

Clinical Development

LCZ696

Clinical Trial Protocol *CLCZ696BCA02 / NCT02690974*

PARASAIL - Prospective, multi-center, open label, post-approval Study Aimed at characterizing the use of LCZ696 at 97 mg sacubitril / 103 mg valsartan bid in patients with HFrEF

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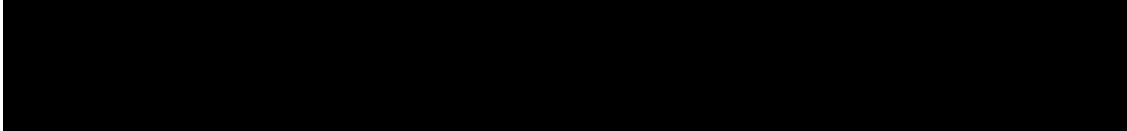
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List of abbreviations

ACE	angiotensin converting enzyme
ACEI(s)	angiotensin converting enzyme inhibitor(s)
AE	adverse event
ALT	alanine aminotransferase
ANP	atrial natriuretic peptide
APP	aminopeptidase P
ARB(s)	angiotensin receptor blocker(s)
ARNi(s)	Angiotensin Receptor Neprilysin Inhibitor(s)
AST	aspartate aminotransferase
AT ₁	angiotensin type 1bid twice a day
BP	blood pressure
CHF	chronic heart failure
CPO	Country Pharma Organization
CRF	Case Report/Record Form (paper or electronic)
CSR	Clinical Study Report
CRO	Contract Research Organization
CV	cardiovascular
DBP	diastolic blood pressure
DMC	Data Monitoring Committee
DS&E	Drug Safety & Epidemiology
EC(s)	Ethics Committee(s)
ECG	Electrocardiogram
EDC	Electronic Data Capture
eGFR	estimated glomerular filtration rate
EOS	end of study
██████	██████
HF	Hearth Failure
ICH	International Conference on Harmonization of Technical Requirements for Registration of Pharmaceuticals for Human Use

IEC	Independent Ethics Committee
IRB	Institutional Review Board
IRT code	Interactive Randomization TechnologyLCZ696 Novartis compound
LVEF	left ventricular ejection fraction
MDRD	Modification of Diet in Renal Disease
mg	milligram
NP(s)	natriuretic peptide(s)
NYHA	New York Heart Association
o.d.	once a day
p.o.	oral
SAE	serious adverse event
SBP	systolic blood pressure
ULN	upper limit of normal

Glossary of terms

Assessment	A procedure used to generate data required by the study
Enrollment	Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e. prior to starting any of the procedures described in the protocol)
Medication number	A unique identifier on the label of each investigational/study drug package in studies that dispense medication using an IRT system
Subject Number	A number assigned to each patient who enrolls into the study
Premature patient withdrawal	Point/time when the patient exits from the study prior to the planned completion of all investigational/study treatment administration and all assessments (including follow-up)
Stop study participation	Point/time at which the patient came in for a final evaluation visit or when study/investigational treatment was discontinued whichever is later
Study drug/ treatment	Any single drug or combination of drugs administered to the patient as part of the required study procedures; includes investigational drug (s), active drug run-ins or background therapy
Study/investigational treatment discontinuation	Point/time when patient permanently stops taking study/investigational treatment for any reason; may or may not also be the point/time of premature patient withdrawal
Variable	Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time points

Amendment 1

Amendment Rationale

ENTRESTO™ (sacubitril/valsartan) is indicated for the treatment of heart failure with reduced ejection fraction (HFrEF) in patients with NYHA Class II or III, to reduce the incidence of cardiovascular death and heart failure. The NYHA classification consists of a Functional Classification that helps assess the severity of the Heart Failure-related symptoms. In order to assess how these symptoms evolve during the subjects' participation to the study, NYHA assessment will be performed by the investigator at every visit and reported in the eCRF.

Since the NYHA assessment needs to be performed at every visit by the investigator, visit 4 (month 3) has now to be performed on site and is no longer optional.

The ENTRESTO™ Product Monograph has been updated in order to use rounded dosage strengths. Therefore, the ENTRESTO™ dosage descriptions in the protocol have been updated accordingly.

According to the American Thoracic Society Guidelines, the Six Minutes Walk Test can be performed once or twice during the same visit, with the first test being used as a practice test. However, the practice test is not mandatory to ensure the reliability of the test. Therefore, the instructions related to the Six Minutes Walk Test have been updated to allow the centers to perform it either once or twice based on their routine practice.

Changes to the protocol

The described changes in the aforementioned amendment rationale are implemented throughout the protocol:

- In Section 6.6.4 and table 6.1, NYHA class assessment will be performed by the Investigator at baseline (visit 1), month 3 (visit 4), month 6 (visit 5) and month 12 (visit 6).
- Table 6.1, the Visit 4 (month 3) is no longer optional and needs to be performed on site.
- Across all applicable sections in the protocol, the initial dosage strengths descriptions, 24.3 mg sacubitril / 25.7 mg valsartan, 48.6 mg sacubitril / 51.4 mg valsartan, 97.2 mg sacubitril / 102.8 mg valsartan has been changed and replaced by the following rounded dosages strengths; 24 mg sacubitril / 26 mg valsartan, 49 mg sacubitril / 51 mg valsartan, 97 mg sacubitril / 103 mg valsartan.
- Appendix 3 (section 15) has been updated to allow the centers to perform the Six

Minutes Walk test either once or twice based on their routine practice.

The opportunity was also taken to make the following changes:

- The last paragraph of section 1.1 stating that *“In addition it will provide guidance on the most effective up-titration approach for achieving and maintaining the optimal therapeutic dose of 300 mg bid.”* has been revised to correct the optimal therapeutic dose which is 200 mg.



- The list of the Adverse Events of special interest that are object of more targeted follow-up activities as per regulatory commitments has been updated in Section 7.1 as follows:

Previous list:

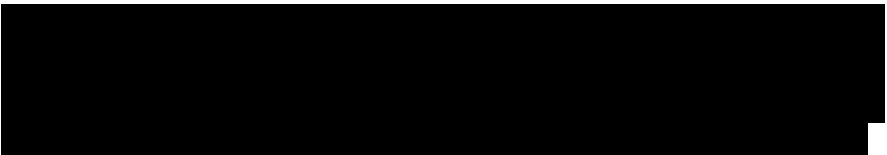
- ✓ Angioedema
- ✓ Cognitive Impairment/Dementia
- ✓ Hepatotoxicity

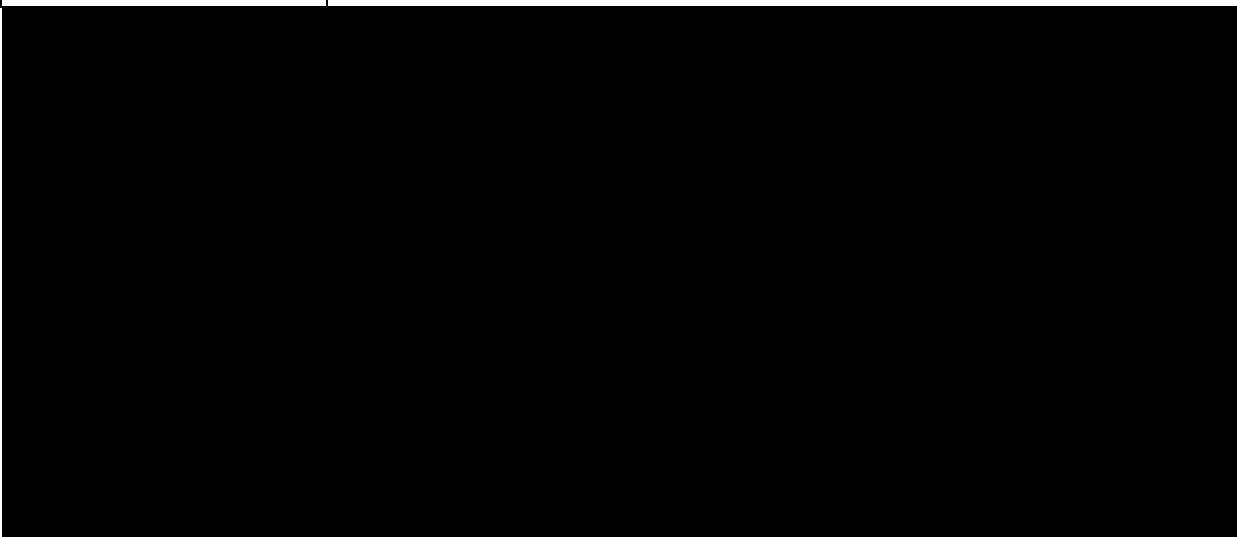
Updated list:

- ✓ Angioedema-related events
- ✓ Cognitive Impairment/Dementia-related events
- ✓ Hepatotoxicity-related events
- ✓ Statin-related events

Protocol synopsis

Protocol number	CLCZ696BCA02
Title	Prospective, multi-center, open label, post-approval Study Aimed at characterizing the use of LCZ696 at 97 mg sacubitril / 103 mg valsartan bid in patients with HFrEF
Brief Title	Prospective Canadian Study Describing the use of LCZ696 in the management of Patients with Heart Failure with Reduced Ejection Fraction (HFrEF).
Sponsor and Clinical Phase	Novartis, Canada Phase IV
Investigation Type	Drug
Study type	Interventional
Purpose and Rationale	<p>Optimal dosage of LCZ696 has been established at 97 mg sacubitril / 103 mg valsartan bid based on results of controlled clinical trials. Up titration of lower doses, beginning at 24 mg sacubitril / 26 mg valsartan bid, has been shown to be an effective approach to achieving optimal dose that is well tolerated by patients. However, generalization of results from controlled clinical trial to the general population is limited. There is therefore a need for the real life assessment of the effectiveness and safety of LCZ696 and the tolerability of the optimal 97 mg sacubitril / 103 mg valsartan bid dose. The current study will address this knowledge gap.</p> <p>The primary purpose of the study will be to describe the tolerability of treatment with the optimal dose of LCZ696 (97 mg sacubitril / 103 mg valsartan bid), over six (6) months, in patients with HFrEF in Canada.</p> <p>The study will also describe the overall tolerability, effectiveness and safety of LCZ696 for the management of HFrEF over 12 months of treatment, as well as describe the patterns of LCZ696 up and down dose titrations occurring during the management of patients with HFrEF.</p>


	
Primary Objective(s) and Key Secondary Objective	To describe the tolerability of LCZ696 at 97 mg sacubitril / 103 mg valsartan bid after 6 months of treatment in patients with HFrEF
Secondary Objectives	In patients with HFrEF: <ul style="list-style-type: none">• To describe the tolerability of LCZ696 at 97 mg sacubitril / 103 mg valsartan bid after 12 months of treatment.• To evaluate the impact of the titration scheme on the tolerability of patients maintained on LCZ696 at 97 mg sacubitril / 103 mg valsartan bid at 6 and 12 months• To describe the impact of LCZ696 on functional exercise capacity, as measured by the Six Minute Walk Test, at 6 and 12 months.• To describe the time of up-titration for each dose (24 mg sacubitril / 26 mg valsartan and 49 mgsacubitril / 51 mg valsartan bid) of LCZ696.• To describe the adherence to guideline recommended dosing of beta-blockers and MRAs at 6 and 12 months of treatment with LCZ696.• To evaluate the overall safety profile of LCZ696 during 12 months of treatment



