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Compound Number:	GSK2798745
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Description:

The purpose of this reporting and analysis plan (RAP) is to describe the planned analyses and output to be included in the Clinical Pharmacology Study Report for Protocol MRI201137. This RAP is intended to describe the analyses required to validate the use of DCE-MRI for evaluating measures of pulmonary oedema in patients with cardiac failure. This document will be provided to the study team members to convey the content of the final Statistical Analysis Complete (SAC) deliverable.

Subject: MRI, heart failure, pulmonary oedema

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The Discovery Biometrics Director (or designee) will give final approval

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LIST OF ABBREVIATIONS

AE	Adverse Event
ALT	Alanine Transaminase
ANCOVA	Analysis of Covariance
AST	Aspartate Transaminase
BMI	Body Mass Index
BNP	B-Type Natriuretic Peptide
CDF	Cumulative Distribution Function
DCE	Dynamic Contrast Enhanced
DLCO	Diffusing Capacity of the Lung for Carbon Monoxide
DLNO	Diffusing Capacity of the Lung for Nitrous Oxide
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
FENa	Fractional excretion of sodium
GSK	GlaxoSmithKline
HF	Heart Failure
HV	Healthy Volunteers
ICH	International Conference on Harmonisation
Kg	Kilogram
Ktrans	Exchange Rate
MedDRA	Medical Dictionary for Regulatory Activities
mL	Milliliter
MRI	Magnetic Resonance Imaging
NO	Nitric Oxide
NT-proBNP	N-terminal of pro-Brain-type Natriuretic Peptide
NYHA	New York Heart Association
RAP	Reporting and Analysis Plan
RBC	Red Blood Cells
RER	Respiratory Exchange Ratio
RPE	Rating of Perceived Exertion
SAE	Serious Adverse Event
SPM	Study Procedures Manual
TRPV4	Transient Receptor Potential Vanilloid 4
VCO_2	Volume of Carbon Dioxide
Ve	Interstitial Volume
VO_2	Volume of Oxygen
Vp	Plasma Volume
WBC	White Blood Cells

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Pharmacology Study Report for Protocol MRI201137.

Revision Chronology:		
2013N186309_00	2014-FEB-04	Original
2013N186309_01	2014-APR-24	Amendment No.: 01 This protocol amendment clarifies the exercise protocol to be conducted, details measures for endpoints, defines the biomarker to be measured (NT-pro BNP), reduces total blood volume to be collected, updates study schematic, adds an interim review of the data, removes collection of AEs as there is no IP included in the study, alters physical exams to brief physical exams, and adds a dyspnoea scale and the Borg Rating of Perceived Exertion.
2013N186309_02	2015-FEB-16	Amendment No.: 02 This protocol amendment changes modifies inclusion criteria, clarifies the exercise protocol, and corrects the footnote numbering in the time and events table.
2013N186309_03	2016-APR-08	Amendment No. 3 adds an evaluation of an additional group of subjects who have been hospitalized for acute decompensated heart failure to determine whether DCE-MRI can detect changes in measures of pulmonary oedema with standard of care treatment. Details for summarizing data from ADHF patients (referred to in this document as group 3) can be found in Section 10.2.6.
2013N186309_03	2016-APR-20	The data analysis for Group 3 has been simplified due to limited number of subjects (n=3) in the study

In addition to following the revision chronology of the study protocol, current reversions are also under the general guidance of "driving efficiency in Clinical Statistics" initiative,

and the outputs are simplified to match with the scale and lack of investigational drug of the study.

All decisions regarding final analysis, as defined in this RAP document, have been made prior to Database Freeze of the study data. After completion of 12 evaluable subjects, an informal interim look will be performed.

2. STUDY OBJECTIVE(S) AND ENDPOINT(S)

2.1. Study Objective(s)

The objectives and endpoints for the study are summarized in the table below:

Objectives	Endpoints
Primary	
• Establish whether DCE-MRI can detect differences in measures of pulmonary oedema or vascular permeability between HF and healthy volunteers (HV) groups.	• Interstitial volume (ve) and exchange rate (ktrans) measured using DCE-MRI in HF patients and HVs at baseline.
• Explore the effect of exercise on DCE-MRI measures of pulmonary oedema and vascular permeability in HF and HV groups.	• Change in interstitial volume (ve) and exchange rate (ktrans) measured using DCE-MRI in HF patients and HVs before and following exercise.
• Explore the effect of standard of care treatment on DCE-MRI measures of pulmonary oedema and vascular permeability in patients with ADHF.	• Change in interstitial volume (ve) and exchange rate (ktrans) measured using DCE-MRI in patients with ADHF during hospitalization and following the resolution of pulmonary oedema.
Secondary	
• Estimate the intra subject variability of DCE-MRI measures of pulmonary oedema and vascular permeability.	• Estimation of the variability in the interstitial volume (ve) and exchange rate (ktrans) within HF patients and HVs between 2 MRI visits approximately 1 week apart.

Objectives	Endpoints
Exploratory	
• Explore the relationship between DCE-MRI measures of pulmonary physiology and disease severity, symptoms, pulmonary function, volume status and renal function	• Correlation of MRI measures with clinical and biochemical measures: dyspnoea score, respiratory rate, NT-proBNP, exercise capacity (including BORG RPE, heart rate, blood pressure and gas exchange endpoints such as peak VO2, Ve/VCO2 slope), DLCO, DLNO, body weight, urine specific gravity, fractional excretion of sodium (FENa), blood urea to creatinine ratio.
• Estimate differences in plasma volume and MR physical properties influenced by the tissue microenvironment relaxation rate, and proton density between HF and HV groups as measured using DCE-MRI	• Plasma volume (vp), T1 relaxation rate, and proton density measured using MRI in HF patients and HVs.
• Explore the distribution of DCE-MRI measures of pulmonary physiology in HF and HV groups both before and after exercise	• Interstitial volume (ve) and exchange rate (ktrans), and other clinical and biochemical measures as listed above if data permit.
• Explore the effect of standard of care treatment on plasma volume and MRI physical properties influenced by the tissue microenvironment relaxation rate, and proton density in patients with ADHF.	• Change in Plasma volume (vp), T1 relaxation rate, and proton density measured using MRI in patients with ADHF during hospitalization and following the resolution of pulmonary oedema;
• Explore the effect of standard of care treatment on ultrasound measures of pulmonary oedema in patients with ADHF.	• Change in B-lines measured using ultrasound in patients with ADHF during hospitalization and following the resolution of pulmonary oedema;
• Explore the distribution of DCE-MRI measures of pulmonary physiology in ADHF patients both before and after standard of care treatment;	• Interstitial volume (ve) and exchange rate (ktrans), and other clinical and biochemical measuresas listed above if data permit;

3. STUDY DESIGN

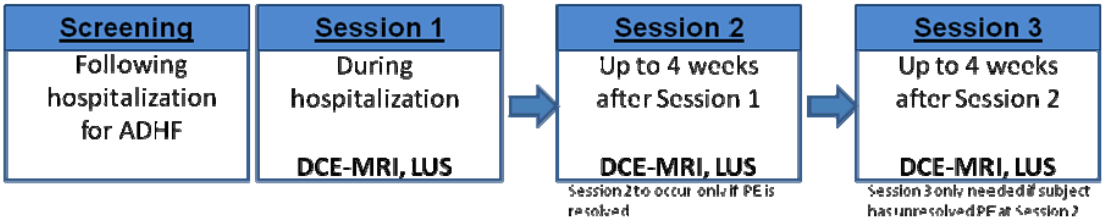
The study will enroll 12 HV and 12 HF patients. First, the DCE-MRI markers of vascular permeability and pulmonary edema will be measured in HV and HF patients at rest to determine whether there is a difference between the two populations. Next, exercise-induced changes relative to rest in interstitial volume and exchange rate will be evaluated in both HV and HF patients. Since exercise increases pulmonary vascular pressure more markedly in patients with left ventricular failure as compared to normal subjects, a greater increase in vascular permeability and pulmonary oedema may be observed in patients with HF as compared to HV.

The study consists of four visits. The first visit will be a Screening Visit during which the subjects will be assessed for their tolerance of lying flat and baseline information will be collected. Within 35 days, subjects will return for the first of two scanning sessions approximately one week apart to determine baseline levels and within subject variability. A third imaging visit will incorporate a bicycle exercise challenge prior to imaging and will occur approximately one to three days after the second imaging session.

All MRI data will be anonymized at site and transferred to Bioxydyn Limited for DCE-MRI data analysis. The 'extended Tofts' tracer kinetic model will be applied to the data to provide measurements of k^{trans} (capillary transfer coefficient of contrast agent - /min), v_e (leakage space - fraction) and v_p (plasma volume - fraction). Median values of k^{trans} and v_e will be provided from each lung (total lung, apical and basal) as well as total lung for subsequent statistical analysis. All values will be corrected for the individual's hematocrit value. If not available, a typical hematocrit value will be assumed.

