THE EFFECTS OF SACUBITRIL/VALSARTAN COMPARED TO VALSARTAN ON LEFT VENTRICULAR REMODELLING IN PATIENTS WITH ASYMPTOMATIC LEFT VENTRICULAR SYSTOLIC DYSFUNCTION AFTER MYOCARDIAL INFARCTION: A RANDOMISED, DOUBLE-BLINDED, ACTIVE-COMPARATOR, CARDIAC-MR BASED TRIAL

RECOVER-LV

STATISTICAL ANALYSIS PLAN

Study Title:	The effects of sacubitril/valsartan compared to valsartan on left ventricular remodelling in patients with asymptomatic left ventricular systolic dysfunction after myocardial infarction: a randomised, double-blinded, active-comparator, cardiac-MR based trial		
Short Title:	RECOVER-LV		
IDs:	EudraCT Number: 2017-003460-13 REC Reference Number: 17/ES/0128 Sponsor's Protocol Number: GN16CA007		
Sponsor:	NHS Greater Glasgow & Clyde and The University of Glasgow		
Funded by:	BHF Project Grant no. PG/17/23/32850 IMP supplied by Novartis Pharmaceuticals UK Ltd.		
Protocol Version:	v7.0	Date:	24th August 2020
SAP Version:	v1.1	Date:	25th August 2020

		Signature	Date
Prepared by:	Bethany Stanley Junior Biostatistician, Robertson Centre for Biostatistics, University of Glasgow		
Approved by:	Dr Alex McConnachie Assistant Director Biostatistics, Robertson Centre for Biostatistics, University of Glasgow		
Chief Investigator:	Professor John McMurray Professor of Cardiology, BHF Glasgow Cardiovascular Research Centre, University of Glasgow		

CONTENTS

ABBREVIATIONS

ACE	Angiotensin-converting-enzyme
ACEi	Angiotensin-converting-enzyme inhibitor
AF	Atrial Fibrillation
BNP	B-Type Natriuretic Peptide
ANP	Atrial Natriuretic Peptide
CABG	Coronary Artery Bypass Graft
CCS	Canadian Cardiovascular Society
cGMP	Cyclic Guanosine Monophosphate
CMR	Cardiovascular Magnetic Resonance imaging
CNP	C-type Natriuretic Peptide
COPD	Chronic Obstructive Pulmonary Disease
CRT	Cardiac Resynchronisation Therapy
DBP	Diastolic Blood Pressure
ECG	Electrocardiogram
ED	Emergency Department
FSH	Follicle-Stimulating Hormone
GDF-15	Growth Differentiation Factor-15
GP	General Practice
HF	Heart Failure
hsTnI	High Sensitive Troponin-I
ICD	Implantable Cardioverter-Defibrillator
LAVI	Left Atrial Volume Index
LVEF	Left Ventricular Ejection Fraction
LVESVI	Left ventricular End-Systolic Volume Index
LVSD	Left Ventricular Systolic Dysfunction
MedDRA	Medical Dictionary for Regulatory Activities
MI	Myocardial Infarction
MMP-9	Matrix Metallopeptidase 9
MR-proADM	Mid-Regional pro-Adrenomedullin
MR-proANP	Mid-Regional pro-Atrial Natriuretic Peptide
MRA	Mineralocorticoid Receptor Antagonist
MRI	Magnetic Resonance Imaging
NT-proBNP	N-terminal-pro hormone B-Type Natriuretic Peptide
NYHA	New York Heart Association
OTC	Over-the-Counter
PT	Preferred Term
QTc	QT interval corrected for heart rate
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SBP	Systolic Blood Pressure
SD	Standard Deviation
SOC	System Organ Class

sST2	Somatostatin Receptor Subtype 2
SUSAR	Suspected Unexpected Serious Adverse Reaction
TIA	Transient ischemic attack
TIMP-1	Tissue Inhibitor Of Metalloproteinases 1

1. INTRODUCTION

1.1. STUDY BACKGROUND

Left ventricular systolic dysfunction (LVSD) and heart failure (HF) remain relatively common among survivors of myocardial infarction. This is because a large proportion of patients are not eligible for reperfusion therapy (i.e. those with non ST-segment elevation myocardial infarction) and many patients suffer recurrent episodes of infarction, leading to cumulative left ventricular damage over time.

