An open-label, multicentre study to evaluate pharmacokinetics, safety and efficacy of zamicastat as adjunctive therapy in pulmonary arterial hypertension (PAH)

Sponsor Project Code: BIA-51058-201
Scope Project Code: 0223BI26.MPB

STATISTICAL ANALYSIS PLAN

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- Added table 15.2.5.1 (section 5.5.5)
- Removed the original SF-6D score from analysis (section 5.5.6)
- Added figures 15.2.1 and 15.2.2 (section 5.5.6)
- Added the definition of TEAEs leading to down-titration and table 15.3.1.7 (section 5.6.1)
- Added table 15.3.5.4.2 (section 5.6.5)

Version Draft 0.3 (24-NOV-2021): Document updated after sponsor's review. Notable changes:

- Added specification that the definition of PAH medications will be reviewed during the DRM (section 5.3)
- Updated the range of nominal compliance to 90%-110% (section 5.4.2)
- Added within-visit shift table for ECG abnormalities (section 5.6.5)

Version Draft 0.4 (06-JAN-2022): Document updated after the Data Review meeting and the sponsor's review. Notable changes:

- Changed definition of FAS to only include patients with non-missing efficacy assessments at MPV3 (Section 3.1)
- Added definition of mFAS (Section 3.1). Efficacy analyses will be performed for both the FAS and MFAS (Section 5.5).
- Added definitions for TAPSE subgroups (Section 3.2). TAPSE subgroup analyses will be performed for selected efficacy parameters (Sections 5.5.1, 5.5.2, 5.5.4)
- Safety data will no longer be summarised at derived visit V3. Actual visits will be used (Section 4.4)
- Added definition of PAH-approved medications and corresponding tables (Section 5.3)
- Right heart catheterisation clinical significance assessments will not be used in statistical analysis (Section 5.5.1)
- Added specification that in case the distance covered during both 6MWT attempts is equal, the first attempt will be considered as baseline (Section 5.5.2)
- Changed unit for biomarket NT-proBNP from pg/mL to ng/L (Section 5.5.3)
- Added specification for interpreting normal, NCS abnormal, and CS abnormal findings for arterial blood gas analysis (Section 5.6.3) and ECG (Section 5.6.5)

Version Draft 0.5 (08-FEB-2022): Document updated after sponsor's review. Notable changes:

- Added the coefficient of variance to standard summary statistics (Section 4.1)

Version Draft 0.6 (17-MAR-2022): Document updated after sponsor's review. Notable changes:

- Amended the definition of PAH-approved medications to include diuretics (Sections 3.1, 5.3)

Version Final 1.0 (22-MAR-2022): Document finalised.

TABLE OF CONTENTS

LIST OF ABBREVIATIONS AND KEY TERMS

Abbreviations	Description of abbreviations
6-MWT	6-minute walk test
λ_z	Terminal rate constant
AE	Adverse event
ALT	Alanine transaminase
AST	Aspartate transaminase
AUC	Area under the curve
AUEC	Area under the effect-time curve
CI	Cardiac index
CL/f	Apparent total clearance
C_{max}	Maximum plasma concentration
C_{min}	Minimum plasma concentration
CO	Cardiac output
CPK	Creatine phosphokinase
CS	Clinically significant
CV	Coefficient of variation
DßH	Dopamine ß-hydroxylase
DBP	Diastolic blood pressure
DPG	Diastolic pressure gradient
DR(M)	Data review (meeting)
DSMB	Data safety monitoring board
ECG	Electrocardiogram
eCRF	Electronic case report form
EDV	Early discontinuation visit
E_{max}	Maximum observed effect on DβH activity
ES	Enrolled set
FAS	Full analysis set
GGT	Gamma-glutamyl transferase
HbA1c	Haemoglobin A1c
HCG	Human chorionic gonadotropin
HTD	Highest tolerated dose
ICF	Informed consent form
IMP	Investigational medicinal product
LDH	Lactate dehydrogenase
LLOQ	Lower limit of quantification
LPLV	Last patient's last visit
MedDRA	Medical Dictionary for Regulatory Activities
mPAP	Mean pulmonary artery pressure
mRSS	Modified Rodnan skin score
NCS	Not clinically significant
NT-proBNP	N-terminal pro brain natriuretic peptide
NYHA/WHO	New York Heart Association/Word Health Organisation
PAC	Pulmonary arterial compliance
PAH	Pulmonary arterial hypertension
PAPs	Pulmonary artery pressure systolic
PAPd	Pulmonary artery pressure diastolic
PAWP	Pulmonary artery wedge pressure
PD	Pharmacodynamic
PK	Pharmacokinetic
PKS	Pharmacokinetic analysis set

PT	Preferred term
PVR	Pulmonary vascular resistance
RAP	Right atrial pressure
RBC	Red blood cell count
RHC	Right heart catheterisation
SAE	Serious adverse event
SAP	Statistical analysis plan
SAS	Statistical Analysis System
SBP	Systolic blood pressure
SF-36	Short Form - 36
S_vO_2	Mixed venous oxygen saturation
SOC	System organ class
SS	Safety set
SVR	Systemic ventricular resistance
$t_{1/2}$	Terminal half-life
TAPSE	Tricuspid annular plane systolic excursion
TEAE	Treatment emergent adverse event
T_{Emax}	Time to occurrence of E_{max}
t_{max}	Time until C_{max}
TPG	Transpulmonary pressure gradient
UV	Unscheduled visit
V	Visit
V_z/f	Apparent volume of distribution
WBC	White blood cell count
WHO	World Health Organization
ZMC	Zamicastat

INTRODUCTION

This statistical analysis plan (SAP) contains a more technical and detailed elaboration of the principal features of the statistical analyses as described in the clinical study protocol versions:

Document, Version	Date
Protocol, Final 1.0	22-JUN-2018
Protocol, Final 2.0	18-JUN-2019
Protocol, Final 2.0 UK	08-JUL-2019
Protocol, Final 2.0 DE	23-SEP-2019
Protocol, Final 3.0	12-MAY-2020

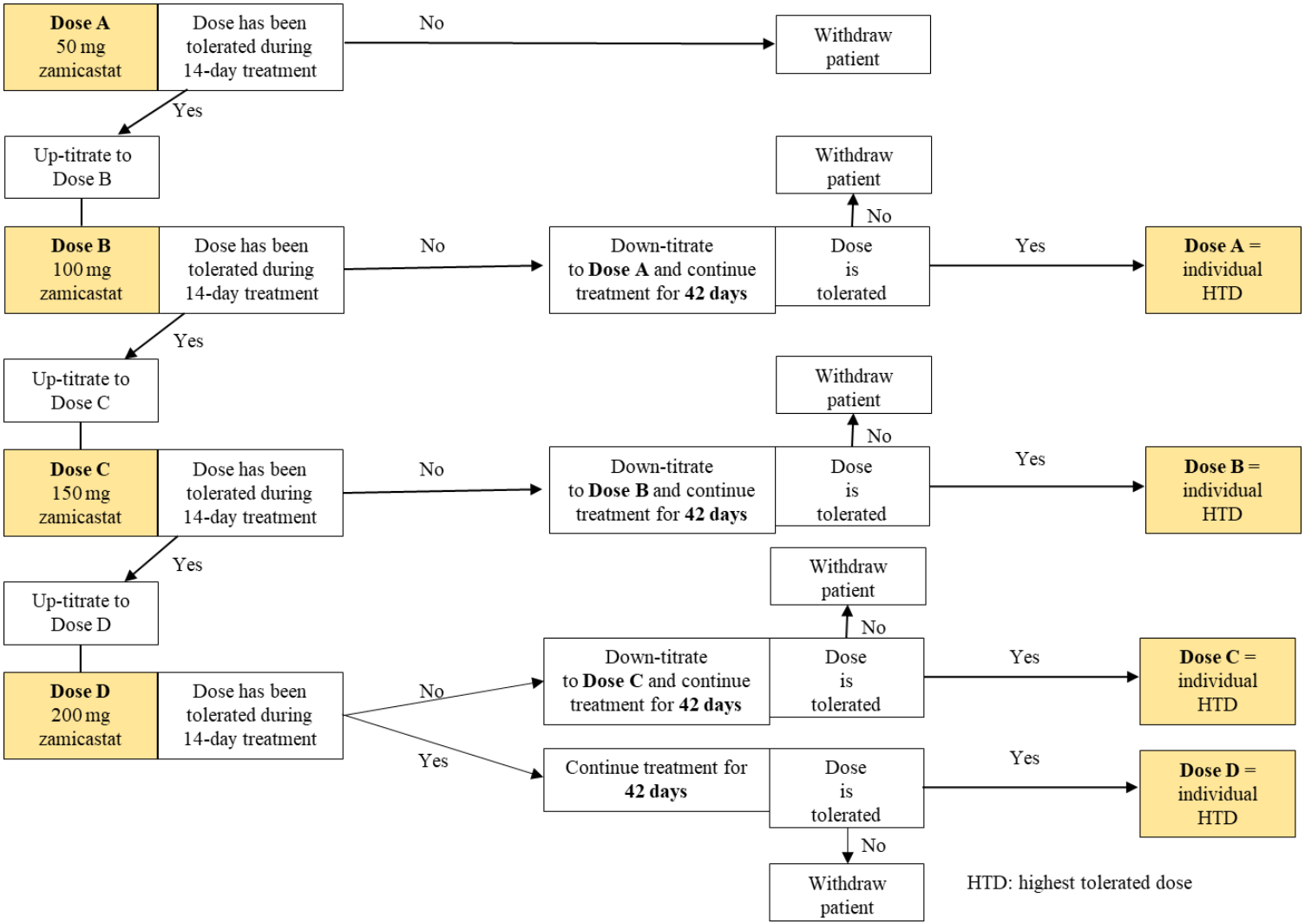
This SAP is written assuming the latest version (**Final 3.0**, 12-MAY-2020). Relevant differences between the protocol versions will be listed in the corresponding subsections of the SAP.

This SAP includes detailed procedures for executing the statistical analysis of the secondary safety, tolerability and efficacy variables and other data, and it is structured according to different data types. The SAP is finalised and signed-off before analysis begins in an open-label study. This SAP supersedes statistical considerations previously defined in the clinical study protocol. Analysis of the primary endpoint (pharmacokinetics (PK)) as well as secondary PK and pharmacodynamics (PD) endpoints is covered in a separate reporting and analysis plan prepared by Quotient Sciences Ltd (Appendix 4).

All analysis data sets and statistical output related to the secondary safety, tolerability and efficacy endpoints will be produced by the statistics department of Scope International AG using SAS® for Windows (SAS Institute Inc., Cary, NC, USA) [1] version 9.4 or higher. The actual version used will be documented in the Validation Plan for Statistical Programming.

1 FLOW CHART AND VISIT SCHEDULE

1.1 Flow Chart



1.2 Schedule of Study Procedures

	Screening	**Dose finding period**			**42-days Maintenance period**			**Follow-up**	
Visit no.	**V1**	**A1**[2]	**A2/B2/C2/D2**	**A3/B3/C3/D3**[5]	**MPV1**[5]	**MPV2**[5]	**MPV3**[2,5]**/ EDV**[1]	**Follow-up down-titration**[7]	**FU**[17]
	Day -12 to -5	**Day 1**	**8 days ±2 after A1/A3/B3/C3**	**14 days ±2 after A1/A3/B3/C3**	**13 days ±2 after D3/down-titration**[19]	**27 days ±2 after D3/ down-titration**[19]	**41 days ±2 after D3/ down-titration**[19]	**14 days ±2 after MPV3/EDV**	**14 days ±2 after last IMP intake**
on-site visit ⊗ / telephone contact ☎	⊗	⊗	☎	⊗	⊗	⊗	⊗	☎	⊗
Initiation procedures									
Informed consent	●								
Demographics	●								
Height	●								
Weight	●						●		
Medical history	●								
Prior medication	●								
Concomitant medication	●	●	●	●	●	●	●	●	●
WHO functional class	●						●		
Inclusion/exclusion criteria	●	●							
Medication									
First IMP administration		●							
Dose increase				●[3]					
Dispense IMP		●		●	●	●	●[7]		
IMP accountability				●	●	●	●		●[7]
Pharmacokinetics/ Pharmacodynamics									
Blood withdrawal (24h profile)		●[4]					●[4,8]		
Blood withdrawal (trough level)				●[14]	●[14]	●[14]			
Blood withdrawal (DβH activity)		●[4]		●[14]	●[14]	●[14]	●[4,8]		
Urinalysis (dopamine and norepinephrine levels, 24h urine collection)[15]		●		●			●[8]		

	Screening	Dose finding period			42-days Maintenance period			Follow-up	
Visit no.	**V1**	**A1[2]**	**A2/B2/C2/D2**	**A3/B3/C3/D3[5]**	**MPV1[5]**	**MPV2[5]**	**MPV3[2,5]/ EDV[1]**	**Follow-up down-titration[7]**	**FU[17]**
	Day -12 to -5	**Day 1**	**8 days ±2 after A1/A3/B3/C3**	**14 days ±2 after A1/A3/B3/C3**	**13 days ±2 after D3/down-titration[19]**	**27 days ±2 after D3/ down-titration[19]**	**41 days ±2 after D3/ down-titration[19]**	**14 days ±2 after MPV3/EDV**	**14 days ±2 after last IMP intake**
on-site visit ⊗ / telephone contact ☎	⊗	⊗	☎	⊗	⊗	⊗	⊗	☎	⊗
Safety									
Adverse events	●	●	●	●	●	●	●	●	●
Vital signs[11] (blood pressure, heart rate, tympanic body temperature)	●	●[12]		●	●	●	●[12]		●
Blood withdrawal (haematology, biochemistry and coagulation)	●			●	●		●		●
Urinalysis	●			●	●		●		●
Physical examination	●			●	●	●	●		
12-lead electrocardiogram	●	●[18]		●	●	●	●[18]		●
Number of digital scars[10]	●			●	●	●	●		
Modified Rodnan Skin Score[10]	●						●		
Blood pregnancy test[6]	●								
Urine pregnancy test[6]		●		●	●	●	●		●
Arterial blood gas analysis[16,21]		●					●[8]		
Efficacy									
SF-36v2	●						●[8]		
6-min walk test/Borg dyspnoea score	●[13]						●[8,20]		
Echocardiography	●						●[8]		
Right heart catheterisation[16,22]		●					●[8]		
Blood withdrawal biomarker	●						●[8]		

1. EDV = early discontinuation visit. An EDV has to be performed within 10 days of early discontinuation. Additionally, patients who will not participate in the extension study will be contacted by phone at the time of last patient's last visit (LPLV) to document their vital status.
2. Patients will be hospitalised for 24 hours.

3. The dose will be increased if the previous dose was considered safe by the investigator according to safety criteria (at A3, B3 and C3).

4. Blood samples for PK and PD to be taken prior to IMP intake as well as 1, 2, 4, 8, 16 and 24 hours after IMP intake (but still prior to next IMP intake).

5. The patient has to be advised not to take the IMP at home on the day of A3, B3, C3, D3, MPV1, MPV2 and MPV3.

6. Only in women of childbearing potential.

7. Only applicable in patients taking 150 mg or 200 mg zamicastat and who will not participate in the extension study. In case a patient will discontinue the study early due to the occurrence of an AE, down-titration is not mandatory, but at the investigator's discretion.

8. Not applicable at EDV.

9. Visits during the Dose-finding period:
Dose A (50 mg zamicastat): visits A1, A2 and A3
Dose B (100 mg zamicastat): visits B2 and B3. These visits will only be performed if the patient was up-titrated to 100 mg zamicastat at A3.
Dose C (150 mg zamicastat): C2 and C3. These visits will only be performed if the patient was up-titrated to 150 mg zamicastat at B3.
Dose D (200 mg zamicastat): D2 and D3. These visits will only be performed if the patient was up-titrated to 200 mg zamicastat at C3.
If the patient's next dose will not be tolerated, the patient will be asked to come to an unscheduled visit (UV) and he/she will be down-titrated to his/her previous dose.

10. In scleroderma patients only.

11. Blood pressure and heart rate will be measured in supine position (two measurements) and afterwards in standing position (one measurement).

12. At A1 and MPV3 blood pressure and heart rate (two measurements in supine and one measurement in standing position) will be measured before IMP intake as well as 4, 8 and 24 hours after IMP intake.

13. Two baseline tests, separated by an interval of at least 30 minutes.

14. Blood samples will be taken prior to IMP intake.

15. 24-hour urine collection will start on the day before the respective visit.

16. Right heart catheterisation and arterial blood gas analysis have to be performed before IMP intake.

17. Applicable in all patients who will not participate in the extension study as well as in patients who discontinued early.

18. At A1 and MPV3 triplicate ECGs recordings will be performed before IMP intake, 4 and 8 hours after IMP intake. At EDV only one ECG recording will be performed.

19. Down-titration can be performed at a scheduled visit or an unscheduled visit (on-site visit or telephone contact) during the dose finding period.

20. 6-MWT has to be performed after arterial blood gas analysis but before right heart catheterisation and IMP intake.

21. Arterial blood gas analysis has to be performed before right heart catheterisation.

22.Right heart catheterisation will only be performed if no results which were measured at the study site from within 90 days before V1 are available.

2 OBJECTIVES AND DESIGN

2.1 Study Objectives

2.1.1 Primary Objective

The primary objective of this study is to evaluate the PK profile of different zamicastat doses in pulmonary arterial hypertension (PAH) patients to find the most promising therapeutic dosage range for the treatment of PAH disease. This SAP does not cover the analysis of the primary objective.