In Session 3 (which will be conducted in 2 visits), subjects will perform two exercise tests. Subjects will first be asked to perform a maximal exercise test limited by dyspnoea or fatigue on a cycle ergometer. At the 2nd visit, subjects will be asked to perform cycle exercise for 10 minutes at 75%-80% of the peak work rate achieved during the maximal exercise to exhaustion test described above.

For subjects with ADHF (Group 3), the study design is shown below:



4. PLANNED ANALYSES

4.1. Interim Analyses

After 12 evaluable subjects (6 HV and 6 HF patients) have completed Sessions 1 and 2, an interim review will be performed. Following the interim review, the study team will decide whether to (a) terminate the study if it is determined that the image quality is poor

(e.g., due to excessive movement during scanning or related to specifics around lung tissue) or the procedures are not well tolerated in the HF group (e.g., inability to lie flat for the duration of the imaging session), or (b) continue the study and enrol an additional 12 evaluable subjects (6 HV and 6 HF patients).

The interim decision will be based on the expert opinion of the Investigator in consultation with the GSK Study Team based on the totality of the data. No formal interim analysis will be reported out.

4.2. Final Analyses

The final planned analyses will be performed after all subjects have completed the study and after database freeze. See Section 9 to Section 10 for all final planned analyses for this study.

5. ANALYSIS POPULATIONS

An evaluable subject is defined as a subject that has MRI data of sufficient quality to enable DCE-MRI modelling in both Session 1 and Session 2.

All enrolled population

The all enrolled population will include all subjects who have signed the informed consent for participation in the study.

Safety population

The safety population will include all enrolled subjects who have initiated Session 1 DCE-MRI scan. All safety analyses will be based on the safety population.

For Group 3, the safety population will include all enrolled subjects who have initiated at least one session of DCE-MRI or LUS scan.

This is the population to be used for all tables, listings, and figures of patients in group 3.

Evaluable population

The evaluable population will include subjects in safety population who are 40 years and older .There is no plan to exclude subjects with major or minor protocol deviations from the analyses. However, subject data will be examined for evidence of protocol deviations in order to assess how well the protocol was followed. If necessary, any decision to exclude any subject from the planned analyses will be determined when the database is released for reporting purposes.

The evaluable populations have been changed in this RAP amendment to limit the analysis populations to subjects with age greater than 40 years old at baseline. At the interim analysis, it was realized that age may confound the results in the HV population. Since HV and HF subjects were not age-matched, limiting the analysis population to similar age range will provide a more appropriate comparison. This analysis will exclude

4 subjects; however, the study has enrolled an additional 5 subjects who are >40 years old in order to have a sufficient number of subjects for comparison. However, in addition to the comparisons using the defined populations in this RAP, a sensitivity analysis for the comparison between two groups on the change from baseline in Ve will be performed using safety population with all subjects who have evaluable MRI data in either Sessions 1 or 2.

The evaluable population definition does not apply to ADHF patients to be included in in group 3 summaries.

This population is not applicable to Group 3.

5.1. Analysis Datasets

Primary Analysis Set

The primary analysis set to evaluate whether DCE-MRI can detect differences in measures of pulmonary oedema or vascular permeability between HV and HF patients will include all subjects in the evaluable population. A sensitivity analysis for Ve will also be performed using the safety population.

This analysis set will also be used to explore the effect of exercise on DCE-MRI measures in HV and HF patients. Missing post-exercise MRI data will not be imputed. This analysis set will be used to estimate the intra-subject variability of DCE-MRI measures of pulmonary oedema and vascular permeability.

Secondary Analysis Set

The secondary analysis set will include all evaluable subjects who have MRI data of sufficient quality from Session 1, 2 or both. This analysis set will be used to estimate the intra-subject variability of DCE-MRI measures of pulmonary oedema and vascular permeability.

No formal hypothesis testing will be performed.

No analysis will be performed for Group 3, so no analysis data sets will be defined.

6. TREATMENT AND OTHER SUB-GROUP DESCRIPTIONS FOR DATA DISPLAYS

Population Group		Final Data Display (i.e. HARP / other)
Code	**Treatment Description**	**Treatment Description**
HV	Healthy Volunteer	Healthy Volunteer
HF	Heart Failure Patient	Heart Failure Patient
ADHF	Acute Decompensated Heart Failure	Acute Decompensated Heart Failure Patient

7. GENERAL CONSIDERATIONS FOR DATA ANALYSES AND HANDLING

7.1. Reporting Conventions

Data manipulations and statistical analyses will be performed using SAS version 9.2 or higher.

All variables will be presented and summarized in tables or graphs. Continuous variables will be summarized using descriptive statistics (mean, standard deviation, median, inter-quartile range (where appropriate), and range). Categorical variables will be summarized using frequency counts and percentages. Associated listings will also be provided. Unless otherwise stated, 95% confidence intervals around the point estimates, as appropriate will be presented.

7.2. Data Management

Data Type	Source	Format of Data	Planned Date of Final File[1]	Responsibility
Safety	Database	IDSL	DBF	CPSSO
PD/biomarker	Study Site	CSV file	DBF	CPSSO

1. This is for study teams to determine upfront if there is a possibility of not meeting the completion of the CPSR within 6 months of LSLV (i.e. novel data that may not be available until several months after LSLV).

7.3. Premature Withdrawal and Missing Data

All subjects who withdraw prematurely from the study will be documented and the reason for their withdrawal recorded in the final Clinical Pharmacology Study Report (CPSR). All available data from subjects who withdraw will be listed and all available planned data will be included in the summaries according to the populations and analysis datasets defined in Section 5.

7.3.1. Missing MRI measurements

Session 1 and Session 2 MRI measurements can be considered baseline pre-exercise data. If Session 2 data is unavailable, Session 1 data will be used. For the purpose of the secondary analysis to estimate intra-subject variability, MRI data will not be imputed.

7.3.2. Missing dyspnoea score and respiratory rate

The last available dyspnoea score or respiratory rate will be carried forward in the case of missing Session 2, and pre-exercise Session 3 measurements. Post-exercise measurements will not be imputed.

Other missing data will not be imputed.

7.4. Baseline Definition

The Session 2 visit will be considered as the baseline visit for MRI measurement endpoints. If Session 2 data is unavailable, Session 1 data will be used. In terms of change from baseline calculation for statistical analysis, tables below defined the baseline for each endpoint of interests:

Parameter	Baseline Collected			Baseline To Be Used in Analysis / Summaries
	Screening	Session 2/1	Session 3	
MRI scan		X	X	Scan 2

Note: For the parameters of MRI scan, if measurements are missing for Scan 2, then Scan 1 measurements will be used as baseline.

Parameter	Baseline Collected			Baseline To Be Used in Analysis / Summaries
	Screening	Session 2/1	Session 3	
Laboratory biomarker	X		Pre-Excercise	Session 3 Pre-Excercise
Respiratory rate		Post-MRI	Pre-Excercise	Session 3 Pre-Excercise
Dyspnoea Scale Scoring		Post-MRI	Pre-Excercise	Session 3 Pre-Excercise
Gas Diffusion, DL_{co}, DL_{no}		Post-MRI	Pre-Excercise	Session 3 Pre-Excercise
Pulmonary function		Post-MRI	Pre-Excercise	Session 3 Pre-Excercise

7.5. Derived and Transformed Data

MRI measures: Median values of k^{trans}, v_e and v_p from multiple images/regions will be calculated for total lung, each lung (left and right) and different lung segments. For each MRI measure parameter there are 7 measurement regions: total lung, left lung, right lung, apical left segment, apical right segment, basal left segment and basal right segment for each MRI measure parameter.

Laboratory Data: The majority of laboratory results will be recorded under a numeric field. Some results may be recorded under a character field where a numeric component

(x) has been preceded by '>' or '<' indicating the true value of x is greater than or less than that given.

To ensure this data is not excluded from any summaries or analysis, any laboratory results recorded as '>x' will be moved to the numeric field with a value of x, similarly results recorded as '<x' will be moved to the numeric field with a value of x. All listings will present the data as recorded.

Age (years): Age will be calculated using the date of the screening visit relative to year of birth, according to the Integrated Data Standard Library (IDSL). In this calculation, date of birth will be imputed based on the assumption that all subjects were born on the 30th June (30 Jun YYYY).