Study Design	<p>This will be a multi-center, open label, prospective post-approval (phase IV) study. Patients with HFrEF that are eligible to be treated with LCZ696 as per the ENTRESTO™ product monograph will be enrolled in the study. The study patients will be enrolled at Canadian community cardiologists and IM specialists sites that treat patients with HFrEF. Follow up will be for 12 months, with the primary endpoint being assessed at 6 months of treatment.</p> <p>The patients will continue on their background treatment with the exception of ACEIs and ARBs that will be replaced with LCZ696, as per recent guidelines, after a 36 hour wash-out period for ACEIs. All patients will be initiated on the lower dose of LCZ696 as per the product monograph and the treating physician's judgement. A starting dose of 24 mg sacubitril / 26 mg valsartan twice daily may be considered in selected patients, for example, those on less than guideline-recommended doses of ACEI or ARB prior to initiation of LCZ696. The dose of LCZ696 should be increased every 2-4 weeks, as tolerated by the patient and in accordance to the product monograph, to the target dose of 97 mg sacubitril / 103 mg valsartan twice daily. If patients experience tolerability issues, e.g. symptomatic hypotension or hyperkalemia, consideration should be given to temporary down-titration of LCZ696 (as per ENTRESTO™ Canadian product monograph). Dose reduction of other concomitant medications including nitrates, CCBs, alpha-blockers and diuretics may be considered to optimize the tolerability of treatment with LCZ696.</p>
Population	<p>The target population of the study will be patients with HFrEF that are candidates for treatment with LCZ696 as per the Canadian product monograph.</p>
Inclusion Criteria	<ul style="list-style-type: none">• Age \geq 18 years and \leq 80 years.• Males or females.• Diagnosis of Heart Failure with reduced Ejection Fraction (LVEF \leq 40%) and NYHA class II or III.

	<ul style="list-style-type: none"> • Stable on any dose of ACEI or ARB before enrolment in the study. • Stable dose of a beta-blocker before enrolment in the study. • Eligible for treatment with LCZ696 as per ENTRESTO™ Canadian product monograph). • Treated as an outpatient. • Signed an informed consent agreeing to participate in the study.
<p>Exclusion Criteria</p>	<ul style="list-style-type: none"> • Symptomatic hypotension and/or a SBP < 100 mmHg at baseline visit. • Estimated GFR < 30 mL/min/1.73m² as measured by the simplified Modification of Diet in Renal Disease (MDRD) formula at baseline visit. • Known history of angioedema related to previous ACEI or ARBs therapy, or history of hereditary angioedema or idiopathic angioedema • Requirement of concomitant treatment with both ACEIs and ARBs. • Concurrent participation in other <i>clinical</i> trials or use of other investigational drugs at the time of enrollment, or within 30 days. • Hypersensitivity to the active substances, sacubitril or valsartan, or to any of the excipients. • Concomitant use of aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR <60ml/min/1.73m²) • History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes. • History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases. • Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test. • Women of childbearing potential, defined as all women

	<p>physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment.</p>
Investigational and Reference Therapy	<p>All patients will be treated with LCZ696 in combination with their background treatments. There is no reference treatment.</p>
Efficacy Assessments	<p>The primary endpoint of the study will be the proportion of patients at the 97 mg sacubitril / 103 mg valsartan bid dose of LCZ696 at 6 months.</p> <p>The following will be secondary endpoints:</p> <ul style="list-style-type: none"> • The proportion of patients on LCZ696 who had required down-titration after reaching the 97 mg sacubitril / 103 mg valsartan bid. • The number of down-titration changes from 97 mg sacubitril / 103 mg valsartan bid during 12 months of treatment. • The proportion of patients who tolerate 97 mg sacubitril / 103 mg valsartan bid at 6 and 12 months of treatment. • Functional capacity as measured by the change from baseline to 6 months and 12 months in the Six Minute Walk Test distance. • Time to up-titration of LCZ696 doses. • Duration of treatment on each dose of LCZ696. • The proportion of patients on guideline recommended dose of beta-blockers and MRAs at baseline, 6 and 12 months.
Safety Assessments	<p>All treatment emergent serious and non-serious adverse events.</p>
Data Analysis	<p>The data analysis for the current study will be primarily descriptive. The primary endpoint of the study will be the proportion of patients on LCZ696 97 mg sacubitril / 103 mg valsartan bid at 6 months of treatment. Ninety five percent (95%) confidence intervals will be calculated for the estimate of this proportion in order to assess precision and make inferences to the target population.</p> <p>Similarly for the proportion of patients on LCZ696 97 mg sacubitril / 103 mg valsartan bid at 12 months, requiring down titration and proportion of patient treated in accordance to</p>

	<p>guideline recommended doses of beta blockers and MRAs will also be assessed for precision with the 95% Confidence Intervals.</p> <p>The number of down titrations during the 12-month treatment periods will be described with a Poisson distribution and the incidence density rate as the number of dose reductions per 100 person – month of follow up.</p> <p>The change in the Six Minute Walk Test from baseline to 6 and 12 months of treatment will be assessed with the 95% confidence intervals and with the Student’s t-test for paired observations.</p> <p>The time to LCZ696 up-titration to 97 mg sacubitril / 103 mg valsartan bid and the duration on treatment for each dose will be assessed with the Kaplan Meier estimator of the survival function.</p>  <p>Safety will be assessed with the incidence of treatment emergent adverse events.</p>
Key words	LCZ696, HFrEF, Tolerability, Effectiveness, Durability of Treatment, Safety.

1 Introduction

1.1 Background

Heart failure (HF) is a common disease with high mortality rate and represents the second leading cause of hospitalizations in patients >65 years of age in Canada (1). Patients with HF usually have poor prognosis, frequent hospitalization and increased risk for mortality. The data from the Framingham cohort suggest a prevalence of 8/1000 in males between the ages of 50-59 that increases to 66/1000 for ages 80-89. The estimates are similar for women at 8.0 and 79/000; respectively (2,3). HF can be classified in two categories, the first one with preserved EF (HFpEF) and the other one with reduced EF (HFrEF), the latter representing the majority at approximately 66% (3,4).

The aim of pharmacologic management of HF is to improve the symptoms and decrease morbidity and mortality. For HFrEF patients angiotensin-converting enzyme inhibitors (ACEIs) or angiotensin receptor blockers (ARBs) for ACEI intolerant patients combined with beta-adrenergic blockers are recommended. If symptoms persists mineralocorticoid receptors antagonists (MRAs) are also added and diuretics used to relieve congestive symptoms as per current Canadian Cardiology Society guidelines (5).

More recently, the recognition of the role of natriuretic peptides (NP) as natriuretics and vasodilators along with the discovery that neprilysin (NEP) inhibition can increase the concentration of NPs, has identified these as potential therapeutic solutions that can produce cardiac, vascular and renal benefits to patients with HF (6)

LCZ696 is the first NEP and angiotensin receptor inhibitor (ARNI). The results of clinical trials have shown marked improvements in the reduction of mortality and cardiac events as well as symptom management in patients treated with LCZ696 when compared to current standard of care (6,7,8) .

PARADIGM-HF was a phase III randomized controlled trial conducted in HFrEF patients that were well controlled on background therapy including ACEIs/ARBs, β -blockers and MRAs. The results of this study showed that, when compared to enalapril, LCZ696 significantly reduced the risk of the composite endpoint of CV death or HF hospitalization by 20% after 27 months (8). In the same study LCZ696 also reduced the risk of all-cause mortality by 16%, and the number of all-cause hospitalizations, CV and HF hospitalizations (including first and recurrent hospitalizations). LCZ696 was also found to be safe well tolerated. These results prompted recent changes to the Canadian Cardiovascular Society HF treatment guidelines, according to which LCZ696 has replaced ACEI inhibitors or ARBs in patients with HFrEF .

The TITRATION randomized controlled study enrolled HFrEF patients who were either naïve or already treated with ACEIs or ARBs treated (with EF \leq 35%) that were on any dose of ACEIs or ARBs managed as in-patients or outpatients before enrolment (9). The study compared a condensed regimen in which the dose of LCZ696 was up titrated from 24 mg sacubitril / 26 mg valsartan bid to 49 mg sacubitril / 51 mg valsartan bid in 3 weeks to a conservative regimen in which the up-titration was conducted over 6 weeks. The results showed that LCZ696 was well tolerated and the majority of patients were able to achieve the 97 mg sacubitril / 103 mg valsartan bid target dose without any dose adjustment or interruption over 12 weeks regardless of the ACEIs or ARBs used at baseline. Among the 466 randomized patients, excluding those who discontinued due to non-AE related reasons, 77.8% in the condensed regimen and 84.3% in the conservative regimen achieved the target LCZ696 97 mg sacubitril / 103 mg valsartan bid dose and had no down-titration or dose interruption (Senni et al, ESC-HF May 2015). The results of this study show that up-titration of LCZ696 from 24 mg sacubitril / 26 mg valsartan to the optimal 97 mg sacubitril / 103 mg valsartan bid is safe and well tolerated in a wide range of patients with HFrEF.

Generalization of the results of controlled clinical trials to the real-life setting is problematic

due to the highly selective patients enrolled and the strict adherence to study protocols used in clinical trials. In addition, the fact that controlled clinical trials are conducted in academic or university research centers and to the community setting enhances the discrepancy between controlled trials and the real world setting. Post Approval Clinical Epidemiological Studies (PACES) can address this knowledge gap. Phase IV studies, are one type of PACES, in which patients are treated by community physicians according to a protocol driven pre-specified regimen, in accordance to regional regulations, guidelines and product monographs. These studies can emulate the real – life setting and can provide valuable evidence regarding treatment effectiveness and safety in the real world. With respect to LCZ696 there is a need for the assessment of real – life effectiveness and safety. In addition, there is a need to describe and assess the effectiveness of up-titration regimens aimed at achieving the optimal dose of 97 mg sacubitril / 103 mg valsartan bid.

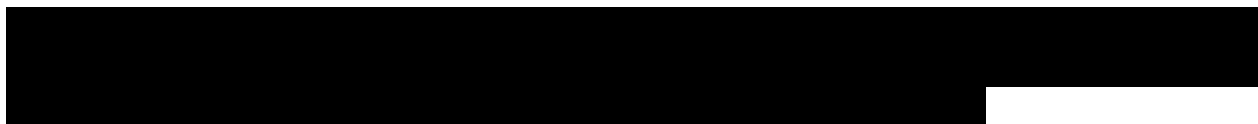
The current study will address this knowledge gap by assessing the tolerability of LCZ696 97 mg sacubitril / 103 mg valsartan bid in Canadian patients with HFrEF treated in community settings. The titration process by which the optimal dose is achieved and any dose reduction or treatment adjustment required will also be described. The study will also assess the therapeutic effectiveness LCZ696 and its overall safety in the real life setting in Canada. The results of this study will have important implications in providing much needed data for the valid evaluation of the benefits of LCZ696 in the management of HFrEF. In addition it will provide guidance on the most effective up-titration approach for achieving and maintaining the optimal therapeutic dose of 200 mg bid.

1.2 Purpose

The results of controlled clinical trials have shown that the optimal dosage of LCZ696 is 97 mg sacubitril / 103 mg valsartan bid. In addition the TITRATION controlled clinical trial has shown that up titration of lower doses, beginning at 24 mg sacubitril / 26 mg valsartan bid, is an effective and well tolerated approach to achieving optimal dose of LCZ696. However, generalization of results from controlled clinical trial to the real – life setting is limited. There is therefore a need for the real life assessment of the effectiveness and safety of LCZ696 and the tolerability of the optimal is 97 mg sacubitril / 103 mg valsartan bid dose. The current study will address this knowledge gap.