2.1.2 Secondary Objectives

The secondary objectives of this study are:

1. To assess further PK parameters including apparent total clearance, terminal half-life and apparent volume of distribution *
2. To assess the safety and tolerability of different zamicastat doses
3. To investigate the effect of different zamicastat doses on plasma dopamine β hydroxylase (DβH) activity*
4. To investigate the effect of different zamicastat doses on urinary catecholamine levels (norepinephrine and dopamine)*
5. To investigate the change in pulmonary haemodynamic parameters
6. To investigate the change in the 6-minute walk test (6-MWT)
7. To investigate the change in biomarkers
8. To investigate the change in cardiac structure and contractibility, assessed by echocardiography
9. To investigate the change in quality of life, assessed by SF-36v2

   * Covered in a reporting and analysis plan prepared by Quotient Sciences Ltd. (Appendix 4).

2.2 Study Endpoints

2.2.1 Primary Endpoint

The following PK parameters (24-hour profile) for zamicastat and its metabolites will be derived after a single dose of 50 mg zamicastat at visit A1 (Day 1):

1. Area under the curve 0-24 h ($AUC_{0\text{-}24h}$)
2. Maximum plasma concentration (C_{max})
3. Time until C_{max} (t_{max})

The following PK parameter (24-hour profile) for zamicastat and its metabolites will be derived at steady-state at the individual HTD and will be taken at visit MPV3:

4. Area under the curve 0-24 h ($AUC_{0\text{-}24h,SS}$)
5. Maximum plasma concentration ($C_{max,SS}$)
6. Time until $C_{max,SS}$ ($t_{max,SS}$)
7. Minimum plasma concentration at the end of the dosing interval ($C_{min,SS}$)

The following PK parameter (trough level) will be derived for each dose at steady-state (visits A3, B3, C3, D3, MPV1, MPV2, MPV3).

8. Minimum plasma concentration at the end of the dosing interval ($C_{min,SS}$)

The analysis of PK parameters is covered in a reporting and analysis plan prepared by Quotient Sciences Ltd. (Appendix 4).

2.2.2 Secondary Endpoints

2.2.2.1 Safety Endpoints

The safety endpoints of this study are:

1. Adverse events
2. Clinically relevant changes in laboratory parameters (haematology, biochemistry, coagulation, urinalysis, arterial blood gas analysis)
3. Clinically relevant changes in vital signs
4. Clinically relevant changes in physical examination
5. Clinically relevant changes in ECG
6. Number of digital scars (only in patients with scleroderma)
7. Skin score (only in patients with scleroderma)

2.2.2.2 Efficacy Endpoints

The secondary efficacy endpoints of this study are the change from baseline to visit MPV3 in:

8. Pulmonary vascular resistance (PVR), right atrial pressure (RAP), mean pulmonary artery pressure (mPAP), cardiac index (CI) and mixed venous oxygen saturation (S_vO_2). Further haemodynamic parameters may also be calculated if considered appropriate.
9. 6-MWT, including Borg dyspnoea score
10. Biomarker (NT-proBNP)
11. Echocardiogram parameters:
    - Tricuspid regurgitation, classified as absent, mild, moderate or severe
    - Right ventricular contractibility, measured via tricuspid annular plane systolic excursion (TAPSE)
    - Pericardial effusion, classified as absent, traces or present
    - Right atrial area (end-systolic), right ventricular end-diastolic area
12. WHO functional class
13. Quality of life (SF-36v2)

2.2.2.3 Pharmacokinetic Endpoints

14. Apparent total clearance (CL/f)
15. Terminal half-life ($t_{1/2}$)
16. Apparent volume of distribution (Vz/f)

The analysis of PK parameters is covered in a reporting and analysis plan prepared by Quotient Sciences Ltd. (Appendix 4).

2.2.2.4 Pharmacodynamic Endpoints

17. Percent inhibition in plasma DβH activity (i.e. % change from baseline of DβH activity) on visits A3/B3/C3/D3, MPV1 and MPV2 (trough samples) and to visits A1 and MPV3 (24-hour profiles)
18. Maximal and minimal observed effect on DβH activity and time to occurrence of E_{max} (T_{Emax}) and E_{min} (T_{Emin}) on visit A1 (Day 1) and MPV3
19. Area under the effect-time curve (AUEC24) for % DβH inhibition on visit A1 (Day 1) and MPV3
20. Change from baseline 24-hour urinary catecholamine levels (norepinephrine and dopamine) on visits A3/B3/C3/D3 and MPV3.

The analysis of pharmacodynamic parameters is covered in a reporting and analysis plan prepared by Quotient Sciences Ltd. (Appendix 4).

2.3 Overall Study Design

This is an open-label, multi-centre study in patients with PAH who are currently on stable treatment with at least one PAH medication. It is planned to evaluate the PK profile (24-hour profile and trough levels) and the safety, tolerability and efficacy of four different zamicastat doses. Each patient will start treatment with the lowest dose (50 mg zamicastat once daily) and the dose will be up-titrated to the individual **highest tolerated dose** (HTD) i.e. up to 200 mg zamicastat once daily.

A data safety monitoring board (DSMB) will periodically review the safety data and will issue a recommendation if the doses can be used as planned.

This study will consist of:

- A screening period, 5 to 12 days: visit V1
- Up to four dose finding periods, 14 days each:
  - o Dose A: visits A1, A2 and A3
  - o Dose B: visits B2 and B3
  - o Dose C: visits C2 and C3
  - o Dose D: visits D2 and D3
- Maintenance period, 42 days: visits MPV1, MPV2 and MPV3
- Follow-up period:
  - o Visit FU (down-titration): 14 days after MPV3 (only for patients taking 150 mg or 200 mg zamicastat who will not participate in the extension study)
  - o Visit FU: 14 days after last IMP intake

After confirmed eligibility, patients will initiate treatment with Dose A (50 mg zamicastat once daily) at visit A1 and will be treated with this dose level for 14 days. If Dose A was considered safe by the investigator, the patient will be up-titrated to Dose B (100 mg zamicastat once daily) at visit A3 and the patient will continue with this dosage for 14 days. Patients not tolerating Dose A have to be withdrawn from the study.

After a positive safety evaluation at visit B3, the patient will be up-titrated to Dose C (150 mg zamicastat once daily) and the patient will continue on this dose level for a further 14 days. If Dose C was tolerated by the patient, he/she will be up-titrated at visit C3 to Dose D (200 mg zamicastat once daily) where the patient will remain for 56 days (14 days dose finding period + 42 days maintenance period).

Patients not tolerating their next dose at any time during the 14-days dose finding period will come immediately to the site or call the investigator (unscheduled visit), unless intolerance was detected during a scheduled visit and the dose will be down-titrated to the patient's previous tolerated dose. Then they will continue this treatment for 42 days during the maintenance period.

The dose which will be taken during the maintenance period will be considered as an individual HTD.

At the end of the maintenance period, the patient will have the opportunity to continue treatment in an extension study (BIA-51058-202), which is described in a separate protocol.

Patients not tolerating their individual HTD during the maintenance period have to be withdrawn from the study.

2.4 Randomisation

No randomisation will be performed in this study.

2.5 Treatment

The study medication is zamicastat (BIA 5-1058). One tablet of the IMP contains 100 mg of zamicastat.

Each patient will start treatment with 50 mg zamicastat once daily (Dose A) at visit A1 and will be up-titrated step by step to the individual HTD i.e. up to 200 mg zamicastat once daily.

Table 1: Dosage regimen

Daily dose	
Dose A	50 mg (half a tablet of 100 mg)
Dose B	100 mg (one tablet of 100 mg)
Dose C	150 mg (one and a half tablet of 100 mg)
Dose D	200 mg (two tablets of 100 mg)

Each next dose will start after 14 days of treatment if the previous dose was considered safe by the investigator. The up-titration is based on the following safety criteria, including but not limited to:

- Absence of symptomatic and/or clinically relevant orthostatic hypotension
- SBP > 95 mmHg or DBP > 50 mmHg
- Absence of clinically significant changes in ECG parameters (heart rate, P-R interval, QRS duration, QT and QTc interval)
- Absence of clinically significant hypersensitivity/skin allergic reactions

Patients not fulfilling the criteria for up-titration after 14 days of treatment with 50 mg zamicastat have to be withdrawn from the study.

If the patient's next dose will not be tolerated by the patient, the dose has to be down-titrated to his/her previous dose and this dose will be considered as the individual HTD, if tolerated by the patient. Treatment at the individual HTD will be for 42 days during the maintenance period.

Zamicastat has to be taken in the morning after breakfast. The patient must not take the tablet at home on visit days (A3/B3/C3/D3, MPV1, MPV2 and MPV3).

Patients taking 150 mg or 200 mg of zamicastat and who will not participate in the extension study will take 100 mg zamicastat for 14 days.

In case a patient will discontinue the study early due to the occurrence of an AE, down-titration is not mandatory, but at the investigator's discretion.

2.6 Sample Size

The clinical study BIA-51058-201 was designed to explore for the first time the pharmacokinetics, safety and efficacy of zamicastat in PAH patients in its potential therapeutic dose range (50 mg to 200 mg). Since this is an exploratory and descriptive study and no powered comparative statistical analysis is planned, study sample size was not formally calculated. Thus, it was considered that 32 patients constitute an appropriate sample to meet the objectives of the study, considering the low prevalence of the disease and the consequent recruitment constraints.

2.7 Blinding

Blinding is not applicable to this study.

3 ANALYSIS SETS AND SUBGROUPS

3.1 Analysis Sets

Within the framework of this study, the following analysis sets are defined and analysed:

The Enrolled Set (ES) will be defined as all patients who provided informed consent.

The Safety Set (SS) will be defined as all patients who belong to ES with at least one IMP administration.

The Full Analysis Set (FAS) will be defined as all patients who belong to SS with at least one efficacy assessment at visit MPV3.

The modified Full Analysis Set (mFAS) will be defined as all patients who belong to FAS with no substantial changes to their regimen of PAH-approved medications (including diuretics) between visits A1 and MPV3. These patients were defined during Data Review (see Data Review Report, Final 1.0, 10-MAR-2022).

The Pharmacokinetic Analysis Set (PKS) and **the Pharmacodynamic (PD) Analysis Set,** as well as all corresponding analyses, are described in the reporting and analysis plan prepared by Quotient Sciences Ltd.

Efficacy analyses will be performed on the FAS and mFAS, and the SS will be used for the analysis of the safety endpoints.

3.2 Subgroup Analysis

Subgroups will be formed to explore the effects of right ventricular dysfunction at baseline on selected efficacy parameters based on echocardiography results at V1. The subgroups are described in Table 2 below.

Statistical analyses using subgroups will be conducted when specifically referred to in relevant subsections of Section 5, as not every endpoint might need further evaluation using subgroups.

Table 2: Subgroup Labels

Number	Description	Label in TLFs
1	Right ventricular contractility (TAPSE) ≤ 17 mm	TAPSE ≤ 17 mm
2	Right ventricular contractility (TAPSE) > 17 mm	TAPSE > 17 mm

4 GENERAL DEFINITIONS AND NAMING CONVENTIONS

In order to avoid ambiguity during the analysis, a number of definitions and conventions for data handling are described here.

4.1 General Methodology and Presentation of the Results

The default summary statistics for quantitative (continuous) variables will be

- the number of patients (n),
- mean,
- standard deviation (SD),
- coefficient of variation (%CV),
- median,
- minimum (min) and maximum (max)

for patients with data.

Mean and median will be presented to one more decimal place than the raw value. The minimum and maximum values will be presented with the same decimal precision as the raw value. SD will be reported to two decimal places greater than the original value, however no more than 3 decimal places will be presented. CV will be reported to one decimal place.

For qualitative (categorical) variables, the frequency count (n) and percentage (%) of patients with non-missing data per category will be the default frequency tabulations. Where appropriate and present, the number of missing values will be displayed as "Missing" category.

Percentage values are to be presented to one decimal place, for example, 52.3%.

The denominator used for calculation of the percentages will be specified in a footnote to the tables for clarification.

4.2 Statistical Output Layout

All titles and column headers (consisting of one or several words) will be capitalised; articles, prepositions, and conjunctions, and "To" in infinitives will not be capitalised, except they are at the beginning of titles or headers.

All pages will be numbered according to the table/listing/figure to which the page belongs to. Every table/listing/figure will be numbered from page 1, "Page X of Y" at the bottom of each page.

The definition of baseline value will be described in a footnote in every TLF where applicable. Other important definitions will also be presented if necessary.

Dates will be listed in the format: yyyy-mm-dd (e.g. 2003-11-20). Times will be listed in the format: hh:mm (e.g. 09:15) or in the format hh:mm:ss if seconds are collected. When date and time are collected, these are listed in the format: yyyy-mm-ddThh:mm (e.g. 2003-11-20T09:15), yyyy-mm-ddThh, or yyyy-mm-ddThh:mm:ss.

Partial missing dates will be listed in the format yyyy-mm (e.g. 2013-11) if only day is missing or in the format yyyy (e.g. 2013) if month and day are missing.

Missing data including missing dates or times will be displayed in listings as blank fields, unless otherwise specified.

Listings will be sorted by patient's number and visit number where applicable, unless specified otherwise.

4.3 Dose Group Names and Labels

Statistical output for baseline characteristics, as well as visit-based safety and efficacy evaluations, will be presented by dose groups. Patients will be allocated to a particular dose group based on their individual HTD, while patients that do not tolerate the 50 mg dose will be allocated to the "No HTD" group for analysis by HTD.

Adverse events and concomitant medications will be summarised based on the concurrent IMP dose, without allocating patients to separate dose groups. Details of assignment of concurrent IMP doses will be further described in the Sections 5.3 and 5.6.1.

The labels to be used in the tables, listings and figures are defined in the table below.

Table 3: Dose Group Labels

Description	Label in TLFs	
	By Concurrent Dose	By HTD
Dose A: 50 mg zamicastat once daily (half a tablet of 100 mg)	ZMC 50 mg	No HTD
		HTD 50 mg
Dose B: 100 mg zamicastat once daily (one tablet of 100 mg)	ZMC 100 mg	HTD 100 mg
Dose C: 150 mg zamicastat once daily (one and a half tablet of 100 mg)	ZMC 150 mg	HTD 150 mg
Dose D: 200 mg zamicastat once daily (two tablets of 100 mg)	ZMC 200 mg	HTD 200 mg

4.4 Visit Names and Labels

This SAP covers only visits which are part of the core study. The extension study (BIA-51058-202) will be covered in a dedicated SAP. The names to be used in the analysis datasets and the labels to be used in the tables, listings and figures for the different study visits are defined below.

Table 4: Visit Names and Labels

Period	Number	Name	Description	Label in TLFs
Screening	100	Visit 1	Screening visit. Day -12 to -5	V1
Dose finding	110	Visit A1	Day 1	A1
	120	Visit A2	8 days ±2 after A1 (phone call)	A2
	130	Visit A3	14 days ±2 after A1	A3
	220	Visit B2	8 days ±2 after A3 (phone call)	B2
	230	Visit B3	14 days ±2 after A3	B3
	320	Visit C2	8 days ±2 after B3 (phone call)	C2
	330	Visit C3	14 days ±2 after B3	C3
	420	Visit D2	8 days ±2 after C3 (phone call)	D2
	430	Visit D3	14 days ±2 after C3	D3
Maintenance	510	Visit MPV1	13 days ±2 after D3/UV for down-titration	MPV1
	520	Visit MPV2	27 days ±2 after D3/UV for down-titration	MPV2
	530	Visit MPV3	41 days ±2 after D3/UV for down-titration	MPV3
Dose finding/ Maintenance	600	Early Discontinuation Visit	Within 10 days of early discontinuation	EDV
Follow-up	610	Follow-up visit [down-titration]	14 days ±2 after MPV3/EDV (phone call)	FUV1
	620	Follow-up visit	14 days ±2 after last IMP intake	FUV2

Unscheduled visits (UV) will be numbered and labelled based on the preceding scheduled visit, e.g. "UV A1.1" for the first unscheduled visit after the scheduled visit A1. Multiple unscheduled visits after the same scheduled visit will be numbered and labelled sequentially.

For patients attending the extension study, adverse events and concomitant medications will only be displayed up to the end date of visit MPV3.

4.5 Day Numbering

All assessment dates will be related to the date of first IMP intake. The date of first IMP intake is referred to as Day 1. Day –1 is the day preceding Day 1 and Day 0 will not be defined. The numbering is such that Day –2 is the day before Day -1, Day 2 is the day after the first IMP intake, etc.

Treatment days may alternatively be numbered with reference to the ongoing study period using the following rules:

- Dates prior to the first IMP intake will be numbered with reference to the date of first IMP intake as described above.
- Dates after the first IMP intake will be numbered with reference to the first day of the ongoing study period using the same rules as described above. Study days during the dose-finding period will be prefixed with the corresponding dose letter (e.g. C-11 for day 11 on the 150 mg dose), study days in the maintenance period will be prefixed with the letter M, and study days in the post-maintenance periods will be prefixed with "DT" and "FU" for the down-titration period and the follow-up period respectively.

For definitions of the study periods, see section 4.6.

4.6 Study Periods

Screening period

The Screening period will be defined as the period from informed consent signature date to the first IMP intake date.

Dose finding period

The dose finding period will be defined as the period from the date of the first IMP intake to the day before visit D3 or the day before IMP down-titration.

The dose finding period will be split into **dose toleration periods** for each dose prescribed for that period. The period will start from the date of the IMP taken at the site at visit A1/A3/B3/C3 to the day before visit A3/B3/C3/D3 or the day before IMP down-titration.

Maintenance period

The maintenance period will be defined as the period between visit D3 or the date of IMP down-titration and the date of the last IMP intake until MPV3 (including the first day of visit). For patients participating in the extension study, the end of the maintenance period will be the end date of visit MPV3.

Down-titration period

The down-titration period is only applicable to patients not participating in the extension study and with an IMP dispensation at visit MPV3/EDV.

The down-titration period will be defined as the period starting on the second day of MPV3 or one day after visit EDV until the date of the follow-up visit for down titration (FUV1).

Follow-up period

The follow-up period is only applicable to patients not participating in the extension study.

The follow-up period will be defined as the period between the day after the last IMP intake until the date of study termination.

