Current Medical Conditions CRF. Changes from screening physical examination findings that meet the definition of an AE will be recorded on the Adverse Events CRF.

ELECTROCARDIOGRAMS

ECGs will be obtained as designated on the Schedule of Procedures/Assessments if subjects come to the study visit in person (Table 4).

Newly occurring Q-waves will be reported and evaluated as potential silent MI; suspected events will be adjudicated by the CEC.

An ECG abnormality may meet the criteria of an AE as described in this protocol (see AEs and Other Events of Interest [Section 9.5.1.5]) and the CRF Completion Guidelines. In these instances, the AE corresponding to the ECG abnormality will be recorded on the Adverse Events CRF.

ECG abnormalities meeting the criteria of SAEs (see SAEs and Other Events of Interest [Section 9.5.1.5]), must be reported to the sponsor in the same manner as SAEs (see Reporting of SAEs [Section 9.5.4.1]). In addition, the ECG report must be provided to the sponsor, as regionally required.

ECHOCARDIOGRAM

Echocardiograms will be obtained on a subset of approximately 3600 subjects at selected sites as designated on the Schedule of Procedures/Assessments (Table 4). Acquisition of new ECHO data in all subjects will cease when at least 1000 subjects have completed the Month 36 echocardiographic assessment. (revised per Amendment 02)

To maintain consistency with echocardiographic assessments conducted in the lorcaserin HCl Phase 3 program, and to allow pooling of Phase 3 data with that from the proposed study, the categories for echocardiographic assessments of aortic and mitral valve regurgitation will remain the same as in the Phase 3 program. Valvular regurgitation as assessed on substudy echocardiogram will be rated absent, trace, mild, moderate, or severe for the aortic, mitral, and tricuspid valves; the rating will be absent or present for the pulmonic valve. (revised per Amendment 01) The evaluations will be based on guidelines from the American Society of Echocardiography. Pulmonary artery pressure will be estimated from the tricuspid regurgitant jet velocity.

In this study, echocardiographic images will be acquired in a subset of subjects to establish the cardiac safety of lorcaserin HCl. Standardized training will be provided for all echocardiographers, and will implement centralized procedures for collecting, analyzing, and reporting echocardiographic data. All echocardiograms will be over-read by 2 blinded central readers (primary and secondary).

Baseline echocardiograms will be performed in between Visits 1 and 2, after the results of screening assessments have been obtained but prior to randomization, and subject eligibility is confirmed.

PREGNANCY TEST

During Screening, blood samples for pregnancy testing will be collected for women of childbearing potential (as defined in Section 9.3.1, Inclusion Criterion No. 5). A urine pregnancy test will be performed at the time of randomization.

TOBACCO HISTORY AND USE

History of tobacco use will be captured at Baseline. Changes in smoking status will be captured yearly thereafter.

9.5.2 Schedule of Procedures/Assessments

9.5.2.1 Schedule of Procedures/Assessments

Table 4 presents the schedule of procedures/assessments for the study.

Table 4 Schedule of Procedures/Assessments in Study APD356-G000-401

Phase	**Pre-randomization**	**Randomization**																		
Period	**Screening**	**Treatment**																	**F/U**	
Visit	1	2[a]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	EOT	EOS	Unsch[b]
Month[c]	Days -30 to -1	Day 1	3	6	9	12	15	18	21	24	28	32	36	40	44	48	52	56		
Assessment (revised per Amendment 01)																				
Informed consent	X																			
Demography	X																			
Medical history	X																			
Cardiovascular history	X																			
Diabetes history	X																			
Tobacco history/use		X				X				X			X			X		X		
Inclusion/ exclusion criteria	X	X																		
Physical examination	X					X				X			X			X		X		
Vital signs	X	X	X	X		X		X		X	X	X	X	X	X	X	X	X	X	X
Height	X																			
Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Waist/hip circumference	X	X				X				X			X			X		X		
Echocardiogram[d]	X			X		X		X		X			X			X				
12-lead ECG		X				X				X			X			X		X		
Hematology laboratory tests[e]	X			X		X				X			X			X		X		
Chemistry laboratory tests [e,f]	X			X		X				X			X			X		X	X	

Table 4 Schedule of Procedures/Assessments in Study APD356-G000-401

Phase	**Pre-randomization**	**Randomization**																		
Period	**Screening**	**Treatment**																	**F/U**	
Visit	1	2[a]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	EOT	EOS	Unsch[b]
Month[c]	Days -30 to -1	Day 1	3	6	9	12	15	18	21	24	28	32	36	40	44	48	52	56		
Assessment (revised per Amendment 01)																				
Serum cystatin C/serum creatinine [f,g]		X				X				X			X			X		X	X	
Urinalysis incl. ACR[f]	X					X				X			X			X		X	X	
PGx sampling (where applicable)		X																		
HbA_{1c} sampling[f]	X	X	X	X		X		X		X		X	X	X	X	X	X	X	X	X
Fasting plasma glucose[f]	X	X		X		X				X			X			X		X	X	X
Fasting insulin level[f]	X	X		X		X				X			X			X		X	X	
Other biomarker sampling (where applicable)		X		X						X								X		
hsCRP	X					X				X			X			X		X		
Fibrinogen		X				X				X			X			X		X		
Urine drug screen	X																			
Pregnancy test[h]	X	X																		
Diet and exercise counseling	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Randomization		X																		
IxRS[e]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Prior/concomitant medications[i]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		

Table 4 Schedule of Procedures/Assessments in Study APD356-G000-401

Phase	**Pre-randomization**	**Randomization**																		
Period	**Screening**	**Treatment**																	**F/U**	
Visit	1	2[a]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	EOT	EOS	Unsch[b]
Month[c]	Days -30 to -1	Day 1	3	6	9	12	15	18	21	24	28	32	36	40	44	48	52	56		
Assessment (revised per Amendment 01)																				
Study drug dispensing[e]		X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X			
Collect study medication[e]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
Drug accounting & compliance [e]			X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X		
AE monitoring [i]	<----------																			---------->
MACE/MACE+ reporting [i]	<----------																			---------->

(revised per Amendment 01)

Notes: Upon Sponsor Notification of Study Completion (ie, trial 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.

Subjects who prematurely discontinue study drug are to complete the EOT visit within approximately 30 days, and will continue in the study for all subsequent study visits until study completion. If the next scheduled visit after EOT assessments is <30 days, subjects can skip that visit and return for the next subsequent visit (eg, if the EOT is 15 days prior to the scheduled Month 36 visit, they can skip Month 36, and come in at Month 40). All procedures and assessments should be performed at subsequent visits until EOS except where footnoted in assessment column. Upon Sponsor Notification of Study Completion, subjects who prematurely 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 30 days of Sponsor Notification of Study Completion will return for an EOS visit approximately 30 days after their last dose of study medication.

ACR = albumin-to-creatinine ratio; AE = adverse event, ECG = electrocardiogram, EOS = end of study; EOT = end of treatment; F/U = Follow-up; HbA_{1c} = glycosylated hemoglobin, hsCRP = high sensitivity C-reactive protein; incl. = including; IxRS = interactive voice and/or web response system; MACE = major adverse cardiovascular events; MACE+ = MACE or hospitalization for unstable angina or heart failure, and any coronary revascularization; PGx = pharmacogenomics, Unsch = unscheduled.

a. Visit 2 = Baseline/Randomization. The first dose should be taken at this visit. (revised per Amendment 01)
b. Assessments are only to be performed if clinically indicated or necessary due to state controlled substance requirements. (revised per Amendment 01)
c. Window ±10 days for all visits after Visit 2, other than the EOS visit which has a window of +10 days. Month is shown unless otherwise indicated; 1 month = approximately 30 days.
d. Only for a subset of subjects at selected sites. Baseline echocardiograms will be performed in between Visits 1 and 2, after the results of screening assessments have been obtained but prior to randomization, and subject eligibility is confirmed. ECHOs will be performed until at least 1000 subjects have completed the Month 36 echocardiographic assessment. (revised per Amendment 02)

Table 4 Schedule of Procedures/Assessments in Study APD356-G000-401

Phase	**Pre-randomization**	**Randomization**																		
Period	**Screening**	**Treatment**																	**F/U**	
Visit	1	2[a]	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	EOT	EOS	Unsch[b]
Month[c]	Days -30 to -1	Day 1	3	6	9	12	15	18	21	24	28	32	36	40	44	48	52	56		
Assessment (revised per Amendment 01)																				

e. For subjects who discontinue study drug early, these assessments will be stopped after the EOT visit.
f. Renal function parameters and glycemic profile should be obtained at all specified visits, regardless of study drug status. (revised per Amendment 01)
g. Serum cystatin C will be measured at Baseline and yearly thereafter in the subpopulation with CKD Stage 1 or 2 at Baseline. Serum creatinine will be measured in chemistry blood samples if chemistry assessments are performed.
h. Serum pregnancy tests will be conducted at Screening. A urine pregnancy test will be conducted at randomization.
i. These assessments should be done if a telephone contact is performed in lieu of a clinic visit.

9.5.3 Appropriateness of Measurements

All clinical assessments are standard measurements used to meet the requirements for conducting a CVOT.

The safety assessments to be performed in this study, including hematology analyses, blood chemistry tests, urinalysis, vital signs and assessment of AEs, are standard evaluations to ensure subject safety. Serial echocardiogram assessments on a subset of subjects at selected sites are included in the study per requirement by the FDA.

9.5.4 Reporting of SAEs, Hypoglycemia, Pregnancy, and Other Events of Interest

9.5.4.1 Reporting of SAEs

All SERIOUS ADVERSE EVENTS, regardless of their relationship to study treatment, must be reported as soon as possible but no later than 24 hours from the time the investigator becomes aware of the event.