The primary purpose of the study will be to describe the tolerability of treatment with the optimal dose of LCZ696 (97 mg sacubitril / 103 mg valsartan bid), over six (6) months, in patients with HFrEF in Canada.

The study will also describe the overall tolerability, effectiveness and safety of LCZ696 in the management of HFrEF over 12 months of treatment, as well as describe the patterns of LCZ696 up and down dose titrations occurring during the management of patients with HFrEF.



2 Study objectives

2.1 Primary

To describe the tolerability of LCZ696 at 97 mg sacubitril / 103 mg valsartan bid, after 6 months of treatment in patients with HFrEF.

2.2 Secondary objectives

In patients with HFrEF:

- To describe the tolerability of LCZ696 at 97 mg sacubitril / 103 mg valsartan bid, after 12 months of treatment.
- To evaluate the impact of the titration scheme on the tolerability of patients maintained on LCZ696 97 mg sacubitril / 103 mg valsartan bid at 6 and 12 months
- To describe the impact of LCZ696 on functional exercise capacity, as measured by the Six Minute Walk Test, at 6 and 12 months.
- To describe the time of up-titration for each dose (24 mg sacubitril / 26 mg valsartan bid / 49 mg sacubitril / 51 mg 51 mg valsartan bid) of LCZ696.
- To describe the adherence to guideline recommended dosing of beta-blockers and MRAs at 6 and 12 months of treatment with LCZ696.
- To evaluate the overall safety profile of LCZ696 during 12 months of treatment.

3 Investigational plan

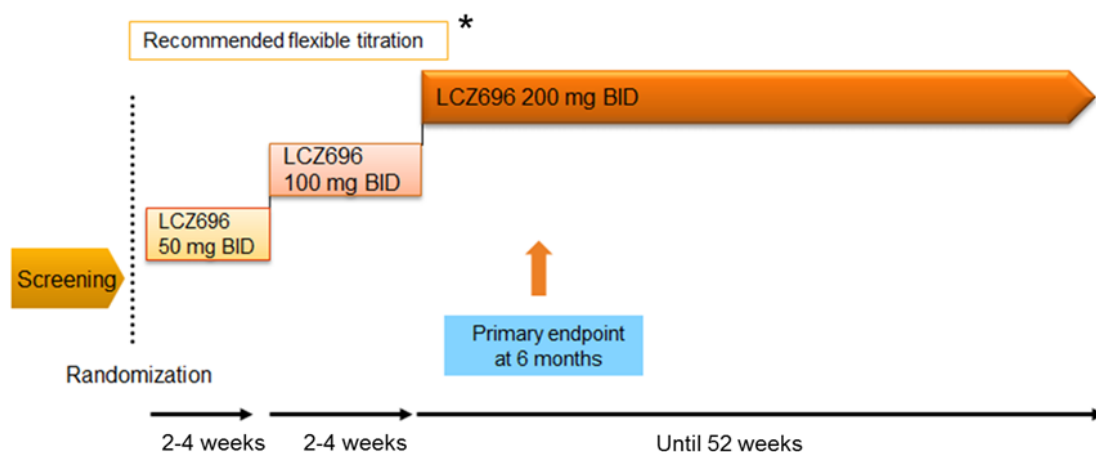
3.1 Study design

This will be a multi-center, open label, prospective post-approval (phase IV) study. Patients with HFrEF that are eligible to be treated with LCZ696 as per the product monograph will be enrolled in the study. The study patients will be enrolled at Canadian community cardiologists and IM specialists that treat patients with HFrEF. Follow up will be for 12

months with assessments at baseline, week 2, week 4, month 3, month 6 and month 12. The primary endpoint will be assessed after 6 months of follow-up.

Potentially eligible patients with HFrEF will be invited to participate in the study and will be asked to sign an informed consent after the purpose, duration and requirements of the study have been explained to them. Treatment with ACEIs will be discontinued for 36 hours and then replaced with LCZ696 at 24 mg sacubitril / 26 mg valsartan bid. NO washout period is need for patients previously treated on ARBs. The dose of LCZ696 will be increased to 49 mg sacubitril / 51 mg valsartan bid within 2-4 weeks of enrolment and to 97 mg sacubitril / 103 mg valsartan bid within 2-4 weeks from the first up titration to 49 mg sacubitril / 51 mg valsartan bid as tolerated by the patient and in accordance to the product monograph (Figure 3-1). All other medications will be used as they were prior to the enrolment in the study; however, the treating physicians may modify the dose of nitrates, CCBs, α -blockers, and diuretics in order to facilitate tolerability of increased LCZ696 doses. Down titration of LCZ696 from the higher doses may be considered, as per the product monograph for patients that experience tolerability issues including, but not limited to, symptomatic hypotension or hyperkalemia.

Figure 3-1 Study design



* Titration scheme in the study protocol will reflect approved Canadian product monograph

- * LCZ696 50 mg bid is the equivalent of 24 mgsacubitril / 26 mg valsartan bid
- * LCZ696 100 mg bid is the equivalent of 49 mg sacubitril / 51 mg valsartan bid
- * LCZ696 200 mg bid is the equivalent of 97 mg sacubitril / 103 mg valsartan bid

3.2 Rationale of study design

This is a single cohort prospective study of HFrEF patients that will be initiated on treatment with LCZ696. Given that the primary purpose of the study is to describe the tolerability of LCZ696 97 mg sacubitril / 103 mg valsartan bid a comparison group is not relevant. Hence

there is no probability of bias in the results caused by the single cohort, no-comparator design.

In addition the study will assess the overall safety and tolerability of LCZ696 over 12 months of treatment, and describe the process by which up-titration to the optimal dose of 97 mg sacubitril / 103 mg valsartan bid is achieved in the real world setting. The assessment of the incremental change in the Six Minute Walk Test since the substitution of ACEIs and ARBs will also be assessed in the study. The single cohort prospective design is appropriate to address these questions.

3.3 Rationale of dose/regimen, route of administration and duration of treatment

All patients will be treated with LCZ696 as a substitution of their current ACEIs or ARBs. The starting dose of LCZ696 will be 24 mg sacubitril / 26 mg valsartan bid that will be up-titrated to 49 mg sacubitril / 51 mg valsartan and then to 97 mg sacubitril / 103 mg valsartan bid as the tolerability of the patient, the product monograph and judgement of the treatment physician. The LCZ696 dose regimen and up-titration algorithm utilized in the current study will be according to the approved Canadian product monograph and has been shown to be efficacious and tolerable in controlled clinical trials.

3.4 Rationale for choice of comparator

Not Applicable.

3.5 Purpose and timing of interim analyses/design adaptations

An interim analysis may be performed after 50 patients have reached 12 weeks of treatment, [REDACTED] and at any time during the study as long as it does not impact the study completion.

3.6 Risks and benefits

The study will be submitted for approval to local and central Independent Review Boards prior to any patient being enrolled. All participating patients will be asked to sign an informed consent prior to undergoing any study related procedures. Patient anonymity will be protected by the exclusive use of study specific identification numbers that will not be linked to personal identifying information. In addition, personal identifying information will never be entered in any study database or study data collection form.

This is an open label study of LCZ696 in patients with HFrEF that will be conducted after approval of the product for marketing in Canada. All treatments will be provided as per the product monograph and the judgement of the physician. Only patients that are eligible for treatment with LCZ696, as per regional policies, treatment guidelines and the product monograph will be enrolled in the study. The risk to the patients is minimized by the close clinical monitoring and option to down-titrate the LCZ696 dose, change the doses of other

medications or terminate treatment. The benefits to the patients include the potentially higher efficacy of LCZ696 in controlling the symptoms of Heart Failure.

4 Population

The target population of the current study is that of patients with HFrEF that are on stable dose of ACEIs and ARBs and for whom treatment with LCZ696 is indicated as per the product monograph and recent guidelines.

4.1 Inclusion criteria

Patients eligible for inclusion in this study have to fulfill **all** of the following criteria:

1. Written informed consent must be obtained before any assessment is performed.
2. Age \geq 18 years and \leq 80 years.
3. Males or females.
4. Diagnosis of Heart Failure NYHA class II-III.
5. Diagnosis of Heart Failure with reduced Ejection Fraction (LVEF \leq 40%) and NYHA class II or III.
6. Stable on any dose of ACEI or ARB prior to enrolment in the study
7. Stable on any dose of a beta-blocker prior to enrolment in the study.
8. Eligible for treatment with LCZ696 (ENTRESTO™) as per Canadian product monograph.
9. Treated as an outpatient.
10. Signed an informed consent agreeing to participate in the study.

4.2 Exclusion criteria

Patients fulfilling **any** of the following criteria are not eligible for inclusion in this study. No additional exclusions may be applied by the investigator, in order to ensure that the study population will be representative of all eligible patients.

1. Symptomatic hypotension and/or a SBP $<$ 100 mmHg at baseline visit.
2. Estimated GFR $<$ 30 mL/min/1.73m² as measured by the simplified Modification of Diet in Renal Disease (MDRD) formula at baseline visit.
3. Known history of angioedema related to previous ACEI or ARBs therapy, or history of hereditary or idiopathic angioedema.

4. Requirement of concomitant treatment with both ACEIs and ARBs.
5. Concurrent participation in other clinical trials or receiving other investigational drugs within 30 days of enrollment.
6. Hypersensitivity to the active substances, sacubitril or valsartan, or to any of the excipients.
7. Concomitant use of aliskiren-containing drugs in patients with diabetes mellitus (type 1 or type 2) or moderate to severe renal impairment (GFR <60ml/min/1.73m²).
8. History of hypersensitivity to any of the study drugs or to drugs of similar chemical classes.
9. History of malignancy of any organ system (other than localized basal cell carcinoma of the skin), treated or untreated, within the past 5 years, regardless of whether there is evidence of local recurrence or metastases.
10. Pregnant or nursing (lactating) women, where pregnancy is defined as the state of a female after conception and until the termination of gestation, confirmed by a positive hCG laboratory test.
11. Women of childbearing potential, defined as all women physiologically capable of becoming pregnant, unless they are using effective methods of contraception during dosing of study treatment. Effective contraception methods include:
 - Total abstinence (when this is in line with the preferred and usual lifestyle of the subject. Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception
 - Female sterilization (have had surgical bilateral oophorectomy with or without hysterectomy) or tubal ligation at least six weeks before taking study treatment. In case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment
 - Male sterilization (at least 6 m prior to screening). For female subjects on the study, the vasectomized male partner should be the sole partner for that subject
 - Barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/ vaginal suppository
 - Use of oral, injected or implanted hormonal methods of contraception or other forms of hormonal contraception that have comparable efficacy (failure rate <1%), for example hormone vaginal ring or transdermal hormone contraception
 - Placement of an intrauterine device (IUD) or intrauterine system (IUS)

- In case of use of oral contraception women should have been stable on the same pill for a minimum of 3 months before taking study treatment.
- Women are considered post-menopausal and not of child bearing potential if they have had 12 months of natural (spontaneous) amenorrhea with an appropriate clinical profile (e.g. age appropriate, history of vasomotor symptoms) or have had surgical bilateral oophorectomy (with or without hysterectomy) or tubal ligation at least six weeks ago. In the case of oophorectomy alone, only when the reproductive status of the woman has been confirmed by follow up hormone level assessment is she considered not of childbearing potential.