Body Mass Index (BMI) (kg/m^2): equals (weight (kg)) / ((height (m))^2)

Study Day: Study day will be defined in reference to the DCE-MRI scan date in the corresponding Session. Session 1 – Day 1 will be the DCE-MRI scan date in Session 1, and Session 2 – Day 1 will be the DCE-MRI scan date in Session 2, etc.

7.5.1. Change from Baseline

The change from baseline will be calculated by subtracting the baseline values from the individual post-exercise values. If either the baseline or post-exercise value is missing, the change from baseline is set to missing as well.

7.6. Values of Potential Clinical Importance

7.6.1. Values of Potential Clinical Importance for Healthy Volunteers

Hematology Analyte	Effect	Relative – Low (Multipliers of LLN)	Relative – High (Multipliers of ULN)
White Blood Cell Count		0.67	1.82
Neutrophil Count		0.83	
Hemoglobin	Male		1.03
	Female		1.13
Hematocrit	Male		1.02
	Female		1.17
Platelet Count		0.67	1.57
Lymphocytes		0.81	

Chemistry Analyte	Effect	Relative – Low (Multipliers of LLN)	Relative – High (Multipliers of ULN)
Albumin (mmol/L)		0.86	
Calcium (mmol/L)		0.91	1.06
Glucose (mmol/L)		0.71	1.41
Magnesium (mmol/L)		0.63	1.03
Phosphorus (mmol/L)		0.80	1.14
Potassium (mmol/L)		0.86	1.10
Sodium (mmol/L)		0.96	1.03
Total CO_2 (mmol/L)		0.86	1.14

Liver Function Test (Healthy Volunteers)

Liver Function Test Analyte	Effect	Potential Clinical Importance (PCI) Range	Unit
ALT/SGPT	High	≥ 2x ULN	U/L
AST/SGOT	High	≥ 2x ULN	U/L
AlkPhos	High	≥ 2x ULN	U/L
T. Bilirubin	High	≥ 1.5x ULN	µmol/L
T. Bilirubin + ALT	High	≥ 1.5x ULN T.Billirubin + ≥ 2x ULN ALT	µmol/L U/L

ECG Values of Potential Clinical Importance (Healthy Volunteers)

ECG Parameter	Potential Clinical Importance Range (PCI)	Unit
Absolute QTc Interval	>450	msec
Increase from Baseline QTc	>60	msec
PR Interval	<110 and >220	msec
QRS Interval	<75 and >110	msec

ECG Parameter	Potential Clinical Importance Range (PCI)	Unit
Absolute QTc Interval	>450 to ≤480	msec
Absolute QTc Interval	>480 to ≤500	msec
Absolute QTc Interval	>500	msec
Increase from Baseline QTc	>30 to ≤60	msec
Increase from Baseline QTc	>60	msec

Vital Sign Values of Potential Clinical Importance (Healthy Volunteers)

VS Parameter	Potential Clinical Importance Range (PCI)	Unit
Systolic Blood Pressure	<85 and >160	mmHg
Diastolic Blood Pressure	<45 and >100	mmHg
Heart Rate	<40 and >110	bpm

Vital Sign Values of Potential Clinical Importance (Healthy Volunteers)

VS Parameter	Potential Clinical Importance Range (PCI)	Unit
Systolic Blood Pressure (Change from Baseline)	Increase ≥ 20 and ≥ 40	mmHg
	Decrease ≥ 20 and ≥ 40	
Diastolic Blood Pressure (Change from Baseline)	Increase ≥ 10 and ≥ 20	mmHg
	Decrease ≥ 10 and ≥ 20	
Heart Rate (Change from Baseline)	Increase ≥ 15 and ≥ 30	bpm
	Decrease ≥ 15 and ≥ 30	

7.6.2. Laboratory Values of Potential Clinical Importance for Heart Failure Patients

Note GI/L = 10^9/L=10^3/µL

Hematology			
Laboratory Test	**Units**	**Change from Baseline of Potential Clinical Concern**	**Potential Clinical Concern Value**
Basophils	GI/L	None	None
Calcitonin	pg/mL	None	>100 pg/mL
Eosinophils	GI/L	None	None
Hematocrit	1	>0.1 decrease	>0.05 below LLN >0.04 above ULN
Hemoglobin	g/L	>25 g/L decrease	>20 g/L below LLN >10 g/L above ULN
Lymphocytes	GI/L	None	<0.5 x LLN
Monocytes	GI/L	None	None
Neutrophils	GI/L	None	<1 GI/L
Platelet Count	GI/L	None	<80 GI/L >500 GI/L
Red Blood Cell Count	TI/L	None	None
White Blood Cell Count	GI/L	None	>1 GI/L below LLN >5 GI/L above ULN

Chemistry			
Laboratory Test	**Units**	**Change from Baseline of Potential Clinical Concern**	**Potential Clinical Concern Value**
Albumin	g/L	None	None
Alkaline Phosphatase	U/L	None	>3 x ULN
ALT	U/L	None	>3 x ULN
AST	U/L	None	>3 x ULN
Bicarbonate (Carbon Dioxide	mmol/L	None	<16 mmol/L > 40 mmol/L

Chemistry			
Laboratory Test	**Units**	**Change from Baseline of Potential Clinical Concern**	**Potential Clinical Concern Value**
Content)			
Blood Urea Nitrogen	mmol/L	None	>2 x ULN
Calcium	mmol/L	None	<1.8 mmol/L >3.0 mmol/L
Chloride	mmol/L	None	None
Creatinine	umol/L	≥50% increase from baseline	>159 umol/L
Direct Bilirubin	umol/L	None	>1.35 x ULN
Gamma Glutamyl Transferase	U/L	None	>3 x ULN
Glucose (fasting)	mmol/L	None	<3 mmol/L >22 mmol/L
Magnesium	meq/L	None	≤1 meq/L
Potassium	mmol/L	None	>0.5 mmol/L below LLN >1.0 mmol/L above ULN
Sodium	mmol/L	None	>5 mmol/L above LN or below LN
Total Bilirubin	umol/L	None	>1.5 x ULN
Total Protein	g/L	None	>15 g/L above or below LN
Uric acid	umol/L	None	>654 umol/L

Liver Function Test	
Laboratory Test	**Potential Clinical Concern Value**
ALT	≥ 2 x ULN ≥ 3 x ULN ≥ 5 x ULN ≥ 8 x ULN ≥ 10 x ULN ≥ 3 x ULN and Total Bilirubin ≥ 2 x ULN
AST	≥ 2 x ULN ≥ 3 x ULN ≥ 5 x ULN ≥ 8 x ULN ≥ 10 x ULN ≥ 3 x ULN and Total Bilirubin ≥ 2 x ULN
Total Bilirubin	≥ 1.5 x ULN ≥ 2 x ULN ≥ 3 x ULN ≥ 5 x ULN ≥ 8 x ULN ≥ 10 x ULN

Vital Signs

Parameter	**Units**	**Change from Baseline of Potential Clinical Concern**	**Potential Clinical Concern Value**
Systolic BP	mmHg	Decrease >30 mmHg Increase >30 mmHg	<100 mmHg >170 mmHg
Diastolic BP	mmHg	Decrease >20 mmHg Increase >20 mmHg	<50 mmHg >110 mmHg
Heart rate	bpm	Decrease >30 bpm Increase >30 bpm	<50 bpm > 120 bpm

ECG

Parameter	Units	Change from Baseline of Potential Clinical Concern	Potential Clinical Concern Value
Heart Rate	bpm	Decrease >30 bpm Increase >30 bpm	Supine: < 50 or > 120 bpm
QRS interval	msec	Increase of > 25% when baseline QRS >100 msec Increase of > 50% when baseline QRS ≤100 msec	>200 msec
QTcB	msec	Increase of > 10% when baseline QTc >440 msec Increase of > 20% when baseline QTc ≤440 msec	>500 msec
QTcF	msec	Increase of > 10% when baseline QTc >440 msec Increase of > 20% when baseline QTc ≤440 msec	>500 msec
PR Interval	msec	Increase of > 25% when baseline PR >200 msec Increase of > 50% when baseline PR ≤200 msec	>300 msec

8. STUDY POPULATION

The precise format and content of the Study Population tables are shown in Section 12.2 of the RAP.

8.1. Disposition

Data displays will be produced to account for all subjects enrolled in the study. This will include the number of subjects enrolled in each population (HV or HF patients), number of subjects who have attempted or completed the DCE-MRI scan at each session, number of early withdrawals and reasons for early withdrawal. Number of subjects in each analysis population as defined in Section 5 will also be summarized.

The tables will use the "All subjects" population unless otherwise specified.