Serious adverse events, regardless of causality assessment, must be collected through the end of study. For those subjects taking study drug at the time of study completion ("Sponsor Notification of Study Completion"), SAEs should be collected for 30 days after the last dose. (revised per Amendment 01) All SAEs must be followed to resolution or, if resolution is unlikely, to stabilization. Any SAE judged by the investigator to be related to the study treatment should be reported to the sponsor regardless of the length of time that has passed since study completion.

The detailed contact information for reporting of SAEs is provided in the Investigator Study File.

For urgent safety issues, please ensure all appropriate medical care is administered to the subject and contact the appropriate study team member listed in the Investigator Study File.

It is very important that the SAE report be as complete as possible at the time of the initial report. This includes the investigator's assessment of causality.

Any follow-up information received on SAEs should be forwarded within 24 hours of its receipt. If the follow-up information changes the investigator's assessment of causality, this should also be noted on the follow-up SAE report.

Preliminary SAE reports should be followed as soon as possible by detailed descriptions including copies of hospital case reports, autopsy reports, and other documents requested by the sponsor.

The investigator must notify his/her IRB/IEC of the occurrence of the SAE, in writing, if required by their institution. A copy of this communication must be forwarded to the sponsor or designated CRO to be filed in the sponsor's Trial Master File.

9.5.4.2 Reporting of Hypoglycemia

Patient-reported episodes of hypoglycemia or decreased blood sugar should be captured on the eCRF according to the following guidelines:

- Mild hypoglycemia is defined as capillary glucose ≥55 to <65 mg/dL (≥3.0 - <3.3 mmol/L) that the subject is able to treat himself/herself; or, if glucose is not measured, symptoms of hypoglycemia that resolve with administration of oral carbohydrates.
- Moderate hypoglycemia is defined as capillary glucose <55 mg/dL (<3.0 mmol/L) that the subject is able to treat himself/herself.
- Severe hypoglycemia is defined as a symptomatic capillary glucose <40 mg/dL (<2.2mmol/L) OR a capillary glucose ≤65 mg/dL AND needed help from another person OR required intravenous glucose
- Catastrophic hypoglycemia is defined as severe hypoglycemia that resulted in life-threatening injury to the subject or another person, hospitalization, and/or death. This should be reported as a SAE.

Additionally, ***adverse events*** of hypoglycemia should be further specified in the eCRF adverse event term as "symptomatic" or "asymptomatic".

See Section 9.4.7.2 for directions on the recommendations for possible adjustment to antihyperglycemic medication doses in response to reported episodes of hypoglycemia.

9.5.4.3 Reporting of Pregnancy and Exposure to Study Drug Through Breastfeeding

Any pregnancy in which the estimated date of conception is either before the last visit or within 30 days of last study treatment or any exposure to study drug through breastfeeding during study treatment or within 30 days of last study treatment must be reported.

If an adverse outcome of a pregnancy is suspected to be related to study drug exposure, this should be reported regardless of the length of time that has passed since the exposure to study treatment.

A congenital anomaly, death during perinatal period, an induced abortion, or a spontaneous abortion are considered to be an SAE and should be reported in the same time frame and in the same format as all other SAEs (see Reporting of SAEs [Section 9.5.4.1]).

Pregnancies or exposure to study drug through breastfeeding must be reported as soon as possible but no later than 24 hours from the date the investigator becomes aware of the pregnancy. The contact information for the reporting of pregnancies and exposure to study drug through breastfeeding is provided in the Investigator Study File. All pregnancies must be followed to outcome. The outcome of the pregnancy must be reported as soon as possible but no later than 24 hours from the date the investigator becomes aware of the outcome.

A subject who becomes pregnant must be discontinued from study treatment.

9.5.4.4 Reporting of Events Associated with Special Situations

(revised per Amendment 01)

REPORTING OF AEs ASSOCIATED WITH STUDY DRUG OVERDOSE, MISUSE, ABUSE, OR MEDICATION ERROR

AEs associated with study drug overdose, misuse, abuse, and medication error refer to AEs associated with uses of the study drug outside of that specified by the protocol. Overdose, misuse, abuse, and medication error are defined as follows:

Overdose	Accidental or intentional use of the study drug in an amount higher than the protocol-defined dose
Misuse	Intentional and inappropriate use of study drug not in accordance with the protocol (revised per Amendment 01)
Abuse	Sporadic or persistent intentional excessive use of study drug accompanied by harmful physical or psychological effects
Medication error	Any unintentional event that causes or leads to inappropriate study drug use or subject harm while the study drug is in the control of site personnel or the subject

All AEs associated with an overdose should be captured on the Adverse Event CRF. AEs associated with overdose, misuse, abuse, or medication error should be reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1) even if the AEs do not meet serious criteria. Abuse is always to be captured as an AE. If the AE associated with an overdose, misuse, abuse, or medication error does not meet serious criteria, it must still be reported in an expedited manner but should be noted as nonserious in the report and on the Adverse Event CRF.

(revised per Amendment 01)

REPORTING OF STUDY-SPECIFIC EVENTS

All study specific AEs of interest should be reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1). (revised per Amendment 01)

The Study-specific events below should always be considered as SAEs and be entered on the Adverse Event CRF and reported using the procedures detailed in Reporting of Serious Adverse Events (Section 9.5.4.1), If the event does not meet other serious criteria, then it should be reported under the serious criteria of Important Medical Event. (revised per Amendment 01)

- **Serotonin syndrome** (must have at least 1 of the following: Spontaneous clonus; Inducible clonus PLUS agitation or diaphoresis; Ocular clonus PLUS agitation or diaphoresis; Tremor PLUS hyperreflexia; Hypertonia PLUS temperature above 38ºC PLUS ocular clonus or inducible clonus) (revised per Amendment 01)

- **Psychosis**

- **Suicidal behavior** (revised per Amendment 01)

- **Priapism**

- **New symptoms or worsening symptoms of valvular heart disease** (revised per Amendment 01)

- **New or worsening symptomatic pulmonary hypertension** (revised per Amendment 01)

- **Malignant neoplasms**, with the exception of basal cell and squamous cell carcinomas of the skin

- **Fibroadenomas of the breast or ductal carcinoma *in sit***

Additionally, the following additional study specific AEs of interest should be reported using the procedures detailed in Reporting of SAEs (Section 9.5.4.1), even if the study-specific event does not meet serious criteria. If the event meets seriousness criteria, it should be reported as an SAE as above. However, if the event listed below does not meet serious criteria, it should be noted as non-serious on the Adverse Event CRF: (revised per Amendment 01)

- **Suicidal ideation (revised per Amendment 01)**

- **Euphoria (revised per Amendment 01)**

- **Asymptomatic new onset or worsened valvular heart disease** as demonstrated by objective assessment, eg, echocardiography or cardiac catheterization. New onset valvular disease is defined as subjects who develop mild or greater aortic insufficiency and moderate or greater grading for all other valvular lesions (eg, mitral regurgitation, aortic stenosis) on imaging in subjects without any valvular disease at Baseline. Worsened valvular disease is defined in subjects who have existing FDA defined valvulopathy at Baseline increase in severity of regurgitation or stenosis as demonstrated by objective assessments (eg, imaging assessments such as magnetic resonance imaging [MRI], echocardiography, or cardiac catherization). (revised per Amendment 01)

- **Asymptomatic new onset or worsened pulmonary hypertension** as documented by echocardiography or cardiac catheterization. New onset of pulmonary hypertension is defined as estimated pulmonary artery or right ventricular systolic pressure greater than

40 mmHg or mean pulmonary artery pressure equal-or-greater than 25 mmHg in the subjects without any pulmonary hypertension at Baseline. Worsening pulmonary hypertension is defined in subjects who have documented objective assessment pulmonary hypertension at Baseline as an increase in pulmonary artery systolic pressure, or mean artery pressure by more than 10 mmHg. (revised per Amendment 01)

9.5.4.5 Expedited Reporting

The sponsor must inform investigators (or, as regionally required, the head of the medical institution) and regulatory authorities of reportable events, in compliance with applicable regulatory requirements, on an expedited basis (ie, within specific time frames). For this reason, it is imperative that sites provide complete SAE information in the manner described above.

9.5.4.6 Breaking the Blind

In the case of a medical emergency where the appropriate treatment of the subject requires knowledge of the study treatment given, the investigator may break the randomization code for an individual subject. In all such cases, the AE necessitating the emergency blind break will be handled as an SAE in accordance with the procedures indicated above. Any broken code will be clearly justified and documented. The medical monitor must be notified immediately of the blind break.

9.5.4.7 Regulatory Reporting of AEs

AEs will be reported by the sponsor or a third party acting on behalf of the sponsor to regulatory authorities in compliance with local and regional law and established guidance. The format of these reports will be dictated by the local and regional requirements.

All studies that are conducted within any European country will comply with European GCP Directive 2005/28/EC and Clinical Trial Directive 2001/20/EC. All SUSARs will be reported, as required, to the competent authorities of all involved European member states.

9.5.5 Completion/Discontinuation of Subjects

9.5.5.1 Premature Discontinuation of Study Drug

A subject may decide to discontinue receiving the study drug at any time for any reason. The investigator may discontinue a subject from receiving the study drug at any time for safety or administrative reasons. The reason for premature discontinuation of study drug will be documented.

Discontinuation from receiving study drug does not mean that the subject is withdrawn from the study. Subjects who prematurely and permanently discontinue study drug are to complete the EOT visit within approximately 30 days as defined in the Schedule of Procedures/Assessments (Table 4). (revised per Amendment 01) 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. It is preferred that these visits are conducted 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 clinic visit at least once per year.