In PARADIGM-HF, a combination of neprilysin inhibitor (sacubitril) and angiotensin receptor blocker (valsartan), reduced the risk of heart failure hospitalisation and death in patients with heart failure due to left ventricular systolic dysfunction or reduced ejection fraction (HF-REF), compared to an angiotensin-converting-enzyme inhibitor (ACEi) (enalapril).

The objective of RECOVER-LV is to obtain information on the cardiac effects of sacubitril/valsartan in patients with LVSD, compared to valsartan alone.

1.2. STUDY OBJECTIVES

1.2.1. PRIMARY OBJECTIVE

To investigate the potential benefit of sacubitril/valsartan vs. valsartan in attenuating adverse left ventricular remodelling in high risk asymptomatic patients post myocardial infarction as a result of residual left ventricular systolic dysfunction.

1.2.2. SECONDARY OBJECTIVES

To provide understanding of the cardiac effects and mechanisms of action of sacubitril/valsartan in patients with LVSD.

1.3. STUDY DESIGN

Randomised, double-blind, clinical trial.

1.4. RANDOMISATION

Section 12.1 of the study protocol states:

"Randomisation will be in a 1:1 ratio and stratified by LVESVI ≤45ml/m^2 / >45ml/m^2 as measured by baseline CMR, and whether or not the patient is being prescribed diuretics at baseline, with the randomisation schedule computer generated by the method of randomised permuted blocks, with random block lengths of 4 and 6."

1.5. SAMPLE SIZE AND POWER

Section 11.1 of the study protocol states:

"A sample size of 100 patients is proposed. This is based on the calculation that 45 patients per treatment group provides >90% power (α level = 0.05) to detect a difference of 6mL/m^2 in LVESVI (standard deviation = 7.8mL/m^2) and accounting for a discontinuation rate of 10% (lost to follow up, development of heart failure or death). A 6mL/m^2 difference in LVESVI represents a minimally important difference."

Recruitment of 100 patients in 18 months requires a monthly recruitment rate of 5.6 patients/month or 1.4 patients/week.

1.6. STUDY POPULATION

Patients aged ≥18 years with asymptomatic left ventricular systolic dysfunction (i.e. no evidence of clinical and/or radiological heart failure) >3 months post-acute myocardial infarction. A full list of inclusion and exclusion criteria is given in section 5.1 of the study protocol.

1.7. STATISTICAL ANALYSIS PLAN (SAP)

1.7.1. SAP OBJECTIVES

The objective of this SAP is to describe the final statistical analyses to be carried out for the randomised controlled trial of the RECOVER-LV study.

1.7.2. GENERAL PRINCIPLES

Data will be summarised for all participants and by randomised treatment group where appropriate. Categorical variables will be summarised with the number of observations and missing values, and number and percentage of participants falling into each category. Continuous variables will be summarised using the number of observations and number missing, mean, standard deviation (SD), median, 25th and 75th quartiles (Q1 and Q3 respectively), minimum and maximum values. Rates of recruitment and retention will be summarised as counts and percentages with 95% confidence intervals.

All efficacy outcomes will be analysed using regression analysis models that are adjusted for the baseline value of the outcome in question and whether or not taking diuretics at baseline. Efficacy outcomes will be summarised at baseline, 12 months and for the change from baseline at 12 months, presented overall and by treatment group. The model's intervention group treatment effect (and 95% CI) and p-value will be presented for outcome results measured at 12 months. All biomarker outcomes will additionally be summarised at 6 months and for the change from baseline at 6 months. Furthermore, a repeated measures linear regression model will be performed for each biomarker outcome, adjusting for the main effects of time-point and randomised group and the interaction between time-point and randomised group. The intervention group

treatment effect and time-point effect (and 95% CIs) will be presented with p-values for these main effects and their interaction.