8.2. Demographic and Baseline Characteristics

Demography data will be summarized for safety population in this study. Disease characteristics data will also be summarized for the HF patients if data are available

These will include the following:

- Year of birth

- Gender
- Race and ethnicity
- Significant past medical history including onset, aetiology, and results of any recent relevant investigations of heart failure, as applicable
- Medication history
- Confirm heart failure class (HF patients only)
- Onset and type of symptoms (HF patients only)
- Years since diagnosis of HF (HF patients only)
- Degree of exercise intolerance-- distance/ stairs/time prior to breathlessness
- Presence of orthopnoea and/or paroxysmal nocturnal dyspnoea
- Peripheral oedema—level above ankle, non-dependent limb

9. SAFETY ANALYSES

The precise format and content of Safety figures, tables and listings are shown in Section 12.3 of the RAP.

The tables will use the "Safety" population unless otherwise specified.

9.1. Statistical Analyses

9.1.1. Extent of Exposure

No treatment (investigational product) will be given in this study. The number of subjects who were exposed to 1 MRI scan, 2 MRI scans, or 3 MRI scans will be summarized. Subjects who completed scan 1 and scan 2, but could not complete scan 3, with reason will be listed. If more than one patient cannot complete scan 3 due to not being able to lie down, an additional exploratory analysis will be undertaken.

9.1.2. Adverse Events

Since no investigational product will be administered in this study, information regarding the occurrence of adverse events will not be routinely collected. Medical occurrences (non-serious events) that begin during the study may be recorded under Medical History/Current Medical Conditions. Non-serious events related to study procedures may also be recorded.

Any SAEs assessed as related to study participation (e.g., protocol-mandated procedures, invasive tests, or change in existing therapy) will be recorded from the time a subject consents to participate in the study up to and including the last visit.

Any SAEs assessed as related to study procedures will be recorded. SAEs will be coded and grouped by system organ class (SOC) and preferred term using the Medical Dictionary for Regulatory Activities (MedDRA).

Based on date/time of onset, session number will be assigned to each SAE and duration from last MRI scan will be calculated.

Session	Definition
0	AEs with onset prior to Session 1 MRI
1	AEs with onset between Session 1 and Session 2 MRI
2	AEs with onset between Session 2 and Session 3 MRI
3	AEs with onset after Session 3 MRI

Frequency of SAEs will be summarized by subject population overall and by session. A SAE will only be counted once within a session.

9.1.3. Deaths and Serious Adverse Events

Deaths, as well as SAEs, if any, leading to discontinuation of the study will be presented in separate listings

9.1.4. Pregnancies (as applicable)

Any pregnancies reported or identified during this study will be listed.

9.1.5. Clinical Laboratory Evaluations

Haematology, clinical chemistry, urinalysis and additional parameters to be tested are listed below. Baseline clinical laboratory data will be collected for all HV and HF patients. Additional laboratory data will be collected before the MRI scan at each session for the HF patients.

Haematology

Platelet Count	*Automated WBC Differential:*
RBC Count	Neutrophils
WBC Count (absolute)	Lymphocytes
Hemoglobin	Monocytes
Hematocrit	Eosinophils
	Basophils

Clinical Chemistry

Urea	Potassium	Total and direct bilirubin
Creatinine	Troponin	eGFR (estimated Glomerular Filtration Rate)
Glucose	Calcium	
Sodium	AST (SGOT)	
Potassium	ALT (SGPT)	

Routine Urinalysis

Specific gravity
pH, glucose, protein, blood and ketone by dipstick
Microscopic examination (if blood or protein is abnormal)

Biomarkers

N-terminal pro-Brain-type Natriuretic Peptide (NT- pro BNP)

*At Screening and in Session 3 only, blood samples for NT-Pro BNP determinations will be drawn before and after the maximal exercise test, before the constant workload exercise test and after MRI scanning only in subjects with HF.

Descriptive statistics and number of subjects with abnormal clinical laboratory values will be summarized by subject population and by session (in HF patients only).

9.2. Other Safety Measures

9.2.1. Vital Signs

Vitals signs, including systolic blood pressure, diastolic blood pressure and heart rate, will be collected at screening, and after MRI scan in Sessions 1 and 2. In Session 3, data will also be collected at the beginning and at the end of the maximal exercise test and the constant workload exercise test. Descriptive statistics for the measurements in all sessions and change from pre-exercise will be provided.

9.2.2. Respiratory rate

Respiratory rate will be collected after MRI scan in Session 1 and Session 2. In Session 3, data will also be collected at the beginning and at the end of the maximal exercise test and the constant workload exercise test. Data will be also collected after MRI scan in constant exercise test. Descriptive statistics for the measurements in all sessions and change from pre-exercise in session 3 will be provided.

9.2.3. Dyspnoea score

Dyspnoea score will be collected after MRI scan in Sessions 1 and 2. In Session 3, data will also be collected before and after the maximal exercise test and the constant workload exercise test. Also data will be collected after MRI scan in constant workload visit. The dyspnoea score data is (0,1,2,3,45), descriptive statistics for the measurements

in all sessions and change from pre-exercise in session 3 will be provided, in addition a bar chart showing the frequency of each score will be presented.

9.2.4. ECG Findings

12-lead ECGs will be obtained at screening. Results will be displayed in the baseline characteristics table described in Section 9.2.

10. VALIDATION ANALYSES

Planned analyses for the primary, secondary and exploratory objectives of the study are described in this section using the evaluable population as the primary analysis population. Listings of all MRI data, clinical and biochemical measures will be produced. Special listings, such as listings that include data from multiple sources or include only a subset of subjects/measurements are described in the corresponding sections below.

10.1. Primary Objectives

10.1.1. Baseline and post exercise Analysis

For the primary endpoints, contrast agent interstitial volume (v_e) and exchange rate (k^{trans}) data for total lung, left and right lung, apical segments and basal segments for each lung (total 7 measurements for each parameter) will be fitted separately using a repeat measure ANOVA model with terms include patient population (HF or HV), visit (i.e. sessions), interaction of patient population and visit, with subject ID as block of the repeat factor. Point estimates and associated 95% confidence intervals (CI) will be constructed to provide a plausible range of values for the following parameters of interest: mean DCE-MRI measurements in HV and HF patients, and the mean difference between the HV and HF groups, at each session, as well as the differences among MRI sessions within each patient population group (HV or HF) See example sas codes below.

```
/* analysis of primary endpoints to compare HF vs HV with Sessions 1 to
3 data */
proc mixed data=mri;
  class subjid atrtgrp visit;
  model mriresn = visit atrtgrp visit*atrtgrp/e3 ddfm=kr outp=pred_one;
  repeated visit/ subject=subjid type=un;
  by mritstu regint;
  LSMEANS  visit*atrtgrp  /CL ALPHA=0.05;
  estimate 'HF - HV at Session 1' atrtgrp 1 -1
                       visit*atrtgrp  1 0 0 -1 0 0/cl alpha = 0.05;
   estimate 'HF - HV at Session 2' atrtgrp 1 -1
                       visit*atrtgrp  0 1  0 0 -1 0/cl alpha = 0.05;
   estimate 'HF - HV at post excercise' atrtgrp 1 -1
                       visit*atrtgrp  0 0 1 0 0 -1/cl alpha = 0.05;
   estimate 'Session 2 - Session 1 in HF' visit -1 1 0
                       visit*atrtgrp  -1 1 0 0 0 0/cl alpha = 0.05;
   estimate 'post excercise - Session 1 in HF' visit -1 0 1
                       visit*atrtgrp  -1 0 1 0 0 0/cl alpha = 0.05;
   estimate 'change from baseline estimates in HF' visit 0 -1 1
                       visit*atrtgrp  0 -1 1 0 0 0/cl alpha = 0.05;
```

```
   estimate 'Session 2 - Session 1 in HV' visit -1 1 0
                        visit*atrtgrp  0 0 0 -1 1 0/cl alpha = 0.05;
   estimate 'post excercise - Session 1 in HV' visit -1 0 1
                        visit*atrtgrp  0 0 0 -1 0 1/cl alpha = 0.05;
   estimate 'Change from baseline estimates in HV' visit 0 -1 1
                        visit*atrtgrp  0 0 0 0 -1 1/cl alpha = 0.05;
   estimate 'HF vs HV of Change from baseline '
                        visit*atrtgrp  0 -1 1 0 1 -1/cl alpha = 0.05;


ods output lsmeans = lsm;
 ods output covparms = cov_one;
 ods output estimates = est;
run;
```