Upon Sponsor Notification of Study Completion, subjects who prematurely 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 30 days of Sponsor Notification of Study Completion will return for an EOS visit approximately 30 days after their last dose of study medication. (revised per Amendment 01)

Unless he or she withdraws consent for any type of follow-up contact, a subject who has ceased to return for visits may be followed up by mail, phone, or other means to gather information such as the reason for failure to return, the status of treatment compliance, the presence or absence of AEs, and clinical courses of signs and symptoms. This information will be recorded in the CRF. Patient finder services will be utilized to identify updated contact information when the site cannot locate a missing subject.

For subjects who prematurely discontinue from study drug, the reasons will be documented in the CRF and source documentation. Study drug disposition information will be collected on the Early Discontinuation from Study Drug CRF.

Restart of Study Drug

Whenever possible, restart of study drug should be encouraged. Subjects discontinued from study drug due to a serious or severe adverse event considered to be related to study drug by the investigator should not be restarted on study drug. Prior to restarting study drug on subjects who have been discontinued, consideration should be given as to whether the subject has developed any conditions (eg, change in medical status, use of concomitant medications, lack of contraception) exclusionary to taking study drug. See specific instructions in Section 9.4.5.1 for instructions on dosing when restarting study drug and Section 9.4.7.2 for instructions concerning restart of study drug for individuals requiring a second non study drug serotonergic agent. Even if a premature EOT visit was completed due to the discontinuation of study drug, this should not prevent complete study follow-up procedures including the final EoT/Closing Visit, following restart of randomized treatment. (revised per Amendment 01)

9.5.5.2 Discontinuation from Study Procedures/Withdrawal of Consent

A subject may elect to discontinue all participation in the study at any time for any reason. (revised per Amendment 01)

Only subjects who refuse any and all types of contact (eg, visits, telephone calls, medical record reviews) will be considered to have withdrawn consent for all clinical follow-up. It is expected that this would be extremely unusual. The site must contact the TIMI Hotline to confirm withdrawal of consent, at which time the Withdrawal of Consent CRF will be made available for

completion. A final assessment for vital status using publically available data will be performed at the end of the study for all subjects who withdraw consent for all clinical follow-up, when allowed by law, regulation, or local authorities.

The investigator may also withdraw a subject from the study only in the event of exceptional circumstances. This must be documented by the site, signed by the investigator, and reviewed by the sponsor/designee before it is considered to take effect.

All subjects who prematurely discontinue all study procedures (ie, withdraw consent) are to complete the EOS Visit procedures indicated in the schedule of procedures/assessments (Table 4).

For subjects who prematurely discontinue from the study, the reasons will be documented in the CRF and source documentation. Study disposition information will be collected on the Subject Disposition CRF.

A subject removed from the study for any reason may not be replaced.

9.5.6 Abuse or Diversion of Study Drug

During the study, the investigator will report any concern about abuse or diversion of study drug.

AEs associated with abuse or diversion will be appropriately reported as AEs and monitored per Section 9.5.1.5. Abuse is always to be captured as an AE.

Sites will be assessed for the appropriateness of study drug storage and retrieval at the time of site selection. Required policies and procedures will be clearly communicated to the site to assess the site's capabilities and adherence to storage, dispensing, reconciliation, and retention of study drug.

9.5.7 Confirmation of Medical Care by Another Physician

The investigator will instruct subjects to inform site personnel when they are planning to receive medical care by another physician. At each visit, the investigator will ask the subject whether he/she has received medical care by another physician since the last visit or is planning to do so in the future. When the subject is going to receive medical care by another physician, the investigator, with the consent of the subject, will inform the other physician that the subject is participating in the clinical study.

9.6 DATA QUALITY ASSURANCE

This study will be organized, performed, and reported in compliance with the protocol, SOPs, working practice documents, and applicable regulations and guidelines. Site audits will be made periodically by the sponsor's or the CRO's qualified compliance auditing team, which is an independent function from the study team responsible for conduct of the study.

9.6.1 Data Collection

Data required by the protocol will be collected on the CRFs and entered into a validated data management system that is compliant with all regulatory requirements. As defined by ICH guidelines, the CRF is a printed, optical, or electronic document designed to record all of the protocol-required information to be reported to the sponsor on each study subject.

Data collection on the CRF must follow the instructions described in the CRF Completion Guidelines. The investigator has ultimate responsibility for the collection and reporting of all clinical data entered on the CRF. The investigator or designee as identified on Form FDA 1572 or equivalent must sign the completed CRF to attest to its accuracy, authenticity, and completeness.

Completed, original CRFs are the sole property of Eisai and should not be made available in any form to third parties without written permission from Eisai, except for authorized representatives of Eisai or appropriate regulatory authorities.

9.6.2 Clinical Data Management

All software applications used in the collection of data will be properly validated following standard computer system validation that is compliant with all regulatory requirements. All data, both CRF and external data (eg, laboratory data), will be entered into a clinical system.

9.7 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. Details of the statistical analyses will be included in a separate statistical analysis plan.

9.7.1 Statistical and Analytical Plans

The statistical analyses of the APD356-G000-401 study data are described in this section. Further details of the analytical plan will be provided in the SAP, which will be finalized before database lock and treatment unblinding for the interim analysis.

9.7.1.1 Study Endpoints

PRIMARY ENDPOINTS

- Time from randomization to first occurrence of MACE (first occurrence of any of the following events: MI, stroke, or CV death)
- 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) (revised per Amendment 02)

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[14] in subjects with prediabetes at Baseline. The diagnostic criteria are met if a subject has unequivocal hyperglycemia (random plasma glucose ≥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} ≥6.5%
    - FPG ≥126 mg/dL (7.0 mmol/L)
    - 2-hour plasma glucose ≥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)

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} ≤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)
- Time from randomization to conversion to T2DM in subjects without any type of diabetes at Baseline (revised per Amendment 01)
- Change from Baseline in HbA_{1c} 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)

- 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 prediabetes at Baseline (revised per Amendments 01 and 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 subjects with T2DM at Baseline (revised per Amendment 02)
- 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

Secondary Safety 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
- Proportion of subjects with FDA-defined valvulopathy confirmed by documented objective assessments at Baseline who demonstrate worsened FDA-defined valvulopathy at 1 year (revised per Amendment 01)
- Change from Baseline in estimated pulmonary artery systolic pressure at 1 year

EXPLORATORY ENDPOINTS

- Change from Baseline in CV risk factors at 1 year and yearly thereafter (eg, body weight, dyslipidemia, insulin level, hypertension, and applicable biomarkers of CV risk and other end-organ diseases)
- Change from Baseline in eGFR and ACR at 1 year, yearly thereafter, and at the end of the study

- 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 $HbA_{1c,}$ 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 (HbA_{1c}>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 (HbA_{1c} >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)

9.7.1.2 Definitions of Analysis Sets

The Safety Analysis Set will be the group of subjects who received at least 1 dose of study drug and had at least 1 postdose safety assessment.

The Intent-to-Treat set (ITT) will be the group of all randomized subjects regardless of whether they took study drug or not.

- Total Time Analysis Set: Using the ITT, events are counted that occur while subjects are on and off treatment. Subjects with no events who discontinue early or complete the study will be censored at their last study contact (see details in the SAP). This will be used for the primary analysis.

- 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 day plus 30 days.

- 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 day.

- 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. Definition of prediabetes will be found in the SAP. (revised per Amendment 01)

- Nondiabetes Analysis Set: This set includes all subjects in the ITT set without a history of any type of diabetes at Baseline. Definition of nondiabetes will be found in the SAP. (revised per Amendment 01)

T2DM Analysis Set: This set will be all subjects in the ITT who have T2DM at Baseline.

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

The PD Analysis Set will be the group of subjects who have both baseline and at least 1 postbaseline assessment of at least 1 PD parameter.

9.7.1.3 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 and treated subjects who completed the study and who discontinued from the study will be summarized according to the primary reason for discontinuation based on data reported on the Subject Disposition (Study Phase) 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. The reasons for discontinuation from the study will be documented in the CRF and source documentation.

Completion of Study Treatment: the number (percent) of randomized and treated subjects who completed study treatment and who discontinued from study treatment will be summarized according to the primary reason for discontinuation, based on data reported on both the Subject Disposition (Study Phase) 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 treatment, and discontinued from study treatment. The reasons for discontinuation from study treatment will be documented in the CRF and source documentation.

9.7.1.4 Demographic and Other Baseline Characteristics

Demographic and other baseline characteristics for the Safety Analysis Set, ITT for subjects who are prediabetic (HbA_{1c} 5.7% to <6.5%) or have normal glucose homeostasis (HbA_{1c} ≤5.6% at Baseline), ITT for subjects who have T2DM at Baseline, and ITT will be summarized for each treatment group using descriptive statistics. 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, HbA_{1c}, and BMI. Categorical variables include sex, age group (<65 years, ≥65 years), race, ethnicity, HbA_{1c} (prediabetes: 5.7% to <6.5%; normal glucose homeostasis: ≤5.6%), BMI (<30 kg/m^2, 30 to <35 kg/m^2, ≥35 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.

9.7.1.5 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 medications that (1) started before the first dose of study drug and were continuing at the time of the first dose of study drug, or

(2) started on or after the date of the first dose of study drug for at least 30 days after study completion/early termination. All medications will be presented in subject data listings.

