



Trial Designs

Design and rationale for the Cardiovascular and Metabolic Effects of Lorcaserin in Overweight and Obese Patients–Thrombolysis in Myocardial Infarction 61 (CAMELLIA-TIMI 61) trial



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ABSTRACT

Objectives: Lorcaserin, a selective serotonin 2C receptor agonist, is an effective pharmacologic weight-loss therapy that improves several cardiovascular risk factors. The long-term clinical cardiovascular and metabolic safety and efficacy in patients with elevated cardiovascular risk are unknown.

Research design and methods: CAMELLIA-TIMI 61 (NCT02019264) is a randomized, double-blind, placebo-controlled, multinational clinical trial designed to evaluate the safety and efficacy of lorcaserin with regard to major adverse cardiovascular events and progression to diabetes in overweight or obese patients at high cardiovascular risk. Overweight or obese patients either with established cardiovascular disease or with diabetes and at least 1 other cardiovascular risk factor were randomized in a 1:1 ratio to lorcaserin 10 mg twice daily or matching placebo. The primary safety objective is to assess for noninferiority of lorcaserin for the composite end point of cardiovascular death, myocardial infarction, or stroke (major adverse cardiovascular event [MACE]) (with noninferiority defined as the upper bound of a 1-sided 97.5% CI excluding a hazard ratio of 1.4) compared with placebo assessed at an interim analysis with 460 adjudicated events. The efficacy objectives, assessed at study completion, will evaluate the superiority of lorcaserin for the primary composite end point of cardiovascular death, myocardial infarction, stroke, hospitalization for unstable angina, heart failure, or any coronary revascularization (MACE+) and the key secondary end point of conversion to diabetes. Recruitment began in January 2014 and was completed in November 2015 resulting in a total population of 12,000 patients. The trial is planned to continue until at least 1,401 adjudicated MACE+ events are accrued and the median treatment duration exceeds 2.5 years.

Conclusion: CAMELLIA-TIMI 61 is investigating the safety and efficacy of lorcaserin for MACEs and conversion to diabetes in overweight or obese patients with established cardiovascular disease or multiple cardiovascular risk factors.

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Obesity has reached epidemic proportions with rates doubling over the last 30 years.¹ Globally, 13% of adults are obese (body mass index [BMI] > 30 kg/m²) with rates as high as 25%–30% in some developed

countries; another 39% of adults are overweight (BMI of 25–30 kg/m²) globally.^{1,2} Obesity is associated with development of life-threatening comorbid diseases, such as hypertension, type 2 diabetes, coronary disease, and heart failure, as well as increased mortality.^{3–6} Weight loss, even in the moderate range (5%–10% of body weight), is associated with lower risk for these comorbid conditions, and observational studies of bariatric surgery have demonstrated an association between significant weight loss (typically greater than achievable with lifestyle or

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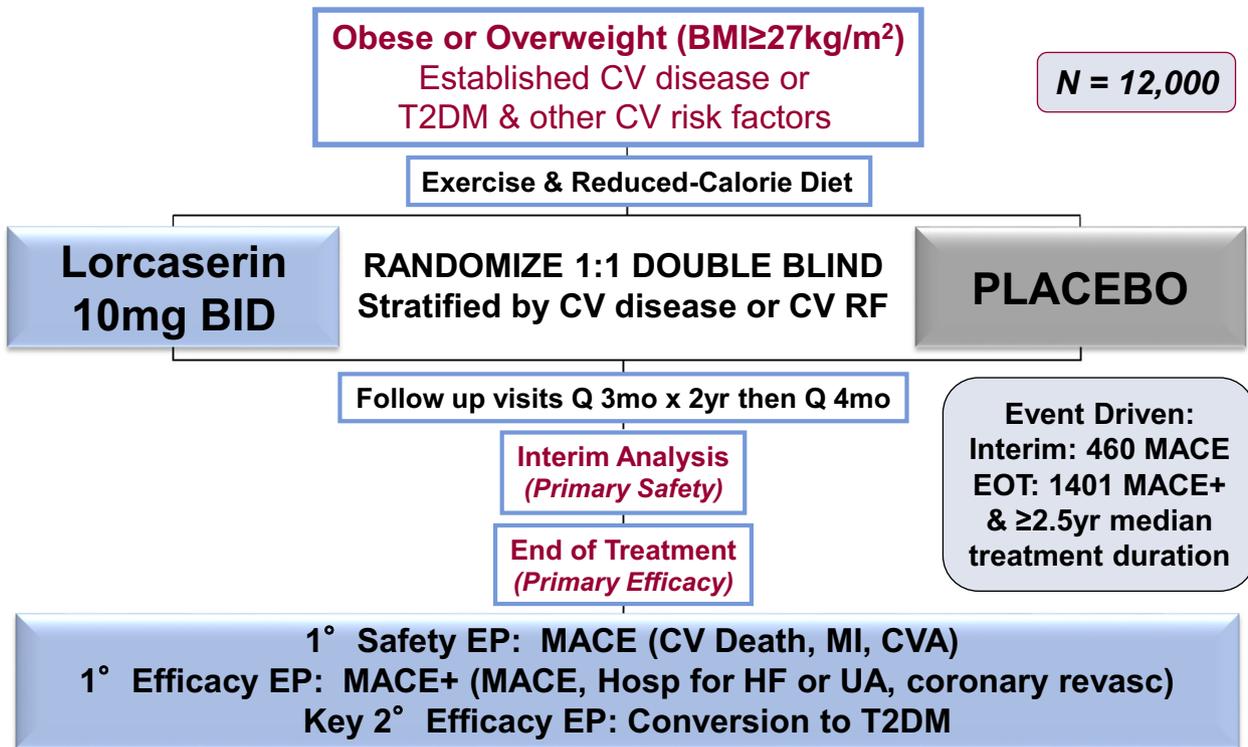