Early discontinuation

For patients who discontinue the study early, the EDV date will be the end date of any ongoing study period.

4.7 Baseline Value

Baseline value

The baseline value for a variable is defined as the last non-missing value collected before the first IMP intake, unless otherwise specified.

See section 5.4.1 Exposure to IMP for definition of first IMP intake.

Absolute change from baseline will be calculated as

$$Absolute\ Change\ from\ Baseline\ at\ Visit\ X = Value\ at\ Visit\ X - Baseline\ Value$$

4.8 Visit Windows

Data will be analysed with the nominal visit number.

4.9 Coding Systems and Conventions

4.9.1 Coding of adverse events and medical history

Adverse event and medical history investigator terms are assigned to a lowest level term (LLT) and a preferred term (PT) and will be classified by high level term (HLT), high level group term (HLGT) and system organ class (SOC) according to the Medical Dictionary for Regulatory Activities (MedDRA), Version 22.0 or higher.

4.9.2 Coding of medications

Medications are classified according to active drug substance using the WHO Drug Global dictionary, version 2019, March, or higher. The WHO drug code has 11 digits. The generic name is defined by the first 6 of the 11 digits. In addition, the Anatomical Therapeutic Chemical (ATC) classes are assigned to the drug code. In this study, ATC codes are defined to the 4th level.

4.10 Handling of Missing Data

No imputations of missing data are planned for this study.

5 STATISTICAL ANALYSIS: DEFINITIONS, DERIVATIONS, CALCULATIONS AND METHODOLOGY

5.1 Patient Disposition

5.1.1 Disposition and Withdrawals

The following disposition data will be collected in the electronic case report form (eCRF):

- date of informed consent
- date of study termination
- did the patient complete the study as scheduled (yes, no)
- will the patient participate in the extension study (yes, no)
- reason for premature study termination

Screening failures will be all patients who have been enrolled in the study (i.e. ICF signed) but discontinue the study before the first IMP intake at visit A1 due to whatever reason (withdrew consent, did not fulfil eligibility criteria, decision of investigator, etc.).

Withdrawals will be all patients who have been enrolled and, for whatever reason, discontinue the study after the first IMP intake at visit A1. Patients may withdraw or may be withdrawn from the study for the following reasons:

- At their own request (withdrawal of consent)
- In the investigator's opinion, for reasons of safety or ethics, continuation in the study would be detrimental to the patient's well-being
- Pregnancy
- Ineligibility/development of an exclusion criterion or inclusion criterion no longer fulfilled
- Intolerable adverse event(s)
- At the specific request of the sponsor
- Major protocol deviations
- Patient non-compliance
- Lost to follow up
- Other reasons

Study completion status will be determined by patient's decision to participate in the extension study. If the question "Will the patient participate in the extension study?" in the eCRF is answered as "Yes", the patient will be considered as a completer. If the patient does not participate in the extension study, then the completion status will be based on the Study Termination page in the eCRF.

The following statistical output will be provided:

Table 15.1.1.1 Analysis Sets – Enrolled Set
Number and percentage of patients included into the enrolled, safety, full analysis, modified full analysis, pharmacokinetic, and pharmacodynamic analysis sets will be provided.

Table 15.1.1.2 Reasons for Exclusions from Analysis Sets – Safety Set
Number and percentage of patients excluded from the full analysis, modified full analysis, pharmacokinetic, and pharmacodynamic analysis sets will be provided. Percentages will be based on the number of patients in the safety set. The reasons of exclusion from the analysis sets will be incorporated into the table.

Table 15.1.2 Screening Failures – Enrolled Set
Counts and percentages of patients who discontinued the study during the screening phase prior to enrolment to the treatment period will be summarised by reasons associated with the discontinuation. Percentage will be based on the number of patients in the enrolled set.

Table 15.1.4 Patient Disposition – Safety Set
Counts and percentages of patients who completed the treatment period as scheduled, withdrawals during the treatment period will be summarised by HTD and overall. Reasons associated with the termination will be included. Percentage will be based on the number of patients in the safety set.

Table 15.1.5.1.1 Number of Patients by Country and Site – Enrolled Set
Table 15.1.5.1.2 Number of Patients by Country and Site – Safety Set
Counts and percentages of patients will be presented by country and by site. Percentage will be based on the number of patients in the specified set.

Table 15.1.5.2 Number of Patients by Visit – Safety Set
Counts and percentages of patients who continue the study will be presented by visit. Percentage will be based on the number of patients in the safety set.

Listing 16.2.1.1.1 Patient Disposition – Safety Set
Patients who enter the treatment period and complete the study as scheduled or as withdrawals will be listed. Reasons for premature study termination will be displayed for withdrawals.

Listing 16.2.1.1.2 Screening Failures – Enrolled Set
Patients who discontinued the study during the screening phase prior to enrolment to the treatment period will be listed. Reasons associated with the discontinuation will be displayed.

Listing 16.2.1.2 Patient Visits – Enrolled Set
All visit dates will be listed by patient.

Listing 16.2.1.4 Exclusions from Analysis Sets – Enrolled Set
Patients excluded from any analysis set and corresponding reasons for exclusion will be listed.

Figure 15.1.1 Flow Chart of Patient Disposition – Enrolled Set
Number of patients will be displayed in flow chart by their disposition.

Figure 15.1.2 Flow Chart of Analysis Sets – Enrolled Set
Number of patients will be displayed in flow chart by analysis sets.

5.1.2 Protocol Deviations

Protocol deviations are deviations from the procedures outlined in the clinical study protocol or from subsequent protocol-related instructions like missed evaluations, incorrect timing of evaluations, non-compliance with IMP and intake of prohibited medications or any non-adherence to the clinical study protocol that impacts patient's rights, safety or welfare. Protocol deviations that may affect the pharmacokinetic and pharmacodynamic outcomes will be discussed during the Data Review Meeting (DRM).

In addition, the study disruption due to the COVID-19 pandemic will be assessed in terms protocol deviations and discussed during the DRM. A separate listing for patients affected by the COVID-19 related study disruption will be provided.

Details regarding the DRM will be provided in Section 6.

The following statistical output will be provided:

Table 15.1.3 Major Protocol Deviations – Safety Set
Number and percentage of patients with major protocol deviations will be summarised by HTD and overall. Protocol deviations will be summarised during the dose finding and maintenance periods and overall. Percentage will be based on the number of patients in the safety set.

Listing 16.2.1.3.1 Major Protocol Deviations – Safety Set
Patients with major protocol deviations will be listed.

Listing 16.2.1.3.2 Patients Affected by the COVID-19 Pandemic – Safety Set
Patients that were affected by the COVID-19 pandemic as well as the details of the deviation will be listed.

5.1.3 Inclusion/Exclusion

The study specific Inclusion/Exclusion Criteria are presented in Section 9.2 and 9.3 of the Clinical Study Protocol.

For each criterion, as appropriate, a response of "Yes/No" is to be obtained at Screening and checked again prior to the first IMP administration, at visit A1.

The following statistical output will be provided:

Listing 16.2.1.3.3 Inclusion Criteria Not Met and Exclusion Criteria Met – Enrolled Set
Listing of inclusion criteria which were not met and exclusion criteria which were met will be presented per patient.

5.2 Demographic and Other Baseline Characteristics

5.2.1 Demographics

The following demographic characteristics will be presented:

- Age (years)
- Gender (Male, Female)
- Race (White, Black or African American, Asian, American Indian or Alaska Native, Native Hawaiian or Other Pacific Islander, Unknown)
- Women of childbearing potential (Yes, No)

Also, the following physical characteristics at baseline will be presented:

- Height (cm)
- Weight (kg)
- Body mass index BMI (kg/m^2)

Body mass index (BMI) will be calculated as follows:

$$BMI\ at\ Visit\ X\ (kg/m^2) = \frac{Body\ weight\ at\ Visit\ X\ (kg)}{[Body\ height\ at\ Visit\ 1\ (m)]^2}$$

The following statistical output will be provided:

Table 15.1.6.1.1 Demographics – Safety Set
Table 15.1.6.1.2 Demographics – Full Analysis Set
Table 15.1.6.1.3 Demographics – Pharmacokinetic Analysis Set
Demographic data will be summarised by HTD and overall in the respective set. Percentage for categorical variables will be based on the respective set.

Table 15.1.6.2.1 Baseline Characteristics – Safety Set
Table 15.1.6.2.2 Baseline Characteristics – Full Analysis Set
Table 15.1.6.2.3 Baseline Characteristics – Pharmacokinetic Analysis Set
Weight, height and BMI data will be summarised by HTD and overall in the respective set.

Listing 16.2.1.5 Demographics and Baseline Characteristics – Enrolled Set
Demographic and baseline characteristic data will be listed for the patients in the enrolled set.

5.2.2 Disease Characteristics

The following information on patient PAH status at baseline will be presented:

- WHO functional class at baseline (see Section 5.5.5)
- The cause of PAH:
  - Idiopathic, in non-vasoreactive patients
  - Heritable: Bone morphogenetic protein receptor type II (BMPR2) mutation and other mutations, in non-vasoreactive patients
  - Drugs and toxin induced, in non-vasoreactive patients
  - Associated with connective tissue disease
  - Associated with simple congenital defects (atrial septal defect and/or ventricular septal defect) if closed > 12 months before inclusion
- Does the patient suffer from scleroderma? (yes, no)

The following statistical output will be provided:

Table 15.1.6.3.1 Disease Characteristics – Safety Set
Table 15.1.6.3.2 Disease Characteristics – Full Analysis Set
Table 15.1.6.3.3 Disease Characteristics – Pharmacokinetic Analysis Set
Disease characteristics data will be presented by HTD and overall in the respective set. Percentage for categorical variables will be based on the number of patients in the respective analysis set.

Listing 16.2.1.6 Disease Characteristics – Enrolled Set
Disease characteristics data will be listed for the patients in the enrolled set.

5.2.3 Medical History

Medical history encompasses relevant prior or ongoing relevant diseases, conditions, hospitalisation and surgical procedures. Medical history records are collected at Visit 1.

Medical history of the patients includes:

- Medical condition/procedure
- Start date
- Stop date
- Ongoing
- Treatment used (yes, no)

Medical history is classified as:

- **Prior medical conditions** are the conditions which started and ended prior to Visit 1.
- **Ongoing medical conditions** are the conditions which are marked as ongoing at Visit 1 or with a stop date at or after Visit 1

In case of partial missing stop dates, a disease will be considered as ongoing at Visit 1, unless the partial date information clearly indicates that the condition stopped prior to Visit 1.

The following statistical output will be provided:

Table 15.1.7.1.1 Prior Medical Conditions – Safety Set
Table 15.1.7.1.2 Prior Medical Conditions – Full Analysis Set
Table 15.1.7.1.3 Prior Medical Conditions – Pharmacokinetic Analysis Set
Table 15.1.7.2.1 Ongoing Medical Conditions – Safety Set
Table 15.1.7.2.2 Ongoing Medical Conditions – Full Analysis Set
Table 15.1.7.2.3 Ongoing Medical Conditions – Pharmacokinetic Analysis Set
Medical history will be summarised displaying counts and percentages of patients having at least one medical condition and will be presented by Primary System Organ Class (SOC) and by Preferred Term (PT) within SOC. SOCs and PT within SOC are to be sorted by descending order of overall incidence. Patients with two or more occurrences of the same condition (as qualified by its PTs) will be counted only once for the respective PT. Percentage will be based on the number of patients in the corresponding analysis set.

Listing 16.2.1.7 Medical History – Enrolled Set
Medical history conditions will be listed for the patients from the enrolled set

5.3 Prior and Concomitant Medications

Prior and concomitant medications and therapies are documented in the eCRF.

The following information is collected:

- Medication / therapy
- Indication (Medical history condition, Adverse event, Other)
- Total daily dose
- Units
- Route

- Frequency
- Start date of medication
- Stop date of medication
- Ongoing (yes, no)

Medications and therapies will be classified as 'prior', 'concomitant' or 'post-treatment' based on start/stop dates:

- **Prior medications/therapies** are defined as those medications/therapies starting and ending prior to the first IMP intake.
- **Concomitant medications/therapies** are defined as medications/therapies started at or after first IMP intake and include medications/therapies started prior to the first IMP intake but continued during the study.
- **Post-treatment medications/therapies** are defined as medications/therapies which started after the last IMP intake.

If the start or stop date of a medication/therapy is incomplete or missing, it will be assumed to be concomitant except if the incomplete start or stop date indicates that the medication/therapy started and ended prior to the first IMP intake or started after the last IMP intake.

PAH medications will be defined as medications where the preferred term for the indication is "pulmonary arterial hypertension", "congenital pulmonary hypertension", or "pulmonary hypertension", as well as any other medications taken for a condition related to PAH. These medications were selected manually during the Data Review (see Data Review Report, Final 1.0, 10-MAR-2022).

In addition, **PAH-approved** medications will be defined as those medications described in the protocol as being an approved PAH therapy (Ambrisentan, Bosentan, Macitentan, Riociguat, Selexipag, Sildenafil, Tadalafil, Epoprostenol intravenous, Iloprost inhaled or Treprostinil intravenous or subcutaneous) and diuretics. PAH-approved medications were selected manually during the Data Review (see Data Review Report, Final 1.0, 10-MAR-2022).

PAH-approved medications will be combined into groups of monotherapy, double therapy, triple therapy, etc., based on the number of PAH-approved medications taken at a given timepoint.

Concomitant medications will be assigned to IMP dose groups based on the prescribed IMP dose at the time of medication intake. If the start or end date indicates that the medication was taken concurrently with multiple doses, it will be assigned to every corresponding dose. If the start or end date is incomplete such that it could belong to more than one dose, the concomitant medication will be assigned to all such doses.

The following statistical output will be provided:

Table 15.1.8.1.1 Prior Medications – Safety Set
Table 15.1.8.1.2 Prior Medications – Full Analysis Set
Table 15.1.8.1.3 Prior Medications – Pharmacokinetic Analysis Set
Table 15.1.8.2.1 Concomitant Medications – Safety Set
Table 15.1.8.2.2 Concomitant Medications – Full Analysis Set
Table 15.1.8.2.3 Concomitant Medications – Pharmacokinetic Analysis Set
The number and percentage of patients with at least one medication within each ATC 2nd level subgroup. Substance name (or combination of substances) will be presented by HTD for prior medication, by dose for concomitant medications and overall in the corresponding analysis set. The ATC 2nd level subgroups and substance drug name within ATC 2nd level subgroup will be ordered by descending overall incidence. Medications that differ at the substance drug name level but belong to the same therapeutic category will be combined.

Table 15.1.8.3.1 Prior PAH Medications – Safety Set
Table 15.1.8.3.2 Prior PAH Medications –Full Analysis Set
Table 15.1.8.3.3 Prior PAH Medications – Pharmacokinetic Analysis Set
Table 15.1.8.4.1 Concomitant PAH Medications – Safety Set
Table 15.1.8.4.2 Concomitant PAH Medications – Full Analysis Set
Table 15.1.8.4.3 Concomitant PAH Medications – Pharmacokinetic Analysis Set
Medications for pulmonary arterial hypertension will be summarised as above.

Table 15.1.8.5.1 PAH-Approved Therapy by Visit – Safety Set
Table 15.1.8.5.2 PAH-Approved Therapy by Visit – Full Analysis Set
Table 15.1.8.5.3 PAH-Approved Therapy by Visit – Pharmacokinetic Analysis Set
The number and percentage of patients with PAH-approved monotherapy, double therapy, and triple therapy will be summarised at visits A1 and MPV3. The substance names for each therapy combination will be presented by HTD and overall in the corresponding analysis set.

Listing 16.2.1.8 Medications and Therapies – Enrolled Set
All medications, prior, concomitant and subsequent, will be listed for the patients from the enrolled set.

5.4 Exposure to IMP and Compliance

5.4.1 Exposure to IMP

Exposure data from the eCRF include:

- First IMP intake
- Last IMP intake before the visit (except unscheduled visits)
- IMP intake at the site (except unscheduled visits)
- Last IMP intake (for withdrawals and patients that do not participate in the extension study)
- Date of IMP down-titration

The overall treatment duration in days will be calculated as follows:

$$Overall\ treatment\ duration\ (days) = last\ IMP\ intake\ date - first\ IMP\ intake\ date + 1$$

The following definitions will be used to calculate the overall treatment duration:

- **The date of the first IMP intake** is the date of the IMP intake as recorded at visit A1.
- **The date of the last IMP intake** depends on the patient's decision to participate in the extension study. If the patient is not participating in the extension study, then the last IMP intake is the date of the last intake recorded at the study termination page. If the patient is participating in the extension study, then the on-site IMP intake at MPV3 will be the date of the last IMP intake.

The duration of the study periods in days will be calculated as follows:

$$Treatment\ period\ duration\ (days) = treatment\ period\ end\ date\ - treatment\ period\ start\ date + 1$$

See Section 4.6 for definitions of study periods.

Overall and by-period treatment duration will be adjusted in the case of occurrence of adverse events with associated IMP interruption periods. The calendar days between and including start and stop dates of IMP interruptions will not count towards treatment duration.

The following statistical output will be provided:

Table 15.1.9.1.1 Treatment Duration (days) – Safety Set
Table 15.1.9.1.2 Treatment Duration (days) – Full Analysis Set
Table 15.1.9.1.3 Treatment Duration (days) – Pharmacokinetic Analysis Set
The default summary statistics of treatment duration will be presented by HTD and overall.

5.4.2 Compliance

The following compliance-related data will be collected in the eCRF:

- date of IMP dispensation
- prescribed IMP dose
- number of tablets dispensed
- dispensed IMP bottle number
- toleration of IMP dose (Yes, No)
- date of IMP down-titration
- date of IMP return
- number of tablets returned
- returned IMP bottle number

The calculation of the compliance will be based on the total number of tablets prescribed, dispensed and returned overall or during particular study period (for definitions of study periods, see Section 4.6).