1.7.3. CURRENT PROTOCOL

The current protocol at the time or writing is version 7.0, dated 24/08/2020. Future amendments to the protocol will be reviewed for their impact on this SAP, which will be updated only if necessary. If no changes are required to this SAP following future amendments to the study protocol, this will be documented as part of the Robertson Centre Change Impact Assessment processes.

1.8. SOFTWARE

All statistical analyses will be carried out using R v4.0.0 [R Development Core Team 2020] or higher versions of this program. The final report will be provided as a password protected PDF document. Listings will be provided as excel files.

2. ANALYSIS

With the exception of analysis detailed in Subsection 2.4.3 Tertiary (exploratory) outcomes below, all analysis described in Section 2, in addition to the tertiary outcome change in ANP, will be produced in the first wave of outputs. The second wave of outputs will include the analysis of the remaining tertiary outcomes outlined.

2.1. STUDY POPULATION

The analysis population will comprise of all subjects randomised into the study.

2.2. SUBJECT DISPOSITION

The number and percentage of participants consenting to take part in the study will be summarised and randomised subjects will be summarised, overall and by randomised treatment group. The cumulative numbers of participants randomised to each treatment group will be reported in tabular form and graphically. The number and percentage of randomised subjects attending each study visit will also be presented with those that did not attend classified as either: Lost to follow-up, died, or did not attend. Reasons for ineligibility for study participation will be summarised for the consenting non-randomised subjects. The number and percentage of subjects withdrawing from the study medication and from study follow-up will be presented alongside the main reasons for withdrawal.

2.3. BASELINE CHARACTERISTICS

The following baseline characteristics will be summarised for all randomised subjects and by randomised intervention group, without formal statistical comparison:

- Cardiac MRI: height (m), weight (kg), BMI (kg/m^2), body surface area (kg/m^2), gadolinium contrast administered
- Physical Exam: NYHA class, third heart sound, pulmonary crepitations (area and location), pleural effusion (location), peripheral oedema (location), any other relevant abnormalities
- Medication history: loop diuretic, thiazide diuretic, ACE inhibitor, angiotensin receptor blocker, beta-blocker (except sotalol), mineralocorticoid receptor antagonist (MRA), statin, anti-platelet, anti-coagulant, nitrate, calcium channel blocker (CCB), alpha blocker, antiarrhythmic
- Vital signs: SBP (mmHg), DBP (mmHg), heart rate (bpm)
- Electrocardiogram results: heart rate (bpm), heart rhythm, PR interval (ms), QRS duration (ms), bundle branch block, QTc interval (ms), ST segment deviation, T wave inversion, Q wave inversion
- Spot urine collection
- Venepuncture: urea, creatinine, potassium, eGFR, haemoglobin, bilirubin, ALT, AST, ALP, hs-troponin I (hsTnI), HbA1c, NTproBNP
- Pregnancy: woman of child-bearing potential, FSH level, pregnancy test done, pregnancy test result
- Symptom Review: heart failure since last review, paroxysmal nocturnal dyspnoea, orthopnoea, dyspnoea at rest, dyspnoea on effort, fatigue, peripheral oedema, emergency admission to hospital, ED visit, urgent clinical visit, GP or other primary care consultation, intervention or treatment change (started or increased dose for all except ICD/CRT)
- Previous Medical History: time since index MI, known coronary artery disease, angina, MI, treatment for MI, CABG/PCI prior to MI, history of hypertension, paroxysmal AF, stroke, TIA, carotid artery disease, peripheral arterial disease, lower limb revascularisation, valve replacement, dizziness / hypotension / falls etc., COPD, asthma, cancer, diabetes, hypothyroidism and hyperthyroidism, smoking (status and pack year), alcohol consumption (intake level, average number of units per week), any other significant medical history

2.4. EFFICACY OUTCOMES

2.4.1. PRIMARY OUTCOME

The change in indexed left ventricular end-systolic volume (LVESVI) from baseline to the 12 month follow-up visit will be summarised overall and by randomised group and compared between randomised groups using a linear regression model adjusted for baseline LVESVI, diuretic use at baseline and time from baseline to the 12 month follow-up visit.

