Division	:	Worldwide Development
Information Type	:	Reporting and Analysis Plan (RAP)
Title	:	Reporting and Analysis Plan for Study to elucidate the association of the Renin-angiotensin system and right ventricular function in mechanically ventilated patients
Compound Number	:	GSK2586881
Effective Date	:	30-JUL-2019

Description:

- The purpose of this RAP is to describe the planned analyses and output to be included in the Clinical Study Report for Protocol 205821.
- The final RAP has been written with the knowledge that the study / project had been terminated early and describes the agreed strategy of only reporting the primary and secondary outcomes.
- This RAP will be provided to the study team members to convey the content of the SAC deliverable.
- This RAP also captures additional clarifications / details to the Critical components version (e.g. clarifies the algorithm for choosing between TTE and TOE results per variable)

RAP Author(s):

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Approver	Date	Review Confirmation Method
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Clinical Statistics and Clinical Programming Line Approvals:

Approver	Date	Approval Method
PPD Director (Respiratory, Clinical Statistics)	30-JUL-2019	e-signature (PharmaTMF)
PPD Programming Manager (Clinical Programming)	29-JUL-2019	e-signature (PharmaTMF)

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1. INTRODUCTION

The purpose of this reporting and analysis plan (RAP) is to describe the analyses to be included in the Clinical Study Report for Protocol 205821.

The study was terminated early and the agreed reporting strategy is to only produce outputs to support the primary and secondary objectives/endpoints. Selected A&R datasets containing the exploratory endpoints may still be produced to enable future access requests and analyses of such endpoints.

Note: All data displays (Tables, Figures & Listings) will use the term "Subject" which reflects CDISC and GSK Data Display Standards terminology, rather than the term "Participant" (although the terms are interchangeable in this RAP document and its associated datasets/outputs).

Revision Chronology:		
2016N294782_00	26-APR-2017	Original
2016N294782_01	02-JUN-2017	Amendment 1
2016N294782_02	27-NOV-2017	Amendment 2
2016N294782_03	27-FEB-2019	Amendment 3

2. SUMMARY OF KEY PROTOCOL INFORMATION

2.1. Changes to the Protocol Defined Statistical Analysis Plan

Except for the planned modelling of the Ang II / Ang(1-7) ratio there were no changes or deviations to the originally planned statistical analysis specified in the protocol amendment 3 (27-FEB-2019).

The protocol originally stated that the ratio of Ang II / Ang(1-7) would be derived for each participant and formally modelled using the same approach as the primary endpoint. However, the statistical model fitting will not take place. Modelling the ratio does not adequately represent aspects of the underlying biology. For example if a participants Ang II and Ang(1-7) values were both 10 pg/mL and another's were both 10000 pg/mL their derived ratios would be identical (one). Modelling a simple ratio naïvely implies the same significance and biological effect for each participant, even though they are at completely different places on the underlying concentration response curves. The additional approach to jointly analyzing Ang II and Ang (1-7) described in the protocol (and in Section 7.2.5.1) will now be the sole approach to modelling Ang II / Ang(1-7) ratios. Note: The simple summary statistics for the Ang II / Ang(1-7) ratios will still be produced because they capture information about enzyme activity.

Protocol amendment #3 (27-FEB-2019) increases the duration that a participant may be mechanically ventilated, before they are included in the study – from ≤24 hours to ≤48 hours. This change has been made to assist enrolment of participants into the study, but the sponsor considers that it will not impact the objectives of the study. Informal checks may be made by the study statistician to confirm this assumption (e.g. visual comparisons

of results grouped by protocol version enrolled under). Any such checks would not be formally documented/reported unless a difference was apparent in which case the likely approach would be to perform additional sensitivity analyses with appropriate adjustments to the original output(s) to account for the protocol version.

At the time of writing the Critical Components RAP recruitment was going to commence under Protocol Amendment #1 and switch to amendment #2 as soon as possible. The initial set of subjects enrolled under amendment #1 have a reduced number of endpoints available because amendment #2 added the following endpoints:

CRF form	Questions / Endpoint
Participant Status	Is the patient being managed with extracoporeal membrane oxygenation?
	Is the patient being managed with extracorporeal CO2 (ECCO2R) removal?
	What is the GI index?
LAB ABGS	PH
	Base excess

The critical components RAP indicated sites may re-consent subjects recruited under protocol amendment #1 and enter any new data into the eCRF and suggested an approach for imputing missing data. However, the missing data approach described in the critical components RAP may not be appropriate to the individual subject's circumstances and so the default will now be to leave any data as missing/not applicable. Only 2x subjects were recruited under protocol amendment #1 (PPD and PPD) so the impact of leaving their data missing/not applicable is unlikely to be influential on the outcome, and following the early termination decision these exploratory endpoints are not going to be analyzed further.

2.2. Study Objective(s) and Endpoint(s)

Exploratory objectives/endpoints have been included for completeness, but due to the early termination of the study will not be analysed further (unless they naturally form part of an output related to a primary or secondary objective, in which case they may be included on a case by case basis).

Objectives	Endpoints
Primary Objectives	**Primary Endpoints**
• To evaluate the association between plasma Ang II levels and RV function in mechanically ventilated participants.	• Ang II levels • Echocardiographic measures: • Ratio of right ventricular to left ventricular end-diastolic area

Objectives	Endpoints
	• Paradoxical septal motion • Pulmonary arterial systolic pressure (PASP) estimated from transtricuspid pressure and right atrial pressure or inferior vena cava (IVC) diameter (whichever is available) Up to and including Day 3 of observation
Secondary Objectives	**Secondary Endpoints**
• To define the incidence of ACP and PCD in mechanically ventilated participants.	• Presence of PCD, ACP (severe PCD) and severe ACP Up to and including Day 3 of observation

• To evaluate the association between plasma Ang(1-7) levels, Ang II/ Ang(1-7) ratio and RV function in mechanically ventilated participants.	• Ang(1-7) levels
	• Ang II/ Ang(1-7) ratio
	• Echocardiographic measures:
	  • Ratio of right ventricular to left ventricular end-diastolic area
	  • Paradoxical septal motion
	  • PASP estimated from transtricuspid pressure and right atrial pressure or IVC diameter (whichever is available)
	Up to and including Day 3 of observation

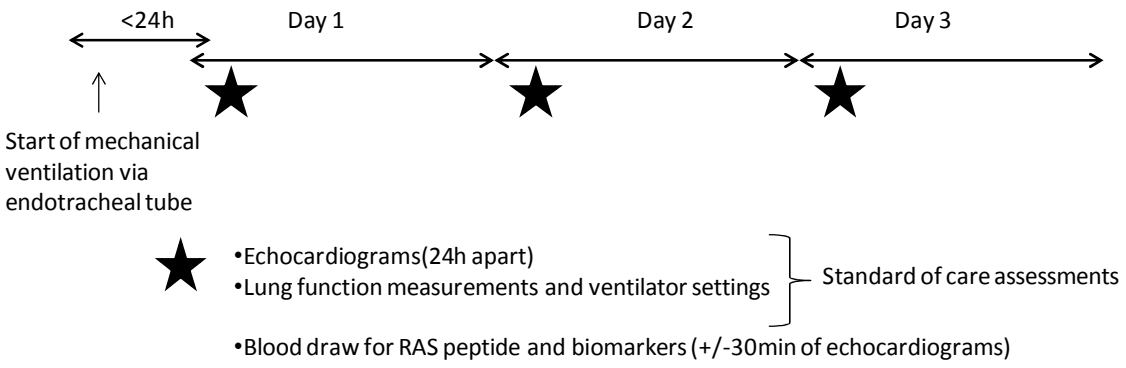
Exploratory Objectives	**Exploratory Endpoints**