9.7.1.6 Primary Safety and and Key Secondary Efficacy Analyses (revised per Amendment 02)

The primary endpoints, MACE, and MACE+, 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). (revised per Amendment 02) For secondary and exploratory endpoints a 2-sided $\alpha = 0.05$ significance level will be used. The MACE analysis ("interim" analysis) will be conducted when 460 adjudicated MACE events have been recorded; the other analyses will be conducted when 1401 adjudicated MACE+ events have been recorded, and the study has completed. (revised per Amendment 02)

Sequential Gatekeeping Testing Procedure (revised per Amendment 02)

The following closed sequential gatekeeping testing procedure (SGTP) will be used to control the family-wise error rate (FWER) at $\alpha = 0.05$ (2-sided) in testing the 2 primary endpoints (MACE and MACE+) and 1 key secondary endpoint, conversion to T2DM. (revised per Amendment 02)

Let H_{01} be the gatekeeping null hypothesis for noninferiority testing of the MACE endpoint using a noninferiority margin of 1.4.

Let H_{02}, and H_{03} be the null hypotheses for superiority testing: MACE+ and conversion to T2DM, respectively. (revised per Amendment 02)

The SGTP testing hierarchy is presented below. (revised per Amendment 02)

- STEP1: At the interim analysis, test the noninferiority hypothesis for MACE, H_{01} ($\alpha = 0.025$, 1-sided). If H_{01} is rejected, then proceed to STEP2, otherwise stop testing and the trial will be stopped.
- STEP2: At study completion, the hypotheses H_{02} ($\alpha = 0.05$, 2-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 3 presents the SGTP. (revised per Amendment 02)

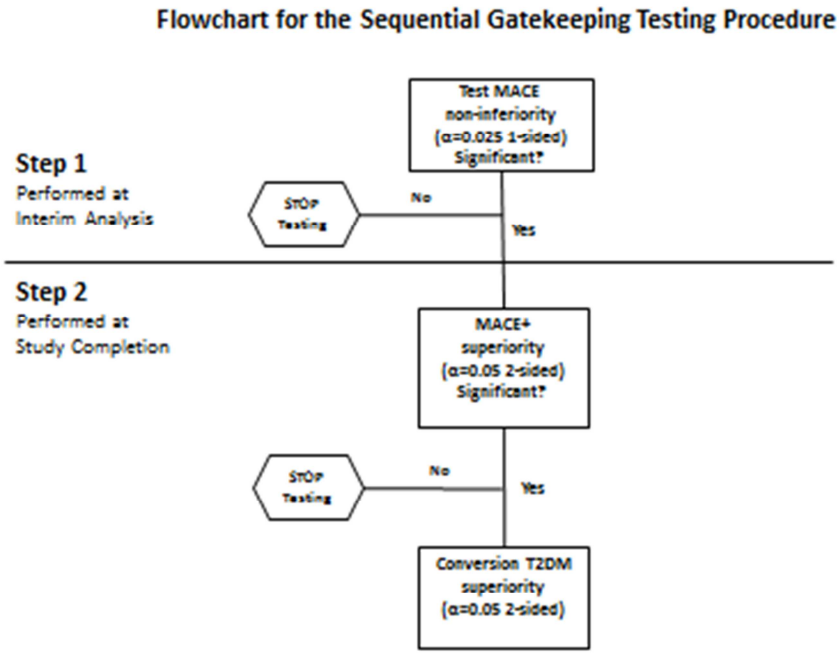


Figure 3 Flowchart for SGTP

MACE = major adverse cardiovascular events, MACE+ = MACE or hospitalization for unstable angina or heart failure, or any coronary revascularization; SGTP = sequential gatekeeping testing procedure; T2DM = type 2 diabetes mellitus.

PRIMARY ENDPOINT ANALYSES

- **Time to MACE:** The estimate of the hazard ratio of lorcaserin HCl to placebo and the corresponding 1-sided 97.5% confidence interval (CI) will be calculated. Noninferiority of lorcaserin HCl to placebo will be declared if the upper limit of the 97.5% CI is less than the noninferiority margin of 1.4. The Total Time Analysis Set will be used as the primary analysis at 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 sensitivity analyses at study completion. (revised per Amendment 02)

- **Time to MACE+:** The estimate of the hazard ratio of lorcaserin HCl to placebo and the corresponding 2-sided 95% CI will be calculated. The Total Time Analysis Set will be used as the primary analysis. (revised per Amendment 02) The On-Treatment Analysis Set and the On-Treatment plus 30 Days Analysis Set will be used as sensitivity analyses.

The incidence rate difference and the incidence rate ratio between lorcaserin and placebo will also be analyzed as supportive analysis for the primary endpoints above at study completion. (revised per Amendment 02)

Sensitivity analysis will be performed at study completion for the MACE and MACE+ endpoints using the Total Time Analysis Set. (revised per Amendment 02) This sensitivity analysis will not count a MACE or MACE+ event that occurs after the subject starts another weight reduction medication or undergoes bariatric surgery. (revised per Amendment 02)

KEY SECONDARY ENDPOINT ANALYSIS (revised per Amendment 02)

- **Time to conversion to T2DM:** The estimate of the hazard ratio of lorcaserin HCl to placebo and the corresponding 2-sided 95% CI will be calculated. The Prediabetes and Total Time Analyses Sets will be used as the primary for this 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).

9.7.1.7 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.

- 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 ≤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)
- 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.

9.7.1.8 Exploratory Endpoints 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 and stratification variable (presence of established CV disease or CV risk factors without established CV disease) as factors. Comparison between lorcaserin HCl and placebo will be made at 1year. The ITT will be used for this analysis.
- 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 and stratification variable (presence of established CV disease or CV risk factors without established CV disease) as factors. Comparison between lorcaserin HCl and placebo will be made at 1 year. The ITT will be used for this analysis.

- 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 2 years and yearly thereafter. 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 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 ITT will be used for this analysis.
- 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 2 years and yearly thereafter. The ITT will be used for this analysis.
- Change from Baseline in HbA_{1c},FPG, fasting insulin levels, and 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 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, in the following subpopulations. (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 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 T2DM Analysis Set will be used for this analysis, in the following subpopulations: (revised per Amendment 01)
    - Subjects with (HbA_{1c} >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 Safety Analysis Set will be used for this analysis. (revised per Amendment 01)

Logistic regression including treatment as factor will be used for the following endpoints. Comparison between lorcaserin HCl and placebo will be made at EOS. (revised per Amendment 01)

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

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

9.7.1.9 Pharmacokinetic, Pharmacodynamic, and Pharmacogenomic/Pharmacogenetic Analyses

PHARMACOKINETIC ANALYSES

Not applicable

PHARMACODYNAMIC ANALYSES

A PD analysis plan may be defined and reported separately.

BIOMARKER ANALYSES

A biomarker analysis plan may be defined and reported separately.

PHARMACOGENOMIC ANALYSES

A pharmacogenomic analysis plan may be defined and reported separately.

9.7.1.10 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.

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.

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). AEs will be coded to the MedDRA lower level term (LLT) closest to the verbatim term. The linked MedDRA PT and primary system organ class (SOC) are also captured in the database.

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

- Re-emerges 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 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. A subject will be counted only once within a SOC and PT, even if the subject experienced more than 1 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 (possibly related, probably related, and not related).

AEs will be summarized by the following subgroups: age (<65 years, ≥65 years), sex (male, female), race (white, black, other), 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 will be summarized separately. In addition, for each AE of interest, Kaplan-Meier curves and median time and 95% CI will be presented. The Safety Analysis Set will be used for this analysis.

LABORATORY VALUES

Laboratory results will be summarized using Système International (SI) units, as appropriate. For all quantitative parameters listed in 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 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 3 (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.

VITAL SIGNS

Descriptive statistics for vital signs parameters (ie, 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.

ECGS

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.

9.7.2 Determination of Sample Size

A sample size of 12,000 subjects should provide the required power for the primary endpoints as follows: (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 (revised per Amendment 02)

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 dropout rate, $\alpha = 0.05$ and a 2-sided test. (revised per Amendment 02)

9.7.3 Interim Analysis

There will be 1 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. The study will continue to accrue events until the required number of MACE+ have occurred. (revised per Amendment 02) Sensitivity analysis at study completion will be performed for the MACE endpoint after all the MACE+ events have accrued. (revised per Amendment 02) At the time of MACE+ analyses, there will be approximately 600 MACE events.

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) Jul 2017. (revised per Amendment 02) 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 (as outlined in the Study Integrity Charter), 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. (revised per Amendment 02)

At the interim analysis for MACE, the estimate of the hazard ratio of lorcaserin HCl to placebo and the corresponding 97.5% CI will be calculated. Noninferiority between lorcaserin HCl and placebo will be declared if the upper limit of the 97.5% CI is less than or equal to the noninferiority margin of 1.4. If the upper limit of the 97.5% CI is greater than 1.4, then lorcaserin HCl will be declared as not noninferior to placebo and the trial will stop.

If noninferiority 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 MACE+ events at approximately 54 months from the start of the study, and a median treatment duration of 2.5 years have accrued. (revised per Amendment 02) The events for MACE+ and T2DM will be tested according to the SGTP described previously, upon study completion.

9.7.4 Other Statistical/Analytical Issues

Not applicable

9.7.5 Procedure for Revising the Statistical Analysis Plan

If the SAP needs to be revised after the study starts, the sponsor will determine how the revision impacts the study and how the revision should be implemented. The details of the revision will be documented and described in the clinical study report.