2.4.2. SECONDARY OUTCOMES

The following outcomes will be analysed as described in section 1.7.2:

- Change in NT-proBNP
- Change in hsTnl
- Change in other cardiac magnetic resonance imaging-based metrics of LV remodelling from baseline to 12 months follow-up:
    - Indexed LV end-diastolic volume (LVEDVI)
    - Indexed left atrial volume by body surface area (LAVI)
    - LV ejection fraction (LVEF)
    - LV mass index

- Change in patient well-being as assessed by a patient global assessment questionnaire at 12 months follow-up

2.4.3. TERTIARY (EXPLORATORY) OUTCOMES

The following outcomes will be analysed as described in section 1.7.2:

- Change in biomarkers of LV remodelling: sST2, Galectin 3, TIMP-1, MMP-9, Type III Procollagen Peptide, GDF-15 and other relevant biomarkers of interest.
- Change in neurohormonal levels: BNP, MR-proANP, C-terminal ANP, CNP, MR-proADM, cGMP, endothelin-1, neprilysin antigen, renin and aldosterone and other relevant biomarkers of interest.
- Change in extracellular volume (ECV), left ventricular global function index (LVGFI), T1 relaxation time and left ventricular strain as measured using cardiac MRI.

2.4.4. SUBGROUP ANALYSIS

Due to the impact of the Covid-19 pandemic on the scheduling of end-of-study MRI scans, all efficacy outcomes outlined in Section 2.4 will be analysed in three subgroups of the randomised population determined by whether the patient had their 12-month MRI scan earlier than planned, on-time or later than planned. A scan will be defined as: on-time if it occurs within a 7-day window around the scheduled 52-week visit date; early if more than 7 days prior; and late if more than 7 days following the scheduled visit date.

2.5. SAFETY OUTCOMES

2.5.1. PREMATURE WITHDRAWAL

The number and percentage of subjects who complete the intervention phase will be reported. The number and percentage of subjects who actively withdraw from study medication and/or the study will be reported and the reasons for withdrawal will be summarised if provided.

2.5.2. ADVERSE EVENTS OF INTEREST

Adverse events of interest include:

- Worsening renal function or acute kidney injury
- Hyperkalaemia
- Symptomatic hypotension
- Symptomatic hypotension with systolic BP <90mmHg
- Angioedema
- Cough

The number and percentage of subjects experiencing one of the adverse events of interest listed will be summarised overall and by randomised treatment group. The Fisher's Exact test will be used to assess whether there is a statistical difference between number of subjects experiencing each event between treatment groups. The following event details will also be summarised and compared between groups: seriousness criteria, severity, relationship to study drug and details of action taken. Full details of these events are provided in section 10.2 of the study protocol.

2.5.3. SERIOUS ADVERSE EVENTS

The number of serious adverse events will be reported and the following event details will be summarised for the randomised population overall and by treatment group: seriousness criteria, severity, relationship to the study drug, expectedness, event outcome and SAE duration (if recovered or fatal).

The number and percentage of subjects experiencing at least one serious adverse event will be reported and summarised by Medical Dictionary for Regulatory Activities (MedDRA) System Organ Class (SOC) and Preferred Term (PT). The Fisher's Exact test will be used to assess whether there is a statistical difference between the number of subjects with each type of event between treatment groups.

The same summaries will be provided for the subsets of serious adverse events that are (a) at least possibly related to the study treatment, (b) Suspected Unexpected Serious Adverse Reactions (SUSARs) and (c) fatal, (d) prior to 1st March 2020 and (e) experienced on or after 1st March 2020.

All serious adverse events will be listed.

3. DOCUMENT HISTORY

This is version 1.1 of the SAP for the RECOVER-LV study, the second version of this document.

4. TABLES, FIGURES AND LISTINGS

Summary tables and figures will be generated prior to database lock. Approval of the content of these documents will then be required for database lock.