• To evaluate the association between plasma Ang II and Ang(1-7) levels and other measures of right ventricular function in mechanically ventilated participants.	• Ang II, Ang(1-7) levels
	• Echocardiographic measures:
	  • Paradoxical septal motion (systolic eccentricity index)
	  • Maximal velocity of s wave (tissue Doppler imaging) at the tricuspid annulus
	  • Fractional area contraction (end diastolic area minus end systolic area normalised to end diastolic area)
	  • Acceleration time of RV ejection flow
	  • Mean acceleration of RV ejection flow (maximum velocity/ acceleration time) at end-expiration and end-inspiration
	  • Inferior vena cava (IVC) diameter at end-expiration (if available)
	  • Respiratory variations of RV velocity time integral (end-expiration minus end-inspiration normalised to end-expiration)
	  • Tricuspid annular plane systolic excursion (TAPSE)
	Up to and including Day 3 of observation
	
	Note: "Mean acceleration of RV ejection flow at end expiration" is omitted from the list of exploratory endpoints in the protocol but is collected as part of the study and may be analysed in the same manner as the above exploratory endpoints

• To evaluate the association between plasma Ang II and Ang(1-7) levels and other measures of cardiac function and pulmonary hemodynamics in mechanically ventilated participants.	• Ang II and Ang(1-7) • Central venous pressure (if available) • Mean arterial pressure • Echocardiographic measures:

Objectives	Endpoints
	• Respiratory variations of diameter of superior vena cava • Cardiac output (pulsed wave Doppler, left ventricle (LV) outflow track) • LV ejection fraction • LV Velocity (E') tissue doppler imaging (TDI) of annulus • LV early to late ventricular filling velocities (E/A) Up to and including Day 3 of observation
• To characterise disease severity by clinical assessment.	• Oxygen saturation (SpO_2) via pulse oximetry • pH of arterial blood gases • PaO_2/FiO_2 ratio • $PaCO_2$ • Peak and plateau ventilator pressure • PEEP • Oxygenation index • Static respiratory system compliance • Mean airway pressure • Driving pressure (plateau pressure – total PEEP) • Clinical Safety labs • Vital Signs Up to and including Day 3 of observation
• To characterise levels of organ dysfunction.	Sequential Organ Failure Assessment (SOFA) score Up to and including Day 3 of observation
• To assess the association of cardiac and inflammatory biomarkers and RV function.	• PCD and ACP status • Biomarkers: for example, cardiac biomarkers (B-type natriuretic peptide (BNP)) or inflammatory biomarkers (cytokines such as IL-6, IL-8 and sTNFR1) may be analysed as sample availability allows Up to and including Day 3 of observation
• To evaluate the association between additional markers of the RAS system (if samples permit) and primary/secondary or exploratory endpoints.	Markers could include but are not limited to: Ang(1-5) in relation to primary, secondary or exploratory endpoints if sufficient sample is available Up to and including Day 3 of observation
• To characterize health outcome measures.	• Duration of intubation • Length of hospital stay • ICU length of stay • Ventilator free days • In ICU and hospital mortality Up to 28 days after first echocardiogram
• To assess lung ventilation and perfusion distribution (in selected site only).	• Lung regional ventilation and perfusion with global inhomogeneity (GI) index Up to and including Day 3 of observation

2.3. Study Design

Overview of Study Design and Key Features **Note: Protocol Amendment #3 extends allowable duration from <24h to <48h (start of mechanical ventilation)**	
	
Design Features	• "Low-interventional" study • No investigational product will be administered • A maximum of 150 participants are anticipated to be enrolled • Participants enrolled following intubation and mechanical ventilation • Participants evaluated over a 3-day period using standard-of-care investigations, including TTE and/or TOE echocardiography • Additional investigations limited to blood samples for RAS peptides and other disease biomarkers • Purpose is to investigate the association of RAS peptides with indicators of right ventricular (RV) function in participants requiring acute mechanical ventilation
Dosing	• Not applicable
Treatment Assignment	• Not applicable
Interim Analysis	• Due to the early termination of the study no interim analysis will take place.

2.4. Statistical Hypotheses / Statistical Analyses

This study is designed to test the hypothesis that an association exists between RAS peptides, primarily plasma Ang II and Ang(1-7) levels, and RV function in mechanically ventilated patients. No formal statistical hypotheses are being tested in this exploratory study.

3. PLANNED ANALYSES

3.1. Interim Analyses

Table 1 Interim analyses

None of the planned interim analyses will take place in study 205821 due to the decision to terminate the study early. The original interim analysis strategy was going to examine data at • IA1: Approximately 25 evaluable subjects (Note: This was scheduled for Jan 2019 but delayed due to technical issues with the assay for RAS peptides and the study was terminated before the RAS data became available) • IA2: Approximately 50 evaluable subjects. • IA3 (Optional): Approximately 100 evaluable subjects

3.2. Final Analyses

The final planned analyses will be performed after the completion of the following sequential steps:

1. All subjects have completed the study as defined in the protocol (i.e. after the last participant has completed their 28-day follow-up).
2. All required database cleaning activities have been completed and final database release and database freeze has been declared by Data Management.
3. Protocol deviation reviews have taken place (See Section 4.1)

(Note: as there is no randomisation and no treatment intervention, the usual steps pertaining to unblinding and release of randomisation codes do not apply.)

4. ANALYSIS POPULATIONS

Population[1]	Definition / Criteria	Analyses Evaluated
Screened	All participants who have been screened.	• To aid construction of Consort diagram in any publication
Enrolled	All participants who had passed screening and who had appropriate informed consent (via any of the processes described in the protocol).	• Summary of Subject Status and Reason for Study Withdrawal • Summary of Study Populations • Summary of Exclusions from the

Population[1]	Definition / Criteria	Analyses Evaluated
		Safety/Completed/ Evaluable Populations
Safety	All participants for whom at least one echocardiograph and/or blood sample has been taken, and who did not retrospectively withdraw the consent.	• Study population (excl. specific tables mentioned below) • Safety
Evaluable	All participants for whom PASP, RV size ratio, Ang II and Ang(1-7) data have been recorded for at least one study time point, and who did not retrospectively withdraw the consent (and who still had at least one study time point of data remaining after accounting for any prohibited concomitant medications (for example but not limited to renin inhibitors, ARBs or ACE inhibitors) – See Section 10.1.1).	• Pharmacodynamic/ Biomarker (excl. disease diagnosis status)
Evaluable with Prohibited Con Meds	All participants in the Evaluable population plus any participants who were excluded from the Evaluable population because of prohibited concomitant medications (for example but not limited to renin inhibitors, ARBs or ACE inhibitors)	• Sensitivity for Primary analysis (conditional on number of prohibited con meds)
Completed[2]	All participants for whom PASP, RV size ratio, Ang II, and Ang(1-7) data have been recorded for all three study days.	• Disease diagnosis status
At Risk	For the purpose of evaluating ACP/PCD and ARDS incidence rates the participants who satisfy 1) PASP and RV size ratio recorded for all three study days (regardless of the Ang II and Ang(1-7) status) and/or 2) databased ACP/PCD and/or ARDS assessment during the study period (even if they do not have three days' worth of study assessments for the above echo outcomes) provided consent is not withdrawn.	• Disease diagnosis status