The total number of tablets prescribed will be calculated as the prescribed daily number of tablets based on the dose (see Section 2.5) multiplied by the length of the dose prescription in calendar days. The total number of prescribed tablets will be adjusted in the case of occurrence of adverse events with associated IMP interruption periods.

The total number of tablets dispensed and returned will be calculated as the sum of all tablets dispensed and all tablets returned during the corresponding study period. The total number of tablets returned will be considered as missing if not all dispensed bottles are returned in the same corresponding period or the returned bottle(s) is from the previous period.

The overall compliance and compliance during each treatment period will be calculated as:

$$Compliance\ \ (\%) = \frac{100 \times (tablets\ dispensed - tablets\ returned)}{tablets\ prescribed}$$

In case an IMP bottle is not returned, the overall compliance will be considered as missing.

The following statistical output will be provided:

Table 15.1.9.2.1 Compliance (%) – Safety Set
Table 15.1.9.2.2 Compliance (%) – Full Analysis Set
Table 15.1.9.2.3 Compliance (%) – Pharmacokinetic Analysis Set
The default summary statistics of compliance will be presented by HTD and overall for the respective analysis set. Number and percentage of patients will also be summarised by compliance categories (< 90%, ≥ 90% and ≤ 110%, >110%) for the respective analysis set.

Listing 16.2.2.1 Drug Accountability – Safety Set
Information related drug accountability will be listed for the patients from the safety set.

Listing 16.2.2.2 Exposure to IMP and Compliance – Safety Set
Information related exposure to IMP and compliance will be listed for the patients from the safety set.

5.5 Analysis of Efficacy Endpoints

The following efficacy related secondary endpoints will be calculated and analysed:

- Right heart catheterisation parameters
- 6-MWT, including Borg dyspnoea score
- Biomarker (NT-proBNT)
- Echocardiogram parameters
- NYHA/WHO functional class
- Quality of life (SF-36v2)

Efficacy data will be analysed exploratively. Continuous measures will be summarised using summary statistics, in addition for the changes from baseline a 95% confidence interval will be provided. Categorical variables will be summarised by using frequency counts and percentages.

5.5.1 Right Heart Catheterisation

Right heart catheterisation (RHC) will be performed at visit A1 and at visit MPV3 before IMP intake to determine the change of haemodynamic parameters in the patients. If available, results from a right heart catheterisation within 90 days before V1 may be used in place of the V1 measurement. The following haemodynamic parameters will be collected:

- Cardiac output (L/min) **(CO)**
- Mixed venous oxygen saturation (%) **(S_vO_2)**
- Pulmonary artery pressure systolic (mmHg) **(PAPs)**
- Pulmonary artery pressure diastolic (mmHg) **(PAPd)**
- Mean pulmonary artery pressure (mmHg) **(mPAP)**
- Pulmonary artery wedge pressure (mmHg) **(PAWP)**
- Right atrial pressure (mmHg) **(RAP)**
- Transpulmonary pressure gradient (mmHg) **(TPG)**
- Diastolic pressure gradient (mmHg) **(DPG)**
- Pulmonary vascular resistance (dyn*s/cm^5) **(PVR)**
- Systemic ventricular resistance (dyn*s/cm^5) **(SVR)**
- Cardiac index (L/min/m^2) **(CI)**
- Pulmonary arterial compliance (mL/mmHg) **(PAC, SV/PP)**
- Heart rate (bpm)
- Stroke volume (mL/beat) **(SV)**
- Stroke volume index (mL/m^2/beat) **(SVI)**

The derived parameters **mPAP**, **TPG**, **DPG**, **PVR**, **PAC**, **SV**, and **SVI** will be recalculated from other parameters using standardised formulae below.

$$mPAP = PAPd + (PAPs - PAPd)/3$$

$$TPG = mPAP - PAWP$$

$$DPG = PAPd - PAWP$$

$$PVR = (mPAP - PAWP)/CO \cdot 80$$

$$PAC = SV/(PAPs - PAPd)$$

$$SV = CO/HR \cdot 1000$$

$$SVI = CI/HR \cdot 1000$$

The recalculated parameter values will be used in summaries and listings.

The clinical significance (yes/no) of any abnormal right heart catheterisation findings will be assessed by the investigator.

Post-DR note: Clinical significance as assessed by the investigator will not be used for statistical analyses (see Data Review Report, Final 1.0, 10-MAR-2022). Instead, right heart catheterisation results

will be assigned a "Low", "Normal" or "High" value according to ranges defined by Table 4. The ranges are based on the Data Validation Plan (Final 3.0, 21-JUL-2020).

Table 5: Right Heart Catheterisation Normal Ranges

Parameter	**Normal Range**
Cardiac output (L/min) **(CO)**	2.5-8.0
Mixed venous oxygen saturation (%) **(S_vO_2)**	60-80
Pulmonary artery pressure systolic (mmHg) **(PAPs)**	25-80
Pulmonary artery pressure diastolic (mmHg) **(PAPd)**	8-16
Mean pulmonary artery pressure (mmHg) **(mPAP)**	≥25
Pulmonary artery wedge pressure (mmHg) **(PAWP)**	≤15
Right atrial pressure (mmHg) **(RAP)**	<14
Transpulmonary pressure gradient (mmHg) **(TPG)**	>12
Diastolic pressure gradient (mmHg) **(DPG)**	>6
Pulmonary vascular resistance (dyn*s/cm^5) **(PVR)**	250-1000
Systemic vascular resistance (dyn*s/cm^5) **(SVR)**	800-1200
Cardiac index (L/min/m^2) **(CI)**	>2
Pulmonary arterial compliance (mL/mmHg) **(PAC; SV/PP)**	0.4-3.8
Heart rate (bpm)	50-100
Stroke volume (mL/beat) **(SV)**	>50
Stroke volume index (mL/m^2/beat) **(SVI)**	>30

Recalculated results will be used for applicable parameters.

The following statistical output will be provided:

Table 15.2.1.1.1 Summary of Right Heart Catheterisation Parameters by HTD – Full Analysis Set
Table 15.2.1.1.2 Summary of Right Heart Catheterization Parameters – Full Analysis Set
Table 15.2.1.1.3 Summary of Right Heart Catheterisation Parameters by HTD – Modified Full Analysis Set
Table 15.2.1.1.4 Summary of Right Heart Catheterization Parameters – Modified Full Analysis Set
The default summary statistics of RHC test results will be presented by HTD and overall at visits A1 and MPV3. The absolute change from baseline will be presented as well. For the changes from baseline a 95% confidence interval will be provided.

Table 15.2.1.1.5 Summary of Right Heart Catheterization Parameters – Modified Full Analysis Set (TAPSE Subgroups)
The default summary statistics of RHC parameters PVR, mPAP, RAP, and CI will be presented by TAPSE subgroup and overall at visits A1 and MPV3. The absolute change from baseline will be presented as well. For the changes from baseline a 95% confidence interval will be provided.

Table 15.2.1.2.1 Incidence of Right Heart Catheterisation Abnormalities – Full Analysis Set
Table 15.2.1.2.2 Incidence of Right Heart Catheterisation Abnormalities – Modified Full Analysis Set
Number and percentage of patients with abnormal values will be displayed by HTD and overall in not CS abnormal and CS abnormal categories. Percentage will be based on the number of patients at specified visit.

Table 15.2.1.3.1 Shift Table of Right Heart Catheterisation Results – Full Analysis Set
Table 15.2.1.3.2 Shift Table of Right Heart Catheterisation Results – Modified Full Analysis Set
Shift tables showing changes in the number and frequency of patients in not CS abnormal and CS abnormal categories between baseline and MPV3 will be provided.

Listing 16.2.3.1 Right Heart Catheterisation Parameters – Enrolled Set
Values of parameters of right heart catheterisation will be listed.

5.5.2 6-Min Walk Test (6-MWT)

The 6-MWT is a self-paced test of walking capacity used to assess aerobic capacity and endurance. It plays a key role in evaluation functional exercise capacity, assessing prognosis and evaluating response to treatment across a wide range of respiratory diseases. The distance covered over a time of 6 minutes is used as the outcome by which to compare changes in performance capacity.

The test will be performed at visit V1 before IMP intake and at visit MPV3 before right heart catheterisation.

At screening, two attempts must be performed, separated by at least 30 minutes. The attempt in which the longer distance was covered will be considered as baseline. In case the distance covered during both attempts is equal, the first attempt will be considered as baseline.

The following parameters will be collected:

- SpO_2 (%) – before and after the test
- Borg Dyspnoea score – before and after the test
- Heart rate (bpm) – before and after the test
- Lap length (m)
- Number of laps completed
- Distance covered (m)
- Time walking (min)
- Oxygen flow rate (L/min)
- Number of stops
- Time stopped (min)

The Borg Dyspnoea score is a patient-reported measure for assessing breathlessness. Symptoms of breathlessness are rated on a scale of 0-10, where 0 indicates no symptoms and 10 indicates the most severe breathlessness.

The differences in SpO_2, the Borg Dyspnoea score, and heart rate between after and before the test will be calculated. These differences will be displayed as additional parameters in summaries.

The following statistical output will be provided:

Table 15.2.2.1 Summary of 6-MWT by HTD – Full Analysis Set
Table 15.2.2.2 Summary of 6-MWT – Full Analysis Set
Table 15.2.2.3 Summary of 6-MWT by HTD – Modified Full Analysis Set
Table 15.2.2.4 Summary of 6-MWT – Modified Full Analysis Set
The default summary statistics of 6-MWT test results will be presented by HTD and overall at visits V1 and MPV3. The absolute change from baseline will be presented as well. For the changes from baseline a 95% confidence interval will be provided.

Table 15.2.2.5 Summary of 6-MWT Distance – Modified Full Analysis Set (TAPSE Subgroups)
The default summary statistics of 6-MWT distance travelled will be summarised by TAPSE subgroup and overall at visits V1 and MPV3. The absolute change from baseline will be presented as well. For the changes from baseline a 95% confidence interval will be provided.

Listing 16.2.3.2-Min Walk Test – Enrolled Set
Values of parameters of 6-Min walk test will be listed.

5.5.3 Biomarker

Blood samples will be collected for biomarker NT-proBNP (pg/mL) evaluation at visits V1 and MPV3. NT-proBNP will be summarized in the unit ng/L for statistical output. No derivations are needed as the conversion factor between these units is 1.

The following statistical output will be provided:

Table 15.2.3.1.1 Summary of Biomarker NT-proBNP (ng/L) by HTD – Full Analysis Set
Table 15.2.3.1.2 Summary of Biomarker NT-proBNP (ng/L) – Full Analysis Set
Table 15.2.3.1.3 Summary of Biomarker NT-proBNP (ng/L) by HTD – Modified Full Analysis Set
Table 15.2.3.1.4 Summary of Biomarker NT-proBNP (ng/L) – Modified Full Analysis Set
The default summary statistics of biomarker NT-proBNP will be presented by HTD and overall at visits V1 and MPV3. The absolute change from baseline will be presented as well. For the changes from baseline a 95% confidence interval will be provided.

Table 15.2.3.2.1 Summary of Biomarker NT-proBNP (ng/L) by Pooled HTD –Full Analysis Set
Table 15.2.3.2.2 Summary of Biomarker NT-proBNP (ng/L) by Pooled HTD – Modified Full Analysis Set
Biomarker NT-proBNP will be summarised as above, with HTD pooled into "HTD < 200 mg" and "HTD 200 mg" groups.

Figure 15.2.1.1 Box-Whisker Plot of NT-proBNP by Pooled HTD – Full Analysis Set
Figure 15.2.1.2 Box-Whisker Plot of NT-proBNP by Pooled HTD – Modified Full Analysis Set
Box-whisker plots of NT-proBNP will be displayed by HTD at visits V1 and MPV3. The HTD will be pooled into "HTD < 200 mg" and "HTD 200 mg" groups. Summary statistics will be displayed below each box.

Listing 16.2.3.3 Biomarker NT-proBNP – Enrolled Set
Values of biomarker NT-proBNP will be listed.

5.5.4 Echocardiography

Transthoracic echocardiography is used to image the effects of PAH on the heart. An echocardiogram (ECHO) will be performed at Visit 1 and MPV3.

The following parameters will be determined:

- Tricuspid regurgitation (absent, mild, moderate or severe)
- Right ventricular contractility (TAPSE) (mm)
- Pericardial effusion (absent, traces or present)
- Right atrial area (end-systolic) (cm^2)
- Right ventricular end-diastolic area (cm^2)

The clinical significance (yes/no) of any abnormal ECHO findings will be assessed by the investigator.

The following statistical output will be provided:

Table 15.2.4.1.1 Summary of Categorical Echocardiography Parameters – Full Analysis Set
Table 15.2.4.1.2 Summary of Categorical Echocardiography Parameters – Modified Full Analysis Set
Number and percentage of patients will be displayed by HTD and overall at visits V1 and MPV3. Percentage will be based on the number of patients at the specified visit.

Table 15.2.4.2.1 Summary of Numerical Echocardiography Parameters by HTD – Full Analysis Set
Table 15.2.4.2.2 Summary of Numerical Echocardiography Parameters – Full Analysis Set
Table 15.2.4.2.3 Summary of Numerical Echocardiography Parameters by HTD – Modified Full Analysis Set
Table 15.2.4.2.4 Summary of Numerical Echocardiography Parameters – Modified Full Analysis Set
The default summary statistics of ECHO parameters will be presented by HTD and overall at visits V1 and MPV3. The absolute change from baseline will be presented as well. For the changes from baseline a 95% confidence interval will be provided.

Table 15.2.4.2.5 Summary of Numerical Echocardiography Parameters – Modified Full Analysis Set (TAPSE Subgroups)
The default summary statistics of ECHO parameters will be presented by TAPSE subgroup and overall at visits V1 and MPV3. The absolute change from baseline will be presented as well. For the changes from baseline a 95% confidence interval will be provided.

Table 15.2.4.3.1 Incidence of Echocardiography Abnormalities – Full Analysis Set
Table 15.2.4.3.2 Incidence of Echocardiography Abnormalities – Modified Full Analysis Set
Number and percentage of patients will be displayed by HTD and overall in Not CS abnormal and CS abnormal categories. Percentage will be based on the number of patients at the specified visit.

Table 15.2.4.4.1 Shift Table of Echocardiography Results – Full Analysis Set
Table 15.2.4.4.2 Shift Table of Echocardiography Results – Modified Full Analysis Set
Shift tables showing changes in the number and frequency of patients in Not CS abnormal and CS abnormal categories between V1 and MPV3 visits will be provided.

Listing 16.2.3.4 Echocardiography – Enrolled Set
Values of echocardiography tests will be listed.

5.5.5 New York Heart Association/Word Health Organisation Functional Class (NYHA/WHO)

Classification of functional status of patients will be performed at Visit 1 and at visit MPV3/EDV by the investigator by using the NYHA/WHO classification system defined below.

Table 6:NYHA/WHO Classes

Class	Description
Class I	Patients with pulmonary hypertension but without resulting limitation of physical activity. Ordinary physical activity does not cause undue dyspnoea or fatigue, chest pain or near syncope.
Class II	Patients with pulmonary hypertension resulting in a slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity causes undue dyspnoea or fatigue, chest pain or near syncope.
Class III	Patients with pulmonary hypertension resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes undue dyspnoea or fatigue, chest pain or near syncope.
Class IV	Patients with pulmonary hypertension with inability to carry out any physical activity without symptoms. These patients' manifest signs of right heart failure. Dyspnoea and/or fatigue may even

The following statistical output will be provided:

Table 15.2.5.1.1 Summary of NYHA/WHO Functional Class – Full Analysis Set
Table 15.2.5.1.2 Summary of NYHA/WHO Functional Class – Modified Full Analysis Set
Number and percentage of patients will be displayed by HTD and overall in each NYHA/WHO functional class. Percentage will be based on the number of patients at the specified visit.

Table 15.2.5.2.1 Shift Table of NYHA/WHO Functional Class – Full Analysis Set
Table 15.2.5.2.2 Shift Table of NYHA/WHO Functional Class – Modified Full Analysis Set
Shift tables showing changes in the number and frequency of patients with respect to the NYHA/WHO functional class between V1 and MPV3/EDV will be provided.

Listing 16.2.3.5 NYHA/WHO Functional Class – Enrolled Set
NYHA/WHO functional class data will be listed by visit.

5.5.6 Quality of Life (SF-36v2)

The 36-item Short Form Survey version 2 (SF-36v2) is used to assess the quality of life. The questionnaire will be completed by the patient at Visit 1 and at MPV3.

SF-36v2 asks 36 questions (items) to measure functional health and well-being from the patient's point of view. All but one (question 2) of the 36 items will be used to score the eight SF-36v2 health domains:

- Physical Functioning (PF)
- Role Limitations due to Physical Health (RP)
- Bodily Pain (BP)
- General Health (GH)
- Vitality (VT)
- Social Functioning (SF)
- Role Limitations due to Emotional Health (RE)
- Mental Health (MH).

A total score will be calculated for each SF-36v2 health domain by taking the sum of the corresponding responses and rescaling it to a range of 0 to 100, where 100 represents the best possible result. Each domain will then be standardised using a general population norm.

The scores of the eight health domains will be used to calculate a physical component summary (PCS) and mental component summary (MCS) score using coefficients based on a principal components analysis of the SF-36v2 domain scores in the general population. The PCS and MCS are summary measures that represent the overall physical and mental health of the patient, with higher scores representing better outcomes.

A subset of items from six domains (PF, RE, SF, BP, MH, VT) will be used to calculate a Utility Index Score, which rates the overall health state from 0.0 (worst health state) to 1.0 (best health state). The updated (SF-6D R2) Utility Index Score will be summarised.