10 REFERENCE LIST

1. World Health Organization Global Strategy on Diet, Physical Activity and Health. Fact Sheet: Obesity and Overweight. 2003.
2. Ogden CL, Carroll, MD, Kit, BK, Flegal KM. Prevalence of Obesity in the United States, 2009-2010. NCHS Data Brief, No, 82. January 2012.
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4. Chan JM, Rimm EB, Colditz GA, Stampfer MJ, Willet WC. Obesity, fat distribution, and weight gain as risk factors for clinical diabetes in men. Diabetes Care 1994;17:961-9.
5. Marx J. Cellular Warriors at the Battle of the Bulge. Science 2003 February 7;299(5608):846-9.
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7. Morton J, Zoungas S, Li Q, Patel AA, Chalmers J, Woodward M, et al. Low HDL Cholesterol and the Risk of Diabetic Nephropathy and Retinopathy. Diabetes Care 2012;35(11):2201-6.
8. Levey AS, Stevens LA, Schmid CH, Zhang YL, Castro AF, 3rd, Feldman HI, et al. A new equation to estimate glomerular filtration rate. Ann Intern Med. 2009;150(9):604-12.
9. Bruno G, Fornengo P, Novelli G, Panero F, Perotto M, Segre O, et al. C-reactive Protein and 5-year Survival in Type 2 Diabetes: the Casale Monferrato Study. Diabetes. 2009 Apr;58(4):926-33.
10. McGoon M, Gutterman D, Steen V, Barst R, McCrory DC, Fortin TA, et al. Screening, Early Detection, and Diagnosis of Pulmonary Arterial Hypertension: ACCP Evidence-Based Clinical Practice Guidelines. Chest. 2004;126:14S-34S.
11. KDIGO Clinical Practice Guideline for the Evaluation and Management of Chronic Kidney Disease. 2012.
12. National Kidney Foundation Kidney Disease Outcome Quality Initiative Clinical Practice Guidelines for Chronic Kidney Disease: Evaluation, Classification, and Stratification. 2002.
13. National Institutes of Health Clinical Guidelines on the Identification, Evaluation, and Treatment of Overweight and Obesity in Adults, September 1998.
14. American Diabetes Association Position Statement: Standards of Medical Care – 2013. Diabetes Care, Volume 36, Supplement 1, January 2013.

11 PROCEDURES AND INSTRUCTIONS (ADMINISTRATIVE PROCEDURES)

11.1 CHANGES TO THE PROTOCOL

Any change to the protocol requires a written protocol amendment or administrative change that must be approved by the sponsor before implementation. Amendments specifically affecting the safety of subjects, the scope of the investigation, or the scientific quality of the study require submission to health or regulatory authorities as well as additional approval by the applicable IRBs/IECs. These requirements should in no way prevent any immediate action from being taken by the investigator, or by the sponsor, in the interest of preserving the safety of all subjects included in the study. If the investigator determines that an immediate change to or deviation from the protocol is necessary for safety reasons to eliminate an immediate hazard to the subjects, the sponsor's medical monitor or appropriate study team member and the IRB/IEC for the site must be notified immediately. The sponsor must notify the health or regulatory authority as required per local regulations.

Protocol amendments that affect only administrative aspects of the study may not require submission to health or regulatory authority or the IRB/IEC, but the health or regulatory authority and IRB/IEC (or if regionally required, the head of the medical institution) should be kept informed of such changes as required by local regulations. In these cases, the sponsor may be required to send a letter to the IRB/IEC and the Competent Authorities (or, if regionally required, the head of the medical institution) detailing such changes.

11.2 ADHERENCE TO THE PROTOCOL

The investigator will conduct the study in strict accordance with the protocol (refer to ICH E6, Section 4.5).

11.3 MONITORING PROCEDURES

The sponsor's/CRO's CRA will maintain contact with the investigator and designated staff by telephone, letter, or email between study visits. Monitoring visits to each site will be conducted by the assigned CRA as described in the monitoring plan. The investigator (or if regionally required, the head of the medical institution) will allow the CRA to inspect the clinical, laboratory, and pharmacy facilities to assure compliance with GCP and local regulatory requirements. The CRFs and subject's corresponding original medical records (source documents) are to be fully available for review by the sponsor's representatives at regular intervals. These reviews verify adherence to study protocol and data accuracy in accordance with local regulations. All records at the site are subject to inspection by the local auditing agency and IRB/IEC review.

In accordance with ICH E6, Section 1.52, source documents include, but are not limited to the following:

- Clinic, office, or hospital charts
- Copies or transcribed health care provider notes which have been certified for accuracy after production
- Recorded data from automated instruments such as IxRS, x-rays, and other imaging reports, (eg, sonograms, computed tomography scans, magnetic resonance images, radioactive images, ECGs, rhythm strips, electroencephalograms, polysomnographs, pulmonary function tests) regardless of how these images are stored, including microfiche and photographic negatives
- Pain, quality of life, or medical history questionnaires completed by subjects
- Records of telephone contacts
- Diaries or evaluation checklists
- Drug distribution and accountability logs maintained in pharmacies or by research personnel
- Laboratory results and other laboratory test outputs (eg, urine pregnancy test result documentation and urine dipsticks)
- Correspondence regarding a study subject's treatment between physicians or memoranda sent to the IRBs/IECs
- CRF components (eg, questionnaires) that are completed directly by subjects and serve as their own source

11.4 RECORDING OF DATA

A CRF is required and must be completed for each subject by qualified and authorized personnel. All data on the CRF must reflect the corresponding source document, except when a section of the CRF itself is used as the source document. Any correction to entries made on the CRF must be documented in a valid audit trail where the correction is dated, the individual making the correction is identified, the reason for the change is stated, and the original data are not obscured. Only data required by the protocol for the purposes of the study should be collected.

The investigator must sign each CRF. The investigator will report the CRFs to the sponsor and retain a copy of the CRFs.

11.5 IDENTIFICATION OF SOURCE DATA

All data to be recorded on the CRF must reflect the corresponding source documents.

11.6 RETENTION OF RECORDS

The circumstances of completion or termination of the study notwithstanding, the investigator (or if regionally required, the head of the medical institution or the designated representative) is responsible for retaining all study documents, including but not limited to the protocol, copies of CRFs, the Investigator's Brochure, and regulatory agency registration documents (eg, Form FDA 1572 or equivalent, ICFs, and IRB/IEC correspondence). In addition, the sponsor will send a list of treatment codes by study subject to the investigator after the clinical database for this study has been locked. The site should plan to retain study documents, as directed by the sponsor, for at least 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 3 years have elapsed since the formal discontinuation of clinical development of the investigational product.

It is requested that at the completion of the required retention period, or should the investigator retire or relocate, the investigator contact the sponsor, allowing the sponsor the option of permanently retaining the study records.

11.7 AUDITING PROCEDURES AND INSPECTION

In addition to the routine monitoring procedures, the sponsor's Clinical Quality Assurance department conducts audits of clinical research activities in accordance with the sponsor's SOPs to evaluate compliance with the principles of ICH GCP and all applicable local regulations. If a government regulatory authority requests an inspection during the study or after its completion, the investigator must inform the sponsor immediately.

11.8 HANDLING OF STUDY DRUG

All study drug will be supplied to the investigator (or a designated pharmacist) by the sponsor. Drug supplies must be kept in an appropriate secure area (eg, locked cabinet) and stored according to the conditions specified on the drug labels. The investigator (or a designated pharmacist) must maintain an accurate record of the shipment and dispensing of the study drug in a drug accountability ledger, a copy of which must be given to the sponsor at the end of the study. An accurate record of the date and amount of study drug dispensed to each subject must be available for inspection at any time. The CRA will visit the site and review these documents along with all other study conduct documents at appropriate intervals once study drug has been received by the site.

All drug supplies are to be used only for this study and not for any other purpose. The investigator (or site personnel) must not destroy any drug labels or any partly used or unused drug supply before approval to do so by the sponsor. At the conclusion of the study and as appropriate during the study, the investigator (or a designated pharmacist) will return all used and unused drug containers, drug labels, and a copy of the completed drug disposition form to the sponsor's CRA.

11.9 PUBLICATION OF RESULTS

All manuscripts, abstracts, or other modes of presentation arising from the results of the study must be reviewed and approved in writing by the sponsor in advance of submission pursuant to the terms and conditions set forth in the executed Clinical Trial Agreement between the sponsor/CRO and the institution/investigator. The review is aimed at protecting the sponsor's proprietary information existing either at the date of the commencement of the study or generated during the study.

The detailed obligations regarding the publication of any data, material results, or other information, generated or created in relation to the study shall be set out in the agreement between each investigator and the sponsor or CRO, as appropriate.

11.10 DISCLOSURE AND CONFIDENTIALITY

The contents of this protocol and any amendments and results obtained during the study should be kept confidential by the investigator, the investigator's staff, and the IRB/IEC and will not be disclosed in whole or in part to others, or used for any purpose other than reviewing or performing the study, without the written consent of the sponsor. No data collected as part of this study will be used in any written work, including publications, without the written consent of the sponsor. These obligations of confidentiality and non-use shall in no way diminish such obligations as set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the sponsor/CRO and the institution/investigator.

All persons assisting in the performance of this study must be bound by the obligations of confidentiality and non-use set forth in either the Confidentiality Agreement or Clinical Trial Agreement executed between the institution/investigator and the sponsor/CRO.

11.11 DISCONTINUATION OF STUDY

The sponsor reserves the right to discontinue the study for medical reasons or any other reason at any time. If a study is prematurely terminated or suspended, the sponsor will promptly inform the investigators/institutions and regulatory authorities of the termination or suspension and the reason(s) for the termination or suspension. The IRB/IEC will also be informed promptly and provided the reason(s) for the termination or suspension by the sponsor or by the investigator/institution, as specified by the applicable regulatory requirement(s).