NOTES :

1. Please refer to Section 10.10: List of Data Displays which details the population to be used for each display being generated.
2. Modifications to the Completed population listed in study protocol to assist with production of summary and incidence rate calculations for ACP/PCD status (include creating a new population "At Risk" to be used with selected incidence rate displays that is independent of the RAS biomarker availability). The remaining completed population is not formally used, but will provide feasibility information (i.e. could we measure items reliably in the "real world" of the ICU)

4.1. Protocol Deviations

Important protocol deviations (including deviations related to study inclusion/exclusion criteria, conduct of the trial, patient management or patient assessment) will be summarised and listed.

Protocol deviations will be tracked by the study team throughout the conduct of the study in accordance with the current version of the Protocol Deviation Management Plan.

1. Data will be reviewed prior to freezing the database to ensure all important deviations are captured and categorised on the protocol deviations dataset.
2. This dataset will be the basis for the summaries and listings of protocol deviations.

A separate summary and listing of all inclusion/exclusion criteria deviations will also be provided. This summary will be based on data as recorded on the inclusion/exclusion page of the eCRF.

5. CONSIDERATIONS FOR DATA ANALYSES AND DATA HANDLING CONVENTIONS

5.1. Study Treatment & Sub-group Display Descriptors

No study treatment is being administered in this study. However, GSK's standard SAS macro reporting tools will still assign each participant a set of treatment variables ("No treatment"). There will not be any treatment comparisons. Tables and Figures will only be presented with a single "No Treatment" column unless they are presented by covariate groupings or subgroups as described in Section 5.3 below.

5.2. Baseline Definitions

At present, no analyses involving a change from baseline are planned since there is no treatment intervention. However, for each endpoint the Baseline will be defined as the earliest evaluable timepoint (if a baseline is required).

5.3. Examination of Covariates, Other Strata and Subgroups

5.3.1. Covariates and Other Strata

The set of potential covariates and other strata that may be used in descriptive summaries and statistical analyses, some of which may also be used for subgroup analyses are large.

To facilitate flexible model building and analyses a A&R dataset(s) of potential covariate and grouping variables should be constructed (called ARDATA.ALLCVTS). It would be expected to contain three records per participant (Study Day 1, Day 2 and Day 3 values for time-varying covariates), with subject-level covariates repeated across the three records (a flagging variable should also be created to subset the main dataset to extract one record per subject if analyses only involve subject-level covariates); an illustrative example is shown below

Subject	Visit	SUBJLEV	AGE	SEX	SAPSII	ARDSX	ARDSI	…
PPD	Day 1	1	35	M	12	N	N	…
	Day 2	0	35	M	12	N	N	…
	Day 3	0	35	M	12	N	N	…
	Day 1	1	43	F	16	Y	N	…
	Day 2	0	43	F	16	Y	Y	…
	Day 3	0	43	F	16	Y	Y	…
	Day 1…	1	54…	M…	7…	N…	N…	…

Guidance for its construction/algorithms are given in Section 10.6.10.

5.3.2. Examination of Subgroups

The following list of subgroups may be used in descriptive summaries and statistical analyses. Additional subgroups of clinical interest may also be considered based on items in ARDATA.ALLCVTS.

- If the percentage of subjects is small within a particular subgroup, then the subgroup categories may be refined prior to producing the final version of the planned output.
- If the category cannot be refined further, then descriptive rather than statistical comparisons may be performed for the particular subgroup.

Subgroup [ARDATA.ALLCVTS Variable]	Categories
ARDS Status [ARDSX]	ARDS, No ARDS (diagnosed at any time in the study)
Any PCD or ACP [PCDACPX & PCDACPI]	Yes; No (where Yes = Participant had disease state of PCD or ACP) Group can be applied across all study visits [PCDACPX] or to specific days [PCDACPI]
No PCD or ACP [NORVDYSX & NORVDYSI]	Yes; No (where Yes = Participant did not have a disease state of PCD or ACP) Group can be applied across all study visits [NORVDYSX] or to specific days [NORVDYSI]
PCD [PCDX & PCDI]	Yes; No (where Yes implies the worst diagnosis received was Moderate PCD across all study visits [PCDX variable] and Yes implies the worst diagnosis received on the corresponding study day was Moderate PCD [PCDI variable])
ACP [ACPX & ACPI]	Yes; No (where Yes implies the worst diagnosis received was Non-severe ACP across all study visits [ACPX variable] and Yes implies the worst diagnosis received on the corresponding study day was Non-severe ACP [ACPI variable])
Severe ACP [SEVACPX & SEVACPI]	Yes; No (where Yes implies the worst diagnosis received was Severe ACP across all study visits [SEVACPX variable] and Yes implies the worst diagnosis received on the corresponding study day was Severe ACP [SEVACPI variable])
ARDS and No PCD or ACP [ARDNOX]	Yes; No (where Yes implies participant received an ARDS diagnosis but never had PCD or ACP at any time in the study)
ARDS and PCD [ARDPCDX]	Yes; No (where Yes implies participant received an ARDS diagnosis but the worst case diagnosis was Moderate PCD at any time in the study)
ARDS and ACP [ARDACPX]	Yes; No (where Yes implies participant received an ARDS diagnosis but the worst case diagnosis was Non-severe ACP at any time in the study)
ARDS and Severe ACP [ARDSACPX]	Yes; No (where Yes implies participant received an ARDS diagnosis and the worst case diagnosis was Severe ACP at any time in the study)

5.4. Multiple Comparisons and Multiplicity

No adjustments for multiplicity will be made.