5 Treatment

5.1 Protocol requested treatment

5.1.1 Investigational treatment

All patients will be treated with the following:

- LCZ696 (sacubitril and valsartan) tablets
- Starting dose of LCZ696 at 24 mg sacubitril / 26 mg valsartan, intermediate dose of 49 mg sacubitril / 51 mg valsartan and highest dose of 97 mg sacubitril / 103 mg valsartan
- Packaging as per commercially available (under the commercial name ENTRESTO™) or as per clinical supplies, (as applicable).

5.1.2 Additional study treatment

No additional treatment beyond investigational treatment is requested for this trial.

Due to the potential risk of angioedema when used concomitantly with an ACEI, LCZ696 must not be started until 36 hours has passed following discontinuation of ACEI therapy.

Patients will terminate treatment with ARBs and may start on LCZ696 at the next schedule dose. All other background treatment for heart failure including diuretics, beta-blockers, and mineralocorticoid receptor antagonists (MRA) should be continued as prescribed.

5.2 Treatment arms

All patients will be treated with LCZ696.

5.3 Treatment assignment, randomization

Not Applicable.

5.4 Treatment blinding

Not Applicable.

5.5 Treating the patient

5.5.1 Patient numbering

Each patient is uniquely identified by a Subject Number which is composed by the site number assigned by Novartis and a sequential number assigned by the investigator. Once assigned to a patient, the Subject Number will not be reused.

Upon signing the informed consent form, the patient is assigned the next sequential number as given by the investigator using the next blank CRF book available from the EDC system.

If a screened patient fails to be enrolled in the study or treated for any reason, the reason will be entered on the Screening Study Disposition CRF.

5.5.2 Dispensing the investigational treatment

Each study site will be supplied by Novartis with the open label study medication, (LCZ696), in sufficient quantity of the three dose levels that may be used during up-titration, (LCZ696 at 24 mg sacubitril / 26 mg valsartan, 49 mg sacubitril / 51 mg valsartan), and 12 month-treatment phase, LCZ696 (97 mg sacubitril/103 mg valsartan).

5.5.3 Handling of study treatment

5.5.3.1 Handling of investigational treatment

Investigational treatment must be received by a designated person at the study site, handled and stored safely and properly, and kept in a secured location to which only the investigator and designees have access. Upon receipt, all investigational treatment should be stored according to the instructions specified on the labels. Clinical supplies are to be dispensed only in accordance with the protocol.

Medication labels will be in the local language and comply with the legal requirements of each country. They will include storage conditions for the investigational treatment but no information about the patient except for the study specific Subject Number.

The investigator must maintain an accurate record of the shipment and dispensing of investigational treatment in a drug accountability log. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial. Patients will be asked to return all unused investigational treatment and packaging at each study visit and at the end of the study or at the time of discontinuation of investigational treatment.

At the conclusion of the study, and as appropriate during the course of the study, the investigator will return all unused investigational treatment, packaging, drug labels, and a

copy of the completed drug accountability log to the Novartis monitor or to the Novartis address provided in the investigator folder at each site.

5.5.4 Handling of other study treatment

Not Applicable.

5.5.5 Instructions for prescribing and taking study treatment

During the baseline visit all patients will be instructed to stop taking their ACEIs for 36 hours prior to taking the first dose of LCZ696. Patient receiving an ARBs will only have to discontinue their medication and start LCZ696 at the next schedule time. All patients will be initiated on LCZ696 at 24 mg sacubitril / 26 mg valsartan that can be up-titrated to LCZ696 49 mg sacubitril / 51 mg valsartan bid after 2-4 weeks and then up-titrated again to 97 mg sacubitril / 103 mg valsartan bid after another 2 - 4 weeks. Timing of LCZ696 up-titration will be dependent on patient tolerability and the judgement of the physician.

If patients experience any lack of tolerability including but not limited to hypotension and hyperkalemia, the dose of LCZ696 may be reduced or treatment suspended or terminated as per the judgement of the treating physician.

All dosages prescribed and dispensed to the patient and all dose changes during the study must be recorded on the Dosage Administration Record CRF.

The investigator should promote compliance by instructing the patient to take the study treatment exactly as prescribed and by stating that compliance is necessary for the patient's safety and the validity of the study. The patient should be instructed to contact the investigator if he/she is unable for any reason to take the LCZ696 as prescribed.

5.5.6 Permitted dose adjustments and interruptions of study treatment

For patients who are unable to tolerate the protocol-specified dosing scheme, dose adjustments and interruptions of LCZ696 are permitted in order to keep the patient on study drug. Attempt will be made to maintain patients on LCZ696 at 97 mg sacubitril / 103 mg valsartan bid. If in the opinion of the investigator, the patient does not tolerate the highest dose of LCZ696, the investigator should consider whether non disease-modifying medication (such as nitrates, CCBs, α -blockers, and diuretics) can be reduced temporarily to permit up-titration and maintenance of a proven efficacious dose of LCZ696.

Attempt should be made to maintain patients on the proposed study drug dose level for as long as duration as possible throughout the trial. If, however, in the opinion of the investigator, the patient does not tolerate the target dose of study drug, the investigator should consider whether non-disease-modifying medication (e.g., CCBs, diuretics, nitrates, α -blockers) can be reduced to rectify the situation, before considering to reduce the dose of the study drug to the next lower dose level. Also, the investigator may adjust doses of disease-modifying medications if it is believed that they are the most likely cause of the adverse effect. If adjustment/elimination of concomitant medications is not possible or does

not alleviate the side effects of concern, the investigator may opt to down-titrate the dose of the study drug to the next lower level (either 24 mg sacubitril / 26 mg valsartan or 49 mg sacubitril / 51 mg valsartan depending which dose the patient is taking). If needed, the study drug may be stopped completely, but the patient should then discontinue the trial.

These changes must be recorded on the Dosage Administration Record CRF.

5.5.7 Rescue medication

Not Applicable.

5.5.8 Concomitant treatment

The investigator should instruct the patient to notify the study site about any new medications he/she takes after the patient was enrolled into the study. All medications, procedures and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient was enrolled into the study must be recorded.

5.5.9 Prohibited Treatment

Any treatments prohibited as per the Canadian Product Monograph (**ENTRESTO™**).

5.5.10 Discontinuation of study treatment and premature patient withdrawal

Patients may voluntarily withdraw from the study for any reason at any time. They may be considered withdrawn if they state an intention to withdraw, fail to return for visits, or become lost to follow-up for any other reason.

If premature withdrawal occurs for any reason, the investigator must make every effort to determine the primary reason for a patient's premature withdrawal from the study and record this information on study completion/discontinuation CRF page. Study treatment must be discontinued.

The investigator should discontinue study treatment for a given patient and/or withdraw the patient from study if, on balance, he/she believes that continuation would be detrimental to the patient's well-being.

Study treatment must be discontinued and the patient withdrawn from the trial under the following circumstances:

- Withdrawal of informed consent.
- Pregnancy.
- Investigator thinks that continuation would be detrimental to the patient's well-being;
- Suspected occurrence of angioedema during the run-in period.
- Any other protocol deviation that results in a significant risk to the patient's safety.

Study medication may be discontinued at the investigator's discretion if any of the following occurs:

- Any severe suspected drug related AE.
- Suspected occurrence of angioedema. A patient with any signs or symptoms of clinically significant angioedema should be thoroughly evaluated by the investigator and constitute a reason for discontinuation of study medication.
- Depending on the serum potassium, blood pressure, or eGFR, patients may need to have their study drug dose or the dose of another concomitant medication reduced or discontinued, or, if appropriate, have potentially contributing agents adjusted.

If premature discontinuation of study occurs, after Visit 1, and after receiving at least one dose of study medication, the patient should return to the clinic as soon as possible for a last follow-up visit, as per routine clinical care. Attempt should be made to perform all assessments listed in [Table 6-1](#) for the Visit 6. If the patient refuses, he/she should be contacted by telephone in place of protocol-specified visits unless the patient expressly refuses such contacts.

For patients who are lost to follow-up (i.e. those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient, e.g. dates of telephone calls, registered letters, etc.

Patients who are prematurely withdrawn from the study will not be replaced by an equal number of newly enrolled patients.

5.5.11 Emergency breaking of treatment assignment

Not Applicable.

5.5.12 Study completion and post-study treatment

Patients will be treated and followed for 12 months in the current study. After the end of follow up or early termination the patients will be treated according to the judgement of their physicians and regional reimbursement policies.

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

5.5.13 Early study termination

The study can be terminated at any time for any reason by Novartis. Should this be necessary, the patient should be seen as soon as possible and treated for a prematurely withdrawn patient, as outlined in section 5.5.10, above. The investigator may be informed of additional procedures to be followed in order to ensure that adequate consideration is given to the protection of the patient's interests. The investigator will be responsible for informing IRBs and/or ECs of the early termination of the trial.

All patients must be informed of the study early termination and be instructed to return for final assessments, as outlined in section 5.5.10, above. All study treatments must be terminated and the patient's must be followed by the physician for appropriate management and reporting of adverse events.

6 Visit schedule and assessments

[Table 6-1](#) lists all of the assessments and indicates with an "x" when the visits are performed. Patients should be seen for all visits on the designated day with an allowed "visit window" of 7 days, or as close to it as possible.

Patients who discontinue study treatment should also return for a final Visit and perform all assessments indicated in Visit 6 of [Table 6-1](#). If they refuse to return for these assessments or are unable to do so, every effort should be made to contact them or a knowledgeable informant by telephone to determine the patient's status as well as whether they have continued on treatment with LCZ696 and the daily dose.

At a minimum, patients will be contacted for safety evaluations during the 30 days following the last study visit or following the last administration of study treatment if there are post-treatment follow-up visits (whichever is later), including a final contact at the 30-day point. Documentation of attempts to contact the patient should be recorded in the source documentation.

Table 6-1 Assessment schedule

Visit number	1	2	3	4	5	6
Time of Visit	day 1	week 2	Week 4	Month 3 (Week 12)	Month 6 (Week 24)	Month 12
Inclusion/Exclusion criteria	x					
Informed consent	x					
Physical examination ¹	x	x ¹	x ¹	x ¹	x ¹	x ¹
Demographics	x					
Medical history	x					
Vital signs (BP, heart rate)	x	x	x	x	x	x
Height	x					
Weight	x	x	x	x	x	x
Pharmacologic treatments ²	x	x	x		x	x
Six Minute Walk Test ³	x				x	x
Dosing information		x	x		x	x
Dispense study medication	x	x	x		x	
Laboratory test ⁴	x		x	x		x
NYHA Class Assessment	x			x	x	x
Adverse events		x	x	x	x	x
Urine pregnancy test for women with childbearing potential	x					x

¹ Short physical exam, as described in [Section 6.6.1](#) and to be captured only in the source documents

² All HF treatments and all concomitant medications used to treat adverse events.

³ Details and instructions in Appendix 3.

⁴ Routine lab test including potassium and serum creatinine for eGFR assessment, if done as part of routine care.

6.1 Information to be collected on screening failures

All patients who have signed informed consent but did not receive any dose of study medication will have CRF completed for the demographics, inclusion/exclusion, and SAE data collected. Adverse events that are not SAEs will be followed by the investigator and collected only in the source data. Patients who discontinue the study after Visit 1 and after

having received a first dose of study medication, should have the study completion/discontinuation page completed, in addition to the above listed CRF.