Figure. CAMELLIA-TIMI 61 Trial Schema.

pharmacologic strategies) and lower rates of myocardial infarction (MI), stroke, heart failure, and death.^{7–11}

Pharmacologic weight-loss strategies are noninvasive adjuncts to lifestyle modification and alternatives to bariatric procedures. Historically, it has been challenging to identify safe and efficacious long-term weight-loss pharmacotherapies, as evidenced by the cardiovascular toxicity of fenfluramine, dexfenfluramine, and sibutramine and the adverse psychiatric profile of rimonabant.^{12–14} Balancing the desire to provide access to effective weight-loss pharmacotherapy with the importance of establishing adequate safety, the US Food and Drug Administration (FDA) has conditionally approved agents for long-term weight management, including lorcaserin, contingent on the ability to exclude an increased risk of adverse cardiovascular outcomes (with the upper bound of the 1-sided 97.5% CI for the hazard ratio < 1.4) in a dedicated postmarketing safety study.¹⁵

Lorcaserin is a selective serotonin 2C (5-HT_{2C}) receptor agonist that is effective for weight management in overweight and obese adults.^{16–18} Lorcaserin is thought to reduce body weight by decreasing appetite through stimulation of 5-HT_{2C} receptors in the hypothalamus, activating the anorexigenic pro-opiomelanocortin pathway.¹⁹ Based on the phase 3 experience in more than 7,500 subjects followed for at least 1 year, lorcaserin was approved by the US FDA in 2012 as an adjunct to a reduced-calorie diet and increased physical activity for chronic weight management in adults with a BMI ≥ 30 kg/m² or with a BMI ≥ 27 kg/m² in the presence of at least 1 weight-related comorbid condition.²⁰ The Cardiovascular And Metabolic Effects of Lorcaserin In Overweight And Obese Patients—Thrombolysis in Myocardial Infarction 61 (CAMELLIA-TIMI 61) study is designed to fulfill the postmarketing requirement to evaluate cardiovascular safety as well as to investigate the long-term cardiovascular and metabolic benefits of lorcaserin in obese or overweight patients at high cardiovascular risk with established atherosclerotic vascular disease or multiple cardiovascular risk factors.

Study design and population

CAMELLIA-TIMI 61 is a randomized, double-blind, placebo-controlled multinational clinical trial designed to evaluate the safety

and efficacy of lorcaserin for long-term treatment of obese or overweight patients at high cardiovascular and metabolic risk (Figure). The primary hypotheses are that lorcaserin is safe and will reduce the incidence of cardiovascular events (major adverse cardiovascular event [MACE]+) as well as prevent progression to new-onset diabetes during long-term follow up. The anticipated duration of the trial is approximately 5 years with a median follow up of 3–4 years; the actual duration of the trial will be based on accrual of a predetermined number of events.

Eligible subjects must be obese or overweight with a BMI ≥ 27 kg/m² with either (1) established cardiovascular disease with or without diabetes or (2) diabetes and at least 1 other cardiovascular risk factor (Table 1). To qualify for established cardiovascular disease criteria, study subjects must be at least 40 years old and have a documented history of atherosclerosis involving the coronary, cerebral, or peripheral vascular system (Table 1). To qualify for the multiple cardiovascular risk factor criteria, study subject must be at least 55 years old (women) or 50 years old (men) and have diabetes and at least 1 of the following other risk factors: dyslipidemia, hypertension, moderate renal insufficiency, an elevated high-sensitivity C-reactive protein, or micro- or macroalbuminuria (Table 1). Key exclusion criteria include moderate to severe pulmonary hypertension, heart failure, or hepatic dysfunction; severe valvular disease or renal dysfunction; planned bariatric surgery; or use of pharmacologic weight-loss therapy (see Table 1 for additional details).

Enrollment was targeted to achieve approximately 20% of the total population in the multiple risk factor stratum and 80% in the established cardiovascular disease stratum to ensure that the study population is at sufficiently high risk to achieve the study objectives. To provide an adequate sample size to power the key secondary efficacy end point of new-onset diabetes, enrollment was restricted to 50% with diabetes enrollment was restricted to 50% with diabetes, including 20% with cardiovascular risk factors only and 30% with established cardiovascular disease. The remaining 50% of subjects enrolled had established cardiovascular disease without diabetes.

Twelve thousand subjects were randomized in a 1:1 ratio to receive either lorcaserin 10 mg twice daily or placebo with stratification by cardiovascular disease status (established cardiovascular disease vs

Table 1
Inclusion and exclusion criteria

Inclusion	Exclusion
1. BMI =27 kg/m ²	- MI or stroke within 1 m of screening
2. Able and willing to comply with a reduced-calorie diet and an increased physical activity program	- Moderate to severe CHF (NYHA class III or IV)
3. Age =40 y with established CV disease defined by at least 1 of the following:	- LVEF < 20%
a. Coronary artery disease (prior MI, prior coronary revascularization, or unrevascularized stenoses of =50% in 2+ territories)	- Moderate to severe pulmonary hypertension (WHO class III and IV)
b. Cerebrovascular disease (prior ischemic stroke or prior carotid revascularization)	- Severe valvular disease (history of corrected severe valve disease permitted)
c. Symptomatic PAD (claudication with an ABI < 0.85 or prior peripheral revascularization)	- Severe renal impairment (eGFR <30 or ESRD)
OR	- Severe hepatic impairment (Child-Pugh score 10 to 15)
Age ≥ 55 y for women or ≥ 50 y for men with T2DM and at least 1 of the following CV risk factors without established CV disease:	- Hemoglobin A1c >10%
a. Hypertension (SBP > 140, DBP >90, or receiving therapy for hypertension)	- Use of the following prior to screening:
b. Dyslipidemia (LDL-C > 130, HDL-C < 40, or receiving lipid-lowering therapy for dyslipidemia)	a. Pharmacologic weight-loss therapy (within 1 m)
c. Renal dysfunction (eGFR 30–60)	b. More than 1 serotonergic agent (within 1 m)
d. hs-CRP > 3 mg/L in the absence of known acute or chronic inflammatory conditions	c. Agents known to increase the risk of cardiac valvulopathy (within 6 m)
e. Albuminuria (spot urinary ACR ≥30)	d. Lorcaserin (within 6 m)
4. Provides written informed consent	- Planned bariatric surgery or bariatric surgery performed within 1 y before screening
	- Alcohol dependence/abuse or recreational drug use in the prior 2 y
	- Pregnancy, lactation, or females of childbearing potential not using a highly effective method of contraception
	- Any condition judged by the investigator to affect safety, interfere with the study assessments, or result in a life expectancy of less than 1 y
	- Participation in another clinical trial with an investigational product during the prior 30 d
	- Concern for inability to comply with the protocol