The investigator reserves the right to discontinue the study should his/her judgment so dictate. If the investigator terminates or suspends a study without prior agreement of the sponsor, the investigator should inform the institution where applicable, and the investigator/institution should promptly inform the sponsor and the IRB/IEC and provide the sponsor and the IRB/IEC with a detailed written explanation of the termination or suspension. Study records must be retained as noted above.

11.12 SUBJECT INSURANCE AND INDEMNITY

The sponsor will provide insurance for any subjects participating in the study in accordance with all applicable laws and regulations.

12 APPENDICES

Appendix 1 WHO Functional Classification of Pulmonary Hypertension

World Health Organization Classification of Functional Status of Patients with PH

Class	Description
I	Patients with PH in whom there is no limitation of usual physical activity; ordinary physical activity does not cause increased dyspnea, fatigue, chest pain, or presyncope.
II	Patients with PH who have mild limitation of physical activity. There is no discomfort at rest, but normal physical activity causes increased dyspnea, fatigue, chest pain, or presyncope.
III	Patients with PH who have a marked limitation of physical activity. There is no discomfort at rest, but less than ordinary activity causes increased dyspnea, fatigue, chest pain, or presyncope.
IV	Patients with PH who are unable to perform any physical activity at rest and who may have signs of right ventricular failure. Dyspnea and/or fatigue may be present at rest, and symptoms are increased by almost any physical activity.
PH = pulmonary hypertension.	

Appendix 2 Classification of Chronic Kidney Disease

Chronic Kidney Disease: A Clinical Action Plan			
Stage	**Description**	**GFR ($mL/min/1.73m^2$)**	**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.

Appendix 3 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 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

	Grade 1	Grade 2	Grade 3	Grade 4
				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).

Appendix 4 APD356-G000-401 Healthy Lifestyle Program

Program Overview

All subjects in Study 401 will participate in a standardized weight management program consisting of intensive multi-component behavior therapy. The therapy will focus on healthy eating, physical activity, and lifestyle changes that will facilitate weight loss and weight maintenance.

The objectives of this program are as follows:

- Develop a moderate-intensity weight management program for all lorcaserin HCl study participants
- Standardize the weight management program across all study sites
- Maximize patient retention

Appendix 5 Biomarker Research

Drug Substance	BELVIQ® (lorcaserin hydrochloride)
Study Code	APD356-G000-401
Edition Number	Version 3
Date	2013-08-28

1 BACKGROUND AND RATIONALE FOR BIOMARKER RESEARCH

Obesity is a major risk factor for cardiovascular (CV) disease and other comorbidities, including diabetes, hypertension and hyperlipidemia. Mounting evidence suggests that excess adiposity leads to increased morbidity via pathologic activation of inflammatory, and subsequently thrombotic and metabolic, pathways. Observations supporting this mechanism are (1) that circulating mediators of inflammation, such as IL-6 and TNF-α, participate in vascular injury and insulin resistance and (2) that several of these inflammatory mediators are secreted by adipocytes and adipose tissue-derived macrophages. These inflammatory processes are reflected in the correlation between adiposity and high sensitivity C-reactive protein (hsCRP), a strong marker of systemic and vascular inflammation associated with cardiovascular risk.

Biomarkers of inflammation, metabolic dysregulation, and atherothrombosis have proven useful in identifying patients at risk of developing incident cardiovascular disease or diabetes as well as recurrent cardiovascular events in patients with stable atherosclerotic disease. However, less is known about the potential of these biomarkers to make similar predictions in the setting of obesity.

In addition to their role in prognostication, biomarkers that identify patients at higher risk for major adverse clinical outcomes can provide opportunity for guiding therapy. Patients at higher risk for cardiovascular events will have the greatest absolute risk reduction for a given relative risk reduction from a therapy and hence require a smaller number needed to treat to prevent a major event. Moreover, pathobiologically relevant biomarkers may identify a specific subset of patients who enjoy a larger relative risk reduction with a given pharmacotherapeutic intervention, and thus an even greater absolute risk reduction.

In addition to established biomarkers, new insights into the mechanistic pathways of obesity, diabetes and atherothrombosis have led to ongoing identification of novel cardiovascular and metabolic biomarkers. Using novel biomarkers that reflect the inflammatory, thrombotic, vascular, metabolic, and hemodynamic mediators of risk in patients with obesity and atherosclerotic risk factors, it may be possible to noninvasively characterize the participation of these different pathobiologic contributors in an individual patient and to monitor response to therapy.

As such, this large study of well-characterized, obese subjects with CV risk factors (including diabetes) or established CV disease presents a unique opportunity to investigate circulating biomarkers for their pathobiologic insight as well as their value for risk stratification, therapeutic guidance and disease monitoring.

The biomarker categories of interest for this study are broadly threefold: (1) those related to adiposity and metabolic dysregulation, (2) those related to dysglycemia and its complications, such as markers of glycation and renal dysfunction, and (3) those related to cardiovascular disease such as markers of atherosclerosis, ischemia, inflammation, thrombosis, hemodynamic stress and lipid dysregulation. Selected examples for each of these areas follow below.

Markers of adiposity include adiponectin, interleukin-6 (IL-6), and resistin. Adiponectin is secreted by adipocytes and is thought to play a role insulin sensitivity, lipid metabolism and inflammation. Interestingly, in patients with established coronary disease (as determined by angiography), lower levels of adiponectin independently predicted major adverse cardiac events. Furthermore, in primary prevention populations, higher concentrations of adiponectin are associated with lower risks of cardiovascular disease and the risk of developing incident T2DM. IL-6 is a pro-inflammatory cytokine released by adipose tissue and is the major stimulant for hepatic generation of CRP. Elevated levels of IL-6 were shown to be associated with increased risk of myocardial infarction in a large cohort of apparently healthy men. A third adipokine, resistin, is thought to mediate insulin resistance and metabolic dysfunction. Several studies have shown a relationship between resistin and major adverse cardiovascular events in both stable CAD and ACS populations.

Markers of dysglycemia and its sequelae include advanced glycation end products (AGEs), receptor for AGE (RAGE) and amino acids/metabolites. In patients with type II diabetes, elevated glucose levels lead to the dysregulation of physiologic metabolic pathways resulting in the production and accumulation of pathologic glycolated proteins, AGEs. Elevated levels of AGE/RAGE have a variety of pathologic consequences such as oxidizing LDL, promoting atherosclerosis, and decreasing NO production. Accordingly, AGE and RAGE have been shown to be prognostic markers for vascular disease in both diabetic and non-diabetic populations. Recent studies found that metabolite levels, specifically several branched chain and aromatic amino acids, can predict development of diabetes in normoglycemic individuals as well as incident cardiovascular disease.

Markers of cardiovascular disease and inflammation include high-sensitivity cardiac troponin, natriuretic peptides, hsCRP and fibrinogen. Cardiac troponin, used commonly for diagnosis of AMI, has been shown to predict worsened cardiovascular outcomes in stable individuals with cardiovascular risk factors. Elevated levels of natriuretic peptides (BNP or the amino-terminal fragment of the prohormone [NT-proBNP]) are closely associated with mortality and/or heart failure across a broad range of individuals, ranging from the general population to patients with acute coronary syndromes and decompensated heart failure. An interesting interplay between natriuretic peptides and obesity has been recognized. Natriuretic peptides levels are lower in obese patients compared with non-obese patients, an effect that may be mediated by increased clearance of natriuretic peptides by adipose tissue. Conversely, it appears that natriuretic peptides may influence adipose tissue through moderation of lipid metabolism. hsCRP, a marker of inflammation, predicts risk of first MI in healthy cohorts and future coronary events in stable patients. Furthermore, elevated hsCRP levels in obesity are prognostic for development of cardiovascular disease and predictive of progression to type II diabetes. Fibrinogen, an acute phase reactant that has a central role in coagulation and platelet aggregation, is a marker for CV risk factors and predicts future cardiovascular disease. Notably, lorcaserin hydrochloride therapy has been shown to decrease hsCRP and fibrinogen levels.

The evaluation of biomarkers in subjects in this trial may provide important insight into pathobiology of obesity, diabetes and cardiovascular disease, improve our ability to risk stratify

subjects, and provide information that can be used to tailor therapy. This study may also provide additional insights into the possible mechanistic pathways leading to CV benefit with lorcaserin hydrochloride.

2. OBJECTIVES

Aim 1: To evaluate the effect of treatment with lorcaserin hydrochloride compared to placebo on the change in baseline biomarkers of adiposity and metabolic dysregulation, dysglycemia and its complications, and CV risk (atherosclerosis, ischemia, inflammation, thrombosis, hemodynamic stress and lipid dysregulation) over the data acquisition period.

We hypothesize that lorcaserin hydrochloride will improve circulating concentrations of biomarkers of these conditions/processes over time compared to placebo.

Aim 2: To evaluate the prognostic performance of established and novel biomarkers of adiposity and metabolic dysregulation, dysglycemia and its complications, and CV risk (atherosclerosis, ischemia, inflammation, thrombosis, hemodynamic stress and lipid dysregulation) individually and in combination (multimarker approach).

We hypothesize that baseline biomarkers can identify subgroups of overweight or obese subjects at increased risk of major adverse cardiovascular outcomes and/or the development of diabetes. Furthermore, we hypothesize that a multi-marker approach can improve discrimination, accuracy, and net reclassification improvement of models predicting the development or progression of these disorders.

Aim 3: To evaluate whether obese subjects identified at higher risk on the basis of biomarkers experience greater absolute and/or relative risk reduction in major adverse cardiovascular outcomes and/or the development of diabetes with lorcaserin HCl versus placebo.