For all patients who have signed informed consent and are entered into the next epoch of the study will have all adverse events **occurring after informed consent is signed** recorded on the Adverse Event CRF.

Investigators will have the discretion to record abnormal test findings on the medical history CRF whenever in their judgement, the test abnormality occurred prior to the informed consent signature.

6.2 Patient demographics/other baseline characteristics

The following demographic and baseline parameters will be ascertained from the patient chart or interview during the baseline visit:

- Demographics:
 - Age (date of birth)
 - Gender
 - Race (ethnic background)
 - Smoking history
 - Alcohol use history
- Medical History
 - Chronic conditions
 - Listing of all cardiovascular chronic conditions
 - Concomitant medications
 - Listing and details of all HF treatments and all concomitant medications used to treat adverse events.
 - Heart Failure History
 - Date of diagnosis
 - Prior treatment for heart failure with duration

6.3 Treatment exposure and compliance

All patients will be treated with LCZ696 at 24 mg sacubitril / 26 mg valsartan, 49 mg sacubitril / 51 mg valsartan and 97 mg sacubitril / 103 mg valsartan bid. The dose prescribed for each patient during the up-titration will be recorded in the CRF. All patients will be instructed to return all unused medication at each visit. The site staff will record the number of tablets returned versus those dispensed at the previous visit, and this information will be used to calculate the number of doses missed. In addition, at each follow up visit, the patients will

be asked how many times they did not take any of their prescriptions for heart disease as instructed by their physicians.

6.4 Efficacy

6.4.1 Primary Efficacy Outcome

The primary outcome measure of the study will be the proportion of patients who have remained on treatment with LCZ696 (at the maximum dose of 200 mg bid; 97 mg sacubitril / 103 mg valsartan) at month 6 of follow up. The proportion will be calculated as the number of patients at the maximum LCZ696 dose, over the total number of patients that received at least one dose of LCZ696.

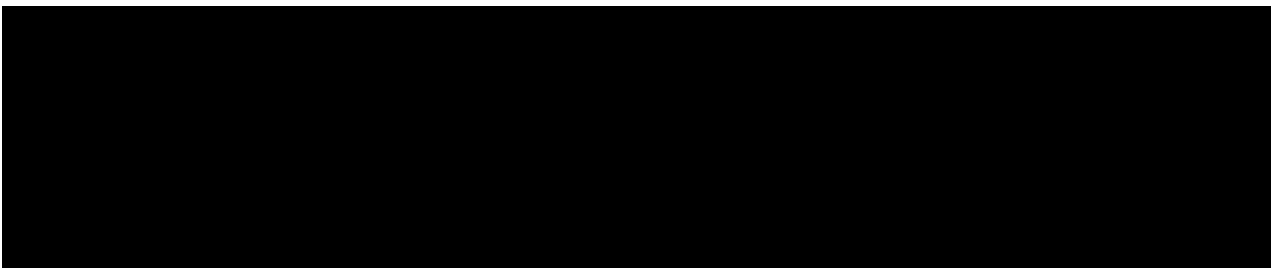
6.4.2 Secondary Efficacy Outcomes

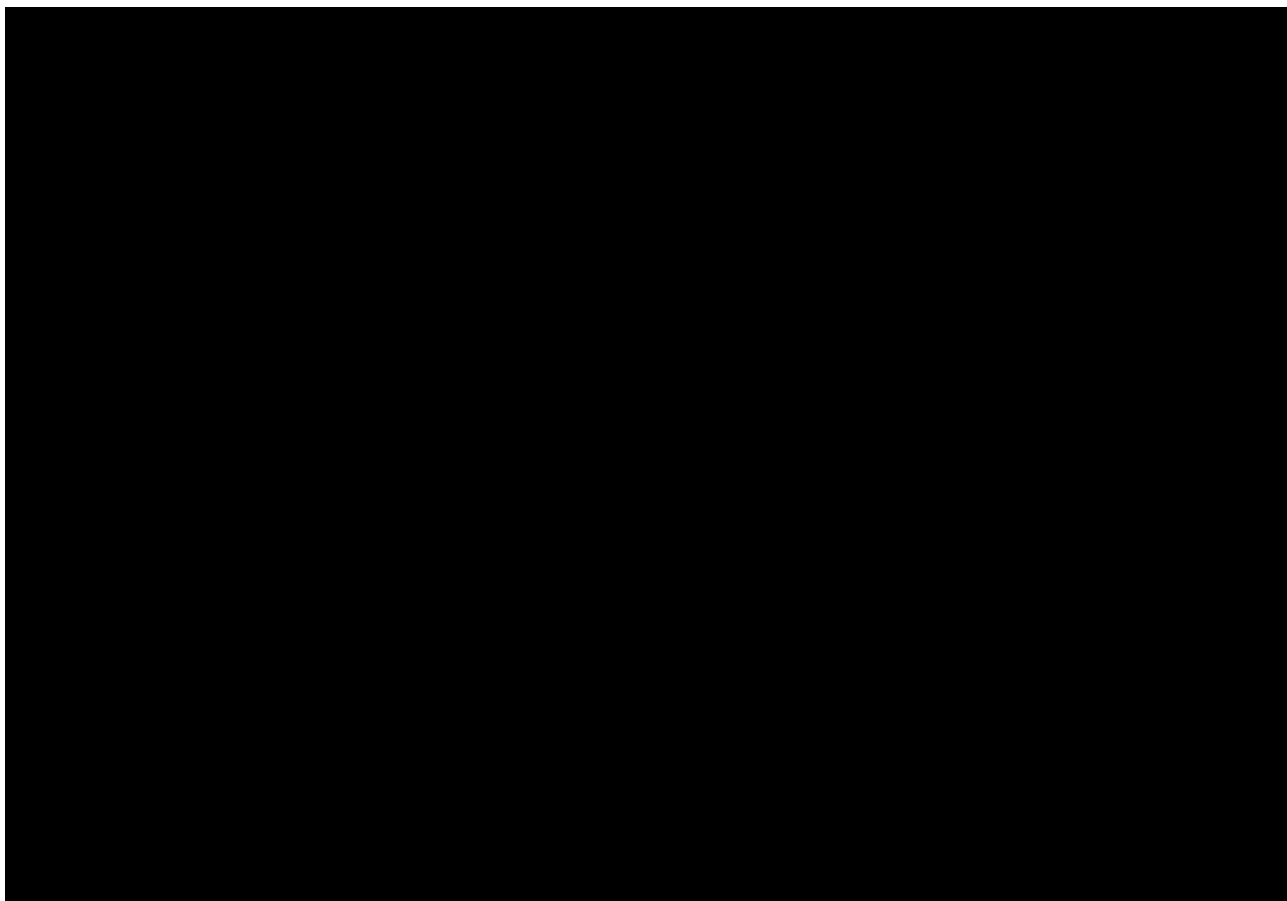
The following secondary outcome measures will be analyzed:

- The proportion of patients who tolerate LCZ696 97 mg sacubitril / 103 mg valsartan bid at 12 months of treatment.
- The proportion of patients on LCZ696 requiring down-titration after reaching the 97 mg sacubitril / 103 mg valsartan dose
- The number of down-titration changes from 97 mg sacubitril / 103 mg valsartan during 12 months of treatment.
- Functional capacity as measured by the change from baseline to 6 months and 12 months in the Six Minute Walk Test*.
- Time to up-titration of LCZ696 doses.
- Duration of treatment on each dose of LCZ696.
- The proportion of patients on guideline recommended dose of beta-blockers and MRAs at baseline, 6 and 12 months.

* The Six Minute Walk Test (SMWT) measures the distance an individual is able to walk over a total of six minutes on a hard, flat surface (Appendix 3). The goal is for the individual to walk as far as possible in six minutes. The individual is allowed to self-pace and rest as needed as they traverse back and forth along a marked walkway (10).

The purpose of the six minute walk is to test exercise tolerance in chronic respiratory disease and heart failure.





6.5 **Appropriateness of efficacy assessments**

The outcome measures are in line with the overall study purpose and objectives. More specifically, the proportion of patients achieving and maintaining treatment with 97 mg sacubitril / 103 mg valsartan bid LCZ696 is the outcome for the primary objective. The time to reaching the dose of 97 mg sacubitril / 103 mg valsartan bid for LCZ696 is relevant in understanding how the up-titration algorithm is applied in the real – life setting. The duration on treatment on 24 mg sacubitril /26 mg valsartan and 49 mg sacubitril / 51 mg valsartan bid LCZ696 is complementary information to the understanding of the real – life implementation of the up-titration scheme for LCZ696. The rate of down – titration of LCZ696 is an indication of tolerability. The change in functional capacity as measured by the six minute walk test, is an important outcome given that it will demonstrate that LCZ696 is not only tolerated at 97 mg sacubitril / 103 mg valsartan bid but also effective in reducing the impact of heart failure.

6.6 **Safety**

The safety assessments include adverse events.

6.6.1 Physical examination

A complete physical examination that will include the examination of general appearance, skin, neck (including thyroid), eyes, ears, nose, throat, lungs, heart, abdomen, back, lymph nodes, extremities, vascular and neurological. If indicated based on medical history and/or symptoms, rectal, external genitalia, breast, and pelvic exams may be performed at the baseline visit.

A short physical exam will include the examination of general appearance and vital signs (blood pressure [SBP and DBP] and pulse) will be conducted for all follow up visits after baseline.

Information for all physical examinations must be included in the source documentation at the study site. Significant findings that are present prior to signing informed consent must be included in the Medical History part of the CRF. Significant findings made after signing the informed consent which meet the definition of an Adverse Event must be recorded on the Adverse Event section of the CRF.

6.6.2 Vital signs

Vital signs include BP and pulse measurements. These will be measured as per the physician's routine practice. However, physicians will be asked to use the same method and instruments, as much as possible, for all assessments of the same patient.

6.6.3 Height and weight

Height in centimeters (cm) and body weight (to the nearest 0.1 kilogram [kg] in indoor clothing, but without shoes) will be measured and recorded at the baseline visit.

6.6.4 NYHA Class assessment

NYHA class will be assessed at baseline (visit 1), at month 3 (visit 4), at month 6 (visit 5) and month 12 (visit 6). NYHA class will be recorded in the CRF and must be included in the source documentations at the study site. At baseline, only patients with heart failure NYHA class II or III can be enrolled in the study

6.6.5 Laboratory evaluations

Laboratory tests will be conducted as per routine care. When results are available these will be recorded in the CRF. Clinically notable laboratory findings are defined in [Appendix 1](#).

6.6.5.1 Hematology

Hematology tests will be conducted as per routine care. When results are available these will be recorded in the CRF.

Hematology tests performed may include the following:

- Hemoglobin

6.6.5.2 Clinical chemistry

Clinical chemistry tests will be conducted as per routine care. When results are available these will be recorded in the CRF.

Blood Chemistry tests performed may include the following:

- ALT (SGPT)
- AST (SGOT)
- BUN
- Creatinine
- CPK
- Alkaline phosphatase
- Potassium
- Chloride
- Uric acid

6.6.5.3 Urinalysis

Not Applicable.

6.6.5.4 Electrocardiogram (ECG)

Electrocardiograms will be conducted as per routine care and documented in the site's source documents.