CV, cardiovascular; PAD, peripheral artery disease; ABI, ankle-brachial index; T2DM, type 2 diabetes mellitus; SBP, systolic blood pressure (mm Hg); DBP, diastolic blood pressure (mm Hg); LDL-C, low-density lipoprotein cholesterol (mg/dL); HDL-C, high-density lipoprotein cholesterol (mg/dL); eGFR, estimated glomerular filtration rate (mL/min/1.73 m²) by the Chronic Kidney Disease Epidemiology Collaboration equation; hs-CRP, high-sensitivity C-reactive protein; ACR, albumin-creatinine ratio (μg/mg); CHF, congestive heart failure; NYHA, New York Heart Association; LVEF, left ventricular ejection fraction; ESRD, end-stage renal dysfunction.

multiple risk factors only). Randomization was performed in a double-blind fashion using a central computerized, Web-based system. Subjects are followed for all clinical end points and adverse events until the end of the study.

The CAMELLIA-TIMI 61 trial is designed to use a 2-step analysis: the primary safety outcome, noninferiority for MACE of lorcaserin versus placebo, will be assessed at an interim analysis once the prespecified number of adjudicated MACE events has accrued (Figure). If noninferiority is met, the trial continues until the other parameters are reached, including a median treatment duration of at least 2.5 years and accrual of the prespecified number of efficacy outcomes.

The study is being performed in accordance with ethical principles in a manner consistent with the Declaration of Helsinki, ICH Good Clinical Practice guidelines, and applicable regulatory requirements. The final study protocol and informed consent have been reviewed and approved by the corresponding health authorities and ethics boards/institutional review boards for all participating study sites. Enrolled subjects gave informed consent for participation in the study.

Treatment protocol and follow-up procedures

Dose selection

Study drug is administered at a dose of lorcaserin 10 mg twice daily or matched placebo based on the results of the BLOOM (Behavioral Modification and Lorcaserin for Overweight and Obesity Management), BLOOM-DM (diabetes-mellitus), and BLOSSOM Phase 3 studies demonstrating this dose to be safe and effective for long-term weight management in overweight patients with at least 1 weight-related comorbidity or obesity.^{16–18} In contrast to the US labeling, which recommends discontinuation of lorcaserin if weight loss is <5% of baseline weight 12 weeks after initiation of therapy, enrolled subjects were expected to remain on study drug even in the absence of significant weight loss to assess for weight-independent metabolic effects of lorcaserin. In August 2015, the protocol was amended to allow subjects who experience nonserious adverse events believed to be related to study drug to

be dosed at 10 mg once instead of twice daily, with the expectation that most subjects would up-titrate to twice daily over time. Lorcaserin 10 mg twice daily is the only regulatory-approved dosing schedule.

Concomitant therapies

It is recommended that all subjects in the CAMELLIA-TIMI 61 study are treated according to standard of care for their cardiovascular risk factors (eg, hypertension, hyperlipidemia, hyperglycemia) and secondary prevention at the discretion of their treating physicians.

Concomitant use of pharmacologic therapies intended for weight loss, including prescription and over-the-counter drugs and herbal preparations, use of 2 or more medications associated with an increased risk of serotonin syndrome (eg, selective serotonin reuptake inhibitors and serotonin-norepinephrine reuptake inhibitors), and agents associated with an increased risk of valvulopathy and/or pulmonary hypertension (eg, cabergoline), is prohibited. If use of any of the prohibited concomitant medications is clinically warranted, study drug should be discontinued until the relevant agent has been discontinued for more than the trial-specified duration.

Healthy lifestyle program

All subjects were encouraged to participate in a standardized weight management program consisting of intensive multicomponent behavior therapy that focuses on diet and physical activity to facilitate weight loss and weight maintenance. As a part of this program, subjects are provided with access to print and/or online dietary and exercise informational materials and tracking capabilities, as well unlimited telephonic access to a registered dietitian.

Visit schedule and follow-up

Randomized subjects return for study visits at 3-month intervals during the first 2 years of follow-up, followed by visits every 4 months thereafter until the end of the study. During follow-up visits, subjects

are assessed for adverse and potential end point events, and blood and urine are sampled for central laboratory testing. All subjects are to undergo an end of treatment visit when permanently discontinuing therapy. It is recommended that all subjects attend the final study visit in person regardless of whether or not they are taking the randomized study treatment. Subjects on study drug at the time of study completion are recommended to complete a final safety assessment 30 days after the end of treatment visit. Vital status assessment will be attempted in all subjects at the end of the trial.