Optum PRO CoRE will be used to generate the following scores:

- SF-36v2 domain scores (0-100 scale)
- SF-36v2 domain scores based on the 2009 US general population norms
- PCS and MCS scores based on the 2009 US general population norms
- SF-6D R2

In addition, interpretations for the norm-based SF-36v2 health domains and PCS and MCS scores will be provided based on benchmarks from the general population cardiac patients:

- "Well Below", if the norm-based score is 10 points or more below the benchmark;
- "Below", if the norm-based score is from 5 to 9 points below the benchmark;
- "Same or Better", if the norm-based score is less than 5 points below the benchmark.

The following statistical output will be provided:

Table 15.2.6.1.1 Summary of SF-36v2 Domain Scores by HTD – Full Analysis Set
Table 15.2.6.1.2 Summary of SF-36v2 Domain Scores – Full Analysis Set
Table 15.2.6.1.3 Summary of SF-36v2 Domain Scores by HTD – Modified Full Analysis Set
Table 15.2.6.1.4 Summary of SF-36v2 Domain Scores – Modified Full Analysis Set
The default summary statistics of SF-36v2 results will be presented by HTD and overall at visits V1 and MPV3. The absolute change from baseline will be presented as well. For the changes from baseline a 95% confidence interval will be provided.

Table 15.2.6.2.1 Summary of Norm-Based SF-36v2 Domain Scores by HTD – Full Analysis Set
Table 15.2.6.2.2 Summary of Norm-Based SF-36v2 Domain Scores– Full Analysis Set
Table 15.2.6.2.3 Summary of Norm-Based SF-36v2 Domain Scores by HTD – Modified Full Analysis Set
Table 15.2.6.2.4 Summary of Norm-Based SF-36v2 Domain Scores – Modified Full Analysis Set
The default summary statistics of SF-36v2 results based on 2009 US norms will be presented by HTD and overall at visits V1 and MPV3. The absolute change from baseline will be presented as well. For the changes from baseline a 95% confidence interval will be provided.

Table 15.2.6.3.1 Summary of SF-36v2 Utility Index Scores by HTD – Full Analysis Set
Table 15.2.6.3.2 Summary of SF-36v2 Utility Index Scores – Full Analysis Set
Table 15.2.6.3.3 Summary of SF-36v2 Utility Index Scores by HTD – Modified Full Analysis Set
Table 15.2.6.3.4 Summary of SF-36v2 Utility Index Scores – Modified Full Analysis Set
The default summary statistics of Utility Index scores will be presented by HTD and overall at visits V1 and MPV3. The absolute change from baseline will be presented as well. For the changes from baseline a 95% confidence interval will be provided.

Table 15.2.6.4.1 Summary of SF-36v2 Cardio Benchmark Interpretation – Full Analysis Set
Table 15.2.6.4.2 Summary of SF-36v2 Cardio Benchmark Interpretation – Modified Full Analysis Set
Number and percentage of patients will be displayed by HTD at visits V1 and MPV3. Percentage will be based on the number of patients at the specified visit.

Table 15.2.6.5.1 Shift Table of SF-36v2 Cardio Benchmark Interpretation – Full Analysis Set
Table 15.2.6.5.2 Shift Table of SF-36v2 Cardio Benchmark Interpretation – Modified Full Analysis Set
Shift tables showing changes in the number and frequency of patients with respect to the Cardio benchmark interpretation between V1 and MPV3 will be provided.

Figure 15.2.2.1 Norm-Based SF-36v2 Domain Scores by Visit – Full Analysis Set
Figure 15.2.2.2 Norm-Based SF-36v2 Domain Scores by Visit – Modified Full Analysis Set
The means of norm-based SF-36v2 domain scores will be presented by HTD at visits V1 and MPV3 using a bar chart. A reference line will be included for the average score in the general population.

Figure 15.2.3.1 SF-36v2 Cardio Benchmark Interpretation by Visit – Full Analysis Set
Figure 15.2.3.2 SF-36v2 Cardio Benchmark Interpretation by Visit – Modified Full Analysis Set
The numbers of patients in each cardio benchmark interpretation category will be displayed by HTD for each domain at visits V1 and MPV3 using a stacked bar chart.

Listing 16.2.3.6 SF-36v2 – Enrolled Set
Summary scores based on the SF-36v2 survey results will be listed.

5.6 Analysis of Safety Endpoints

Safety will be assessed by evaluation of the following variables:

- Adverse events
- Clinically relevant changes in laboratory parameters (haematology, biochemistry, coagulation, urinalysis, arterial blood gas analysis)
- Clinically relevant changes in vital signs
- Clinically relevant changes in ECG
- Physical examination findings
- Number of digital scars (only in patients with scleroderma)
- Modified Rodnan Skin score (only in patients with scleroderma)

5.6.1 Adverse Events

AEs will be coded according to latest Medical Dictionary for Regulatory Activities (MedDRA®) Version 22.0.

Adverse events' data include:

- adverse event name
- start/stop dates
- ongoing
- severity (mild, moderate, severe)
- relationship (not related, unlikely, possible, probable, definite)
- action taken with study medication (dose not changed, dose reduced, drug interrupted, drug withdrawn, not applicable, unknown)
- other actions (none, medication required, tests required, withdrawn from the study, hospitalisation required or prolonged, other specification)

- outcome of event (recovered/resolved, recovering/resolving, not recovered/not resolved, recovered/resolved with sequelae, fatal, unknown)
- AE of special interest (yes or no)
- seriousness (yes or no)
- start/stop dates of drug interruption

All AEs will be presented in listings.

Summaries of adverse events will include AEs defined as **treatment-emergent adverse events (TEAEs)**, defined as AEs with the first onset or worsening after the first IMP intake and not more than 14 days after the last IMP intake.

If the start date of an AE is incomplete or missing, it will be assumed to be treatment-emergent except if the incomplete start date or the stop date indicates that the event started or ended prior to the first IMP intake or started later than 14 days after last IMP intake.

AEs will be further assigned to the following categories:

- **Serious Adverse Events (SAEs):** defined as AEs considered by the investigator as serious.
- **Adverse Event of Special Interest (AESIs):** defined as AEs assessed by the investigator as being of special interest.
- **Related TEAEs**: defined as AEs assessed as being "Possible", "Probable" or "Definite" to IMP and include the events with missing IMP relationship assessment.
- **Unrelated TEAEs**: defined as AEs assessed as being "Not related" or "Unlikely" to be related to IMP.
- **Severe TEAEs**: defined as AEs assessed as being "Severe" in intensity and include the events with missing severity assessment.
- **TEAEs leading to down-titration:** defined as AEs where "Action taken with study medication" is indicated as "dose reduced".
- **TEAEs leading to discontinuation:** selected as those events where "Action taken with study medication" is indicated as "drug withdrawn" or "other actions" is "discontinued from study".
- **TEAEs leading to death:** selected as those events where outcome of event is indicated as "fatal".

Adverse events will be assigned to IMP dose groups based on the prescribed IMP dose at the date of AE onset. AEs with an onset date on the same day as a down-titration will be assigned to the previous dose. If the AE onset date is incomplete such that it could belong to more than one prescribed dose, the AE will be assigned to all such doses.

The following statistical output will be provided:

Table 15.3.1.1 Overall Summary of TEAEs – Safety Set
An overview of TEAEs:

- TEAE
- Non-serious TEAE
- Serious TEAE
- TEAEs of special interest
- Related TEAE
- Related serious TEAE
- Mild TEAE
- Moderate TEAE
- Severe TEAE
- TEAE leading to down-titration
- TEAE leading to discontinuation
- Serious TEAE leading to discontinuation

- Related TEAE leading to discontinuation
- TEAE leading to death

will be displayed during the trial as well as the dose finding, maintenance, and down-titration periods by dose and overall for the patients in the safety set.

Table 15.3.1.2 Incidence of TEAEs – Safety Set
Table 15.3.1.3 Incidence of Serious TEAEs – Safety Set
Table 15.3.1.4 Incidence of TEAEs of Special Interest – Safety Set
Table 15.3.1.5 Incidence of Related TEAEs – Safety Set
Table 15.3.1.6 Incidence of Related Serious TEAEs – Safety Set
Table 15.3.1.7 Incidence of TEAEs Leading to Down-Titration – Safety Set
Table 15.3.1.8 Incidence of TEAEs Leading to Discontinuation – Safety Set
Table 15.3.1.9 Incidence of TEAEs Leading to Death – Safety Set

TEAEs occurring during the trial as well as the dose finding, maintenance, and down-titration periods will be summarised by concurrent dose and overall via the numbers of adverse events, as well as counts and percentages of patients having experienced adverse events during the dose finding and maintenance periods and overall. Percentages will be based on the number of patients in the safety set. Here and in the tables below the SOCs and PTs within each SOC will be ordered by descending overall incidence.

In addition, the following will be provided summarised by SOC and PT for the safety set for each dose and overall:

Table 15.3.1.10 Incidence of TEAEs by Severity – Safety Set
Table 15.3.1.11 Incidence of TEAEs by Relationship to IMP – Safety Set

All adverse event data will be listed as follows:

Listing 16.2.4.1.1 Adverse Events: MedDRA Coding
Listing 16.2.4.1.2 Adverse Events: General – Enrolled Set
Listing 16.2.4.1.3 Non-Serious Adverse Events – Safety Set
Listing 16.2.4.1.4 Serious Adverse Events – Safety Set
Listing 16.2.4.1.5 TEAEs of Special Interest – Safety Set
Listing 16.2.4.1.6 AEs Leading to Discontinuation – Safety Set
Listing 16.2.4.1.7 AEs Leading to Death – Safety Set

All AEs will be displayed by patient including the PT of an AE, start and stop dates, duration and other characteristics of AEs.

5.6.2 Clinical Laboratory Evaluation

Clinical laboratory values for haematology, coagulation, biochemistry and urinalysis will be collected at screening (V1), visits A3/B3/C3/D3, MPV1, MPV3/EDV and FUV2 for each laboratory parameter.

Blood pregnancy test values will be collected only for women with childbearing potential at screening (V1) and urine pregnancy test will be collected at visits A1, A3/B3/C3/D3, MPV1, MPV2, MPV3/EDV and FUV2. For patients enrolled under protocol version final 1.0, urine pregnancy test will be evaluated at visits A1, A3/B3/C3/D3, MPV1, MPV2, MPV3/EDV.

The following parameters will be collected:

- **Haematology:** haemoglobin, haematocrit, red blood cell count (RBC), white blood cell count (WBC), differential - neutrophils, eosinophils, lymphocytes, monocytes and basophils, and platelet count.
- **Coagulation:** prothrombin time test (INR).
- **Biochemistry:** sodium, potassium, chloride, calcium, phosphate, blood urea nitrogen, aspartate transaminase (AST), alanine transaminase (ALT), gamma-glutamyl transferase (GGT), lactate dehydrogenase (LDH), alkaline phosphatase (ALP), creatine phosphokinase (CPK), creatinine, glucose, C-reactive protein, albumin, total protein, total cholesterol, low-density lipoprotein-cholesterol, high-density lipoprotein-cholesterol, triglycerides, and total bilirubin (bilirubin will be fractionated direct/indirect if elevated), haemoglobin A1c (HbA1c).

- **Urinalysis:** pH, specific gravity, protein, blood, glucose, ketones, bilirubin, urobilinogen, leucocytes and nitrites (local dipstick). Microscopy and other appropriate tests (as needed) will be performed if dipstick indicates any relevant abnormality.

Haematology, coagulation and biochemistry test results will be assigned an LNH classification according to whether the value is lower than (L), within (N) or higher than (H) the reference range for that parameter as provided by the corresponding laboratory.

For urinalysis shift tables, all parameters except pH and specific gravity will be assigned a "normal"/"abnormal" category based on the recorded result. "Negative" and "normal" results will be considered as normal, and any positive results will be considered as abnormal.

Clinical significance of laboratory values will be evaluated by the investigator.

The following statistical output will be provided:

Table 15.3.2.1.1.1 Summary of Clinical Laboratory Tests: Haematology by HTD– Safety Set
Table 15.3.2.1.1.2 Summary of Clinical Laboratory Tests: Haematology – Safety Set
Table 15.3.2.1.2.1 Summary of Clinical Laboratory Tests: Biochemistry by HTD – Safety Set
Table 15.3.2.1.2.2 Summary of Clinical Laboratory Tests: Biochemistry – Safety Set
Table 15.3.2.1.3.1 Summary of Clinical Laboratory Tests: Coagulation by HTD – Safety Set
Table 15.3.2.1.3.2 Summary of Clinical Laboratory Tests: Coagulation – Safety Set
The default summary statistics of clinical laboratory test results will be presented by HTD and overall at V1, A3/B3/C3/D3, MPV1, MPV3/EDV and FUV2. The absolute change from baseline will be presented as well.

Table 15.3.2.1.4 Summary of Clinical Laboratory Tests: Urinalysis – Safety Set
Number and percentage of patients will be displayed by HTD and overall at V1, A3/B3/C3/D3, MPV1, MPV3/EDV and FUV2. Percentage will be based on the number of patients at the specified visit.

Table 15.3.2.2.1 Clinical Laboratory Tests: Incidence of Haematology Abnormalities – Safety Set
Table 15.3.2.2.2 Clinical Laboratory Tests: Incidence of Biochemistry Abnormalities – Safety Set
Table 15.3.2.2.3 Clinical Laboratory Tests: Incidence of Coagulation Abnormalities – Safety Set
Number and percentage of patients for each laboratory parameter will be displayed by HTD and overall in Low, CS Low, Normal, High and CS High categories. Percentage will be based on the number of patients at specified visit.

Table 15.3.2.2.4 Clinical Laboratory Tests: Incidence of Urinalysis Abnormalities – Safety Set
Number and percentage of patients for each laboratory parameter will be displayed by HTD and overall in Normal, Abnormal and CS abnormal categories. Percentage will be based on the number of patients at specified visit.

Table 15.3.2.3.1 Clinical Laboratory Tests: Shift Table of Haematology Results – Safety Set
Table 15.3.2.3.2 Clinical Laboratory Tests: Shift Table of Biochemistry Results – Safety Set
Table 15.3.2.3.3 Clinical Laboratory Tests: Shift Table of Coagulation Results – Safety Set
Shift tables showing changes in the number and frequency of patients with respect to the normal range between baseline and MPV3/EDV will be provided.

Table 15.3.2.3.4 Clinical Laboratory Tests: Shift Table of Urinalysis Results – Safety Set
Shift tables showing changes in the number and frequency of patients in Normal, Abnormal and CS abnormal categories between baseline and MPV3/EDV will be provided.

Listing 16.2.4.2.1 Laboratory Data: Haematology – Enrolled Set
Listing 16.2.4.2.2 Laboratory Data: Biochemistry – Enrolled Set
Listing 16.2.4.2.3 Laboratory Data: Coagulation – Enrolled Set
Values of laboratory tests will be listed.

Listing 16.2.4.2.4 Laboratory Data: Urinalysis – Enrolled Set
All urinalysis (dipstick) data will be listed.

Listing 16.2.4.2.5 Laboratory Data: Microscopy – Enrolled Set
All microscopy data will be listed.

Listing 16.2.4.2.6 Laboratory Data: Pregnancy Tests – Enrolled Set
Data of pregnancy tests will be listed.

5.6.3 Arterial Blood Gas Analysis

Arterial blood gas analysis will be performed at visit A1 and MPV3 before first IMP intake.

The following parameters of Arterial blood gas analysis will be collected:

- Fraction of inspired oxygen (%) **(FiO_2)**
- pH
- oxygen partial pressure (mmHg) **(pO_2)**
- carbon dioxide partial pressure (mmHg) **(pCO_2)**
- bicarbonate (mEq/L)
- base excess (mEq/L) **(BE)**
- arterial oxygen saturation (%) **(SaO_2)***
- sodium (mEq/L)
- potassium (mEq/L)
- lactate (mEq/L)

* - Collected as "O2 content (%)" in earlier eCRF versions.

If arterial blood gas analysis is not performed, then peripheral oxygen saturation (%) will be collected.

The clinical significance (yes/no) of any abnormal Arterial blood gas analysis findings will be assessed by the investigator. Parameter values without a clinical significance evaluation will be considered as "Normal", and values with "No" or "Yes" clinical significance evaluations will be considered as "NCS Abnormal" and "CS Abnormal", respectively.

The following statistical output will be provided:

Table 15.3.3.1.1 Summary of Arterial Blood Gas Analysis by HTD – Safety Set
Table 15.3.3.1.2 Summary of Arterial Blood Gas Analysis – Safety Set
The default summary statistics of Arterial blood gas analysis parameters will be presented by HTD and overall at visits A1 and MPV3. The absolute change from baseline will be presented as well. For the changes from baseline a 95% confidence interval will be provided.

Table 15.3.3.2 Incidence of Arterial Blood Gas Analysis Abnormalities – Safety Set
Number and percentage of patients with abnormal values will be displayed by HTD and overall in Not CS abnormal and CS abnormal categories. Percentage will be based on the number of patients at specified visit.

Table 15.3.3.3 Shift Table of Arterial Blood Gas Analysis Results – Safety Set
Shift tables showing changes in the number and frequency of patients in Not CS abnormal and CS abnormal categories between baseline and MPV3/EDV will be provided.

Table 15.3.3.4.1 Summary of Peripheral Oxygen Saturation (%) by HTD – Safety Set
Table 15.3.3.4.2 Summary of Peripheral Oxygen Saturation (%) – Safety Set
The default summary statistics of peripheral oxygen saturation (%) will be presented by HTD and overall at visits A1 and MPV3. The absolute change from baseline will be presented as well. For the changes from baseline a 95% confidence interval will be provided.

Listing 16.2.4.3 Arterial blood gas analysis – Enrolled Set
Values of arterial blood gas analysis and peripheral oxygen saturation (%) will be listed.

5.6.4 Vital Signs

Vital signs will be collected at screening (V1), visits A1, A3/B3/C3/D3, MPV1, MPV2, MPV3/EDV and FUV2. Blood pressure and heart rate will be measured in supine position (two measurements) and afterwards in standing position (one measurement). Tympanic body temperature will also be assessed.