6.6.6 Pregnancy and assessments of fertility

All pre-menopausal women who are not surgically sterile (women of child-bearing potential) will have a local urine pregnancy test conducted at screening and/or pre-dose and at the end of the trial, (Visit 6). If a local urine pregnancy test at screening shows a positive result, then a serum β -hCG test must be done. If positive, the patient should not enter in the study or should be discontinued from the study.

6.6.7 Appropriateness of safety measurements

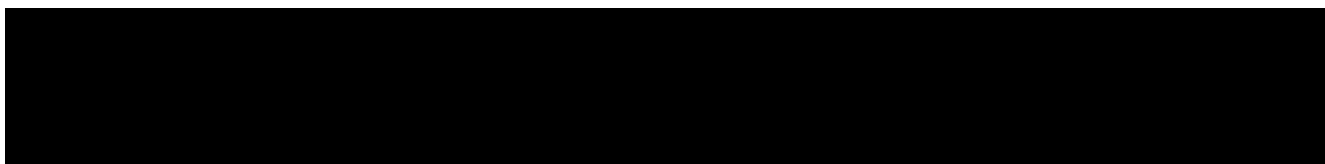
The safety assessments selected are standard for this indication/patient population.

6.7 Other assessments

In additional renal (GFR) function tests may be performed, as per routine clinical care.

6.7.1 Resource utilization

Not Applicable.



6.7.3 Pharmacokinetics

Not Applicable.

6.7.4 Pharmacogenetics/pharmacogenomics

Not Applicable.

6.7.5 Other biomarkers

Not Applicable.

7 Safety monitoring

7.1 Adverse events

An adverse event (AE) is any untoward medical occurrence (i.e., any unfavorable and unintended sign [including abnormal laboratory findings], symptom or disease) in a subject or clinical investigation subject *after providing written informed consent* for participation in the study. Therefore, an AE may or may not be temporally or causally associated with the use of a medicinal (investigational) product.

The occurrence of adverse events should be sought by non-directive questioning of the patient at each visit during the study. Adverse events also may be detected when they are volunteered by the patient during or between visits or through physical examination, laboratory test, or other assessments.

Abnormal laboratory values or test results constitute adverse events only if they fulfill at least one of the following criteria:

- they induce clinical signs or symptoms,
- they are considered clinically significant,
- they require therapy.

Clinically significant abnormal laboratory values or test results should be identified through a review of values outside of normal ranges/clinically notable ranges, significant changes from baseline or the previous visit, or values which are considered to be non-typical in patient with underlying disease. Investigators have the responsibility for managing the safety of individual patient and identifying adverse events. Alert ranges for labs and other test abnormalities are included in [Appendix 1](#).

Adverse events should be recorded in the Adverse Events CRF under the signs, symptoms or diagnosis associated with them accompanied by the following information.

- the severity grade:
 - mild: usually transient in nature and generally not interfering with normal activities
 - moderate: sufficiently discomforting to interfere with normal activities
 - severe: prevents normal activities

- its relationship to the study treatment (no/yes)
- its duration (start and end dates) or if the event is ongoing an outcome of not recovered/not resolved should be reported.
- whether it constitutes a serious adverse event (SAE)
- action taken regarding study treatment
- whether other medication or therapies have been taken (concomitant medication/non-drug therapy)
- its outcome (not recovered/not resolved; recovered/resolved; recovering/resolving, recovered/resolved with sequelae; fatal; or unknown)

An SAE is any adverse event (appearance of (or worsening of any pre-existing) undesirable sign(s), symptom(s) or medical conditions(s) which meets any one of the following criteria

- is fatal or life-threatening
- results in persistent or significant disability/incapacity
- constitutes a congenital anomaly/birth defect
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
 - routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
 - elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since signing the informed consent
 - treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a SAE given above and not resulting in hospital admission
 - social reasons and respite care in the absence of any deterioration in the patient's general condition
- is medically significant, i.e. defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above.

All malignant neoplasms will be assessed as serious under “medically significant” if other seriousness criteria are not met.

For LCZ696, there are events which are the object of more targeted follow-up activities as per regulatory commitments. The local Novartis DS&E Department will perform the follow-up: on the following events regardless of seriousness:

- Angioedema-related events
- Cognitive Impairment/Dementia-related events
- Hepatotoxicity-related events
- Statin-related events

Unlike routine safety assessments, SAEs are monitored continuously and have special reporting requirements; see Section 7.2.

All adverse events should be treated appropriately. Treatment may include one or more of the following: no action taken (i.e. further observation only); study treatment dosage adjusted/temporarily interrupted; study drug(s) permanently discontinued; concomitant medication given; non-drug therapy given. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study treatment, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the ENTRESTO™ Product Monograph. This information will be included in the patient informed consent and should be discussed with the patient during the study as needed.

The investigator should also instruct each patient to report any new adverse event (beyond the protocol observation period) that the patient, or the patient's personal physician, believes might reasonably be related to study treatment. This information should be recorded in the investigator's source documents, however, if the AE meets the criteria of an SAE, it must be reported to Novartis.

7.2 Serious adverse event reporting

To ensure patient safety, every SAE, regardless of causality, occurring after the patient has provided informed consent and until 30 days after the last study visitation of study treatment must be reported to Novartis within 24 hours of learning of its occurrence. Any SAEs experienced after the 30 days period should only be reported to Novartis if the investigator suspects a causal relationship to study treatment.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

Information about all SAEs (either initial or follow up information) is collected and recorded in English on the paper Serious Adverse Event Report Form or the electronic Serious Adverse Event Form within the OC/RDC system (where available). The Investigator must assess the relationship to each specific component of the study treatment (if the study treatment consists of several components).

SAEs (initial and follow-up) that are recorded *on the paper SAE form* should be faxed within 24 hours of awareness of the SAE to the local Novartis Drug Safety and Epidemiology

Department. The telephone and fax number of the contact persons in the local department of Drug Safety and Epidemiology, specific to the site, are listed in the investigator folder provided to each site. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site. Follow-up information should be provided using a new paper SAE Report Form stating that this is a follow-up to a previously reported SAE

SAEs (initial and follow-up) that are recorded *electronically* in the OC/RDC system should be entered, saved and e-signed within 24 hours of awareness of the SAE or changes to an existing SAE. These data will automatically be submitted to Novartis Drug Safety & Epidemiology immediately after investigator signature or 24 hours after entry, whichever occurs first.

Follow-up information provided should describe whether the event has resolved or continues, if and how it was treated, whether the treatment code was broken or not and whether the patient continued or withdrew from study participation. Each re-occurrence, complication, or progression of the original event should be reported as a follow-up to that event regardless of when it occurs.

If the SAE is not previously documented in the Product Monograph (new occurrence) and is thought to be related to the study treatment a Drug Safety and Epidemiology Department associate may urgently require further information from the investigator for Health Authority reporting. Novartis may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the use of LCZ696 that this SAE has been reported. Suspected Unexpected Serious Adverse Reactions (SUSARs) will be collected and reported to the competent authorities and relevant ethics committees in accordance with Directive 2001/20/EC or as per national regulatory requirements in participating countries.

7.3 Liver safety monitoring

To ensure patient safety and enhance reliability in determining the hepatotoxic potential of an investigational drug, a standardized process for identification, monitoring and evaluation of liver events has to be followed.

Liver events are divided into two categories:

- Liver events of special interest (AESI) which consist of LFTs elevations
- Medically significant liver events which are considered as serious adverse events (SAEs) and which consist of marked elevations of LFTs and / or pre-specified adverse events.

Please refer to [Table 14-1](#) in [Appendix 2](#) for complete definitions of liver events.

Any liver event which meets the criteria for “**medically significant**” event as outlined in [Table 14-1](#) of [Appendix 2](#) should follow the **standard procedures for SAE reporting** as described in [Section 7.2](#).

Every liver event as defined in [Table 14-1](#) of [Appendix 2](#) should be followed up by the investigator or designated personal at the trial site as summarized below. Detailed information is outlined in [Table 14-2](#) in [Appendix 2](#).

- Repeating the LFT to confirm elevation as appropriate
- Discontinuation of the investigational drug if appropriate
- Hospitalization of the patient if appropriate
- A causality assessment of the liver event via exclusion of alternative causes (e.g., disease, co-medications)
- An investigation of the liver event which needs to
- be followed until resolution.

These investigations can include serology tests, imaging and pathology assessments, hepatologist's consultancy, based on investigator's discretion. All follow-up information, and the procedures performed should be recorded on appropriate CRF pages, including the liver event overview CRF pages.

7.4 Pregnancy reporting

To ensure patient safety, each pregnancy occurring while the patient is on study treatment must be reported to Novartis within 24 hours of learning of its occurrence. The pregnancy should be followed up to determine outcome, including spontaneous or voluntary termination, details of the birth, and the presence or absence of any birth defects, congenital abnormalities, or maternal and/or newborn complications.

Pregnancy should be recorded on a Clinical Trial Pregnancy Form and reported by the investigator to the local Novartis Drug Safety and Epidemiology Department. Pregnancy follow-up should be recorded on the same form and should include an assessment of the possible relationship to the study treatment.

Any SAE experienced during pregnancy must be reported on the SAE Report Form.

7.5 Prospective suicidality assessment

Not Applicable.

7.6 Unusual Lack of Efficacy

Unusual lack of efficacy is defined as a technical failure of a compound to meet its efficacy goals, to produce the expected intended effect, and is subject to quality assurance testing to confirm that the manufacturing of the compound is appropriate. Therefore, lack of efficacy should be sent within 24 hours of awareness to the local Novartis Drug Safety and Epidemiology Department at [REDACTED]. The original copy of the e-mail correspondence should be kept at the study site.

Clinical judgement should be exercised by a qualified health care professional to determine if the problem reported is related to the product itself, rather than one of treatment selection or disease progression since health products cannot be expected to be effective in 100% of the patients. One example of unusual failure in efficacy is a previously well-stabilized condition that deteriorates when the patient changes to a different brand or receives a new prescription

The following situations are examples when unusual lack of efficacy is considered:

- The patient's disease was stable and controlled. Suddenly, an unexplainable loss of efficacy is reported, with no change in the drug dosage or the severity of the medical condition.
- The loss of efficacy happened despite proper dosage administration and adequate duration of therapy, as per labeling instructions.
- The loss of efficacy happened after switching to a new batch of medication.
- The loss of efficacy reported is in association with some specific units within the same package / box, only.

8 Data review and database management

8.1 Site monitoring

Before study initiation, at a site initiation visit or at an investigator's meeting, a Novartis representative will review the protocol and CRFs with the investigators and their staff. During the study, the field monitor will visit the site regularly to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that the study treatment is being stored, dispensed, and accounted for according to specifications. Key study personnel must be available to assist the field monitor during these visits.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, electrocardiograms, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient's file. If applicable, data not requiring a separate written record will be defined before study start and will be recorded directly on the CRFs. The investigator must also keep the original informed consent form signed by the patient (a signed copy is given to the patient).

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. Novartis monitoring standards require full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and of data that will be used for all primary variables. Additional checks of the consistency of the source data with the CRFs are performed

according to the study-specific monitoring plan. No information in source documents about the identity of the patients will be disclosed.

8.2 Data collection

Designated investigator staff will enter the data required by the protocol into the Electronic Case Report Forms using fully validated software that conforms to 21 CFR Part 11 requirements. Designated investigator site staff will not be given access to the EDC system until they have been trained.