Study end points

The primary safety end point of the trial is a composite of cardiovascular death, MI, or stroke. The primary efficacy end point is a composite of cardiovascular death, MI, stroke, hospitalization for unstable angina, heart failure, or any coronary revascularization (MACE+). The key secondary efficacy end point is conversion to diabetes (based on the 2013 American Diabetes Association Guidelines) in subjects with prediabetes at baseline.²¹ Definitions of the primary and key secondary end points are detailed in [Appendix A](#).

Other efficacy and safety objectives include glycemic control (hypo- and hyperglycemia), renal function, weight loss, blood pressure, dyslipidemia, and inflammatory markers. Because of the theoretical concerns or observed increases in several adverse events with other weight-loss therapies, serotonin agonists, or preclinical studies with lorcaserin, assessments of specific adverse events of special interest are being undertaken. These include cardiac valvulopathy, pulmonary hypertension, malignancies, breast fibroadenomas, ductal carcinoma in situ, serotonin syndrome, euphoria or psychosis, suicidal ideation or behavior, and priapism.

Adjudication of the primary and key secondary end points is performed according to the definitions in the CAMELLIA-TIMI 61 Clinical Endpoints Committee (CEC) Charter ([Appendix A](#)) by an independent, blinded, and trained CEC with board certification in Cardiology, Neurology, or Endocrinology depending on the event type.

Statistical considerations

The primary safety analysis of CAMELLIA-TIMI 61 is based on the time from randomized treatment assignment to the first occurrence of any element of the primary safety end point of CV death, MI, or stroke (MACE) and assessed for noninferiority of lorcaserin to placebo according to the intention-to-treat principle. This analysis is conducted by the independent Data Monitoring Committee (DMC) at an interim analysis after at least 460 adjudicated MACE events have occurred. Upon review of the data, the DMC will communicate an overall qualitative recommendation to trial leadership and the sponsor that either (1) noninferiority between lorcaserin and placebo is declared and the trial should continue or (2) lorcaserin is declared as inferior to placebo and the trial is recommended to be stopped. No other information such as data by treatment group, point estimates, or CI will be communicated. The sponsor then communicates this recommendation to the US FDA. If the FDA required further information, such as unblinded interim results, data sets, or programs, this could be provided by the DMC independent statistical group via a firewalled representative from the sponsor. The trial leadership, including remaining sponsor representatives, and all study investigators and participants will remain blinded to the interim results other than knowing the DMC overall qualitative recommendation.

At trial completion, the primary and key secondary efficacy end points will be assessed in a hierarchical fashion ([Appendix B](#)). The primary and key secondary efficacy analyses will be performed according to an intention-to-treat principle.

The sample size of 12,000 was determined based on an estimated 1.5% annual background rate of MACE from studies in similar populations, a 15-month accrual period, and 5% annual rate of dropout.^{13,22,23} The interim analysis occurs after accrual of 460 adjudicated MACE

events, providing 95% power to exclude a noninferiority margin of 1.4 using the upper bound of the 1-sided 97.5% CI ($\alpha = .025$). In the original protocol, MACE+ and conversion to diabetes were co-primary efficacy end points with a multiple testing procedure where α was split between end points and could be recycled to the other efficacy end point in the event of significance ([Appendix B](#), Figure 1). It was estimated that 808 new-onset diabetes events (in the 6,000 patients without diabetes at baseline) and 1,401 MACE+ events would occur approximately 50 months from the start of the trial and would provide 90% power to detect a 25% risk reduction in new-onset diabetes at an $\alpha = .005$ and 85% power to detect a 15% risk reduction in MACE+ at an $\alpha = .045$ on 2-sided testing, assuming a 15-month accrual and 5% dropout.

To maintain trial timelines, the Sponsor amended the protocol in March 2017, prior to the DMC interim analysis review, to change conversion to diabetes to a key secondary efficacy end point due to a lower-than-anticipated rate of new-onset diabetes. In addition, the population for analysis of this objective was changed to the approximately 4,000 subjects at higher risk for conversion due to the presence of prediabetes at baseline ([Appendix B](#), Figure 2). In the amended protocol, assuming noninferiority of lorcaserin versus placebo for MACE, the study will close after a minimum of 2.5-year median treatment duration and 1,401 adjudicated MACE+ events have occurred which will provide >85% power to detect a 15% risk reduction in MACE+ for 2-sided $\alpha = .05$. At the time of study completion, it is estimated that there will be approximately 400 events of conversion to diabetes, providing 86% power to detect a 25% risk reduction for a 2-sided $\alpha = .05$.

Biomarker, genetic, and echocardiographic assessments

A series of scientific substudies is planned in subjects randomized in selected countries, including serial echocardiographic assessments and collection of samples for pharmacogenetics and biomarker analyses.

Subjects provided written informed consent for participation in the serial biomarker (up to 4 samples over the duration of the trial) and genetic sample collection, where permissible by local regulations. Genetic and biomarker assessments in this trial may provide important insight into pathobiology of obesity, diabetes, and cardiovascular disease; improve the ability to risk stratify subjects; and provide information that can be used to tailor therapy.

The echocardiographic substudy enrolled more than 4,300 subjects in North America with a goal of evaluating serial echocardiograms for the development and/or progression of pulmonary hypertension or FDA-defined *valvulopathy* (defined as mild or greater aortic regurgitation or moderate or greater mitral regurgitation).²⁴ These data will be pooled with echocardiographic data from the phase 3 lorcaserin program to assess for a noninferiority boundary of 1.5.

Echocardiographic examinations are obtained locally following specialized CAMELLIA-TIMI 61 echocardiographer training and certification. Images are processed and read centrally at a core facility. Per protocol, echocardiograms are obtained at baseline and every 6 months for the first 2 years, then annually thereafter. The substudy will cease when at least 1,000 subjects have undergone an echocardiogram 36 months after randomization.