10.2. Secondary Objectives

For the secondary endpoint, the estimation of the within subject variability of DCE-MRI measures of pulmonary edema and vascular permeability between study visits will be calculated based on the mixed model described in Section 10.1.1, but with Session 1 and 2 data, with log_e transformation. For the by patient population estimates, a repeated measure ANOVA model will be fitted with visit as the effect effects. The within subject variability (coefficient of variation) can then be estimated as 100*sqrt(exp(mse)-1), where MSE is the mean square error from the mixed effects model. Example sas codes as follows:

```
/* analysis of primary endpoints to assess variability of primary
endpoints with Sessions 1 to 2 data (secondary endpoint of the analysis
*/
/* estimate overall within subject variability */
data mri_Session12;
   set mri;
   if visit in ('SESSION 1' 'SESSION 2');
   if mriresn>0 then lg_mriresn=log(mriresn);
   run;
proc mixed data=mri_Session12;
  class subjid atrtgrp visit;
  model lg_mriresn = visit atrtgrp visit*atrtgrp/e3 ddfm=kr
outp=pred_one;
  random subjid;
  by mritstu regint;
  ods output covparms = cov_one;
 run;
data cvb1;
     set cov_one;
      where CovParm="Residual";
   mse=estimate;
 keep  mritstu regint mse;
  data cvb2;
      set cov_one;
      where CovParm="SUBJID";
 subj=estimate;
 keep mritstu regint subj;
data covp0;
     merge cvb1 cvb2;
```

```
       by mritstu regint;
       cvw=compress(put(100*sqrt(exp(mse)-1),5.1));
    keep mritstu regint cvw;
run;

proc sort data=mri_Session12;
    by  mritstu regint atrtgrp;
/*obtain within subject varibility by patient population */
proc mixed data=mri_Session12;
  class subjid atrtgrp visit;
  model lg_mriresn = visit /e3 ddfm=kr outp=pred_one;
  random subjid;
 by mritstu regint atrtgrp;
 ods output covparms = cov_one1;
 run;
data cvb11;
     set cov_one1;
      where CovParm="Residual";
   mse=estimate;
 keep  mritstu regint atrtgrp mse;
  data cvb12;
      set cov_one1;
      where CovParm="SUBJID";
 subj=estimate;
 keep mritstu regint atrtgrp subj;
data covp01;
     merge cvb11 cvb12;
       by mritstu regint atrtgrp;
       cvw=compress(put(100*sqrt(exp(mse)-1),5.1));
      keep mritstu regint atrtgrp cvw;
run;
```

10.3. Exploratory Analysis

10.3.1. Exploratory analyses on other MRI scan measurements

DCE-MRI measurements, including change from baselines, will be summarized by visit. The corresponding mean (SE) plots with separate line for HF and HV will be provided also.

A Spaghetti plot for each parameter, with scan session along the horizontal axes, a line for each subject (differentiate HV and HF by different symbol) representing values for the parameter on the vertical axes, will be provided.

Listings with DCE-MRI measurements will be presented.

The distribution of DCE-MRI measures of pulmonary physiology (interstitial volume (v_e), exchange rate (k^{trans}) and Plasma volume (v_p)) in HV and HF patients both before and after exercise will be plotted using a scatter plot.

10.3.2. Comparison of DLco/DLno parameters at baseline by group (HV, HF)

The similar analysis as for the primary endpoint (Section 10.1.1) will be presented for the parameters of gas diffusion DLco/DLno such as DLNO, DMCO, at baseline and post exercise if data permit.

10.3.3. Comparison of effect of exercise at Scan 3 by group (HV, HF)

The analysis will be based on the Evaluable population. The change from baseline parameters of interest on pre-exercise test to post-exercise test in Scan 3 will be fitted separately using a mixed effect model with subject as a random effect, patient population (HF or HV) as fixed effects. Point estimates and associated 95% confidence intervals (CI) will be constructed to provide a plausible range of values for the mean change from baseline measurements in HV and HF patients in Session 3, and the mean difference between the HV and HF groups. Gas diffusion DLco/DLno and lung function parameters in constant exercise session at Scan 3. Change from baseline pre-exercise workload test to post-exercise test is defined as:

DLco/DLno : Scan 3 post MRI – Scan 3 pre-exercise

Lung function: Scan 3 post MRI – Scan 3 pre-exercise

In addition, NT-ProBNP (heart failure patients only), Dyspnoea Score, Respiratory Rate, parameters for gas diffusion and DLco/DLno will be summarized by planned time and group (HV, HF) at Scan 3 by separate exercise session. The corresponding mean (SE) plots will be provided also.

(keep if already programmed)

10.3.4. Comparison of exercise test parameters at Scan 3 by group (HV, HF)

The similar analysis as for the primary endpoint (Section 10.3.6) will be presented for exercise test on parameters of interests including Ve/Vco2 ratio at Scan 3 in maximal test and constant exercise session separately. See below for the example sas codes for the analysis:

```
proc mixed data=VEVCo2;
  class subjid atrtgrp ptm;
  model AVAL = ptm atrtgrp ptm*atrtgrp/e3 ddfm=kr outp=pred_one;
  repeated PTM/ subject=subjid type=un;
  LSMEANS  PTM*atrtgrp  /CL ALPHA=0.05;
  estimate 'HF - HV at CONSTANT WORKLOAD ' atrtgrp 1 -1
                       PTM*atrtgrp  1 0 -1  0/cl alpha = 0.05;
  estimate 'HF - HV at MAXIMAL EXERCISE' atrtgrp 1 -1
                       PTM*atrtgrp  0 1 0 -1/cl alpha = 0.05;
  estimate 'MAXIMAL EXERCISE - CONSTANT WORKLOAD in HF' PTM -1 1
                       PTM*atrtgrp  -1 1 0 0/cl alpha = 0.05;
  estimate 'MAXIMAL EXERCISE - CONSTANT WORKLOAD in HV' PTM -1 1
                       PTM*atrtgrp  0 0 -1 1/cl alpha = 0.05;
 ods output lsmeans = lsm;
```

```
 ods output covparms = cov_one;
 ods output estimates = est;
run;
```

10.3.5. Relationship between change from baseline MRI scan primary endpoint (Ve, Ktrans) and change from baseline of NT-ProBNP, DLco/DLno and Ve/VCo2

Change from baseline NT-ProBNP at Scan 3 is defined as:

post constant workload exercise test –pre constant workload exercise test

The change from baseline DLco/DLno, Ve/VCo2 is defined as:

Scan 3 post MRI – Scan 3 pre-exercise

The following plots will be presented, for each component of interest as defined above:

A scatter plot, with change from baseline (Ve, Ktrans) on the horizontal axes and change from baseline NT-ProBNP, or DLco/DLno, VE/VCO2 on the vertical axes, using different colours for each population if data permit, i.e. HV and HF will be presented, as appropriate to the data.

10.3.6. Analysis of Group 3 patients

For Group 3, all PD endpoints (DCE-MRI measures, lung ultrasound (B Line count), NT proBNP, dyspnoea score, and respiratory rate, etc) will be listed as appropriate. Demographic and safety (AE's if any) will still be summarized according to IDSL standards (see deliverable priority column "Group 3 SAC" for specifics in Section 12.1, note to aviod duplicated TFL numbers, all group 3 tables and listings, please add 30 into the TOC numbers. For instance for Table 9.1, use Table 9.31)

Should the following variables not being captured/calculated from the source data, they have to be calculated as followings:

LUS Score = Total line count over all zones (i.e. sum up the line counts for all zones for the subject and visit);

Inferior vena Cava Collapsability Index, IVCCI = (IVC max –IVC min)/IVC max;

Inferior vena cava diameter index , IVCDI = IVC max/ BSA

11. REFERENCES

European Community for Coal and Steel (ECCS), Lung Volumes and Forced Ventilatory Flows. Quanjer PH, Tammeling GJ, Cotes JE, Pedersen OF, Peslin R, Yernault J-C, 1993. 6(16):25-40.

Hankinson, JL, Odencrantz, JR, Fedan, KB. Spirometic Reference Values from a Sample of the General U.S. Population. Am J Resp Crit Care, 1999. 159:179-187.

Polgar. Pulmonary Function Testing in Children: Techniques and Standards. Philadelpahia: Sanders, 1971.

Schuirmann DJ. 1987. A comparison of the two one-sided tests procedure and the power approach for assessing the equivalence of average bioavailability, J Pharmacokinet and Biopharm, 15, 657-680.