At visits A1 and MPV3, blood pressure and heart rate will be measured before IMP intake as well as 4, 8 and 24 hours after IMP intake. For patients enrolled under protocol version final 1.0, vital signs were only evaluated before IMP intake.

Systolic and diastolic blood pressure and pulse rate will be summarised by measurement position. The mean value of measurements in the supine position at a given timepoint will be used in summaries. **Orthostatic changes** in vital sign parameters will also be calculated as the difference between the measurement in the standing position and the mean of the supine measurements. The orthostatic changes will be displayed after each corresponding parameter's standing position results in summaries.

To evaluate the short-term effects of the IMP on vital sign parameters, the absolute change from the pre-dose value within the corresponding visit will be calculated for each parameter at visits A1 and MPV3. Additionally, the difference in the within-visit changes will be evaluated for each corresponding timepoint between visits MPV3 and A1.

Physical measurements – height and weight will be assessed at visit V1. Weight will also be measured at MPV3/EDV. BMI will be calculated from available data (see Section 5.2.1 for calculation).

The following statistical output will be provided:

Table 15.3.4.1.1 Summary of Vital Signs by HTD– Safety Set
Table 15.3.4.1.2 Summary of Vital Signs – Safety Set
Vital sign parameters will be summarised including change from baseline at each timepoint by HTD and overall.

Table 15.3.4.2 Summary of Vital Signs by Pooled HTD – Safety Set
Vital sign parameters will be summarised as above, with HTD pooled into "HTD < 200 mg" and "HTD 200 mg" groups.

Table 15.3.4.3.1 Summary of Short-Term IMP Effect on Vital Signs by HTD – Safety Set
Table 15.3.4.3.2 Summary of Short-Term IMP Effect on Vital Signs – Safety Set
The observed values and absolute changes from the pre-dose value will be summarised for each vital sign parameter at each timepoint by HTD and overall.

Table 15.3.4.4.1 Summary of Change in Short-Term IMP Effect on Vital Signs by HTD – Safety Set
Table 15.3.4.4.2 Summary of Change in Short-Term IMP Effect on Vital Signs – Safety Set
The changes from pre-dose values and the differences in changes from pre-dose values will be summarised between corresponding timepoints at visits A1 and MPV3 by HTD and overall.

Table 15.3.4.5.1 Summary of Physical Measurements by HTD – Safety Set
Table 15.3.4.5.2 Summary of Physical Measurements – Safety Set
Physical measurements will be summarised including change from baseline at each timepoint by HTD and overall.

Figure 15.3.1 Vital Signs Median Change from Baseline – Safety Set
The median changes from baseline of vital signs parameters at each post-baseline timepoint will be displayed by will be displayed by HTD. The HTD will be pooled into "HTD < 200 mg" and "HTD 200 mg" groups.

Listing 16.2.4.4 Vital Signs and Physical Measurements – Enrolled Set
Values of vital signs and physical measurements will be listed.

5.6.5 12-Lead Electrocardiogram (ECG) Data

A simultaneous 12-lead resting electrocardiogram (ECG) will be collected at screening (V1), A1, A3/B3/C3/D3, MPV1, MPV2, MPV3/EDV and FUV2. At visits A1 and MPV3 triplicate ECG recordings will be performed at following time points - before IMP intake as well as 4 and 8 hours after IMP intake. At EDV only one ECG recording will be performed. For patients enrolled under protocol version final 1.0, ECG assessments were only collected once at visits V1, A3/B3/C3/D3, MPV1, MPV3/EDV.

Following parameters will be assessed:

- Heart rate (bpm)
- P-R interval (msec)
- QRS duration (msec)
- QTcF interval (msec)
- QT interval (msec)
- P pulmonale
- Right axis deviation
- RV hypertrophy
- RV strain
- Right bundle branch block
- Heart rhythm (normal, abnormal)

For patients enrolled under protocol version final 1.0, heart rhythm was not collected.

Clinical significance (yes/no) of any abnormal ECG data findings will be assessed by the investigator. Parameter values without a clinical significance evaluation will be considered as "Normal", and values with "No" or "Yes" clinical significance evaluations will be considered as "NCS Abnormal" and "CS Abnormal", respectively.

Where multiple ECG recordings are performed within a visit or timepoint, ECG parameters will be summarised as follows. For numeric parameters, the mean of collected values will be used in summaries. For abnormality assessments, the worst value within the visit/timepoint will be used.

To evaluate the short-term effects of the IMP on ECG parameters, the absolute change from the pre-dose value within the corresponding visit will be calculated for each parameter at visits A1 and MPV3. Additionally, the difference in the within-visit changes will be evaluated for each corresponding timepoint between visits MPV3 and A1.

The following statistical output will be provided:

Table 15.3.5.1.1 Summary of ECG Assessments by HTD – Safety Set
Table 15.3.5.1.2 Summary of ECG Assessments – Safety Set
ECG parameters will be summarised including change from baseline at each visit by HTD and overall.

Table 15.3.5.2.1 Summary of Short-Term IMP Effect on ECG Assessments by HTD – Safety Set
Table 15.3.5.2.2 Summary of Short-Term IMP Effect on ECG Assessments – Safety Set
The observed values and absolute changes from the pre-dose value will be summarised for each vital sign parameter at each timepoint by HTD and overall.

Table 15.3.5.3.1 Summary of Change in Short-Term IMP Effect on ECG Assessements by HTD – Safety Set
Table 15.3.5.3.2 Summary of Change in Short-Term IMP Effect on ECG Assessements – Safety Set
The changes from pre-dose values and the differences in changes from pre-dose values will be summarised between corresponding timepoints at visits A1 and MPV3 by HTD and overall.

Table 15.3.5.4.1 Incidence of ECG Abnormalities – Safety Set
Number and percentage of patients with Not CS abnormal and CS abnormal ECG parameters assessments will be displayed by HTD and overall. Percentage will be based on the number of patients at specified visit.

Table 15.3.5.4.2 Shift Table of ECG Abnormalities – Safety Set
Shift tables showing changes in the number and frequency of patients in not CS abnormal and CS abnormal categories between baseline and MPV3/EDV will be provided. The worst abnormality assessment collected during MPV3/EDV will be selected for each patient. Percentage will be based on the number of patients in the safety set.

Table 15.3.5.4.3 Shift Table of Within-Visit ECG Abnormalities – Safety Set
Shift tables showing changes in the number and frequency of patients in not CS abnormal and CS abnormal categories between the pre-dose measurement and each post-dose measurement at each visit.

The worst abnormality assessment collected during the corresponding timepoint will be selected for each patient. Percentage will be based on the number of patients in the safety set.

Listing 16.2.4.5 Electrocardiogram – Enrolled Set
Values of simultaneous 12-lead resting electrocardiogram tests will be listed.

5.6.6 Physical Examination Findings

Physical examinations will be performed at Visit 1, visits A3/B3/C3/D3, MPV1, MPV2, MPV3/EDV on relevant body systems (appearance, skin, eyes, ears-nose-throat, lungs-chest, heart, abdomen, extremities, other). Clinical significance (yes/no) of any abnormal physical examination findings and specification of clinically significant abnormality findings will be assessed by the investigator.

The following statistical output will be provided:

Table 15.3.6 Summary of Physical Examination Findings – Safety Set
Number and percentage of patients with not CS abnormal and CS abnormal physical examinations findings will be displayed at each visit by HTD and overall. Percentage will be based on the number of patients at the specified visit.

Listing 16.2.4.6 Physical Examinations – Enrolled Set
Values of physical examination will be listed.

5.6.7 Number of Digital Scars

Number of digital scars will be documented in patients with scleroderma only.

At Visit 1 the investigator will document the number of existing digital scars at the fingers and toes. At visits A3/B3/C3/D3, MPV1, MPV2 and MPV3/EDV the investigator will examine fingers and toes of the patient and will document the number of digital scars. Additionally, the clinical examination will be supported by interviewing the patient.

For patients enrolled with protocol version 1.0 the investigator documented only the number of new scars at post-baseline visits, therefore the total number of scars will be derived adding number of scars at baseline and new scars.

The following statistical output will be provided:

Table 15.3.7.1 Summary of Scleroderma Scarring by HTD – Safety Set
Table 15.3.7.2 Summary of Scleroderma Scarring – Safety Set
The default summary statistics of number of digital scars will be presented by HTD and overall at each visit. The absolute change from baseline will be presented as well.

Listing 16.2.4.7 Number of Digital Scars – Enrolled Set
Number of scars will be listed by visit.

5.6.8 Modified Rodnan Skin Score (mRSS)

The mRSS is a measure of skin thickness and is used as an outcome measure for scleroderma.

The score consists of an evaluation of patient's skin thickness rated by clinical palpation using a scale from 0 to 3 (0=normal skin; 1=mild thickness; 2=moderate thickness; 3=severe thickness) for each of 17 surface anatomic areas of the body: face, anterior chest, abdomen, (right and left separately) fingers, forearms, upper arms, tights, lower legs, dorsum of hands and feet. These individual values are added, and the sum is defined as the total skin score.

The investigator will document the total skin score at Visit 1 and visit MPV3/EDV.

The following statistical output will be provided:

Table 15.3.8.1 Summary of mRSS by HTD – Safety Set
Table 15.3.8.2 Summary of mRSS – Safety Set
The default summary statistics of modified Rodnan score will be presented by HTD and overall at each visit. The absolute change from baseline will be presented as well.

Listing 16.2.4.8 Modified Rodnan Skin Score – Enrolled Set
Values of mRSS will be listed.

6 DATA REVIEW

The aims of the Data Review (DR) are:

- to identify major/minor protocol deviations, that may affect the pharmacokinetic or pharmacodynamic outcomes, or the treatment of the patients
- to identify impacts of the COVID-19 pandemic on the study conduct
- to solve any outstanding issues in the SAP
- to discuss any open data issues

The DR will be performed after data entry and following a database lock. All decisions made during the DR will be documented in the DR report before the closure of the database.

An appropriate clinical study team, including a physician, will review potential protocol deviations and relevant information regarding those deviations to determine a possible impact on pharmacokinetic endpoints. The status, major or minor, of each protocol deviation will be documented in the DR report. A patient may have one or more major protocol deviations resulting in the exclusion of that patient from the PKS set.

Protocol deviations will, if possible, be validated against data recorded in the eCRF. Where an answer for an inclusion/exclusion tick box differs from the algorithmic check of the criteria, the algorithmic check will overrule the tick box.

Additionally, protocol deviations will be reviewed by the medical monitor and will be categorized according to their impact on the PK analysis into following groups: major, minor and case by case decision.

Protocol deviations of the following categories and respective data listings will be reviewed during the DR.

Inclusion Criteria

No.	Inclusion Criteria Deviation	Major/ Minor/ Case by case review
PD#01.	Male or female patients aged 18 to 75 years, inclusive. *Protocol Versions Final 1.0 and 2.0:* Male or female patients aged 18 to 65 years.	Case by case
PD#02.	Able to comprehend and willing to sign an informed consent form (ICF).	Major
PD#03.	Diagnosis of PAH (pulmonary arterial hypertension WHO Group 1) documented by RHC with a mPAP ≥ 25 mmHg, a PAWP ≤ 15 mmHg and a PVR > 3 WU [8,9]: a) Idiopathic, in non-vasoreactive patients b) Heritable: Bone morphogenetic protein receptor type II (BMPR2) mutation and other mutations, in non-vasoreactive patients c) Drugs and toxin induced, in non-vasoreactive patients d) Associated with connective tissue disease e) Associated with simple congenital defects (atrial septal defect and/or ventricular septal defect) if closed > 12 months before inclusion.	Case by case
PD#04.	*Added in Protocol Version Final 3.0:* The patient's last right heart catheterisation results, which were measured at the study site, must not be older than 90 days before V1 (will be considered as baseline value). Otherwise a right heart catheterisation has to be performed as part of the study at visit A1.	Minor

No.	Inclusion Criteria Deviation	Major/ Minor/ Case by case review
PD#05.	WHO functional class II or III as judged by the investigator.	Case by case
PD#06.	Stable treatment with at least one of the following approved PAH therapies for at least 90 days prior to V1: Ambrisentan, Bosentan, Macitentan, Riociguat, Selexipag, Sildenafil, Tadalafil, Epoprostenol intravenous, Iloprost inhaled or Treprostinil intravenous or subcutaneous. *Protocol Version Final 1.0:* Stable treatment with at least one of the following approved oral PAH therapies within 3 months before V1: Ambrisentan, Bosentan, Macitentan, Riociguat, Selexipag, Sildenafil or Tadalafil.	Case by case
PD#07.	*Added in Protocol Version Final 3.0:* For women: Agree not to donate ova from the time of informed consent until 30 days after the last IMP intake. For men: Agree not to donate sperm from the time of informed consent until 90 days after the last IMP intake.	Minor

Exclusion Criteria

No.	Exclusion Criteria Deviation	Major/ Minor/ Case by case review
PD#08.	Contraindication to zamicastat, i.e. known hypersensitivity to ingredients of zamicastat formulation.	Minor
PD#09.	Two or more consecutive measurements of SBP < 95 mmHg or DBP < 50 mmHg measured at V1. *Protocol Version Final 2.0* Two or more consecutive measurements of SBP < 95 mmHg or DBP < 50 mmHg. *Protocol Version Final 1.0:* Persistent hypotension defined as SBP < 95 mmHg or DBP < 50 mmHg.	Minor
PD#10.	Uncontrolled diabetes mellitus with HbA1c ≥ 8.5% within the last three months or at screening. *Protocol Version Final 1.0:* Uncontrolled diabetes mellitus.	Minor
PD#11.	PAH WHO Group 1 due to portal hypertension, human immunodeficiency virus (HIV) infection and schistosomiasis.	Case by case
PD#12.	Any disease known to cause pulmonary hypertension other than PAH WHO Group 1. *Protocol Version Final 1.0:* Any disease known to cause pulmonary hypertension other than PAH WHO Group 1 e.g. obstructive lung diseases, parasitic disease affecting the pulmonary system, sickle cell anaemia, left heart disease.	Case by case
PD#13.	*Added in Protocol Version Final 2.0:*	Case by case

No.	Exclusion Criteria Deviation	Major/ Minor/ Case by case review
	Obstructive lung disease: Forced Expiratory Volume in 1 second/Forced Vital Capacity (FEV1/FVC) < 60% and FEV1 < 60% of predicted value after bronchodilator administration.	
PD#14.	Restrictive lung disease: Total Lung Capacity (TLC) < 70% of predicted value, as demonstrated and documented by previous spirometry data which, in the opinion of the investigator, represent the clinical state of the patient at the time of the screening visit. *Added in Protocol Version Final 2.0:* Restrictive lung disease: Total Lung Capacity (TLC) < 70% of predicted value.	Case by case
PD#15.	History of moderate to severe hepatic impairment (Child-Pugh B and C).	Case by case
PD#16.	Estimated glomerular filtration rate (eGFR) < 30 mL/min/1.73 m^2 (measured at V1).	Case by case
PD#17.	Use of the following prohibited medication or treatments during study participation: calcium channel blockers (CCBs) if used for the treatment of PAH in vasoreactive patients; drugs containing a catechol group that is metabolised by DβH e.g. rimiterole, isoprenaline, dopamine, dopexamine or dobutamide or α- and/or β-blockers.	Case by case
PD#18.	Current or previous (within the past year) alcohol or substance abuse excluding caffeine or nicotine.	Minor
PD#19.	Presence of any other significant or progressive/unstable medical condition that, in the opinion of the investigator, would compromise evaluation of the study treatment or may jeopardise the patient's safety, compliance or adherence to protocol requirements.	Case by case
PD#20.	For women: Pregnancy or breast-feeding. Women of childbearing potential (as defined in Section 4.2) unable or unwilling to undergo pregnancy tests and practice highly effective contraceptive measures in combination with a barrier method e.g. condom (without spermicidal foam/gel/film/cream/suppository or fat- or oil-containing lubricants), occlusive cap (diaphragm or cervical/vault caps) with spermicidal gel/film/cream/suppository from the time of informed consent until 30 days after last IMP intake. Highly effective methods for women are surgical intervention (e.g. bilateral tubal occlusion), non-hormonal implantable intrauterine device, true sexual abstinence (i.e. when this is in line with the preferred and usual lifestyle of the patient) and vasectomised partner (provided that the partner is the sole sexual partner of the patient and the partner has received medical assessment of the surgical success). Periodic abstinence (e.g. calendar, ovulation, symptothermal, post-ovulation methods), hormonal contraceptives and withdrawal are not acceptable methods of contraception. For men: Male patients who are sexually active with a partner of childbearing potential must use, with their partner, a condom plus an approved acceptable contraceptive measure from the time of informed consent until 90 days after the last IMP intake. The following methods are acceptable methods of contraception: partner's use of combined (oestrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal); partner's use of progestogen-only hormonal contraception (oral, injectable/implantable,	Minor

No.	Exclusion Criteria Deviation	Major/ Minor/ Case by case review
	intrauterine hormone-releasing system); partner's use of implantable intrauterine device; surgical sterilisation (for example, vasectomy or bilateral tubal occlusion). *Protocol Version Final 2.0:* For women: Pregnancy or breast-feeding. Women of childbearing potential unable or unwilling to undergo pregnancy tests and practice acceptable contraceptive measures from the time of informed consent until 30 days after last IMP intake. Acceptable methods for women are surgical intervention (e.g. bilateral tubal occlusion), non-hormonal implantable intrauterine device, double-barrier methods, true sexual abstinence (i.e. when this is in line with the preferred and usual lifestyle of the patient) and vasectomised partner (provided that the partner is the sole sexual partner of the patient and the partner has received medical assessment of the surgical success). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods), hormonal contraceptives and withdrawal are not acceptable methods of contraception. For men: Male patients who are sexually active with a partner of childbearing potential must use, with their partner, a condom plus an approved acceptable contraceptive measure from the time of informed consent until 90 days after the last IMP intake. The following methods are acceptable methods of contraception: partner's use of combined (oestrogen and progestogen-containing) hormonal contraception associated with inhibition of ovulation (oral, intravaginal, transdermal); partner's use of progestogen-only hormonal contraception (oral, injectable/implantable, intrauterine hormone-releasing system); partner's use of implantable intrauterine device; surgical sterilisation (for example, vasectomy or bilateral tubal occlusion). *Protocol Version Final 1.0:* For women: Pregnancy or breast-feeding. Women of childbearing potential unable or unwilling to undergo pregnancy tests and practice acceptable contraceptive measures. Acceptable methods for women are surgical intervention (e.g. bilateral tubal occlusion), intrauterine device, double-barrier methods and true sexual abstinence (i.e. when this is in line with the preferred and usual lifestyle of the patient). Periodic abstinence (e.g., calendar, ovulation, symptothermal, post-ovulation methods) and withdrawal are not acceptable methods of contraception.	
PD#21.	Previous participation in any other drug investigational study within the past 30 days (or five half-lives of investigational medicinal product [IMP] whichever is longer) prior to V1.	Case by case
PD#22.	Vulnerable patients according to Section 1.61 of the ICH guideline for Good Clinical Practice E6	Minor

Additional Study Conduct Deviations

No.	Deviation	Major/ Minor/ Case by case review
PD#23.	Down-titration dose not according to the protocol.	Case by case
PD#24.	Up-titration safety criteria deviations	Minor
PD#25.	IMP compliance <90% or >110% by period or overall	Case by case
PD#26.	Schedule deviations of visits with scheduled IMP dispensations	Case by case
PD#27.	Time deviations of scheduled assessments (ECG, Vital signs, blood withdrawal for PK/PD) at A1 and MPV3	Case by case
PD#28.	Deviations in sequences of assessments/tests/procedures	Minor
PD#29.	Prohibited medications/therapies	Case by case
PD#30.	Adverse events with possible impact on primary endpoint.	Case by case
PD#31.	Missing/incomplete blood withdrawal for PK, blood and urinalysis sampling for PD	Case by case
PD#32.	Missing/incomplete test/examination assessments: vital signs, physical measurements, NYHA/WHO functional class, laboratory tests, physical examination, ECG, number of digital scars, modified Rodnan Skin Score, SF-36v2, 6-min walk test, echocardiography, right heart catheterisation, blood withdrawal biomarker	Minor
PD#33.	Protocol deviations documented by CRAs and selected by medical monitors for discussion during DR	Case by case

Reference listings will be made available to help with the review of the protocol deviations. The specific content and format of listings to be reviewed during the DR meeting (including any additional requirements that may be necessary to aid in review) will be determined outside the scope of this SAP.