Study organization

The executive committee, composed of members of the TIMI Study Group, other leading academic experts, and the sponsor (Eisai), oversees all aspects of the trial ([Appendix C](#)). The executive committee is responsible for the scientific content of the protocol and its implementation. A DMC is responsible for independent assessment of the study and periodic reviews of accumulating safety data from the trial, including the assessment of noninferiority for MACE at the interim analysis, adverse events of special interest, and general safety and tolerability. A CEC blinded to study treatment adjudicates the elements of the primary and key secondary end points.

Table II
Baseline characteristics

	N = 12,000
Demographics	
Age, y (mean ± SD)	64 ± 8
Age ≥ 75 y	9
Female	36
White	89
BMI, kg/m ² (median, IQR)	35 (32–39)
Weight, kg (mean ± SD)	105 ± 21
Region	
North America	82
Central and South America	3
Europe	8
Asia Pacific	7
Coexisting conditions	
Diabetes	54
Hypertension	90
Hyperlipidemia	93
eGFR <60 mL/min	21
Coronary artery disease	68
Peripheral artery disease	3.5
Cerebrovascular disease	9.4
Cardiovascular strata	
Multiple risk factor (diabetes with at least 1 other risk factor)	25
Established cardiovascular disease	75

Data based on interim snapshot taken in March 2017 after completion of enrollment but during ongoing trial and data cleaning. Number denotes proportion (%) unless otherwise specified.

The study was designed by the TIMI Study Group in conjunction with the executive committee and the trial sponsors. Data analysis will be conducted by the TIMI Study Group with validation by the trial sponsor. The TIMI Study Group will have free and complete access to all trial data and will submit the results of the study for publication in a peer-reviewed medical journal.

The CAMELLIA-TIMI 61 study is supported by a research grant from Eisai. The trial has been registered under number NCT02019264.

Current status

The CAMELLIA-TIMI 61 study is being conducted in 8 countries and 485 sites. Recruitment began in January 2014 and was completed in November 2015. The initial baseline characteristics of the 12,000 subject trial cohort are presented in Table II. The DMC has met every 6–12 months over the duration of the trial and has recommended continuing as planned at each meeting.

Discussion

Weight management strategies for adults with obesity, such as diet, exercise, surgical interventions, and pharmacotherapies, can improve cardiovascular risk factors, including blood pressure, cholesterol, and hyperglycemia.^{10,11,16} In unblinded, nonrandomized studies, bariatric surgery has been associated with durable improvements in cardiovascular risk factor control as well as lower rates of major adverse cardiovascular events in the setting of significant and sustained weight loss on the order of 15%–25% from baseline at 10 years.^{7,8,25} In contrast, in the Look AHEAD study, randomization to intensive lifestyle intervention versus standard of care resulted in a net weight loss of 2.5% from baseline at 10 years and did not decrease the rate of major adverse cardiovascular events in patients with type 2 diabetes and obesity.²⁶ Furthermore, no pharmacological weight-loss medication has ever been demonstrated to reduce the risk of cardiovascular events.

The early experience with weight-loss pharmacotherapies has been challenging because of unacceptable safety profiles. Peripheral activation of the 2B serotonin receptor subtypes (5HT-2BR) on cardiovascular tissues by fenfluramine and its derivatives resulted in development of pulmonary hypertension and valvular heart disease.⁷ The

norepinephrine and serotonin reuptake inhibitor, sibutramine, increased heart rate and blood pressure through its sympathomimetic effects, leading to higher rates of stroke and MI.¹³ Blockade of the endocannabinoid receptor with rimonabant was safe from a cardiovascular perspective but resulted in unacceptably high rates of serious, neuropsychiatric adverse effects.¹⁴

Given the significant morbidity and mortality associated with obesity, there remains a strong clinical need to identify effective weight-loss agents that are at a minimum safe from a cardiovascular standpoint but also that have the potential to improve cardiovascular outcomes through weight loss or modification of other cardiovascular risk factors. The newer generation of agents, including lorcaserin, is efficacious for weight loss, and smaller studies did not suggest CV risk; however, cardiovascular safety has not been definitively tested in adequately powered clinical trials. To this end, the regulatory authorities now require all new weight-loss agents to undergo a rigorous long-term cardiovascular safety assessment in obese or overweight patients at high cardiovascular risk.

As described, the CAMELLIA-TIMI 61 trial is designed to assess cardiovascular safety via an interim analysis, thereby fulfilling the postmarketing requirement, and then to evaluate cardiovascular and metabolic efficacy. Provision of interim data to regulatory authorities may pose challenges to the confidentiality and integrity of the study, as evidenced by the LIGHT study.²⁷ In the LIGHT study, a pharmacologic weight-loss agent, naltrexone-bupropion, was evaluated for cardiovascular safety in a 2-stage design whereby noninferiority for a hazard ratio of 2.0 would be assessed in a confidential interim analysis for consideration of regulatory approval. After public release of confidential interim data by the sponsor, the FDA concluded that the LIGHT study would not be adequate to meet the postmarketing requirement, and the trial was terminated prematurely.

To protect the integrity and confidentiality of the CAMELLIA-TIMI 61 study, a careful data sharing plan was developed for the interim, noninferiority assessment. As outlined, after review of unblinded interim data, the DMC would provide the FDA (via the sponsor) with an overall qualitative statement regarding whether noninferiority was declared and a recommendation for trial continuation, without provision of any unblinded data (eg, point estimates). If the FDA required further information, this could be provided by the DMC independent statistical group via a firewalled representative from the sponsor, who would not be involved in trial conduct otherwise. Unblinded data would not be disclosed to any other individuals or regulatory authorities, a strategy that is in accordance with FDA guidance.²⁸

In light of the documented improvements in cardiovascular risk factors that are associated with weight loss, it is reasonable to hypothesize that pharmacologic weight-loss agents may have the potential to improve cardiovascular outcomes. Liraglutide, a long-acting GLP-1 receptor agonist with an indication for use in diabetes (1.2 mg or 1.8 mg daily) as well as chronic weight management (3.0 mg daily), demonstrated a significant 13% reduction in the composite of cardiovascular death, MI, or stroke compared to placebo when studied with the diabetic dosing in patients with type 2 diabetes in the setting of a ~2.5% net weight loss.²⁹ It is not known whether the cardiovascular benefit is mediated through direct action through local GLP-1 receptor agonism, risk factor modification (eg, reductions in fasting glucose, hemoglobin A1c, blood pressure, and weight), other mechanisms, or a combination of these.