5.5. Display order of Echocardiography endpoints (source: SI.CV)

Whenever multiple Echocardiography endpoints (found in the CV dataset) are required within the same Table/Listing/Figure and the display ordering is not explicitly stated the following display ordering should be apply:

Priority Order of presentation	**CVTSTCD**	**Description (Note: the actual label/text would be taken from dataset manager at the time of reporting)**
1 (1st in T/L/F)	AH001CAL	Pulmonary Artery Systolic Pressure
NA	AH001	Pulmonary Artery Systolic Pressure (eCRF)
2	AK001	Ratio of RV to LV End-Diastolic Area
3	AK002	Paradoxical Septal Motion
4	AK015	Have PCD or ACP
5	AK016	Severity of PCD or ACP
6	AK003	Systolic Eccentricity Index
7	AK006	Max Velocity S Wave at Tricuspid Annulus
8	AK007	Fractional Area Contraction
9	AK008	Acc Time of RV Ejection Flow (Tacc)
10	TAPSE	Tricuspid Annular Plane Systol Excursion
11	AK004	Transtricuspid Pressure Gradient (TPG)
12	AK009	Mean Acc of RV Ejection Flow at End Exp
13	AK010	Mean Acc of RV Ejec Flow at End Exp-Insp
14	AK005	IVC Diameter at End Expiration
15	AK011	Respiratory Variations of RV VTI
16	AK012	Respiratory Variations of SVC Diameter
17	CARDOUT	Cardiac Output (CO)
18	LVEJ	Left Ventricular Ejection Fraction
19	AK013	LV Velocity (E') Tissue of Annulus
20	AK014	LV Early to Late Filling Velocities
21	ERATRIAP	Estimated Right Atrial Pressure
22	AI001	Measured Right Atrial Pressure
23	RAP	Right Atrial Pressure
24	AD003	Central Venous Pressure (CVP)
NA	AH001src	<Do not display; variable used to track source of PASP>
Note: Only display AH001CAL but label it using the AH001 label text (this is because the auto derived eCRF value for PASP; supplied as AH001; may not capture all data cases reliably and so will be re-calculated)		

5.6. Other Considerations for Data Analyses and Data Handling Conventions

Other considerations for data analyses and data handling conventions are outlined in the appendices:

Section	Component
10.3	Appendix 3: Assessment Windows
10.4	Appendix 4: Study Phases and Treatment Emergent Adverse Events
10.5	Appendix 5: Data Display Standards & Handling Conventions
10.5	Appendix 6: Derived and Transformed Data
10.7	Appendix 7: Reporting Standards for Missing Data
10.8	Appendix 8: Values of Potential Clinical Importance

6. STUDY POPULATION ANALYSES

6.1. Overview of Planned Study Population Analyses

The study population analyses will be based on the Enrolled population, unless otherwise specified.

Study population analyses including analyses of participant disposition, protocol deviations, demographic and baseline characteristics, and prior and concomitant medications will be based on GSK Core Data Standards. Details of the planned displays are presented in Appendix 10: List of Data Displays.

Note: Local French law prohibits the collection of Race information, so the race/ethnicity variables would be blank in the datasets and displays.

7. PHARMACODYNAMIC AND BIOMARKER ANALYSES

7.1. Primary Pharmacodynamic/Biomarker Analyses

7.1.1. Endpoint / Variables

The following variables may be included in the statistical model:

- Independent variable of interest:
  - Ang II on Study Days 1, 2 and 3 (after any imputations)
- Dependent (bivariate) variable of interest:
  - PASP on Study Days 1, 2 and 3
  - RV size ratio on Study Days 1, 2 and 3
- Potential covariates (to be explored, order listed indicates expected importance):
  - Centre
  - Age at screening
  - Sex
  - Use of vasopressors on Study Days 1, 2 and 3
  - PEEP on Study Days 1, 2 and 3
  - Proning status on Study Days 1, 2 and 3
  - BMI at screening
  - Concurrent use of inhaled nitric oxide on Study Days 1, 2 and 3
  - Mean airway pressure on Study Days 1, 2 and 3
  - Tidal Volume on Study Days 1, 2 and 3
  - ECMO on Study Days 1, 2 and 3
  - ECCO2R on Study Days 1, 2 and 3
  - SAPS II at screening
  - PaO2/FiO2 on Study Days 1, 2 and 3

Additionally, the presence/absence of paradoxical septal motion on Study Days 1, 2 and 3 may be assessed on an informal visual basis.

Note: Since the study was terminated early there may not be sufficient information in the collected data to explore covariate analyses and the covariate exploration process may not take place at all.

7.1.2. Summary Measure

The posterior predictive probability of RV dysfunction in a hypothetical individual for a pre-determined “pre-dose” Ang II value,

The posterior predictive probability of RV dysfunction in a hypothetical individual for a pre-determined “post-dose” Ang II value, and

The difference between the above two probabilities.

7.1.3. Population of Interest

The primary pharmacodynamic analyses will be based on the Evaluable population, unless otherwise specified.

7.1.4. Strategy for Intercurrent (Post-Randomization) Events

Intercurrent events which may lead to missing data for all variables (such as death) would not impact the primary analysis since the planned modelling assumes no lag between RAS peptide concentrations and effect on RV dysfunction (i.e. RAS concentrations on day 1 are not used to predict RV dysfunction on day 2 and if death occurs between day 1 and day 2 this will not impact the planned modelling).

Intercurrent events such as taking a non-permitted con med may require exclusion of post medication data if the con med had the potential to confound the true relationship between RAS peptide and RV dysfunction.

Intercurrent events that result in missing data for one or more of the variables required for the primary analysis (e.g. ECHO view not suitable, lost RAS sample) will result in the exclusion of the impacted timepoint as there is not sufficient information to postulate a suitable imputation model.

7.1.5. Statistical Analyses / Methods

The purpose of the primary analysis is to evaluate the association of biomarkers of the Renin Angiotensin System (RAS), specifically Ang II but secondarily Ang(1-7) with measures of RV function (specifically PASP and RV size ratio in the primary model, and also paradoxical septal motion on a more informal visual basis), whilst taking into account any observable variables that may confound the relationship between the two concepts.

RV function will be measured using PASP and RV size ratio. The general principle underlying all the analyses of RV function and RAS peptide biomarkers will be:

- model the joint distribution of PASP and RV size ratio as a function of the RAS peptide(s) in question (together with confounding variables also included as covariates),
- choose reference values of the RAS peptide(s) in question and estimate a posterior distribution of PASP and RV size ratio for those given values, and
- use the posterior distribution to determine the probability of RV dysfunction (for a future individual participant), defined (following the definition of moderate/severe pulmonary circulatory disease given in Boissier, 2013) as:
    - PASP > 40 mmHg
    - RV size ratio > 0.6

The advantage of this method is that all the information on the continuous scales of PASP and RV size ratio is maintained throughout the modelling process, and that dichotomising

participants into binary categories takes place at the end after the modelling has been done.

In order to evaluate the estimated effect of administering rhACE2 on RV outcomes (via its effect on the RAS peptides), predictions for the probability of RV dysfunction will be calculated for specific, pre-determined values of RAS peptide measurements that represent reasonable estimates for each RAS peptide both before and after dosing with rhACE2 in this patient population. These values will be hereafter referred to as *reference values* (the first reference value, hereafter referred to as the *pre-dose reference* and the second reference value, hereafter referred to as the *post-dose reference* reflect). Note: the terminology "pre-dose" and "post-dose" should not be taken to imply that investigational product is used in this study; these values should be taken as being borrowed from that interventional study. Furthermore, the term "reference values" in this context should not be interpreted as upper or lower limits to the normal range. They represent the best guess available for a patient's typical experience before and after rhACE2 administration.

Initially, the basic model described below would be attempted. If model convergence issues are encountered with that model it is unlikely that more complicated models involving covariates would fit, and covariate exploration may not be attempted. However, if covariate exploration is attempted the addition of covariates would be dependent on a combination of changes in DIC and expert judgement (including the biological rationale for the covariate and/or global structures of other statistical models fitted to comparable data types). To simplify reporting only model outputs from the final selected model would be formally reported (included in the CPSR), but a description / short justification for the selected model would be included in the CPSR.