7 INTERIM ANALYSIS

No interim analysis is planned for this study.

8 CHANGES TO THE ANALYSIS AS LAID DOWN IN THE PROTOCOL AND AMENDMENTS

No changes to the analysis as laid down in the clinical study protocol and protocol amendment(s) were made.

9 REFERENCES

1. SAS® Institute Inc., Cary, North Carolina, United States of America, Version 9.4.
2. MedDRA – Medical Dictionary for Regulated Activities. International Federation of Pharmaceutical Manufacturers Associations (IFPMA), c/o TRW, VAR1/8A/MSSO, 12011 Sunset Hills Road, Reston, VA 20190-3285, USA, Version 22.0, 1 March 2019.
3. WHODrug Global dictionary. World Health Organization Collaborating Center for International Drug Monitoring, P.O. Box 26, S-751 03 Uppsala, Sweden, version 2019, March.
4. Optum, Inc 1301 Atwood Avenue, Suite 311 N Johnston, R.I. 02919, U.S.A, Pro Core Version 1.4

10 APPENDICES

The following documents are attached as appendices to the SAP:

1. 0223_TableShells_1.0_20220322.docx
2. 0223_ListingShells_1.0_20220322.docx
3. 0223_FigureShells_1.0_20220322.docx
4. QSC202579 (BIA-51058-201) RAP_20Feb2020_Finalv1.0.pdf

10.1 Tables

Appendix tables defined below will be provided in separate .rtf files for each output.

No	Table Identifier, Title	Output file
Demographic and Study Population Data		
1	Table 15.1.1.1 Analysis Sets – Enrolled Set	BIA-T-150101010000-anlset-enr.rtf
2	Table 15.1.1.2 Reasons for Exclusion from Analysis Sets – Safety Set	BIA-T-150101020000-reas-excl-ss.rtf
3	Table 15.1.2 Screening Failures – Enrolled Set	BIA-T-150102000000-scrfail-enr.rtf
4	Table 15.1.3 Major Protocol Deviations – Safety Set	BIA-T-150103000000-protdev-ss.rtf
5	Table 15.1.4 Patient Disposition – Safety Set	BIA-T-150104000000-disp-ss.rtf
6	Table 15.1.5.1.1 Number of Patients by Country and Site – Enrolled Set	BIA-T-150105010100-countrysite-enr.rtf
7	Table 15.1.5.1.2 Number of Patients by Country and Site – Safety Set	BIA-T-150105010200-countrysite-ss.rtf
8	Table 15.1.5.2 Number of Patients by Visit – Safety Set	BIA-T-150105020000-visits-ss.rtf
9	Table 15.1.6.1.1 Demographics – Safety Set	BIA-T-150106010100-dm-ss.rtf
10	Table 15.1.6.1.2 Demographics – Full Analysis Set	BIA-T-150106010200-dm-fas.rtf
11	Table 15.1.6.1.3 Demographics – Pharmacokinetic Analysis Set	BIA-T-150106010300-dm-pks.rtf
12	Table 15.1.6.2.1 Baseline Characteristics – Safety Set	BIA-T-150106020100-basechar-ss.rtf
13	Table 15.1.6.2.2 Baseline Physical Characteristics – Full Analysis Set	BIA-T-150106020200-basechar-fas.rtf
14	Table 15.1.6.2.3 Baseline Physical Characteristics – Pharmacokinetic Analysis Set	BIA-T-150106020300-basechar-pks.rtf
15	Table 15.1.6.3.1 Disease Characteristics – Safety Set	BIA-T-150106030100-diseasechar-ss.rtf
16	Table 15.1.6.3.2 Disease Characteristics – Full Analysis Set	BIA-T-150106030200-diseasechar-fas.rtf
17	Table 15.1.6.3.3 Disease Characteristics – Pharmacokinetic Analysis Set	BIA-T-150106030300-diseasechar-pks.rtf
18	Table 15.1.7.1.1 Prior Medical Conditions – Safety Set	BIA-T-150107010100-mh-prior-ss.rtf
19	Table 15.1.7.1.2 Prior Medical Conditions – Full Analysis Set	BIA-T-150107010200-mh-prior-fas.rtf
20	Table 15.1.7.1.3 Prior Medical Conditions – Pharmacokinetic Analysis Set	BIA-T-150107010300-mh-prior-pks.rtf
21	Table 15.1.7.2.1 Ongoing Medical Conditions – Safety Set	BIA-T-150107020100-mh-ongoing-ss.rtf
22	Table 15.1.7.2.2 Ongoing Medical Conditions – Full Analysis Set	BIA-T-150107020200-mh-ongoing-fas.rtf
23	Table 15.1.7.2.3 Ongoing Medical Conditions – Pharmacokinetic Analysis Set	BIA-T-150107020300-mh-ongoing-pks.rtf
24	Table 15.1.8.1.1 Prior Medications – Safety Set	BIA-T-150108010100-priormed-ss.rtf
25	Table 15.1.8.1.2 Prior Medications – Full Analysis Set	BIA-T-150108010200-priormed-fas.rtf
26	Table 15.1.8.1.3 Prior Medications – Pharmacokinetic Analysis Set	BIA-T-150108010300-priormed-pks.rtf
27	Table 15.1.8.2.1 Concomitant Medications – Safety Set	BIA-T-150108020100-conmed-ss.rtf

28	Table 15.1.8.2.2 Concomitant Medications – Full Analysis Set	BIA-T-150108020200-conmed-fas.rtf
29	Table 15.1.8.2.3 Concomitant Medications – Pharmacokinetic Analysis Set	BIA-T-150108020300-conmed-pks.rtf
30	Table 15.1.8.3.1 Prior PAH Medications – Safety Set	BIA-T-150108030100-priormed-pah-ss.rtf
31	Table 15.1.8.3.2 Prior PAH Medications – Full Analysis Set	BIA-T-150108030200-priormed-pah-fas.rtf
32	Table 15.1.8.3.3 Prior PAH Medications – Pharmacokinetic Analysis Set	BIA-T-150108030300-priormed-pah-pks.rtf
33	Table 15.1.8.4.1 Concomitant PAH Medications – Safety Set	BIA-T-150108040100-conmed-pah-ss.rtf
34	Table 15.1.8.4.2 Concomitant PAH Medications – Full Analysis Set	BIA-T-150108040200-conmed-pah-fas.rtf
35	Table 15.1.8.4.3 Concomitant PAH Medications – Pharmacokinetic Analysis Set	BIA-T-150108040300-conmed-pah-pks.rtf
36	Table 15.1.8.5.1 PAH-Approved Therapy by Visit – Safety Set	BIA-T-150108050100-pahappr-byvis-ss.rtf
37	Table 15.1.8.5.2 PAH-Approved Therapy by Visit – Full Analysis Set	BIA-T-150108050200-pahappr-byvis-fas.rtf
38	Table 15.1.8.5.3 PAH-Approved Therapy by Visit – Pharmacokinetic Analysis Set	BIA-T-150108050300-pahappr-byvis-pks.rtf
39	Table 15.1.9.1.1 Treatment Duration (days) – Safety Set	BIA-T-150109010100-trtdur-ss.rtf
40	Table 15.1.9.1.2 Treatment Duration (days) – Full Analysis Set	BIA-T-150109010200-trtdur-fas.rtf
41	Table 15.1.9.1.3 Treatment Duration (days) – Pharmacokinetic Analysis Set	BIA-T-150109010300-trtdur-pks.rtf
42	Table 15.1.9.2.1 Compliance (%) – Safety Set	BIA-T-150109020100-compl-ss.rtf
43	Table 15.1.9.2.2 Compliance (%) – Full Analysis Set	BIA-T-150109020200-compl-fas.rtf
44	Table 15.1.9.2.3 Compliance (%) – Pharmacokinetic Analysis Set	BIA-T-150109020300-compl-pks.rtf
Efficacy Data		
45	Table 15.2.1.1.1 Summary of Right Heart Catheterisation Parameters by HTD – Full Analysis Set	BIA-T-150201010100-rhc-htd-fas.rtf
46	Table 15.2.1.1.2 Summary of Right Heart Catheterization Parameters – Full Analysis Set	BIA-T-150201010200-rhc-tot-fas.rtf
47	Table 15.2.1.1.3 Summary of Right Heart Catheterisation Parameters by HTD – Modified Full Analysis Set	BIA-T-150201010300-rhc-htd-mfas.rtf
48	Table 15.2.1.1.4 Summary of Right Heart Catheterization Parameters – Modified Full Analysis Set	BIA-T-150201010400-rhc-tot-mfas.rtf
49	Table 15.2.1.1.5 Summary of Right Heart Catheterization Parameters – Modified Full Analysis Set (TAPSE Subgroups)	BIA-T-150201010500-rhc-tapse-mfas.rtf
50	Table 15.2.1.2.1 Incidence of Right Heart Catheterisation Abnormalities – Full Analysis Set	BIA-T-150201020100-rhc-abnorm-fas.rtf
51	Table 15.2.1.2.2 Incidence of Right Heart Catheterisation Abnormalities – Modified Full Analysis Set	BIA-T-150201020200-rhc-abnorm-mfas.rtf
52	Table 15.2.1.3.1 Shift Table of Right Heart Catheterisation Results – Full Analysis Set	BIA-T-150201030100-rhc-shift-fas.rtf
53	Table 15.2.1.3.2 Shift Table of Right Heart Catheterisation Results – Modified Full Analysis Set	BIA-T-150201030200-rhc-shift-mfas.rtf
54	Table 15.2.2.1 Summary of 6-MWT by HTD – Full Analysis Set	BIA-T-150202010000-6mwt-htd-fas.rtf
55	Table 15.2.2.2 Summary of 6-MWT – Full Analysis Set	BIA-T-150202020000-6mwt-tot-fas.rtf
56	Table 15.2.2.3 Summary of 6-MWT by HTD – Modified Full Analysis Set	BIA-T-150202030000-6mwt-htd-mfas.rtf
57	Table 15.2.2.4 Summary of 6-MWT – Modified Full Analysis Set	BIA-T-150202040000-6mwt-tot-mfas.rtf

58	Table 15.2.2.5 Summary of 6-MWT Distance – Modified Full Analysis Set (TAPSE Subgroups)	BIA-T-150202050000-6mwt-tapse-mfas.rtf
59	Table 15.2.3.1.1 Summary of Biomarker NT-proBNP (ng/L) by HTD – Full Analysis Set	BIA-T-150203010100-biomarker-htd-fas.rtf
60	Table 15.2.3.1.2 Summary of Biomarker NT-proBNP (ng/L) – Full Analysis Set	BIA-T-150203010200-biomarker-tot-fas.rtf
61	Table 15.2.3.1.3 Summary of Biomarker NT-proBNP (ng/L) by HTD – Modified Full Analysis Set	BIA-T-150203010300-biomarker-htd-mfas.rtf
62	Table 15.2.3.1.4 Summary of Biomarker NT-proBNP (ng/L) – Modified Full Analysis Set	BIA-T-150203010400-biomarker-tot-mfas.rtf
63	Table 15.2.3.2.1 Summary of Biomarker NT-proBNP (ng/L) by Pooled HTD –Full Analysis Set	BIA-T-150203020100-biomarker-htdpool-fas.rtf
64	Table 15.2.3.2.2 Summary of Biomarker NT-proBNP (ng/L) by Pooled HTD – Modified Full Analysis Set	BIA-T-150203020200-biomarker-htdpool-mfas.rtf
65	Table 15.2.4.1.1 Summary of Categorical Echocardiography Parameters– Full Analysis Set	BIA-T-150204010100-echo-cat-fas.rtf
66	Table 15.2.4.1.2 Summary of Categorical Echocardiography Parameters – Modified Full Analysis Set	BIA-T-150204010200-echo-cat-mfas.rtf
67	Table 15.2.4.2.1 Summary of Numerical Echocardiography Parameters by HTD – Full Analysis Set	BIA-T-150204020100-echo-num-htd-fas.rtf
68	Table 15.2.4.2.2 Summary of Numerical Echocardiography Parameters – Full Analysis Set	BIA-T-150204020200-echo-num-tot-fas.rtf
69	Table 15.2.4.2.3 Summary of Numerical Echocardiography Parameters by HTD – Modified Full Analysis Set	BIA-T-150204020300-echo-num-htd-mfas.rtf
70	Table 15.2.4.2.4 Summary of Numerical Echocardiography Parameters – Modified Full Analysis Set	BIA-T-150204020400-echo-num-tot-mfas.rtf
71	Table 15.2.4.2.5 Summary of Numerical Echocardiography Parameters – Modified Full Analysis Set (TAPSE Subgroups)	BIA-T-150204020500-echo-num-tapse-mfas.rtf
72	Table 15.2.4.3.1 Incidence of Echocardiography Abnormalities – Full Analysis Set	BIA-T-150204030100-echo-abnorm-fas.rtf
73	Table 15.2.4.3.2 Incidence of Echocardiography Abnormalities – Modified Full Analysis Set	BIA-T-150204030200-echo-abnorm-mfas.rtf
74	Table 15.2.4.4.1 Shift Table of Echocardiography Results – Full Analysis Set	BIA-T-150204040100-echo-shift-fas.rtf
75	Table 15.2.4.4.2 Shift Table of Echocardiography Results – Modified Full Analysis Set	BIA-T-150204040200-echo-shift-mfas.rtf
76	Table 15.2.5.1.1 Summary of NYHA/WHO Functional Class – Full Analysis Set	BIA-T-150205010100-whofc-fas.rtf
77	Table 15.2.5.1.2 Summary of NYHA/WHO Functional Class – Modified Full Analysis Set	BIA-T-150205010200-whofc-mfas.rtf
78	Table 15.2.5.2.1 Shift Table of NYHA/WHO Functional Class – Full Analysis Set	BIA-T-150205020100-whofc-shift-fas.rtf
79	Table 15.2.5.2.2 Shift Table of NYHA/WHO Functional Class – Modified Full Analysis Set	BIA-T-150205020200-whofc-shift-mfas.rtf
80	Table 15.2.6.1.1 Summary of SF-36v2 Domain Scores by HTD – Full Analysis Set	BIA-T-150206010100-sf36-htd-fas.rtf
81	Table 15.2.6.1.2 Summary of SF-36v2 Domain Scores – Full Analysis Set	BIA-T-150206010200-sf36-tot-fas.rtf
82	Table 15.2.6.1.3 Summary of SF-36v2 Domain Scores by HTD – Modified Full Analysis Set	BIA-T-150206010300-sf36-htd-mfas.rtf
83	Table 15.2.6.1.4 Summary of SF-36v2 Domain Scores – Modified Full Analysis Set	BIA-T-150206010400-sf36-tot-mfas.rtf
84	Table 15.2.6.2.1 Summary of Norm-Based SF-36v2 Scores by HTD – Full Analysis Set	BIA-T-150206020100-sf36-norm-htd-fas.rtf
85	Table 15.2.6.2.2 Summary of Norm-Based SF-36v2 Scores – Full Analysis Set	BIA-T-150206020200-sf36-norm-tot-fas.rtf
86	Table 15.2.6.2.3 Summary of Norm-Based SF-36v2 Domain Scores by HTD – Modified Full Analysis Set	BIA-T-150206020300-sf36-norm-htd-mfas.rtf
87	Table 15.2.6.2.4 Summary of Norm-Based SF-36v2 Domain Scores – Modified Full Analysis Set	BIA-T-150206020400-sf36-norm-tot-mfas.rtf