There are several mechanisms by which lorcaserin could theoretically improve cardiovascular and metabolic outcomes. The phase 3 program demonstrated a net 3%–4% weight loss from baseline for lorcaserin over, with 38% to 47% and 16% to 22% patients experiencing ≥5% and ≥ 10% weight loss, respectively, depending on the particular study.^{16–18} Furthermore, there were significant concurrent improvements in glycemia, insulin resistance, blood pressure, inflammatory markers, and lipids in patients with adequate control at baseline.^{16–18} Additionally, although weight loss is known to improve insulin sensitivity and blood glucose levels, lorcaserin may also result in weight-loss-independent

effects on glucose homeostasis. Preclinical data suggest that central and neurohormonal signaling pathways downstream of the 5HT-2C receptor can suppress hepatic gluconeogenesis, which may result in improved glycemic control in patients with diabetes and prevention of new-onset diabetes in those at risk.³⁰ Furthermore, in BLOOM-DM, fasting plasma glucose decreased with lorcaserin compared to placebo as early as after 2 weeks initiation of therapy, prior to any significant weight loss.³¹ It is not known whether these observations were due to decreased energy intake and/or an alternative mechanism, such as suppression of hepatic gluconeogenesis.

Lorcaserin has minimal cross-reactivity with other serotonin receptor subtypes and does not alter the release or metabolism of serotonin; as a result, it is not believed to pose a significant risk for adverse events such as pulmonary hypertension, valvulopathy, or serotonin syndrome.^{32,33} Therefore, the experimental data and clinical experience from the phase 3 studies support testing the hypothesis that agonism of the 5HT-2C receptor with lorcaserin may safely improve cardiovascular outcomes and glycemic parameters. The CAMELLIA-TIMI 61 study is designed and adequately powered to exclude excess cardiovascular risk as well as to assess for cardiovascular and glycemic efficacy.

Disclosures

The TIMI Study Group reports grant support through Brigham and Women's Hospital from Eisai, Amgen, AstraZeneca, Daiichi-Sankyo, GlaxoSmithKline, Intarcia, Janssen, MedImmune, Merck, Novartis, Pfizer, Poxel, and Takeda. Mr Abrahamsen and Drs Bohula, Scirica, Fanola, Wiviott, and Sabatine are members of the TIMI Study Group. Drs Inzucchi, Keech, McGuire, and Smith participated as executive committee members for the CAMELLIA-TIMI 61 trial. Drs Francis, Miao, Perdomo, and Satlin are employees of Eisai. In addition, Dr Bohula reports personal fees from Merck, Daiichi Sankyo, and Servier. Dr Scirica reports personal fees from AstraZeneca, Biogen Idec, Boehringer Ingelheim, Covance, Dr Reddy's Laboratory, Elsevier Practice Update Cardiology, GlaxoSmithKline, Lexicon, Merck, NovoNordisk, Sanofi, and St Jude's Medical and equity in Health [at] Scale. Dr McGuire reports clinical trial leadership roles for AstraZeneca, Sanofi Aventis, Janssen, Boehringer Ingelheim, Merck & Co, Novo Nordisk, Lexicon, Eisai, GlaxoSmithKline, Esperion and consultancy for AstraZeneca, Sanofi Aventis, Lilly US, AstraZeneca, Boehringer Ingelheim, Merck & Co, Pfizer, Novo Nordisk, Metavant. Dr Inzucchi has served as a consultant to Janssen, Alere, and vTv Therapeutics and participated on other clinical trial steering, executive, or publications committees for Boehringer Ingelheim, Astra-Zeneca, Novo Nordisk, Sanofi, and Daiichi Sankyo. Dr Wiviott reports personal fees from AstraZeneca, Bristol Myers Squibb, Arena, Aegerion, Angelmed, Janssen, Xoma, ICON Clinical, Boston Clinical Research Institute, Eli Lilly/Daiichi Sankyo, and Boehringer Ingelheim and grants from Amgen. Dr Sabatine reports personal fees from Amgen, CVS Caremark, Esperion, Intarcia, Ionis, Janssen, MedImmune, and Merck.

Appendix A. Definitions of the primary and secondary end points

A.1. Death

All deaths reported postenrollment will be recorded and adjudicated. Deaths will be subclassified by cardiovascular, noncardiovascular, or undetermined primary cause. Cardiovascular death includes death due to acute myocardial infarction, heart failure, stroke, cerebrovascular procedures, cardiovascular hemorrhage, other cardiovascular causes (eg, pulmonary embolism, aortic syndrome, peripheral arterial disease), and sudden cardiac death.