Automatic validation procedures within the system check for data discrepancies during and after data entry and, by generating appropriate error messages, allow the data to be confirmed or corrected online by the designated investigator site staff. The Investigator must certify that the data entered into the electronic Case Report Forms are complete and accurate. After database lock, the investigator will receive copies of the patient data for archiving at the investigational site.

8.3 Database management and quality control

Novartis staff review the data entered into the CRFs by investigational staff for completeness and accuracy and instruct the site personnel to make any required corrections or additions. Queries are sent to the investigational site using an electronic data query. Designated investigator site staff is required to respond to the query and confirm or correct the data. If the electronic query system is not used, a paper Data Query Form will be faxed to the site. Site personnel will complete and sign the faxed copy and fax it back to Novartis staff that will make the correction to the database. The signed copy of the Data Query Form is kept at the investigator site.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Concomitant procedures, non-drug therapies and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

8.4 Data Monitoring Committee

Not Applicable.

8.5 Adjudication Committee

Not Applicable.

9 Data analysis

9.1 Analysis sets

The Full Analysis Set (FAS) will be comprised of all patients that have received at least one dose of LCZ696. The Per-Protocol (PP) Analysis Set will be comprised of the patients that

complete the 6 month and 12 month follow up assessments depending on the time period analyzed. The primary analysis will be based on the FAS. The analyses will be repeated for the PP Analysis Set if there is a more than 10% difference between the FAS and PP samples. Patients in the FAS will also comprise the Safety Population. All analyses will be performed in both the FAS and PP Analysis Sets, unless otherwise specified.

9.2 Patient demographics and other baseline characteristics

Descriptive statistics will be reported for patient demographics and baseline characteristics. This will include the mean, median, standard deviation and 95% confidence interval of the mean for continuous scale variables. Frequency distributions with 95% confidence intervals around the estimate of proportions will be reported for categorical variables.

9.3 Treatments

All LCZ696 doses administered to the patients will be recorded in the CRF. The number of tablets dispensed at the previous visit minus the number of tablets returned by patients at each study visits, will be used as a measure of the number of tablets taken between study visits.

9.4 Analysis of the primary and key secondary variable(s)

9.4.1 Variable(s)

9.4.1.1 Primary Outcome Analysis

The primary outcome measure of the study will be the proportion of patients remaining on treatment with LCZ696 97 mg sacubitril / 103 mg valsartan at six months of follow up. The proportion will be calculated as the number of patients at 97 mg sacubitril / 103 mg valsartan over the total number of patients that received at least one dose of ENTRESTO™.

9.4.1.2 Secondary Outcome Analyses

The following secondary outcome measures will be analyzed:

1. The proportion of patients who tolerate the LCZ696 dose of 97 mg sacubitril / 103 mg valsartan mg bid at 12 months of treatment.
2. The proportion of patients on LCZ696 who had required down-titration after reaching the 97 mg sacubitril / 103 mg valsartan
3. The number of down-titration changes from 97 mg sacubitril / 103 mg valsartan during 12 months of treatment.
4. Functional capacity as measured by the change from baseline to 6 months and 12 months in the Six Minute Walk Test.
5. Time to up-titration of LCZ696 doses.
6. Duration of treatment on each dose of LCZ696.

7. The proportion of patients on guideline-recommended doses of beta-blockers and MRAs at baseline, 6 and 12 months.

9.4.2 Statistical model, hypothesis, and method of analysis

The data analysis for the current study will be primarily descriptive. Therefore there are no a-priori hypothesis being tested.

9.4.3 Primary Efficacy Analysis

The primary efficacy outcome will be assessed by the proportion of patients on LCZ696 97 mg sacubitril / 103 mg valsartan bid at 6 months of treatment. Ninety five percent (95%) confidence intervals will be calculated for the estimate of this proportion in order to assess precision and make inferences to the target population.

9.4.4 Secondary Efficacy Analyses

Similarly, for the secondary efficacy outcomes, the proportion of patients on LCZ696 97 mg sacubitril / 103 mg valsartan bid at 12 months, the proportion of patients requiring down titration, and the proportion of patients treated in accordance to guideline recommended doses of beta blockers and MRAs, will also be assessed for precision with the 95% Confidence Intervals.

The number of down titrations during the 12 month treatment periods will be described with a Poisson distribution and the incidence density rate (IDR) as the number of dose reductions per 100 person – month of follow up.

The change in the Six Minute Walk Test from baseline to 6 and 12 months of treatment will be assessed with the 95% confidence intervals and with the Student's t-test for paired observations.

The time to LCZ696 up-titration to 97 mg sacubitril / 103 mg valsartan bid and the duration on treatment for each dose will be assessed with the Kaplan Meier estimator of the survival function.



9.4.6 Handling of missing values/censoring/discontinuations

There will be no replacement or imputation of missing values. All analysis will be conducted on observed cases only. For patients lost to follow up after achieving the LCZ696 dose of 97 mg sacubitril / 103 mg valsartan bid, the conservative approach will be used according to

which they will be considered as not staying on treatment. A sensitivity analysis will be conducted to assess the impact of this assumption by using only the PP patients.

9.4.7 Supportive analyses

Not Applicable.

9.5 Analysis of secondary variables

9.5.1 Efficacy variables

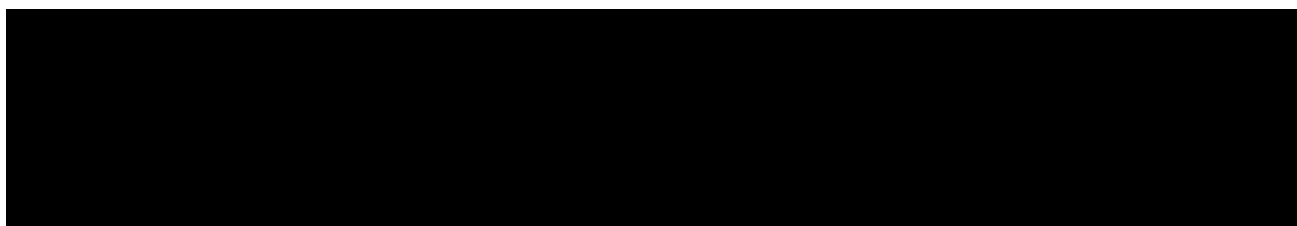
Not Applicable.

9.5.2 Safety variables

Adverse events (AEs) will be classified according to the MedDRA dictionary of terms (Version 18.1 or newer) and summarized using the total number of AEs, the total number and percentage of patients who experience an AE overall, and the number and percent of patients who experience an AE within each system organ class (SOC) and preferred terms (PTs) within individual SOCs. Analysis of the number of patients who experience each AE will be performed in the following manner: patients experiencing the same AE multiple times will only be counted once for the corresponding PT; similarly, if a patient experiences multiple AEs within the same SOC, that patient will be counted only once for that SOC. A similar table will be produced for serious adverse events (SAEs), AEs with reasonable probability to be related to the study treatment (definitely related, probably related, possibly related), and SAEs with reasonable probability to be related to the study treatment. Finally, a summary table reporting the breakdown of the total number of AEs by seriousness (serious, non-serious), severity (mild, moderate, severe), relationship to study medication (definitely related, probably related, possibly related, unlikely related, definitely not related), action taken, and outcome will be prepared. The Safety Analysis will be carried out on the Safety Population only.

9.5.3 Resource utilization

Not Applicable.



9.5.5 Pharmacokinetics

Not Applicable.

9.5.6 **Pharmacogenetics/pharmacogenomics**

Not Applicable.

9.5.7 **Biomarkers**

Not Applicable.

9.5.8 **PK/PD**

Not Applicable.

9.6 **Sample size calculation**

The primary outcome measure for the current study will be the proportion of patients on 97 mg sacubitril / 103 mg valsartan bid of LCZ696 at 6 months of treatment. The data from clinical trials have shown that at 12 weeks (3 months) approximately 80% of patients have achieved this dose. In this current real – life study of 6 months (primary endpoint) a reasonable estimate of patients achieving this dose would be 70%.

Given that this is a single cohort, prospective study in which all patients are receiving the same treatment and the objective is to describe the proportion of patients reaching 97 mg sacubitril / 103 mg valsartan bid LCZ696, sample size requirements are based on the precision of the estimate. This is assessed with the 95% confidence interval. A reasonable level of precision is one with a 95% confidence interval width (ω) that is between 5 and 15% of the point estimate. With 300 patients enrolled in the study, the 95% Confidence Interval width will be $\pm 5.2\%$ which is equivalent to 7.4% of the point estimate of 70%, with upper and lower limits of 64.8% – 75.2% respectively. This is within the limits of reasonable precision.

10 **Ethical considerations**

10.1 **Regulatory and ethical compliance**

This clinical study was designed and shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC, US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor, and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

10.2 **Informed consent procedures**

Eligible patients may only be included in the study after providing written, IRB/IEC-approved informed consent, or, if incapable of doing so, after such consent has been provided by a legally acceptable representative of the patient. In cases where the patient's representative gives consent, the patient should be informed about the study to the extent possible given his/her understanding. Informed consent must be obtained before

conducting any study-specific procedures (i.e. all of the procedures described in the protocol). The process of obtaining informed consent should be documented in the patient source documents.

Novartis will provide to investigators in a separate document a proposed informed consent form that complies with the ICH GCP guideline and regulatory requirements and is considered appropriate for this study. Any changes to the proposed consent form suggested by the investigator must be agreed to by Novartis before submission to the IRB/IEC, and a copy of the approved version must be provided to the Novartis monitor after IRB/IEC approval.

Women of child bearing potential should be informed that taking the study treatment may involve unknown risks to the fetus if pregnancy were to occur during the study and agree that in order to participate in the study they must adhere to the contraception requirement for the duration of the study. If there is any question that the patient will not reliably comply, they should not be entered in the study.

10.3 Responsibilities of the investigator and IRB/IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Institutional Review Board/Independent Ethics Committee/Research Ethics Board (IRB/IEC) before study start. A signed and dated statement that the protocol and informed consent have been approved by the IRB/IEC must be given to Novartis before study initiation. Prior to study start, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the study in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to Novartis monitors, auditors, Novartis Clinical Quality Assurance representatives, designated agents of Novartis, IRBs/IECs, and regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform Novartis immediately that this request has been made.

10.4 Publication of study protocol and results

Novartis assures that the key design elements of this protocol will be posted in a publicly accessible database such as clinicaltrials.gov. In addition, upon study completion and finalization of the study report the results of this trial will be either submitted for publication and/or posted in a publicly accessible database of clinical trial results.

11 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator contact Novartis or its agents, if any, monitoring the trial to request approval of a protocol deviation, as requests to approve deviations will not be granted.

This protocol defines the study objectives, the study procedures and the data to be collected on study participants. Under no circumstances should an investigator collect additional data or conduct any additional procedures for any research related purpose involving any investigational drugs.


If the investigator feels a protocol deviation would improve the conduct of the study this must be considered a protocol amendment, and unless such an amendment is agreed upon by Novartis and approved by the IRB/IEC it cannot be implemented. All significant protocol deviations will be recorded and reported in the CSR.

11.1 Protocol Amendments

Any change or addition to the protocol can only be made in a written protocol amendment that must be approved by Novartis, Health Authorities where required, and the IRB/IEC. Only amendments that are required for patient safety may be implemented prior to IRB/IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this study, even if this action represents a deviation from the protocol. In such cases, Novartis should be notified of this action and the IRB/IEC at the study site should be informed within 10 working days or less, if required by local regulations.