88	Table 15.2.6.3.1 Summary of SF-36v2 Utility Index Scores by HTD – Full Analysis Set	BIA-T-150206030100-sf36-util-htd-fas.rtf
89	Table 15.2.6.3.2 Summary of SF-36v2 Utility Index Scores – Full Analysis Set	BIA-T-150206030200-sf36-util-tot-fas.rtf
90	Table 15.2.6.3.3 Summary of SF-36v2 Utility Index Scores by HTD – Modified Full Analysis Set	BIA-T-150206030300-sf36-util-htd-mfas.rtf
91	Table 15.2.6.3.4 Summary of SF-36v2 Utility Index Scores – Modified Full Analysis Set	BIA-T-150206030400-sf36-util-tot-mfas.rtf
92	Table 15.2.6.4.1 Summary of SF-36v2 Cardio Benchmark Interpretation – Full Analysis Set	BIA-T-150206040100-sf36-cardio-fas.rtf
93	Table 15.2.6.4.2 Summary of SF-36v2 Cardio Benchmark Interpretation – Modified Full Analysis Set	BIA-T-150206040200-sf36-cardio-mfas.rtf
94	Table 15.2.6.5.1 Shift Table of SF-36v2 Cardio Benchmark Interpretation – Full Analysis Set	BIA-T-150206050100-sf36-cardio-shift-fas.rtf
95	Table 15.2.6.5.2 Shift Table of SF-36v2 Cardio Benchmark Interpretation – Modified Full Analysis Set	BIA-T-150206050200-sf36-cardio-shift-mfas.rtf
Safety Data		
96	Table 15.3.1.1 Overall Summary of TEAEs – Safety Set	BIA-T-150301010000-teae-sum-ss.rtf
97	Table 15.3.1.2 Incidence of TEAEs – Safety Set	BIA-T-150301020000-teae-ss.rtf
98	Table 15.3.1.3 Incidence of Serious TEAEs – Safety Set	BIA-T-150301030000-tesae-ss.rtf
99	Table 15.3.1.4 Incidence of TEAEs of Special Interest – Safety Set	BIA-T-150301040000-teae-si-ss.rtf
100	Table 15.3.1.5 Incidence of Related TEAEs – Safety Set	BIA-T-150301050000-teae-rel-ss.rtf
101	Table 15.3.1.6 Incidence of Related Serious TEAEs – Safety Set	BIA-T-150301060000-tesae-rel-ss.rtf
102	Table 15.3.1.7 Incidence of TEAEs Leading to Down-Titration – Safety Set	BIA-T-150301070000-teae-dt-ss.rtf
103	Table 15.3.1.8 Incidence of TEAEs Leading to Discontinuation – Safety Set	BIA-T-150301080000-teae-disc-ss.rtf
104	Table 15.3.1.9 Incidence of TEAEs Leading to Death – Safety Set	BIA-T-150301090000-teae-death-ss.rtf
105	Table 15.3.1.10 Incidence of TEAEs by Severity – Safety Set	BIA-T-150301100000-teae-bysev-ss.rtf
106	Table 15.3.1.11 Incidence of TEAEs by Relationship to IMP – Safety Set	BIA-T-150301110000-teae-byrel-ss.rtf
107	Table 15.3.2.1.1.1 Summary of Clinical Laboratory Tests: Haematology by HTD– Safety Set	BIA-T-150302010101-lbh-htd-ss.rtf
108	Table 15.3.2.1.1.2 Summary of Clinical Laboratory Tests: Haematology– Safety Set	BIA-T-150302010102-lbh-tot-ss.rtf
109	Table 15.3.2.1.2.1 Summary of Clinical Laboratory Tests: Biochemistry by HTD – Safety Set	BIA-T-150302010201-lbb-htd-ss.rtf
110	Table 15.3.2.1.2.2 Summary of Clinical Laboratory Tests: Biochemistry – Safety Set	BIA-T-150302010202-lbb-tot-ss.rtf
111	SetTable 15.3.2.1.3.1 Summary of Clinical Laboratory Tests: Coagulation by HTD – Safety Set	BIA-T-150302010301-lbco-htd-ss.rtf
112	Table 15.3.2.1.3.2 Summary of Clinical Laboratory Tests: Coagulation – Safety Set	BIA-T-150302010302-lbco-tot-ss.rtf
113	Table 15.3.2.1.4 Summary of Clinical Laboratory Tests: Urinalysis – Safety Set	BIA-T-150302010400-lbu-ss.rtf
114	Table 15.3.2.2.1 Clinical Laboratory Tests: Incidence of Haematology Abnormalities – Safety Set	BIA-T-150302020100-lbh-abnorm-ss.rtf
115	Table 15.3.2.2.2 Clinical Laboratory Tests: Incidence of Biochemistry Abnormalities – Safety Set	BIA-T-150302020200-lbb-abnorm-ss.rtf
116	Table 15.3.2.2.3 Clinical Laboratory Tests: Incidence of Coagulation Abnormalities – Safety Set	BIA-T-150302020300-lbco-abnorm-ss.rtf
117	Table 15.3.2.2.4 Clinical Laboratory Tests: Incidence of Urinalysis Abnormalities – Safety Set	BIA-T-150302020400-lbu-abnorm-ss.rtf
118	Table 15.3.2.3.1 Clinical Laboratory Tests: Shift Table of Haematology Results – Safety Set	BIA-T-150302030100-lbh-shift-ss.rtf
119	Table 15.3.2.3.2 Clinical Laboratory Tests: Shift Table of Biochemistry Results – Safety Set	BIA-T-150302030200-lbb-shift-ss.rtf

120	Table 15.3.2.3.3 Clinical Laboratory Tests: Shift Table of Coagulation Results – Safety Set	BIA-T-150302030300-lbco-shift-ss.rtf
121	Table 15.3.2.3.4 Clinical Laboratory Tests: Shift Table of Urinalysis Results – Safety Set	BIA-T-150302030400-lbu-shift-ss.rtf
122	Table 15.3.3.1.1 Summary of Arterial Blood Gas Analysis by HTD– Safety Set	BIA-T-150303010100-artbg-htd-ss.rtf
123	Table 15.3.3.1.2 Summary of Arterial Blood Gas Analysis – Safety Set	BIA-T-150303010200-artbg-tot-ss.rtf
124	Table 15.3.3.2 Incidence of Arterial Blood Gas Analysis Abnormalities – Safety Set	BIA-T-150303020000-artbg-abnorm-ss.rtf
125	Table 15.3.3.3 Shift Table of Arterial Blood Gas Analysis Results – Safety Set	BIA-T-150303030000-artbg-shift-ss.rtf
126	Table 15.3.3.4.1 Summary of Peripheral Oxygen Saturation (%) by HTD– Safety Set	BIA-T-150303040100-po2-htd-ss.rtf
127	Table 15.3.3.4.2 Summary of Peripheral Oxygen Saturation (%) – Safety Set	BIA-T-150303040200-po2-tot-ss.rtf
128	Table 15.3.4.1.1 Summary of Vital Signs by HTD – Safety Set	BIA-T-150304010100-vs-htd-ss.rtf
129	Table 15.3.4.1.2 Summary of Vital Signs – Safety Set	BIA-T-150304010200-vs-tot-ss.rtf
130	Table 15.3.4.2 Summary of Vital Signs by Pooled HTD – Safety Set	BIA-T-150304020000-vs-htdpool-ss.rtf
131	Table 15.3.4.3.1 Summary of Short-Term IMP Effect on Vital Signs by HTD – Safety Set	BIA-T-150304030100-vs-visitchg-htd-ss.rtf
132	Table 15.3.4.3.2 Summary of Short-Term IMP Effect on Vital Signs – Safety Set	BIA-T-150304030200-vs-visitchg-tot-ss.rtf
133	Table 15.3.4.4.1 Summary of Change in Short-Term IMP Effect on Vital Signs by HTD – Safety Set	BIA-T-150304040100-vs-effchg-htd-ss.rtf
134	Table 15.3.4.4.2 Summary of Change in Short-Term IMP Effect on Vital Signs – Safety Set	BIA-T-150304040200-vs-effchg-tot-ss.rtf
135	Table 15.3.4.5.1 Summary of Physical Measurements by HTD – Safety Set	BIA-T-150304050100-physmeas-htd-ss.rtf
136	Table 15.3.4.5.2 Summary of Physical Measurements – Safety Set	BIA-T-150304050200-physmeas-tot-ss.rtf
137	Table 15.3.5.1.1 Summary of ECG Assessments by HTD – Safety Set	BIA-T-150305010100-ecg-htd-ss.rtf
138	Table 15.3.5.1.2 Summary of ECG Assessments – Safety Set	BIA-T-150305010200-ecg-tot-ss.rtf
139	Table 15.3.5.2.1 Summary of Short-Term IMP Effect on ECG Assessments by HTD – Safety Set	BIA-T-150305020100-ecg-visitchg-htd-ss.rtf
140	Table 15.3.5.2.2 Summary of Short-Term IMP Effect on ECG Assessments – Safety Set	BIA-T-150305020200-ecg-visitchg-tot-ss.rtf
141	Table 15.3.5.3.1 Summary of Change in Short-Term IMP Effect on ECG Assessements by HTD – Safety Set	BIA-T-150305030100-ecg-effchg-htd-ss.rtf
142	Table 15.3.5.3.2 Summary of Change in Short-Term IMP Effect on ECG Assessements – Safety Set	BIA-T-150305030200-ecg-effchg-tot-ss.rtf
143	Table 15.3.5.4.1 Incidence of ECG Abnormalities – Safety Set	BIA-T-150305040100-ecg-abnorm-ss.rtf
144	Table 15.3.5.4.2 Shift Table of ECG Abnormalities – Safety Set	BIA-T-150305040200-ecg-shift-ss.rtf
145	Table 15.3.5.4.3 Shift Table of Within-Visit ECG Abnormalities – Safety Set	BIA-T-150305040300-ecg-shift-visit-ss.rtf
146	Table 15.3.6 Summary of Physical Examination Findings – Safety Set	BIA-T-150306000000-pe-ss.rtf
147	Table 15.3.7.1 Summary of Scleroderma Scarring by HTD – Safety Set	BIA-T-150307010000-sclero-htd-ss.rtf
148	Table 15.3.7.2 Summary of Scleroderma Scarring – Safety Set	BIA-T-150307020000-sclero-tot-ss.rtf
149	Table 15.3.8.1 Summary of mRSS by HTD – Safety Set	BIA-T-150308010000-mrss-htd-ss.rtf
150	Table 15.3.8.2 Summary of mRSS – Safety Set	BIA-T-150308020000-mrss-tot-ss.rtf

10.2 Listings

Appendix listings defined below will be provided to the sponsor in separate .rtf files for each output.

No	Listing Identifier, Title	Output file
Demographic and Study Population Data		
1	Listing 16.2.1.1.1 Patient Disposition – Safety Set	BIA-L-1602010101-disp-ss.rtf
2	Listing 16.2.1.1.2 Screening Failures – Enrolled Set	BIA-L-1602010102-scrfail-enr.rtf
3	Listing 16.2.1.2 Patient Visits – Enrolled Set	BIA-L-1602010200-visits-enr.rtf
4	Listing 16.2.1.3.1 Major Protocol Deviations – Safety Set	BIA-L-1602010301-protdev-ss.rtf
5	Listing 16.2.1.3.2 Patients Affected by the COVID-19 Pandemic – Safety Set	BIA-L-1602010302-protdev-covid-ss.rtf
6	Listing 16.2.1.3.3 Inclusion Criteria Not Met and Exclusion Criteria Met – Enrolled Set	BIA-L-1602010303-ie-enr.rtf
7	Listing 16.2.1.4 Exclusions from Analysis Sets – Enrolled Set	BIA-L-1602010400-anlset-excl-enr.rtf
8	Listing 16.2.1.5 Demographics and Baseline Characteristics – Enrolled Set	BIA-L-1602010500-demo-enr.rtf
9	Listing 16.2.1.6 Disease Characteristics – Enrolled Set	BIA-L-1602010600-diseasechar-enr.rtf
10	Listing 16.2.1.7 Medical History – Enrolled Set	BIA-L-1602010700-mh-enr.rtf
11	Listing 16.2.1.8 Medications and Therapies – Enrolled Set	BIA-L-1602010800-conmed-enr.rtf
12	Listing 16.2.2.1 Drug Accountability– Safety Set	BIA-L-1602020100-da-ss.rtf
13	Listing 16.2.2.2 Exposure to IMP and Compliance – Safety Set	BIA-L-1602020200-imp-compl-ss.rtf
Efficacy Data		
14	Listing 16.2.3.1 Right Heart Catheterization Parameters – Enrolled Set	BIA-L-1602030100-rhc-enr.rtf
15	Listing 16.2.3.2 6-Min Walking Test – Enrolled Set	BIA-L-1602030200-6mwt-enr.rtf
16	Listing 16.2.3.3 Biomarker NT-proBNP – Enrolled Set	BIA-L-1602030300-biomarker-enr.rtf
17	Listing 16.2.3.4 Echocardiography – Enrolled Set	BIA-L-1602030400-echo-enr.rtf
18	Listing 16.2.3.5 NYHA/WHO Functional Class – Enrolled Set	BIA-L-1602030500-whofc-enr.rtf
19	Listing 16.2.3.6 SF-36v2 – Enrolled Set	BIA-L-1602030600-sf36-enr.rtf
Safety Data		
20	Listing 16.2.4.1.1 Adverse Events: MedDRA Coding	BIA-L-1602040101-aecod.rtf
21	Listing 16.2.4.1.2 Adverse Events: General – Enrolled Set	BIA-L-1602040102-ae-enr.rtf
22	Listing 16.2.4.1.3 Non-Serious Adverse Events – Safety Set	BIA-L-1602040103-nsae-ss.rtf
23	Listing 16.2.4.1.4 Serious Adverse Events – Safety Set	BIA-L-1602040104-sae-ss.rtf
24	Listing 16.2.4.1.5 TEAEs of Special Interest - Safety Set	BIA-L-1602040105-teae-si-ss.rtf
25	Listing 16.2.4.1.6 AEs Leading to Discontinuation – Safety Set	BIA-L-1602040106-ae-disc-ss.rtf
26	Listing 16.2.4.1.7 AEs Leading to Death – Safety Set	BIA-L-1602040107-ae-death-ss.rtf
27	Listing 16.2.4.2.1 Laboratory Data: Haematology – Enrolled Set	BIA-L-1602040201-lbh-enr.rtf
28	Listing 16.2.4.2.2 Laboratory Data: Biochemistry – Enrolled Set	BIA-L-1602040202-lbb-enr.rtf
29	Listing 16.2.4.2.3 Laboratory Data: Coagulation – Enrolled Set	BIA-L-1602040203-lbco-enr.rtf
30	Listing 16.2.4.2.4 Laboratory Data: Urinalysis – Enrolled Set	BIA-L-1602040204-lbu-enr.rtf

31	Listing 16.2.4.2.5 Laboratory Data: Microscopy – Enrolled Set	BIA-L-1602040205-lbmicro-enr.rtf
32	Listing 16.2.4.2.6 Laboratory Data: Pregnancy Tests – Enrolled Set	BIA-L-1602040206-lbpreg-enr.rtf
33	Listing 16.2.4.3 Arterial Blood Gas Analysis – Enrolled Set	BIA-L-1602040300-artbg-enr.rtf
34	Listing 16.2.4.4 Vital Signs – Enrolled Set	BIA-L-1602040400-vs-enr.rtf
35	Listing 16.2.4.5 Electrocardiogram – Enrolled Set	BIA-L-1602040500-ecg-enr.rtf
36	Listing 16.2.4.6 Physical Examinations – Enrolled Set	BIA-L-1602040600-pe-enr.rtf
37	Listing 16.2.4.7 Number of Digital Scars – Enrolled Set	BIA-L-1602040700-scars-enr.rtf
38	Listing 16.2.4.8 Modified Rodnan Skin Score – Enrolled Set	BIA-L-1602040800-mrss-enr.rtf

10.3 Figures

Appendix figures defined below will be provided to the sponsor in separate .rtf files for each output.

No	Figure Identifier, Title	Output file
Demographic and Study Population Data		
1	Figure 15.1.1 Flow Chart of Patient Disposition – Enrolled Set	BIA-F-15010100-disp-enr.rtf
2	Figure 15.1.2 Flow Chart of Analysis Sets – Enrolled Set	BIA-F-15010200-anlset-enr.rtf
Efficacy Data		
3	Figure 15.2.1.1 Box-Whisker Plot of NT-proBNP by Pooled HTD – Full Analysis Set	BIA-F-15020101-biomarker-htdpool-fas.rtf
4	Figure 15.2.1.2 Box-Whisker Plot of NT-proBNP by Pooled HTD – Modified Full Analysis Set	BIA-F-15020102-biomarker-htdpool-mfas.rtf
5	Figure 15.2.2.1 Norm-Based SF-36v2 Domain Scores by Visit – Full Analysis Set	BIA-F-15020201-sf36-norm-fas.rtf
6	Figure 15.2.2.2 Norm-Based SF-36v2 Domain Scores by Visit – Modified Full Analysis Set	BIA-F-15020202-sf36-norm-mfas.rtf
7	Figure 15.2.3.1 SF-36v2 Cardio Benchmark Interpretation by Visit – Full Analysis Set	BIA-F-15020301-sf36-cardio-fas.rtf
8	Figure 15.2.3.2 SF-36v2 Cardio Benchmark Interpretation by Visit – Modified Full Analysis Set	BIA-F-15020302-sf36-cardio-mfas.rtf
Safety Data		
9	Figure 15.3.1 Vital Signs Median Change from Baseline – Safety Set	BIA-F-15030100-vs-med-ss.rtf

SIGNATURES

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