12. ATTACHMENTS

12.1. Table of Contents for Data Display Specifications

For the Clinical Study Report the following section numbering will apply:

Section 9: Study Population

Section 10: Safety

Section 11: Other Safety

Section 12: Efficacy

Listed below are the planned figures, tables and listings to be produced for inclusion in the MRI201137 clinical study report:

- The 'IDSL No. / Example Shell"' column refers to the relevant example in the Integrated Data Standards Library (IDSL) database
- Unless otherwise indicated, these refer to the core IDSL data standards located under:
    - 'Data Standards' → 'By Component' in the IDSL database

12.2. Study Population and Disposition

12.2.1. Study population

Listings

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
9.1	Safety	IE3	Listing of Analysis populations		Programmer	SAC, Group 3 SAC

12.2.2. Disposition

Tables

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
9.1	Safety	ES1	Summary of Subject Disposition		Programmer	SAC, Group 3 SAC

Listings

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
9.2	Safety	ES2	Listing of Reasons for Study Withdrawal		Programmer	SAC, Group 3 SAC

12.2.3. Demography and Baseline Characteristics

Tables

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
9.2	Safety	DM1	Summary of Demographic Characteristics	Include all variables collected.	Programmer	SAC, Group 3 SAC
9.3	Safety	DM5	Summary of Race and Racial Combinations		Programmer	SAC

Listings

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
9.3	Safety	DM2	Listing of Demographic Characteristics	Include all variables collected.	Programmer	SAC, Group 3 SAC
9.4	Safety	DM9	Listing of Race		Programmer	SAC, Group 3 SAC

12.3. Safety

12.3.1. Exposure to MRI

Tables

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
10.1	Safety	EX1	Summary of Exposure to MRI	Present subjects who were exposed to 1, 2, or 3 MRI scans	Programmer	SAC

Listings

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
10.1	Safety	EX3	Listing of Exposure to MRI	Present all MRI data.	Programmer	SAC, Group 3 SAC

12.3.2. Laboratory Data

Tables

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
10.2	Safety	LB1	Summary of Laboratory Values by session and overall	Include all Laboratory values collected, by Session 0, 1, 2, 3,include immediately before and after both exercise tests	Programmer	SAC Group 3 SAC
10.3	Safety	LB2	Summary of Abnormal Laboratory Values by session and overall		Programmer	SAC
10.4	Safety	UR1	Summary of Urinalysis Data by Session and overall		Programmer	SAC

Listings

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
10.2	Safety		Listing of Laboratory Data	Include all lab values, at all-time points.	Programmer	SAC, Group 3 SAC
10.3	Safety	LB5	Listing of Laboratory Data for Subjects with Abnormalities of Potential Clinical Concern	Include Session variable	Programmer	SAC, Group 3 SAC

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
10.4	Safety	LB13	Listing of Laboratory Test Reference Ranges	Include Session variable	Programmer	SAC, Group 3 SAC

12.4. Other Safety

12.4.1. Vital Signs

Tables

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
10.5	Safety	VS1	Summary of Vital Signs by Session	Include all vital signs variables collected and all time points i.e. screening, after MRI scan 1 and 2, and immediately pre and post maximal and constant workload exercise tests.	Programmer	SAC, Group 3 SAC
10.6	Safety	VS1	Summary of change from pre-exercise for vital signs		Programmer	SAC

Listings

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
10.5	Safety	VS4	Listing of Vital Signs	Include change from pre-exercise and session variable.	Programmer	SAC, Group 3 SAC

12.4.2. ECG

Tables

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
10.7	Safety	EG1	Summary of ECG findings at screening		Programmer	SAC
10.8	Safety	EG2	Summary of ECG values at screening		Programmer	SAC, Group 3 SAC

Listings

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
10.6	Safety	EG3	Listing of ECG values at screening		Programmer	SAC, Group 3 SAC
10.7	Safety	EG5	Listing of ECG findings at screening		Programmer	SAC, Group 3 SAC

12.5. Efficacy

12.5.1. Primary endpoint

Tables

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
11.1	Evaluable	Example A	Analysis of contrast agent interstitial volume (v_e) and exchange rate (k^{trans}) data	For Total lung, Left lung, Right lung, Left lung apical,Left lung basal,Right lung apical, Right lung basal	Statistician	SAC
11.2	Safety	Example A	Analysis of contrast agent interstitial volume (v_e) and exchange rate (k^{trans}) data	For Total lung, Left lung, Right lung, Left lung apical,Left lung basal,Right lung apical, Right lung basal	Statistician	SAC
11.3	Evaluable	VS1	Summary of change from baseline of contrast agent interstitial volume (v_e) and exchange rate (k^{trans}) data	For Total lung, Left lung, Right lung, Left lung apical,Left lung basal,Right lung apical, Right lung basal	Programmer	SAC

Figures

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
11.101	Evaluable	Example B	Mean (SE) Plot of contrast interstitial volume (v_e) and exchange rate (k^{trans}) data	For Total lung, Left lung, Right lung, Left lung apical,Left lung basal,Right lung apical, Right lung basal. Separate line for HF and HV.	Programmer	SAC

12.5.2. Secondary endpoint

Tables

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
11.4	Evaluable	Example A	Analysis of within subject variability of DCE-MRI measures of pulmonary edema and vascular permeability	Amend footnote to: Analysis performed using mixed effect model with subject (nested within scanning session) treated as a random effect, patient population (HF or HV) and scanning session (Session 1 and 2) as fixed effects.	Statistician	SAC

12.5.3. Exploratory endpoint

12.5.3.1. Exploratory analysis of DCE-MRI measurements: Plasma volume (v_p), T_1 relaxation rate, proton density

Tables

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
11.5	Evaluable	DM1	Summary of DCE-MRI measurements interstitial volume (v_e), exchange rate (k^{trans}) (Plasma volume (v_p), T_1 relaxation rate, proton density, by visit.	Replace demographic variables with Plasma volume (Vp), T1 relaxation rate, proton density by visit.	Programmer	SAC
11.6	Evaluable	DM1	Summary of lung ultrasound total B-line scores by visit.	Replace demographic variables with LUS B-line total scores (counts).	Programmer	

Figures

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
11.102	Evaluable	Example B	Mean (SE) Plot for DCE-MRI measure interstitial volume (v_e).	For Total lung, Left lung, Right lung, Left lung apical,Left lung basal,Right lung apical, Right lung basal. Separate line for HF and HV patients across 3 scans.	Programmer	SAC
11.103	Evaluable	Example B	Mean (SE) Plot for DCE-MRI measure exchange rate (k^{trans})	For Total lung, Left lung, Right lung, Left lung apical,Left lung basal,Right lung apical, Right lung basal. Separate line for HF and HV patients across 3 scans.	Programmer	SAC

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
11.104	Evaluable	Example B	Mean (SE) Plot for DCE-MRI measure Plasma volume (v_p).	For Total lung, Left lung, Right lung, Left lung apical,Left lung basal,Right lung apical, Right lung basal. Separate line for HF and HV patients across 3 scans.	Programmer	SAC
11.105	Evaluable	Example B	Mean (SE) Plot for DCE-MRI measure T_1 relaxation rate.	For Total lung, Left lung, Right lung, Left lung apical,Left lung basal,Right lung apical, Right lung basal. Separate line for HF and HV patients across 3 scans.	Programmer	SAC
11.106	Evaluable	Example B	Mean (SE) Plot for DCE-MRI measure proton density.	For Total lung, Left lung, Right lung, Left lung apical,Left lung basal,Right lung apical, Right lung basal. Separate line for HF and HV patients across 3 scans.	Programmer	SAC
11.201	Evaluable	Example C	Spaghetti plot of interstitial volume (v_e) by scan session	For Total lung, Left lung, Right lung, Left lung apical,Left lung basal,Right lung apical, Right lung basal. Interstitial volume (V_e) on the vertical axes, scan session on the horizontal axes, and different symbols for HF and HV patients. (3 Scans)	Programmer	SAC
11.202	Evaluable	Example C	Spaghetti plot of exchange rate (k^{trans}) by scan session	For Total lung, Left lung, Right lung, Left lung apical,Left lung basal,Right lung apical, Right lung basal. Exchange rate (k^{trans}) on the vertical axes, scan session on the horizontal axes, and different symbols for HF and HV patients.	Programmer	SAC
11.301	Evaluables	Example D	Scatter plot of change from baseline interstitial volume (v_e) and change from baseline Pro-BNP		Programmer	SAC

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
11.302	Evaluables	Example D	Scatter plot of change from baseline interstitial volume (v_e) and change from baseline DLno/DLco		Programmer	SAC
11.303	Evaluables	Example D	Scatter plot of change from baseline interstitial volume (v_e) and change from baseline Ve/VCo2		Programmer	SAC
11.304	Evaluables	Example D	Scatter plot of change from baseline exchange rate (k^{trans}) and Change from baseline Pro-BNP		Programmer	SAC
11.305	Evaluables	Example D	Scatter plot of change from baseline exchange rate (k^{trans}) and Change from baseline DLno/DLco		Programmer	SAC

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
11.306	Evaluables	Example D	Scatter plot of change from baseline exchange rate (k^{trans}) and Change from baseline Ve/VCo2		Programmer	SAC