12 References

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- (13) Packer M (2001) Proposal for a new clinical end point to evaluate the efficacy of drugs and devices in the treatment of chronic heart failure. *J Cardiac Fail*; 7: 176-182.

13 **Appendix 1: Clinically notable laboratory values and vital signs**

Clinically notable laboratory abnormalities for selected tests based on a percent change from baseline:

Hematology

RBC count	>50% increase, >20% decrease
Hemoglobin	>50% increase, >20% decrease
Hematocrit	>50% increase, >20% decrease
WBC count	>50% increase, >50% decrease
Platelet count	>75% increase, >50% decrease

Blood Chemistry

ALT (SGPT)	>150% increase
AST (SGOT)	>150% increase
BUN	>50% increase
Creatinine	>50% increase
Total bilirubin	>100% increase
CPK	>300% increase
Alkaline phosphatase	>100% increase
Potassium	>20% increase, >20% decrease
Chloride	>10% increase, >10% decrease
Calcium	>10% increase, >10% decrease
Uric acid	>50% increase

14 Appendix 2: Liver event definitions and follow-up requirements

Table 14.1 Liver Event Definitions

	Definition/ threshold
Adverse event of special interest	
Laboratory values	ALT or AST > 3 x ULN ALP > 2 x ULN TBL > 1.5 x ULN
Medically significant event (SAE)	
Laboratory values	ALT or AST > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction]) ALP > 5 x ULN (with or without TBL > 2 x ULN [mainly conjugated fraction]) TBL > 3 x ULN Potential Hy's Law cases (defined as ALT/AST > 3 x ULN <u>and</u> TBL > 2 x ULN [mainly conjugated fraction] <u>without</u> notable increase in ALP to > 2 x ULN)
Adverse events	Any clinical event of jaundice (or equivalent term) ALT or AST > 3 x ULN accompanied by general malaise, fatigue, abdominal pain, nausea, or vomiting, or rash with eosinophilia Any event that links to a preferred term (PT) in the MedDRA dictionary falling under the SMQ sub-module "Drug-related hepatic disorders – severe events only"* or any "Hy's law case" PT

* These events cover the following: hepatic failure, fibrosis and cirrhosis, and other liver damage-related conditions; the non-infectious hepatitis; the benign, malignant and unspecified liver neoplasms

Table 14-2 Liver Event Follow Up Requirements

Criteria	Event type	Actions required	Follow-up monitoring
Potential Hy's Law case ^a	Medically significant	Discontinue the study drug immediately Hospitalize, if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γ GT until resolution ^c (frequency at investigator discretion)
ALT or AST			
> 8 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γ GT until resolution ^c (frequency at investigator discretion)
> 5 to \leq 8 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists for <i>more than 2 weeks</i> , discontinue the study drug Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γ GT until resolution ^c (frequency at investigator discretion)
> 3 x ULN accompanied by symptoms ^b	Medically significant	Discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γ GT until resolution ^c (frequency at investigator discretion)
> 3 to \leq 5 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Investigator & Novartis Repeat LFT once or twice in the week If elevation persists, establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
\leq 3 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
ALP (isolated)			
> 5 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, report to Novartis as an SAE Establish causality	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
> 2 to \leq 5 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Investigator & Novartis	Investigator discretion Monitor LFT within 1 to 4 weeks or at next visit

Criteria	Event type	Actions required	Follow-up monitoring
		Repeat LFT once or twice in the week If elevation persists, establish causality	
≤ 2 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
TBL (isolated)			
> 3 x ULN	Medically significant	Repeat LFT within 48 hours If elevation persists, discontinue the study drug immediately Hospitalize if clinically appropriate Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution ^c (frequency at investigator discretion) Test for hemolysis (e.g., reticulocytes, hemoglobin, unconjugated [indirect] bilirubin)
> 1.5 to ≤ 3 x ULN (patient is asymptomatic)	AESI	Central laboratory to report to Novartis Repeat LFT once or twice in the week If elevation persists, establish causality	investigator discretion Monitor LFT within 1 to 4 weeks or at next visit
≤ 1.5 x ULN (patient is asymptomatic)	N/A	Repeat LFT at next visit	
Preferred terms			
Jaundice	Medically significant	Discontinue the study drug immediately Hospitalize the patient Report to Novartis as an SAE Establish causality	ALT, AST, TBL, Alb, PT, ALP and γGT until resolution ^c (frequency at investigator discretion)
“Drug-related hepatic disorders - severe events only” SMQ AE	Medically significant	Discontinue the study drug hospitalization if clinically appropriate Report to Novartis as an SAE Establish causality	Investigator discretion

^a Elevated ALT/AST > 3 x ULN and TBL > 2 x ULN but with no notable increase in ALP to > 2 x ULN

^b General malaise, fatigue, abdominal pain, nausea, or vomiting, rash with eosinophilia

^c Resolution is defined as an outcome of one of the following: return to baseline values, stable values at three subsequent monitoring visits at least 2 weeks apart, remain at elevated level after a maximum of 6 months, liver transplantation, and death.

15 Appendix 3: Study Assessments and Questionnaires

15.1 Six Minute Walk Test

> Key Points

- The 6MWT must be performed once or else twice to account for a learning curve.
- *Note: consistency in administering the test is imperative. If the test was performed once at baseline it should be performed once at all subsequent visits, if performed twice at baseline it should be performed twice at all subsequent visits.
- If the two tests are performed on the same day, at least 30 minutes rest should be allowed between tests.

*Note: debilitated individuals may require tests to be performed on separate days, preferably less than one week apart.

- Results of both tests are recorded with the best result used to determine functionality.
- A health professional trained in CPR with the ability to run the test must be present.

> Required Equipment

- Walking Track or Area
 - The walking track or area must be the same for all tests for a patient
 - The track may be a continuous track (oval or rectangular) or a point-to-point area (stop- turn around-go back).
 - The track or area should be flat with no blind turns, traffic or obstacles.
 - The minimum walking length of 25m (82 feet) should be marked in meter (feet) increments.

*Note: If you do not have access to a 25m track, make sure you use the same point-to- point area for all tests (be aware that the distance walked may be less due to the patient having to slow down and turn more often in the six minutes).

- Stethoscope, vital sign equipment, pulse oximeter
- Stop watch
- Portable oxygen delivery system
- Chairs in position for the patient to rest
- Dyspnea scale

> Before the 6MWT

- Ensure that you have already obtained a medical history for the patient and have

taken into account any precautions or contraindications to exercise testing.

- Instruct the patient to dress comfortably, wear appropriate footwear and to avoid eating for at least two hours before the test (where possible or appropriate).
- Any prescribed inhaled bronchodilator medication should be taken within one hour of testing or when the patient arrives for testing.
- The patient should rest for at least 15 minutes before beginning the test.
- A comfortable ambient temperature and humidity should be maintained for all tests.
- Record:
 - Blood pressure
 - Heart rate
 - Oxygen saturation
 - Dyspnea score

** Note: Show the patient the dyspnea scale (e.g., Borg scale) and give consistent instructions on how to obtain a score.*

- **Instructions to the Patient**

**Note: Instructions must be consistent.*

(Read out loud the instructions to the patient.)

- Describe the walking track or area to the patient.
- Explain the objective of the test.
- Provide instructions on what to do and what not to do during the test.
- Emphasize reporting any untoward effects.
- Sample instructions:

“You are now going to do a six-minute walking test. The object of this test is to walk as quickly as you can for six minutes around the track (or up and down the corridor etc... depending on your track set up) so that you cover as much ground as possible. You may slow down if necessary. If you stop, I want you to continue to walk again as soon as possible. You will be kept informed of the time and you will be encouraged to do your best. Your goal is to walk as far as possible in six minutes. Please do not talk during the test unless you have a problem or if I ask you a question. You must let me know if you have any chest pain or dizziness. When the six minutes is up I will ask you to stop where you are. Do you have any questions?”

> **Begin the Test** by instructing the patient to start walking and start the stop watch.

> **During the Test**

- Monitor the patient for untoward signs and symptoms.
- Use standard encouragements during the test. Example:
 - At minute one: “Five minutes remaining. Do your best!”
 - At minute two: “Four minutes remaining. You're doing well- keep it up!”
 - At minute three: “Half way point. Three minutes remaining!”
 - At minute four: “Two minutes remaining. You're doing well- keep it up!”
 - At minute five: “One minute remaining. Do your best!”

> **At the End of the 6MWT**

- Put a marker on the distance walked.

- Have the patient sit down or if the patient prefers, allow to the patient to stand.
**Note: The measurements taken before and after the test should be taken with the patient in the same position.*
- Immediately record oxygen saturation (SpO₂)%, heart rate, and dyspnea rating on the recording sheet.
- Measure the excess distance with a tape measure and add up the total distance.
- The patient should remain in a clinical area for at least 15 minutes following an uncomplicated test.

>Clinical Notes

Normally the clinician does not walk with the patient during the test to avoid the problem of setting the walking pace. The pulse oximeter should be applied immediately if the patient chooses to rest and at completion of the six-minute walking period. Any delay may result in readings being recorded that are not representative of maximum exercise response.

In some instances, the clinician may choose to walk with the patient for the entire test (e.g., if continuous oximetry is desired). If this is the case the clinician should try to walk slightly behind the patient to avoid setting the walking pace. Alternatively, if the oximeter is small and lightweight, it may be attached to the patient and checked throughout the test without interfering with walking pace.

> If the Patient Stops During the Six Minutes

- Allow the patient to sit in a chair if they wish.
- Measure the SpO₂% and heart rate.
- Ask the patient why they stopped.
- Record the time the patient stopped (but keep the stop watch running).
- Encourage the patient to begin walking as soon as he/she is feeling better and offer encouragement every 15 seconds if necessary.
- Monitor the patient for untoward signs and symptoms.

>Stop the Test in the Event of Any of the Following

- Chest pain suspicious for angina.
- Evolving mental confusion or lack of coordination.
- Evolving light-headedness.
- Intolerable dyspnea.
- Leg cramps or extreme leg muscle fatigue.
- Persistent SpO₂ < 85%.
- Any other clinically warranted reason.

> Predicted Normal Values for the 6MWT

The following predictive equation uses the reference values determined from a study

that performed two 6MWTs and recorded the best result: (For more details see Troosters T, Gosselink R, Decramer M. Six minute walk distance in healthy elderly subjects. Eur Respir J. 1999;14: 270-274).

- Predicted six-minute walk distance in healthy elderly = 631 ± 93 meters
- Predictive equation: $6MWD_{pred} = 218 + (5.14 \times \text{height}_{cm} - 5.32 \times \text{age}) - 1.80 \times \text{weight}_{kg} + 51.31 \times \text{gender}$

Note: Gender is factored into the equation by male = 1, female = 0.

> 6MWT as an Outcome Measure

The change in the distance walked in the 6MWT can be used to evaluate the efficacy of an exercise training program or to trace the natural history of change in exercise capacity over time.

The minimum clinically important difference (i.e., improvement) in the distance walked in a 6MWT has been estimated as 54 meters (with 95% confidence limits of 37 to 71 meters) (For further details, see Redelmeier, 1997).

However, this improvement in 6MWT distance may not occur in patients who walk a very short distance in their 6MWT before pulmonary rehabilitation. For these patients, it may be more reasonable to evaluate efficacy based on the percent change rather than a change in a set number of meters. However, the actual percent change that equates to a clinical improvement has not yet been established - further research is required.

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