We hypothesize that subjects with the highest risk biomarker profiles will observe greatest benefit from treatment with lorcaserin hydrochloride.

Aim 4: To evaluate the prognostic significance of the change in the levels of established and novel biomarkers of adiposity, inflammation, hemodynamic stress, myocardial ischemia/necrosis and metabolism between baseline and 6 month, and whether changes in biomarker concentration identify subjects with greater benefit with lorcaserin HCl versus placebo.

We hypothesize that the change in levels of biomarkers between baseline and 6 months can identify subgroups of overweight or obese subjects at increased risk of major adverse cardiovascular outcomes and/or the development of diabetes, who are likely to derive greater benefit from treatment with lorcaserin HCl.

3 BIOLOGIC RESEARCH PLAN AND PROCEDURES

This appendix to the Clinical Study Protocol has been subjected to peer review according to Eisai standard procedures. Collection of the biomarker samples will be bound by the sample

principles and processes outlined in the main study protocol. Sample collection for biomarker analysis is required as per the study protocol unless the collection and use of the samples is prohibited by specific country laws.

3.1 Selection of biologic research population

3.1.1 Study selection record

All subjects will be asked to participate in this biologic research (except where prohibited by local regulations). Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main Clinical Study Protocol.

3.1.2 Inclusion criteria

For inclusion in this biologic research, subjects must fulfill all of the inclusion criteria described in the main Clinical Study Protocol.

3.1.3 Exclusion criteria

Exclusion from this biologic research may be for any of the exclusion criteria specified in the main Clinical Study Protocol.

3.1.4 Discontinuation of subjects from this biologic research

Subjects may withdraw from this biologic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in the main Clinical Study Protocol.

3.2 Collection of samples for biologic research

All subjects in participating countries will be asked to participate in this biologic research at Visit 2. If the patient agrees to participate, blood samples will be taken at Visit 2 (Randomization/Baseline) and the remaining visits indicated on the schedule in the main Clinical Study Protocol.

- Blood samples for isolation of serum and plasma will be obtained as follows:
  - Visit 2: Serum (10-mL draw); EDTA-anticoagulated plasma (6-mL draw x 2)
  - Remaining visits: Serum (10-mL draw); EDTA-anticoagulated plasma (6-mL draw)
- Samples will be frozen at -20°C or colder until shipped to the central laboratory on dry ice.

These procedures are detailed in the Laboratory Manual of Operations.

3.3 Coding and storage of samples

The biomarker samples will be labeled (or "coded") with a study specific code to maintain patient confidentiality. Samples do not carry any patient identifying information. Samples will be stored for up to 20 years after the completion of the study (defined as submission of the clinical study report [CSR] to the appropriate regulatory agencies). At the end of the storage period,

samples will be destroyed. Samples may be stored longer if a Health Authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

3.4 Analytic Plan

3.4.1 Biomarkers of interest

Analysis will be performed of biomarkers of adiposity and metabolic dysregulation, dysglycemia and its complications, and CV risk (atherosclerosis, ischemia, inflammation, thrombosis, and hemodynamic stress) to address the specific 4 aims listed above. A detailed analytic plan will be developed. Candidate biomarkers are listed below, from which a subset will be measured based on the scientific evidence at the time of testing.

Biomarkers of Adiposity/Obesity and Metabolic Dysregulation:

- Adipokines (eg, adiponectin, leptin, resistin, angiotensinogen, IL-6, TNF-α)
- Mediators of appetite (eg, Orexin A, neuropeptide Y, α-melanocyte stimulating hormone, agouti-related protein)
- Biomarkers of Lipid Dysregulation/Insulin Resistance (eg, Lipoproteins and modified/oxidized lipoproteins, Lp(a))

Dysglycemia and its complications

- Glycation end products and associated receptors (eg, AGE, RAGE)

Biomarkers of Cardiovascular Risk

Biomarkers of Oxidative Stress:

- Myeloperoxidase
- ADMA and other arginine metabolism products

Biomarkers of Endothelial Function:

- VCAM-1, ICAM-1, vWF, E-selectin

Biomarkers of Ischemia/Injury:

- Cardiac troponin, FABP

Biomarkers of Inflammation and Atherothrombosis:

- hs-CRP
- Fibrinogen
- phospholipases (eg, Lp-PLA2 and sPLA2)
- metalloproteinases (eg, PAPP-A, MMP-9, MMP-11)
- cytokines (eg, IL-1β, IL-1Ra, IL-6, IL-18, GDF-15, PlGF)
- chemotactic molecules (eg, MCP-1)
- sCD40L

Biomarker of Renal Dysfunction:

- Cystatin-C, FGF-23, NGAL

Biomarkers of Hemodynamic Stress:

- Natriuretic peptides (eg, BNP, ANP and their NT-prohormones)
- MR-adrenomedullin, C-terminal proendothelin 1, copeptin
- ST-2
- Galectin-3

Specific biomarkers to be tested will depend on the totality of published data at the time analyses are ready to commence. Other markers of these processes may be added or substituted as new evidence comes to light. In addition to analysis of existing biomarkers, proteomics and metabolomic analyses may be performed on samples to develop and test novel protein markers of cardiovascular outcomes. The biomarker samples may be used for discovery and/or validation to identify biomarkers that, for evaluation of response and/or safety-related outcomes as well as for use in diagnostic development.

Sample processing and analysis will be performed by laboratories under the direction of the Sponsor and/or designee. Processing, analysis, and storage will be performed at secure laboratory facilities to protect the validity of the data and maintain subject privacy. Samples will only be used for the purposes described in this protocol.

3.4.2 Biomarker Testing

Biomarkers will be measured in all subjects at baseline with serial testing at three additional timepoints. Testing at serial timepoints may be expanded.

4 ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this biologics research component, are outlined in Section 5 of the main Clinical Study Protocol.

Informed consent
The biologic component of this study is optional and the patient may participate in other components of the main study without participating in the biologic component. The principal investigator(s) is responsible for ensuring that consent is given freely and that the patient understands that they may freely discontinue from the biologic aspect of the study at any time.

Right to Withdraw
If, during the time the samples are stored, a participant would like to withdraw his/her consent for participation in this research, Eisai or its agents will destroy the samples. Information from any assays that have already been completed at the time of withdrawal of consent will continue to be used as necessary to protect the integrity of the research project.

Subject Privacy and Return of Data
No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. All biomarker samples will be coded.

The Sponsor will take steps to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The Sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- Clinical research organizations retained by the Sponsor;
- Independent ethics committees or institutional review boards that have responsibility for this research study;
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

Given the research nature of the biomarker analysis, it will not be possible to return individual data to subjects. The results that may be generated are not currently anticipated to have clinical relevance to the patients or their family members. Therefore, these results will not be disclosed to the subjects or their physicians.

5 DATA MANAGEMENT

Biomarker data from the designated laboratory will be merged with the clinical database for statistical analysis.

The results from this biologic research may be reported in the CSR for the main study, or in a separate report as appropriate.

Some or all of the clinical datasets from the main study may be merged with the biologic data in a suitable secure environment separate from the clinical database.

6 STATISTICAL ANALYSIS PLAN

The biomarker analyses are exploratory in nature. A sample size of approximately 10,000 subjects (assuming 80%-90% participation) will provide 80% power to detect a relative risk of ≥1.2 for the primary endpoint of MACE and secondary endpoint of MACE+ for subjects above versus those below the median level of a biomarker. These values are in keeping with risk estimates and interactions seen with other biomarkers and represent the thresholds of clinical importance.

Appendix 6 Pharmacogenetic Research

Drug Substance	BELVIQ® (lorcaserin hydrochloride)
Study Code	APD356-G000-401
Edition Number	Version 2
Date	2013-08-28

1 BACKGROUND AND RATIONALE

Subjects enrolled in this clinical study will have the option to have samples collected for genetic analysis. Genetic variations affect the risk of developing cardiovascular disease (eg, myocardial infarction) and metabolic disease (eg, diabetes). Furthermore, genetic variants may alter the clinical efficacy and/or the safety profile of specific pharmacotherapy, either directly by affecting the pharmacokinetics or pharmacodynamics of the drug in question, or indirectly by altering the risk of developing outcomes the drug may prevent.

2 GENETIC RESEARCH OBJECTIVES

The objective of this research is to collect deoxyribonucleic acid (DNA) for research into genes/genetic variation that may influence response (eg, distribution, safety, tolerability and efficacy, including effects on obesity and the development and progression of secondary complications of obesity) to treatment with lorcaserin and genetic factors that may influence susceptibility to obesity, cardiovascular disease, and diabetes mellitus, and/or associated cardiovascular conditions and their risk factors.

The pharmacogenomic samples may be used to identify genetic factors that may influence a subject's exposure to the study drug, as well as genetic factors that may have an effect on clinical response or potential adverse events related to study treatment, and to explore the role of genetic variability in response/resistance. Samples may be analyzed to determine a subject's genotypes or sequence for a number of genes or non-coding regulatory regions. The research may include the investigation of polymorphisms in genes that are likely to influence the study drug pharmacokinetics or therapeutic response.

3 GENETIC RESEARCH PLAN AND PROCEDURES

3.1 Selection of genetic research population

3.1.1 Study selection record

All subjects will be asked to participate in this genetic research. Participation is voluntary and if a subject declines to participate there will be no penalty or loss of benefit. The subject will not be excluded from any aspect of the main study.

3.1.2 Inclusion criteria

For inclusion in this genetic research, subjects must fulfill all of the inclusion criteria described in the main Clinical Study Protocol and:

- Provide informed consent for the genetic sampling and analyses.