12.5.3.2. Comparison of DLco/DLno gas diffusion parameters at baseline by group (HF, HV)

Tables

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
11.6	Evaluable	DM1	Summary of gas diffusion, lung function parameters by visit.		Programmer	SAC
11.7	Evaluable	Example A	Analysis of gas diffusion parameters: parameters DLno, DLco, and DLno/DLco ratio at baseline.	Using mixed model to compare all parameters of interest between HF and HV if data permit.	Statistician	SAC

Figures

11.401	Evaluable	Example B	Mean (SE) Plot for gas diffusion (DLno, DLco and DLco/DLno) , lung function parameter	Separate line for HF and HV patients across 3 scans, a separate plot for each gas diffusion, lung function parameter	Programmer	SAC
11.501	Evaluable	Example C	Spaghetti plot of gas diffusion parameter by scan session (DLno, DLco and DLco/DLno)	Gas diffusion parameter on the vertical axes, scan session on the horizontal axes, and different symbols for HF and HV patients, a separate plot for each gas diffusion parameter	Programmer	SAC

12.5.3.3. Comparison of Dyspnoea Score at baseline by group (HV, HF)

Tables

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
11.8	Evaluable	DM1	Summary of Dyspnoea score by visit and session	Use dyspnoea variables at each planned time point, including immediately before and after both exercise tests.	Programmer	SAC

Figures

11.6	Evaluable	Example F	Frequency bar plot of Dyspnoea score by visit		Programmer	SAC

12.5.3.4. Comparison of Respiratory Rate at baseline by group (HV, HF)

Tables

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
11.9	Evaluable	DM1	Summary of Respiratory rate by visit	Use respiratory rate at each planned time point.	Programmer	SAC

Figures

11.7	Evaluable	Example B	Mean (SE) Plot for respiratory rate by visit.	Separate line for HF and HV patients across 3 scans.	Programmer	SAC

12.5.3.5. Comparison of effect of exercise at Scan 3 by group (HV, HF)

Tables

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
11.10	Evaluable	Example A	Analysis of effect of exercise (session 3) on gas diffusion parameters	Amend footnote to: Analysis performed using a mixed effect model, subject is random effect, (HF or HV) as fixed effects. With change from pre-exercise gas diffusion parameters DLno, DMco, for both exercise tests.	Statistician	SAC

12.5.3.6. Comparison of exercise test parameters at Scan 3 by group (HV, HF)

Tables

No.	Population	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
11.11	Evaluable	DM1	Summary of exercise test parameters	Use the data collected at scan 3, no pre/post or change from baseline values.	Programmer	SAC
11.12	Evaluable	Example A	Analysis of exercise test parameters of interest (Ve/Vco2 ratio at Scan 3 by HF and HV.	Use the data collected at scan 3, no pre/post or change from baseline values.	Statistician	SAC

12.5.3.7. Relationship between exercise parameters (Ve/Vco2) vs gas diffusion DLno/DLco parameters at scan 3

Listings

No.	Population[1]	IDSL No. / Example Shell	Title	Additional Programming Notes	Responsibility	Deliverable Priority
11.1	Evalauble		Listing of DCE-MRI scan data	Include all variables collected, i.e. interstitial volume, exchange rate, pulmonary edema and vascular permeability.	Programmer	SAC. Group 3 SAC
11.2	Evalauble		Listing of dyspnoea score	Include all variables collected.	Programmer	SAC, Group 3 SAC
11.3	Evalauble		Listing of respiratory rate	Include all variables collected.	Programmer	SAC, Group 3 SAC
11.4	Evalauble		Listing of NT-proBNP measurements	Include all variables collected.	Programmer	SAC, Group 3 SAC
11.5	Evalauble		Listing of exercise capacity measurements	Include all variables collected.	Programmer	SAC, Group 3 SAC
11.6	Evalauble		Listing of DLco and DLno measurements	Include all variables collected.	Programmer	SAC, Group 3 SAC
11.7	Evalauble		Listing of plasma volume (v_p)	Include all variables collected.	Programmer	SAC, Group 3 SAC
11.8	Evalauble		Listing of T_1 relaxation rate and proton density	Include all variables collected.	Programmer	SAC
11.7	Evalauble		Listing of Lung Ultrasound Data and Score	Include all variables collected, including B-line counts, total scores as well as by thoracic zones	Programmer	Group 3 SAC

[1] Evaluable population is not applicable to Group 3, using Safety population for Group 3 displays

12.6. Data Display Specifications (Example Shells)

Example : Example A
Protocol : 2013N186309_02
Population : Completers

Table *X.X*

Analysis of contrast agent interstitial volume (v_e) and exchange rate (k^{trans}) data for total lung, left lung, right lung, left apical segments, right apical segment and left basal segments and right basal segment

Pls update this mock table with headers something as the following:

		Comparisons (Grp1 vs Grp0)		LSMean (Se)		Point estimates	
Parameter	Region	Group1	Group0	Group1	Group0	and 95% CI	p-value
Ve	Left Lung	HF (n=)	HV (n=)	xxx.xx(xx.x)	xxx.xx(xx.xx)	xx.xx(xx.xx, xx.xx)	0.xx
		Post Exercise	Session 2				
		in HF (n=)	in HF (n=)	xxx.xx(xx.x)	xxx.xx(xx.xx)	xx.xx(xx.xx, xx.xx)	0.xx

Example : Example A (Secondary Objective)

Protocol: 201137 Page 1 of 6

Population: Evaluable

Table 11.3
Analysis of within subject variability of DCE-MRI measures of pulmonary edema and vascular permeability

Comparisons: (Session 2 Vs Session 1)

MRI test(Unit)	Region of interest	Population	GeoMean (Se in log) Session2	Session1	Point estimates (Ratio)and 95% CI	Coef. of Variation p-value	by pop	overall
Transfer rate from plasma to extracellular space (EES) (Ktrans) (1/MIN)	Lungs	Heart Failure (n=12)	0.187 (0.129)	0.206 (0.193)	0.908 (0.634, 1.300)	0.5789	32.4	43.3

Example : Example B Page 1 of n

Protocol : 2013N186309_02

Population : Completers

Figure *X.X*

Mean (SE) Plot, Analysis performed using a Mixed effect model with subject (nested within scanning session) treated as a random effect, patient population (HF or HV) and Scanning Session (Session 1 and 2) as fixed effects