At the time of writing, the reference values for Ang II (and for completeness Ang(1-7) and Ang(1-5)) were as follows:

	ANG II (pg/mL)	**ANG 1-7 (pg/mL)**	**ANG 1-5 (pg/mL) Optional endpoint**
“Pre-dose” reference value	30.0	2.0	n/a
“Post-dose” reference value	8.0	30.0	n/a

An additional sensitivity analysis (to be computed alongside the above) in case the reference study values are discordant with the observed values will use the observed data to determine the references as follows

Sensitivity	ANG II (pg/mL)	ANG 1-7 (pg/mL)	ANG 1-5 (pg/mL) Optional endpoint
Sensitivity "Pre-dose" reference value	Upper Quartile of Observed ANG II	Lower Quartile of Observed ANG 1-7	Lower Quartile of Observed ANG 1-5
Sensitivity "Post-dose" reference value	Lower Limit of Quantification	Upper Quartile of Observed ANG 1-7	Upper Quartile of Observed ANG 1-5

The relationship between Ang II (as the explanatory variable) and the joint bivariate distribution of PASP and RV size ratio (the outcome variables) will be analysed using a Bayesian multivariate linear regression model.

The multivariate normal model is specified as follows:

$$\begin{pmatrix} y_{it1} \\ y_{it2} \end{pmatrix} \sim MVNormal\left(\begin{pmatrix} \mu_{it1} \\ \mu_{it2} \end{pmatrix}, \Sigma \right)$$

where y_{itj} represents the observed value for the ith participant, the tth time-point and the jth outcome (i.e. $j = 1$ representing PASP and $j = 2$ representing RV size ratio), μ_{itj} represents the expected value for the ith participant, tth time-point ($t = 1,2,3$) and the jth outcome ($j=1$ and $j=2$ as above), and Σ represents a variance-covariance (vcov) matrix for the two outcome variables.

The expected values, μ_{itj}, are modelled as follows:

$$\mu_{itj} = \alpha_j + \beta_j x_i + \gamma_{tj} z_{it}$$

where:

- α_j is the intercept term for the jth outcome (i.e. PASP or RV size),
- β_j represents the vector of slope coefficients for all participant-level variables in the model for the jth outcome,
- x_i represents the vector of observed participant-level variables values for the ith participant (if applicable – initial model structures would not involve such covariates but Age at Screening and Sex would be added first to be consistent with the study protocol),
- γ_{tj} represents the matrix of slope coefficients for all timepoint-level variables in the model for the jth outcome at time-point t,
- z_{it} represents the matrix of observed time-point-level variables for the ith participant at time-point t (e.g. log10- transformed RAS).

The vcov matrix $\boldsymbol{\Sigma}$ is specified within each study participant, as a Kronecker product of the inter- and intra-marker vcov matrices $\boldsymbol{Sigma}$ and $\boldsymbol{Tigma}$, respectively:

$$\boldsymbol{\Sigma} = \boldsymbol{Sigma} \otimes \boldsymbol{Tigma}$$

(the notation $\otimes$ represent the Kronecker product)

The $\boldsymbol{y_{i=1,2}}$ inter-marker vcov matrix

$$\boldsymbol{Sigma} = \begin{pmatrix} \sigma^2_{y_1} & \sigma_{y_1 y_2} \\ \sigma_{y_1 y_2} & \sigma^2_{y_2} \end{pmatrix}$$

assumes a constant inter-marker bivariate correlation, $\rho_{y_1 y_2} = \sigma_{y_1 y_2} / \sqrt{\sigma^2_{y_1} \sigma^2_{y_2}}$, across $\boldsymbol{y_{t,i=1,2}}$ measured at the same $\boldsymbol{t}$. The $\boldsymbol{Sigma}$ vcov matrix structure, when $\boldsymbol{\sigma_{y_1 y_2} = 0}$, implies independence between both markers.

The $\boldsymbol{y_{i=1,2}}$ inter-marker vcov matrix assumed as

$$\boldsymbol{Tigma} = \begin{pmatrix} 1 & \rho & \rho^2 \\ \rho & 1 & \rho \\ \rho^2 & \rho & 1 \end{pmatrix}$$

implies an intra-marker AR(1) process structure with common correlation parameter $\boldsymbol{\rho}$. The dimension of the $\boldsymbol{T}$ is determined by the number of timepoints ($\boldsymbol{t = 1,2,3}$) the $\boldsymbol{y_{i=1,2}}$ marker measurements are measured at. Note: Initial simulation work showed an UN (Unstructured) form of vcov for $\boldsymbol{Tigma}$ results in convergence issues due to parameter estimation issues; hence why AR(1) is preferred. A potential drawback to using Kronecker product is that it forces the inter-marker relationship though time to be the same for both response variables; but the Kronecker product requires estimation of fewer parameters (improved chance of model convergence) and recognises the repeated measures (time) structure whilst allowing it to be handled as a nuisance parameter in the final inferences (albeit with the previous caveat).

Given the above assumptions the $\begin{pmatrix} y_{it1} \\ y_{it2} \end{pmatrix}$ vcov structure is derived as follows:

$$\boldsymbol{\Sigma} = \boldsymbol{Sigma} \otimes \boldsymbol{Tigma} =$$

$$\begin{pmatrix} \sigma^2_{y_1} & \sigma_{y_1 y_2} \\ \sigma_{y_1 y_2} & \sigma^2_{y_2} \end{pmatrix} \otimes \begin{pmatrix} 1 & \rho & \rho^2 \\ \rho & 1 & \rho \\ \rho^2 & \rho & 1 \end{pmatrix} = \begin{pmatrix} \sigma^2_{y_1} * \begin{pmatrix} 1 & \rho & \rho^2 \\ \rho & 1 & \rho \\ \rho^2 & \rho & 1 \end{pmatrix} & \sigma^2_{y_1 y_2} * \begin{pmatrix} 1 & \rho & \rho^2 \\ \rho & 1 & \rho \\ \rho^2 & \rho & 1 \end{pmatrix} \\ \sigma_{y_1 y_2} * \begin{pmatrix} 1 & \rho & \rho^2 \\ \rho & 1 & \rho \\ \rho^2 & \rho & 1 \end{pmatrix} & \sigma^2_{y_2} * \begin{pmatrix} 1 & \rho & \rho^2 \\ \rho & \mathbf{1} & \rho \\ \rho^2 & \rho & 1 \end{pmatrix} \end{pmatrix}$$

Uninformative prior distributions are assigned for α, β, γ, $Sigma$ and $Tigma$ as follows:

- For each α_j outcome variable a normal distribution with mean zero, large variance (e.g. 1E6) would be used as a non-informative prior,
- each element in the vector β is assigned a distribution with the same specifications as for α,
- each element in the matrix γ is assigned a distribution with the same specifications as for α and the elements of β,
- S, defined as the inverse of $Sigma$, is assigned an uninformative Wishart prior distribution: $S \sim Wishart(R, df)$ where: $R = \begin{pmatrix} 0.01 & 0 \\ 0 & 0.01 \end{pmatrix}$ and $df = 3$.
- The $Tigma$ parameter ρ is assigned uninformative uniform prior distribution over $[-1,1]$ interval.
- Note: Simulations suggest that the model convergence is improved if the response variables (or more specifically their covariance parameter estimates) are roughly on the same scale (range). Therefore, if required, the response variables may be re-scaled for model fitting, but model inferences/results should be displayed using the original scale of the response variable.
- Note: Simulation work suggests that model convergence may also be sensitive to the software used (due to the complexities of estimating the vcov parameters and the limitations of Gibbs samplers being most efficient when the priors are conjugate to the likelihood of the parameters; once a Kronecker Product vcov is involved the conjugacy is not spotted automatically by most software). The first intent is to use SAS PROC MCMC, but if that does not work then R may be used (e.g. an appropriate package that implements JAGS) and if R fails then Stan may be used. Although a Bayesian implementation of the above model is desired if convergence issues are encountered then SAS PROC MIXED may be used to estimate the required model parameters (it may also as part of the QC checking of the model)
- Note: For IA1 (and IA2 and final analysis, if required) model simplification may occur to improve model convergence (e.g. γ parameter would only contain terms for the RAS peptides and not other time dependent terms such as separate slopes for each visit and endpoint combination).
- The initial model structure would consist of nine parameters, a slope and intercept for the two linear regressions of RAS biomarker level against outcome (PASP or RV Size raio) (four parameters), four parameters of $Sigma$, and one parameter (ρ) for $Tigma$

Estimates for the posterior distributions of coefficients in the model will be obtained using an MCMC simulation running a suitable number of chains for an appropriate number of iterations each to ensure satisfactory convergence of the MCMC sampling algorithm. Nominally, a minimum of 3 chains would be used to produce the Gelman-Rubin diagnostics, though these numbers may be adjusted as necessary and chain

convergence may require separate model runs (e.g. SAS PROC MCMC requires separate model runs to assess the Gelman-Rubin chain convergence (with a zero burn in); but the final MCMC model used for inference requires a non-zero burn in; necessitating separate modelling runs. However, the final model run should utilise one of the sets of starting parameters used in the Gelman-Rubin investigations).

The corresponding secondary pharmacodynamic analyses (using Ang(1-7), and optionally Ang(1-5), in place of Ang II) and a model including Ang II and Ang(1-7) as joint independent variables of interest may be used to support the primary analysis. Details are provided in Section 7.2.

Posterior estimates for the predictive probability of RV dysfunction will be made for the two sets of reference values of Ang II described above (exception is if joint modelling using Ang II and Ang(1-7) is being attempted). If other covariates are included in the final inference model these predictions should be made using the observed mean value for continuous variables and the observed mode value for categorical variables (exception being terms like CENTRE or SEX which would be predict for the average of the corresponding levels). Note: Observed margins may be used if there is a good clinical rationale to do so (assessed on a covariate by covariate basis).

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.1.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.1.5.1. Statistical Methodology Specification

Endpoint / Variables
• See above
Model Specification
• See above
Model Checking & Diagnostics
• "Bayesian Statistics Best Practice at GSK – Clinical Trials using Bayesian Inference" (effective 20-Apr-2017) gives guidance on model checking and diagnostics that would be applicable to the MCMC modelling in this study.
Model Results Presentation
• See above
Subgroup Analyses
• Not planned.
Sensitivity and Supportive Analyses
• See above. Only the final (chosen) model form would be used to produce the Tables/Listings/Figure outputs supporting the CPSR. • If the joint modelling strategy fails then an alternative strategy would be to derive the RV

dysfunction status for each participant (using the same criteria) and analyse the collection of derived binary outcomes, accounting for the repeated measures made on each participant (e.g. logistic regression modelling techniques). The final logit model (including any covariates) would be used to determine the probabilities (and differences) for the sets of "pre and post" dose Ang II reference values to be fed into the decision-making criteria. Any such approach wold be documented in the CSR.

7.2. Secondary Efficacy Analyses

7.2.1. Endpoint / Variables

The variables to be included in the secondary pharmacodynamic analysis are the same as for the primary pharmacodynamic analysis, with the addition of the following independent variables:

- Ang(1-7) on Study Days 1, 2 and 3
- (Optionally) Ang(1-5) on Study Days 1, 2 and 3 (if the correlation between Ang(1-7) and Ang(1-5) values is not too high – otherwise the analysis would not be expected to add additional insights/value)
- Note: The planned modelling using similar techniques to the primary analysis for the Ang II/Ang(1-7) response on Study Days 1, 2 and 3 will not be attempted.

Incidence rates would be assessed across

i) the entire study (the outcome taking the value of the worst case observed) and
ii) on an individual visit basis (Note: Screening and Day 1 data would be combined and labelled as Day 1; the worst case outcome used in any combination)

The following rates would be assessed

- Incidence rates of ARDS diagnosis
- Incidence rates of PCD or ACP (any right ventricular dysfunction; regardless of PCD or ACP severity level)
- Incidence rates of PCD (Moderate PCD (not severe enough to qualify as ACP))
- Incidence rates of Non-severe ACP
- Incidence rates Severe ACP

Additionally, the worst case PCD/ACP diagnosis across the study would be combined with the ARDS diagnosis to form the following categories

- ARDS and No PCD or ACP
- ARDS and PCD
- ARDS and Non-Severe ACP
- ARDS and Severe ACP

7.2.2. Summary Measure

For the Ang(1-7) and Ang(1-5) endpoints described above:

- The posterior predictive probability of RV dysfunction for pre-determined "pre-dose" Ang II and Ang(1-7) values (or Ang(1-5)),

- The posterior predictive probability of RV dysfunction for pre-determined "post-dose" Ang II and Ang(1-7) values (or Ang(1-5)), and
- The difference between the two (Note: Although the difference will still be computed as Pre-Post for Ang(1-7) and Ang(1-5) negative values would be a favourable outcome).

For the incidence rate variables

- The At Risk population would be used to filter the individuals going into the subsequent analysis dataset
- For rates relating to an individual visit
    - The big N value would not represent distinct participants but instead represents the maximum number of visits in the analysis dataset (derived by counting the number of subject visits where any ARDS or PCD/ACP assessment was made (expecting three visits per subject – but may reduce if subjects withdraw/die before day 3))
    - the little n value would represent the number of completed visits for that item
    - Freq. represents the number of positive occurrences (Subjects with a Yes response)
    - Rate (%) = 100 * Freq. / n [little n]
    - The 95% CI for the rate (%) should be derived using Wilson Score interval with continuity correction methodology
- For rates relating to the entire study
    - The big N value represents the number of participants for whom an ARDS or PCD/ACP assessment was made at any time in the study
    - Freq. represents the number of positive occurrences (Subjects with a Yes response)
    - Rate (%) = 100 * Freq. / N [big N]
    - The 95% CI for the rate (%) should be derived using Wilson Score interval with continuity correction methodology

Any modifications to the above would be described in the CSR.

7.2.3. Population of Interest

The secondary pharmacodynamic analyses will be based on the Evaluable population, unless otherwise specified.