3.1.3 Exclusion criteria

Exclusion from this genetic research may be for any of the exclusion criteria specified in the main Clinical Study Protocol or any of the following:

- Previous bone marrow transplant
- Whole blood transfusion within 120 days of genetic sample collection

3.1.4 Discontinuation of subjects from this genetic research

Subjects may withdraw from this genetic research at any time, independent of any decision concerning participation in other aspects of the main study. Voluntary discontinuation will not prejudice further treatment. Procedures for discontinuation are outlined in the main Clinical Study Protocol.

3.2 Collection of samples for genetic research

The blood sample (10 ml EDTA) for genetic research will be obtained from the subjects at Visit 2 (Randomization/Baseline). Although genotype is a stable parameter, early sample collection is preferred to avoid introducing bias through excluding subjects who may withdraw due to an adverse event (AE). If for any reason the sample is not drawn at baseline, it may be taken at any visit until the last study visit at the discretion of the investigator and site staff.

Only 1 sample should be collected per subject for genetics during the study. Samples will be collected, labeled, stored and shipped as detailed in the Laboratory Manual of Operations

3.3 Coding and storage of DNA samples

No subject-identifying information (eg, initials, date of birth, government identifying number) will be associated with the sample. The DNA samples will be double coded. Double-coding involves removing the initial code (subject ID) and replacing with another code such that the subject can be re-identified by use of 2 code keys. The key linking the sample ID to the subject number will be maintained separately from the sample. Laboratory personnel performing genetic analysis will not have access to the key.

All genetic samples will be stored under secure conditions with restricted access at Eisai, the designated vendor, and/or a contracted third party working with them on this study. Samples will be stored for up to 20 years after the completion of the study (defined as submission of the clinical study report [CSR] to the appropriate regulatory agencies). At the end of the storage period, samples will be destroyed. Samples may be stored longer if a Health Authority (or medicinal product approval agency) has active questions about the study. In this special circumstance, the samples will be stored until the questions have been adequately addressed.

3.4 Genetic testing

There are genetic variants that increase the risk of the development of particular disease states (eg, degrees of obesity, cardiovascular disease, and type 2 diabetes mellitus), and lorcaserin may offer particular benefit among patients with these polymorphisms. Genes will be evaluated both in relation to the disease state and to the properties of the study drug, and testing may include:

1. Body mass index and obesity: FTO, BDNF, MC4R.

2. Cardiovascular disease as well as the risk of recurrent events: CDKN2A, SORT1, and CXCL12; additionally, a genetic risk score derived from 13 common variants has been successfully used to stratify risk for incident cardiovascular disease and MI in prospective

cohorts. An additional 13 loci have now been identified, and these composite scores can also be used.

3. Development and severity of type 2 diabetes mellitus: TCF7L2, WFS1, and KCNQ1 as well as a composite genetic score will be evaluated.

4. Drug disposition and putative drug target: HTR2C.

5. Unbiased genetic studies may add further understanding of the mechanisms related to degrees of obesity, cardiovascular disease, and type 2 diabetes mellitus as well as lorcaserin's modification of these particular entities. Discovery studies using a gene array could be performed.

4 ETHICAL AND REGULATORY REQUIREMENTS

The principles for ethical and regulatory requirements for the study, including this genetics research component, are outlined in the main Clinical Study Protocol.

4.1 Informed consent

The genetic component of this study is optional and the subject may participate in other components of the main study without participating in the genetic component. To participate in the genetic component of the study the subject must sign and date both the consent form for the main study and the genetic component of the study. Subjects may freely discontinue from the genetic aspect of the study at any time.

4.2 Subject data protection

Individual genotype results will not be provided to subjects, any insurance company, any employer, their family members, general physician or any other third party, unless required to do so by law.

Samples will only be used for the purposes described in this protocol. Laboratories contracted to perform the analysis will not retain rights to the samples beyond those necessary to perform the specified analysis and will not transfer or sell those samples.

5 DATA MANAGEMENT

Any genotype data generated in this study will be in appropriate secure system within Eisai, the designated vendor, and/or a contracted third party working with them on this study.

Steps will be taken to ensure that data are protected accordingly and confidentiality is maintained as far as possible. Data from subjects enrolled in this study may be analyzed worldwide, regardless of location of collection.

The Sponsor and its representatives and agents may share coded data with persons and organizations involved in the conduct or oversight of this research. These include:

- Clinical research organizations retained by the Sponsor;
- Independent ethics committees or institutional review boards that have responsibility for this research study;
- National regulatory authorities or equivalent government agencies

At the end of the analysis, results may be presented in a final report which can include part or all of the coded data, in listing or summary format. Other publication (eg, in peer-reviewed scientific journals) or public presentation of the study results will only include summaries of the population in the study, and no identified individual results will be disclosed.

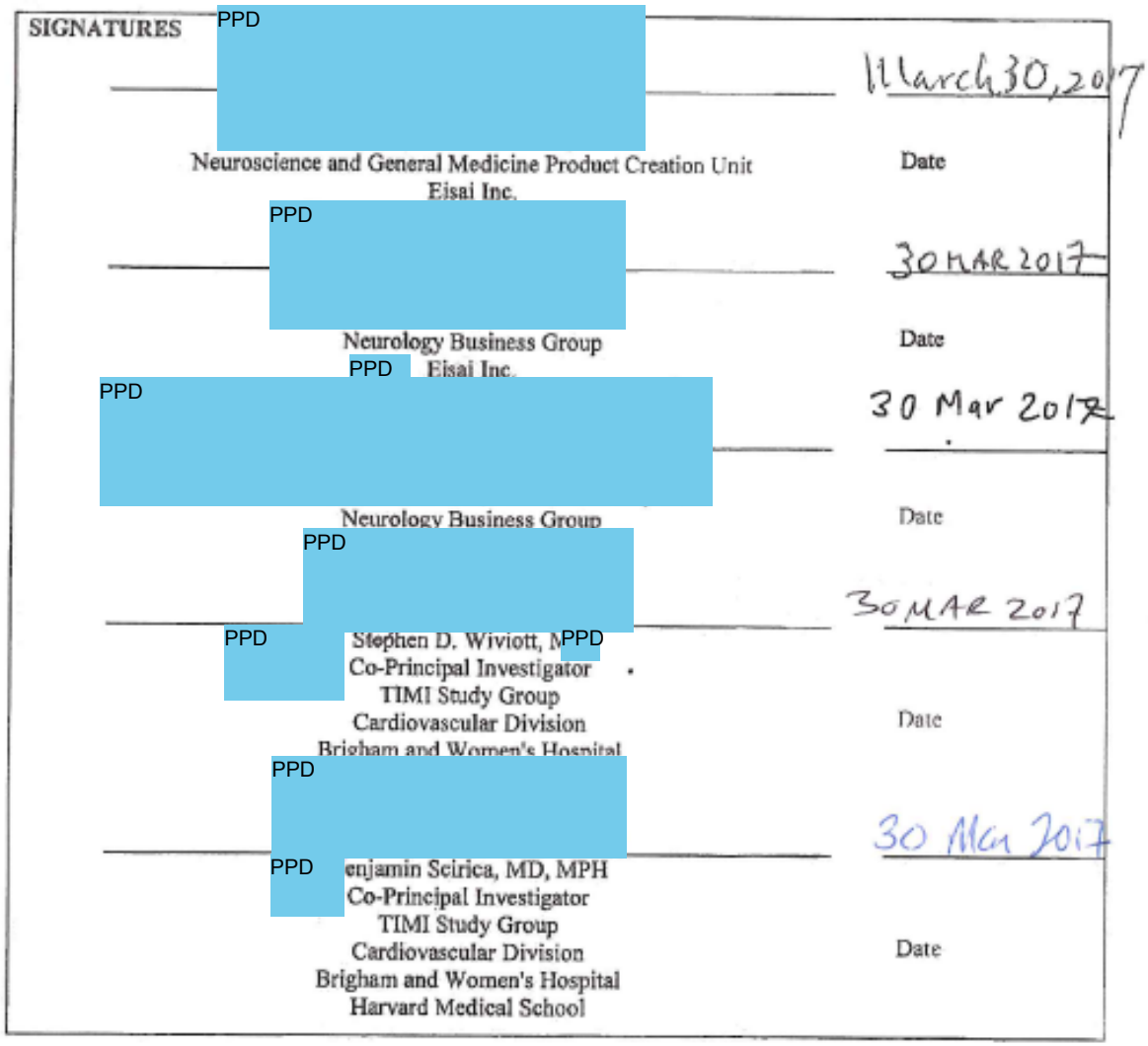
The genetic material is for research use only and not clinical care. Therefore, these results will not be disclosed to the subjects or their physicians.

6 STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The number of subjects that will agree to participate in the genetic research is unknown. It is therefore not possible to establish whether sufficient data will be collected to allow a formal statistical evaluation or whether only descriptive statistics will be generated. A statistical analysis plan will be prepared where appropriate.

PROTOCOL SIGNATURE PAGE

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
Investigational Product Name:	APD356/BELVIQ (lorcaserin hydrochloride)
IND Number:	69888
EudraCT Number:	2013-000324-34



INVESTIGATOR SIGNATURE PAGE

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
Investigational Product Name:	APD356/BELVIQ (lorcaserin hydrochloride)
IND Number:	69888
EudraCT Number:	2013-000324-34

I have read this protocol and agree to conduct this trial in accordance with all stipulations of the protocol and in accordance with International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) and all applicable local Good Clinical Practice (GCP) guidelines, including the Declaration of Helsinki.

Medical Institution

Investigator	Signature	Date