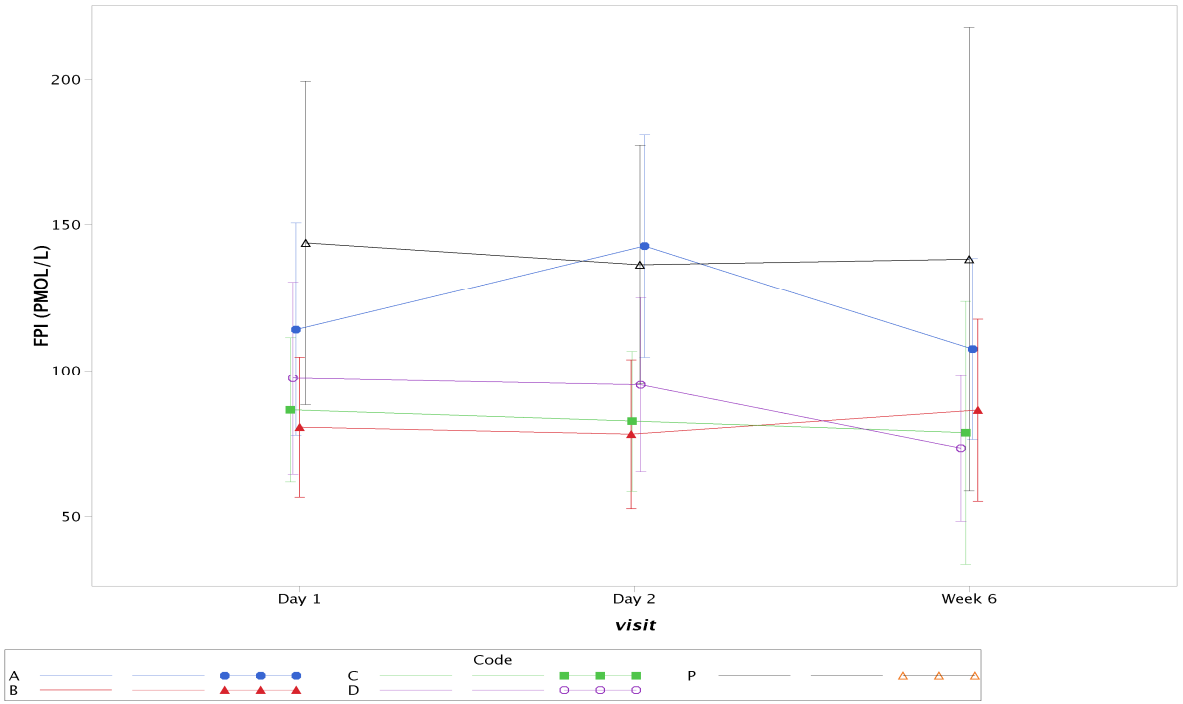
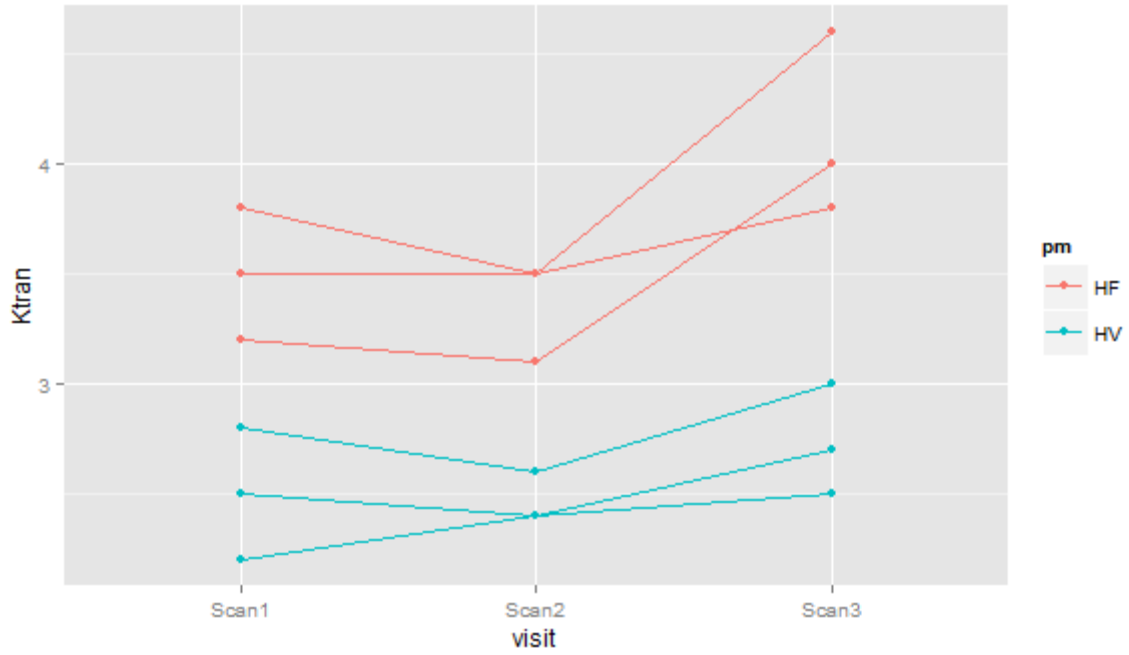
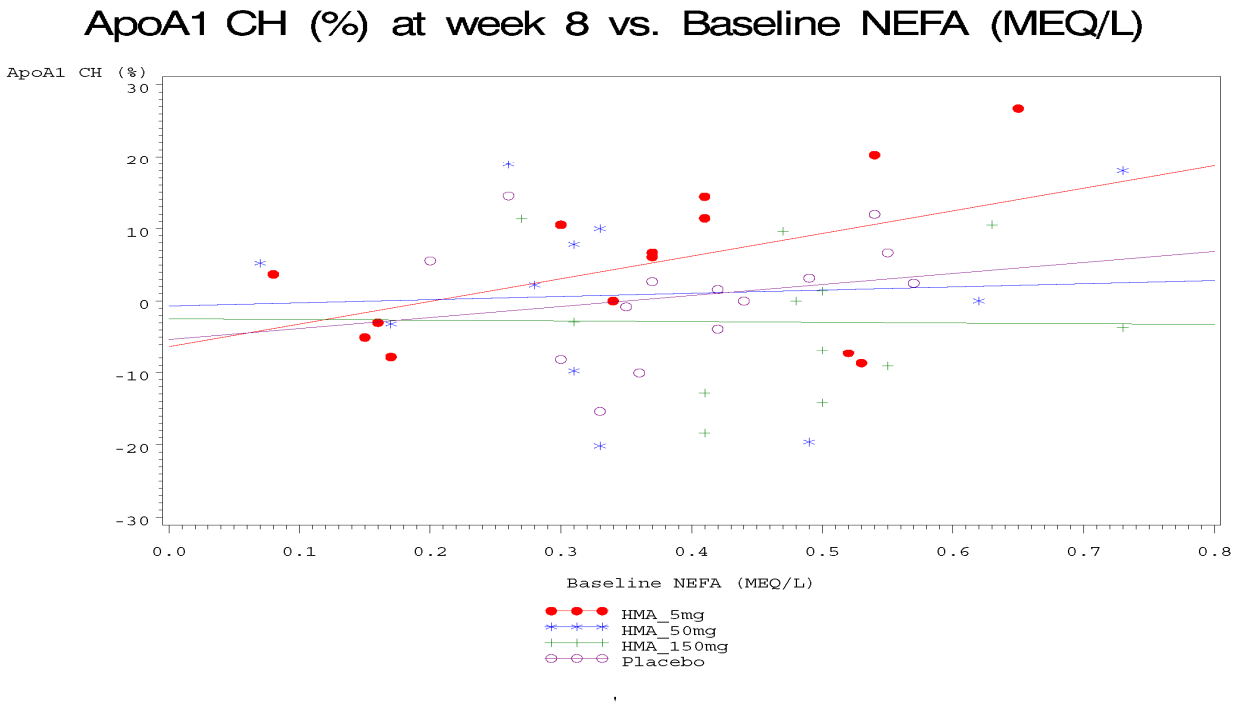


Figure *X.X*



Example : Example D
Protocol : 2013N186309_02
Population : Completers

Figure *X.X*



Amend title to "Scatter plot of var 1 vs var 2.
Amend axes labels to appropriate variable names
Amend legend text to Healthy Volunteers and Heart Failure patients.

Example: Example E
Protocol: 2013N186309_02
Population: Completers

Table xx.xx

Correlation of Change from Baseline in MRI Parameters and Change from Baseline NT-proBNP Analysis

	Parameter 1	Parameter 2	Group	Pearson's Correlation (P-value)	Spearman's Correlation (P-value)
Left Lung					
Apical segment	MRI Parameter	NT-proBNP Parameter	Healthy volunteers	x.xxxx (0.xxxx)	x.xxxx (0.xxxx)
	MRI Parameter	NT-proBNP Parameter	Heart failure	x.xxxx (0.xxxx)	x.xxxx (0.xxxx)
Basal segment	MRI Parameter	NT-proBNP Parameter	Healthy volunteers	x.xxxx (0.xxxx)	x.xxxx (0.xxxx)
	MRI Parameter	NT-proBNP Parameter	Heart failure	x.xxxx (0.xxxx)	x.xxxx (0.xxxx)
Total	MRI Parameter	NT-proBNP Parameter	Healthy volunteers	x.xxxx (0.xxxx)	x.xxxx (0.xxxx)
	MRI Parameter	NT-proBNP Parameter	Heart failure	x.xxxx (0.xxxx)	x.xxxx (0.xxxx)
Right Lung					

Apical segment	MRI Parameter	NT-proBNP Parameter	Healthy volunteers	x.xxxx (0.xxxx)	x.xxxx (0.xxxx)
	MRI Parameter	NT-proBNP Parameter	Heart failure	x.xxxx (0.xxxx)	x.xxxx (0.xxxx)
Basal segment	MRI Parameter	NT-proBNP Parameter	Healthy volunteers	x.xxxx (0.xxxx)	x.xxxx (0.xxxx)
	MRI Parameter	NT-proBNP Parameter	Heart failure	x.xxxx (0.xxxx)	x.xxxx (0.xxxx)
Total	MRI Parameter	NT-proBNP Parameter	Healthy volunteers	x.xxxx (0.xxxx)	x.xxxx (0.xxxx)
	MRI Parameter	NT-proBNP Parameter	Heart failure	x.xxxx (0.xxxx)	x.xxxx (0.xxxx)
Total both lungs	MRI Parameter	NT-proBNP Parameter	Healthy volunteers	x.xxxx (0.xxxx)	x.xxxx (0.xxxx)
	MRI Parameter	NT-proBNP Parameter	Heart failure	x.xxxx (0.xxxx)	x.xxxx (0.xxxx)

Example : Example D
Protocol : 2013N186309_02
Population : Evaluable

Frequency bar plot of Dyspnoea score by visit