A.2. Definition of MI

The definition of MI is based on the third universal definition and requires the combination of (1) evidence of myocardial necrosis and (2)

supportive information derived from the clinical presentation or diagnostic procedures (eg, electrocardiogram, myocardial or coronary imaging), as follows:

- Spontaneous MI: detection of a rise and/or fall of cardiac biomarker values (preferably cardiac troponin [cTn]) with at least 1 value above the 99th percentile upper reference limit (URL) and with at least 1 of the following:
 - Symptoms of ischemia
 - New or presumed new significant ST-segment–T wave (ST-T) changes or new left bundle-branch block (LBBB).
 - Development of pathological Q waves in the electrocardiogram (ECG).
 - Imaging evidence of new loss of viable myocardium or new regional wall motion abnormality is required.
 - Identification of an intracoronary thrombus by angiography or autopsy.
- MI resulting in death when biomarker values are unavailable: sudden unexpected cardiac death, often with symptoms suggestive of myocardial ischemia and presumed new ischemic ECG changes or new LBBB, but death occurring before blood samples could be obtained, before cardiac biomarker could rise, or in rare cases cardiac biomarkers were not collected.
- Percutaneous coronary intervention (PCI)–related MI: elevation of cTn values $>5 \times$ 99th percentile URL in patients with normal baseline values (≤ 99 th percentile URL) or a rise of cTn values $>20\%$ if the baseline values are elevated and are stable or falling. In addition, (a) symptoms suggestive of myocardial ischemia, (b) new ischemic ECG changes or new LBBB, (c) angiographic loss of patency of a major coronary artery or a side branch or persistent slow or no-flow or embolization, or (d) imaging demonstration of new loss of viable myocardium or new regional wall motion abnormality is required.
- Coronary artery bypass graft (CABG)–related MI: elevation of cardiac biomarker values $>10 \times$ 99th percentile URL in patients with normal baseline cTn values (≤ 99 th percentile URL). In addition, (a) new pathological Q waves or new LBBB, (b) angiographic documented new graft or new native coronary artery occlusion, or (c) imaging evidence of new loss of viable myocardium or new regional wall motion abnormality is required.
- Silent or prior MI: based on electrocardiogram, imaging, or pathologic findings.

A.3. Definition of stroke

Stroke is defined as an acute episode of focal or global neurological dysfunction caused by brain, spinal cord, or retinal vascular injury as a result of hemorrhage or infarction. Infarction may be documented by brain imaging, persistence of symptoms beyond 24 hours, or death within 24 hours. Evidence of central nervous system injury without recognized neurologic dysfunction will not be adjudicated as cerebrovascular events. Stroke will be subclassified when possible as one of the following:

- *Ischemic stroke*: defined as an acute episode of focal cerebral, spinal, or retinal dysfunction caused by infarction of central nervous system tissue. This may include hemorrhage as a consequence of ischemic stroke (ie, ischemic stroke with hemorrhagic transformation).
- *Hemorrhagic stroke*: defined as an acute episode of focal or global cerebral or spinal dysfunction caused by intraparenchymal, intraventricular, or subarachnoid hemorrhage. This does not include subdural hematomas.
- *Undetermined stroke*: defined as an acute episode of focal or global neurological dysfunction caused by presumed brain, spinal cord, or

retinal vascular injury as a result of hemorrhage or infarction but with insufficient information to allow categorization as A or B.

A.4. Definition of hospitalization for unstable angina

Unstable angina requiring hospitalization is defined as ischemic discomfort of at least 10 minutes' duration at rest or in an accelerating pattern associated with a decline in exercise capacity without an elevation in cardiac biomarkers that prompts an unscheduled hospitalization within 24 hours of the most recent symptoms with the presence of at least 1 of the following:

- New or worsening ST or T wave changes on resting ECG (in the absence of confounders, such as left bundle branch block (LBBB) or left ventricular hypertrophy (LVH)).
- Definite evidence of inducible myocardial ischemia on imaging (eg, exercise stress testing, stress echocardiography, myocardial scintigraphy, or cardiac magnetic resonance imaging) that is believed to be responsible for the myocardial ischemic signs/symptoms.
- Angiographic evidence of new or worse $\geq 70\%$ lesion and/or thrombus in an epicardial coronary artery that is believed to be responsible for the myocardial ischemic symptoms/signs.
- Need for coronary revascularization procedure (PCI or CABG) for the presumed culprit lesion(s) during an unscheduled hospitalization, or subsequent to transfer to another institution without interceding home discharge.

A.5. Definition of heart failure

Heart failure includes hospitalization for heart failure and urgent outpatient visits.

Hospitalization for heart failure is defined by hospitalization for the primary diagnosis of heart failure with all of the following:

1. Documentation of new or worsening symptoms due to heart failure on presentation,
2. Objective evidence of new or worsening heart failure, consisting of at least 2 physical examination findings or 1 physical examination finding and at least 1 diagnostic laboratory or imaging finding, and
3. Initiation or intensification of treatment specifically for heart failure.

An *urgent heart failure visit* is defined as an event that meets all of the following:

1. The patient has an urgent, unscheduled office/practice or emergency department visit for a primary diagnosis of HF but not meeting the criteria for an HF hospitalization.
2. All signs and symptoms for HF hospitalization (ie, symptoms, physical examination findings/diagnostic evidence of new or worsening HF, as indicated above) must be met.
3. The patient receives initiation or intensification of treatment specifically for HF, with the exception of oral diuretic therapy, which will not be sufficient.

A.6. Definition of coronary revascularization

Coronary revascularization includes PCI and surgical revascularization. *PCI* is defined by placement of an angioplasty guide wire, balloon, or other device (eg, stent, atherectomy catheter, brachytherapy delivery device, or thrombectomy catheter) into a native coronary artery or

CABG for the purpose of mechanical coronary revascularization. Assessment of the severity of coronary lesions with the use of intravascular ultrasound, coronary flow reserve (CFR) or fractional flow reserve (FFR) mandating insertion of a guide wire will **NOT** be considered PCI.