All analyses involving incidence rate endpoints will be based on the At Risk population unless otherwise specified.

7.2.4. Strategy for Intercurrent (Post-Randomization) Events

Since there is no investigational product in the study simplistic approaches will be taken to deal with intercurrent events. Any data driven alternative strategies implemented would be described in the CSR.

7.2.5. Statistical Analyses / Methods

The secondary statistical analyses are divided into three subcategories, with the first being variations on the primary analysis: analyses following the same form as the primary analysis but using a different RAS peptide measurement in place of Ang II.

The second subcategory models the joint association of Ang II and Ang(1-7) on RV function (Note: if the observed data ranges do not permit parameter estimation/model convergence of the proposed model then simpler alternative models may not be attempted; but if they are any methodology would be described in the CSR).

The third subcategory of the secondary analyses is an estimate of disease incidence within the mechanically ventilated population.

Details of the planned displays are provided in Appendix 10: List of Data Displays and will be based on GSK data standards and statistical principles.

Unless otherwise specified, endpoints / variables defined in Section 7.2.1 will be summarised using descriptive statistics, graphically presented (where appropriate) and listed.

7.2.5.1. Supportive Models to the Primary analysis, using other RAS peptides in place of Ang II

Supportive models to the primary analysis will be conducted following the same methodology as the primary analysis models (see Section 7.1) but with changes as described below.

The first supportive model will include Ang(1-7) as a time-point-level covariate instead of Ang II, and the corresponding reference value from Section 7.1.5.

Note: An optional supportive model would include Ang(1-5) as a time-point-level covariate instead of Ang II, and the corresponding reference value from Section 7.1.5. This model may be attempted if the Ang II and Ang(1-7) modelling does not produce a clear/consistent outcome and/or the observed level of correlation between Ang(1-5) and Ang(1-7) data is deemed likely to result in a different conclusion (*a priori* expectation Ang(1-7) and Ang(1-5) data will be highly correlated, and so any modelling would be expected to produce similar conclusions and duplication would not add value).

7.2.5.2. Combined model of the joint association of Ang II and Ang (1-7) with RV function

Endpoint / Variables
• PASP and RV Size Ratio on Day 1, Day 2 and Day 3 where available • Time matched concentration of Ang II (Denoted as A in model specification) • Time matched concentration of Ang (1-7) (Denoted as B in model specification)
Model Specification
The relationship between Ang II and Ang(1-7) (as joint explanatory variables) and the

joint bivariate distribution of PASP and RV size ratio (the outcome variables) will be analysed using a Bayesian multivariate non-linear regression model.

For simplicity, the repeated measures aspect of the data structure is not being modelled by first intent and Hill coefficients are assumed to be 1. If data permit, a similar strategy to the primary analysis that accounts for repeated measures may be attempted (e.g. Kronecker product with an AR(1) structure for Tigma), but only the model used for final inference would be reported. If data do not permit the planned model to be fitted no further modelling is proposed. However, if alternative model(s) are attempted and successful, they would be described in the CSR).

The multivariate normal model is specified as follows (for maximum flexibility time has been left in the parameter definitions) :

$$\begin{pmatrix} y_{it1} \\ y_{it2} \end{pmatrix} \sim MVNormal\left(\begin{pmatrix} \mu_{it1} \\ \mu_{it2} \end{pmatrix}, \Sigma \right)$$

where y_{itj} represents the observed value for the ith participant, the tth time-point and the jth outcome (i.e. $j = 1$ representing PASP and $j = 2$ representing RV size ratio), μ_{itj} represents the expected value for the ith participant, tth time-point ($t = 1,2,3$) and the jth outcome ($j=1$ and $j=2$ as above), and Σ represents a variance-covariance (vcov) matrix for the two outcome variables.

The expected values, μ_{itj}, are modelled as follows:

$$\mu_{itj} = \frac{Basal_j + Max_{Bj}\frac{[B]}{EC_{50jB|A=0}} + Max_{Aj}\frac{[A]}{EC_{50jA|B=0}} + Max_{ABj}\frac{[A][B]}{EC_{50jA|B=0}EC_{50jB|A\to\infty}}}{1 + \frac{[B]}{EC_{50jB|A=0}} + \frac{[A]}{EC_{50jA|B=0}} + \frac{[A][B]}{EC_{50jA|B=0}EC_{50jB|A\to\infty}}}$$

Where,
$Basal_j$ is the response in the absence of A and B for the jth outcome
Max_{Aj} is the response to saturating concentrations of A in the absence of B for the jth outcome
Max_{Bj} is the response to saturating concentrations of B in the absence of A for the jth outcome
Max_{ABj} is the response in the presence of saturating concentrations of both ligands for the jth outcome
$EC_{50jA|B=0}$ is the EC_{50} of A in the absence of B for the jth outcome
$EC_{50jB|A=0}$ is the EC_{50} of B in the absence of A for the jth outcome
$EC_{50jB|A\to\infty}$ is the EC_{50} of B in the presence of saturating concentrations of A for the jth outcome
[A] is time matched concentration of AngII (to aid review $[A_{it}]$ notation not used)
[B] is time matched concentration of Ang(1-7) (to aid review $[B_{it}]$ notation not used)

Also note that $EC_{50jA|B=0}$ x $EC_{50jB|A\to\infty}$ = $EC_{50jB|A=0}$ x $EC_{50jA|B\to\infty}$, so the equation is symmetrical in A & B.

The vcov structure for $\Sigma_{(6x6)}$ is constructed using the same approach as the primary analysis model but with an Identity matrix used for Tigma by first intent

$$\boldsymbol{\Sigma = Sigma \otimes Tigma =}$$

$$\begin{pmatrix} \sigma^2_{y_1} & \sigma_{y_1y_2} \\ \sigma_{y_1y_2} & \sigma^2_{y_2} \end{pmatrix} \otimes \begin{pmatrix} 1 & 0 & 0 \\ 0 & 1 & 0 \\ 0 & 0 & 1 \end{pmatrix} and$$

$$Var \begin{pmatrix} y_{t11} \\ y_{t21} \\ y_{t31} \\ y_{t12} \\ y_{t22} \\ y_{t32} \end{pmatrix} = \begin{pmatrix} \begin{pmatrix} \sigma^2_{y_1} & 0 & 0 \\ 0 & \sigma^2_{y_1} & 0 \\ 0 & 0 & \sigma^2_{y_1} \end{pmatrix} & \begin{pmatrix} \sigma^2_{y_1y_2} & 0 & 0 \\ 0 & \sigma^2_{y_1y_2} & 0 \\ 0 & 0 & \sigma^2_{y_1y_2} \end{pmatrix} \\ \begin{pmatrix} \sigma^2_{y_1y_2} & 0 & 0 \\ 0 & \sigma^2_{y_1y_2} & 0 \\ 0 & 0 & \sigma^2_{y_1y_2} \end{pmatrix} & \begin{pmatrix} \sigma^2_{y_2} & 0 & 0 \\ 0 & \sigma^2_{y_2} & 0 \\ 0 & 0 & \sigma^2_{y_2} \end{pmatrix} \end{pmatrix}$$