A.7. Definition of new-onset diabetes

The criteria for diagnosis of diabetes, which are based on the 2013 American Diabetes Association guidelines,²¹ are as follows:

1. Symptoms (eg, polyuria, polydipsia, polyphagia, unexplained weight loss) of diabetes and casual/random (any time of day without regard to time since last meal) plasma glucose levels of ≥ 200 mg/dL (11.1 mmol/L)

OR

2. Fasting (no energy intake for at least 8 hours) plasma glucose (FPG) level ≥ 126 mg/dL (7.0 mmol/L) on 2 occasions separated by at least 1 calendar day

OR

3. Hemoglobin A1c level $\geq 6.5\%$ (ideally using an NGSP³-certified method and standardized to the Diabetes Control and Complications Trial [DCCT] assay when available) on 2 occasions separated by at least 1 calendar day

OR

4. At least 2 of the following:

- a. Hemoglobin A1c $\geq 6.5\%$ (ideally using an NGSP³-certified method and standardized to the DCCT assay when available)
- b. FPG (no energy intake for at least 8 hours) level ≥ 126 mg/dL (7.0 mmol/L)
- c. Two-hour plasma glucose level ≥ 200 mg/dL (11.1 mmol/L) during an oral glucose tolerance test (OGTT) (OGTT performed as per WHO criteria with glucose load of 75 g anhydrous glucose dissolved in water)

OR

5. One of the following:

- a. Hemoglobin A1c $\geq 6.5\%$ (ideally using an NGSP³-certified method and standardized to the DCCT assay when available)
- b. FPG (no energy intake for at least 8 hours) level ≥ 126 mg/dL (7.0 mmol/L)
- c. Two-hour plasma glucose level ≥ 200 mg/dL (11.1 mmol/L) during an OGTT (OGTT performed as per WHO criteria with glucose load of 75 g anhydrous glucose dissolved in water)
- d. Random plasma glucose ≥ 200 mg/dL (11.1 mmol/L)

AND

Use of oral or injected diabetes medication for the purpose of diabetes control. Note that the use of diabetes medication for prediabetes with the intent of preventing diabetes does not meet the definition, and these events will require confirmatory central laboratory testing.

Appendix B

Multiple Testing Procedure

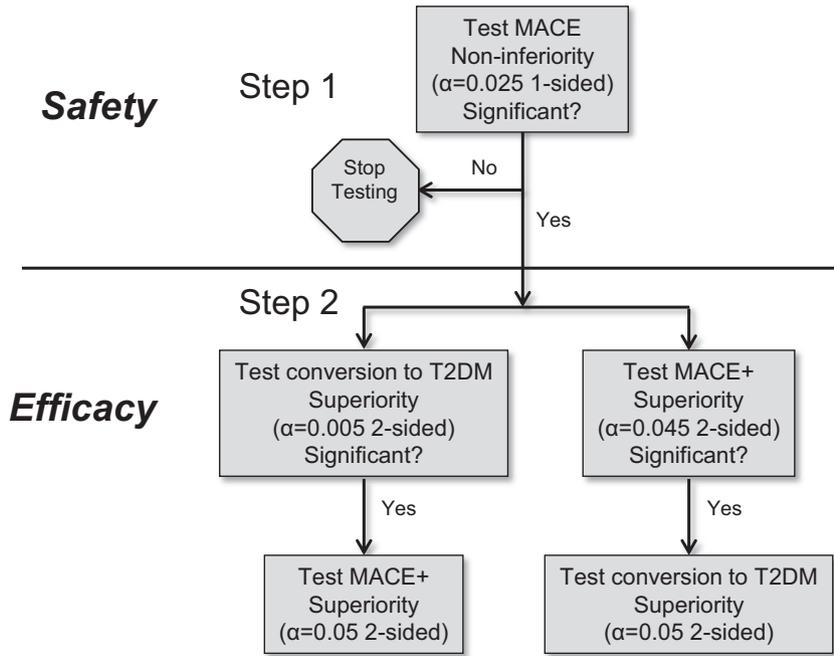


Figure 1. Original multiple testing procedure.

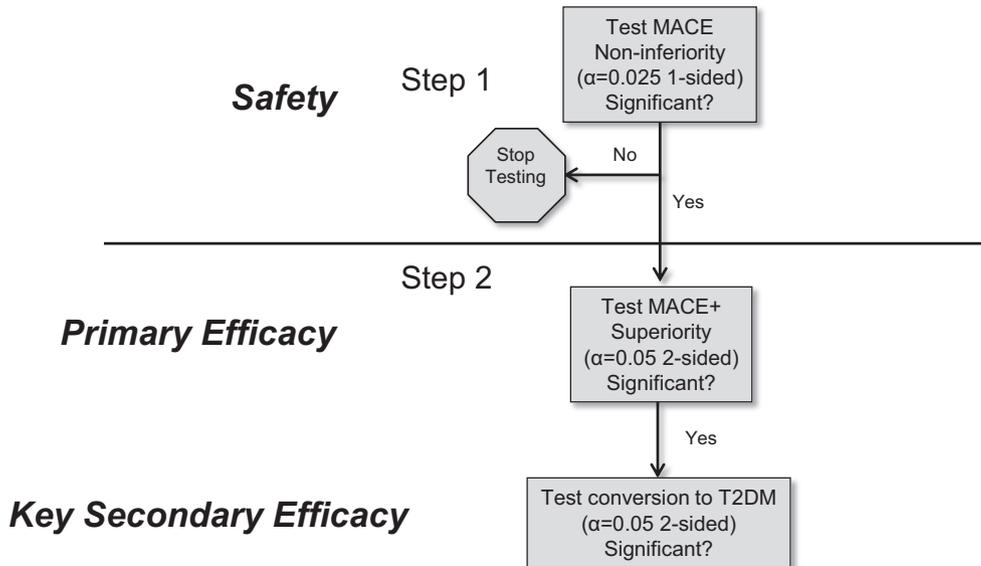


Figure 2. Amended sequential gatekeeping testing procedure.

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