Uninformative prior distributions are assigned for the parameters as follows:

- Model parameters $Basal_j$, Max_{Aj}, Max_{Bj}, Max_{ABj}, $EC_{50jA|B=0}$, $EC_{50jB|A=0}$ and $EC_{50jB|A\to\infty}$ (for j=1 (PASP) and 2 (RV Size ratio)) will each be assigned a prior of Normal(Mean=0, Var=1^E6). Note: By first intent these are all independent prior statements and correlation structures between related parameters would be expected to be observed in the observed posterior covariances of the model parameters (see Sensitivity analyses sections for alternative prior structures if model convergence issues are encountered).
- $\boldsymbol{S}$, defined as the inverse of $\boldsymbol{Sigma}$, is assigned an uninformative Wishart prior distribution: $\boldsymbol{S \sim Wishart(R, df)}$ where: $\boldsymbol{R} = \begin{pmatrix} 0.01 & 0 \\ 0 & 0.01 \end{pmatrix}$ and $\boldsymbol{df = 3}$.
-

Model Checking & Diagnostics

- As per Primary analysis

Model Results Presentation

- Once the model parameters have been estimated analogous predictions of the Posterior Probability of RV dysfunction (and differences between pre and post dose AngII levels) would be obtained as per Primary analysis. However, twice the number of items would be produced because there would be a need to condition on the two "pre and post dose" values for Ang(1-7) for each set of Ang II values.

Subgroup Analyses

- Not planned

Sensitivity and Supportive Analyses

- If model convergence issues are encountered the prior structure may be modified to group related sets of parameters together using a MVN (multivariate normal distribution). Two MVN priors distributions may be set up (one for each j) using parameters $Basal_j$, Max_{Aj}, Max_{Bj}, Max_{ABj}, $EC_{50jA|B=0}$, $EC_{50jB|A=0}$ and $EC_{50jB|A\to\infty}$. The MVN mean would be a vector of zeros and the prior for the vcov matrix of the model parameters would be an inverse-wishart with R=Identity (7x7) and df=7.
- An AR(1) structure may be attempted for the Tigma vcov matrix and would use an uninformative uniform prior distribution over -1,1 interval for parameter ρ

7.2.5.3. Analysis of disease incidence within the mechanically ventilated population

The incidence of ACP and PCD in the population will be presented as summary tables, by study day, and overall (i.e. diagnosis at any time during the three-day study period).

Descriptive statistics (N (population), #Occurrences (Freq.), number at risk (n), Incidence Rate and 95% CI for Rate (methodology for 95% CI: Wilson Score interval with continuity correction))

7.3. Exploratory Efficacy Analyses

No exploratory analyses are planned due to the early termination of the study.

8. SAFETY ANALYSES

The safety analyses will be based on the Safety population, unless otherwise specified. The details of the planned displays are provided in Appendix 10: List of Data Displays.

8.1. Adverse Events Analyses

Only Serious Adverse Events (SAEs) relating to study procedures or any GSK medications are being recorded and reported in this study. SAEs will be presented as a summary table and a listing, and will be based on GSK Core Data Standards.

8.2. Clinical Laboratory and Other Safety Analyses

Chemistry and Haematology Laboratory evaluations and Vital Signs test results will be presented as summary tables and listings. Additionally, all values of potential clinical importance will be presented as listings, together with all other measurements of the same test in the same participant. These displays will be based on GSK Core Data Standards.

9. REFERENCES

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10. APPENDICES

10.1. Appendix 1: Protocol Deviation Management and Definitions for Evaluable Population

10.1.1. Exclusions from Evaluable Population

Subjects with major/important protocol deviations will be considered for exclusion from Evaluable Population. The Protocol Deviation Management Plan (PDMP) will be used to determine major/important protocol deviations that will lead to exclusion from the Evaluable Population (Note: In the event the PDMP retains the template text / default terminology which refers to "per protocol population" it would be interpreted as the "Evaluable population" for study 205821).

In addition, a subject meeting any of the following criteria will be excluded from the Evaluable population (or if more applicable, only the relevant timepoint(s) excluded):

Number	Exclusion Description
01	Participants whose day 1, day 2 and day 3 samples were all lost or for whom the post sample processing was unable to produce evaluable results would be excluded from the evaluable population If a single day (or two days) are impacted by the above reason(s) then the participant shall remain in the evaluable population, but the impacted time points would be removed from the analysis.
02	If a single day (or two days) are impacted by the ECHO results that are later deemed of insufficient quality (e.g. this may be discovered by independent review/adjudication of source notes) then those data points would be removed from the analysis (but the participant would remain in the evaluable population). If all of the day 1, day 2 and day 3 ECHO results are impacted in this way then the participant would be removed from the evaluable population.
03	If the participant takes a prohibited concomitant medication that, in the opinion of the GSK medical monitor, may confound / interfere with the estimation of the true relationship between RAS peptides and an endpoint then any post con-med observations would be removed from the corresponding analysis.

10.2. Appendix 2: Schedule of Activities

10.2.1. Protocol Defined Schedule of Events

Procedure	Study Period					Notes
	Screening[1]	Day 1	Day 2	Day 3	Up to day 28	
Start of mechanical ventilation	X					
Inclusion/exclusion criteria	X					Reason for intubation (underlying diagnosis e.g. sepsis, pneumonia) to be collected where possible.
Informed consent (ICF)	X					Consent process will be followed as outlined in Informed Consent Process (Section 12.3.3)
Demography	X					If it is not possible to collect at screening can be collected at any point during the study.
Height and weight	X					Collected for the purposes of evaluating BMI. Clinical estimates are acceptable if direct measurement is not possible.
Medical history	X					If possible to collect, includes medication and cardiovascular risk factors. If it is not possible to collect at screening can be collected at any point during the study.
Diagnosis of pulmonary circulatory dysfunction (PCD) and acute cor pulmonale (ACP)		X	X	X		As per echocardiographic output.
Participant status	X	X	X	X		Intubation status, proned status; diagnosis of acute respiratory distress syndrome (ARDS) including severity at time of diagnosis (if available). Post screening status to be assessed at the same time point as echocardiogram (± 1 hour).
Participant management	X	X	X	X		Management with extracorporeal membrane oxygenation (ECMO) and extracorporeal CO_2 ($ECCO_2R$) removal. Post screening status to be assessed at the same time point as echocardiogram (± 1 hour).

Procedure	Study Period					Notes
	Screening[1]	Day 1	Day 2	Day 3	Up to day 28	
Simplified acute physiology score (SAPS II)	X					To be taken at time of intubation.
Sequential Organ Failure (SOFA) score	X	X	X	X		
Echocardiogram		X	X	X		Transthoracic echocardiogram (TTE) and/or transoesophageal echocardiogram (TOE). First echocardiogram must be completed within 48 hours of starting mechanical ventilation (but ≤24 hours, whenever possible); the following echocardiograms will be undertaken as per standard of care 24 hours apart (± 2 hours) on subsequent consecutive days (Day 2 and 3).
Vital signs	X[3]	X	X	X		Blood pressure (mean arterial, systolic and diastolic), heart rate, body temperature to match echocardiogram time points (± 30 minutes)[2].
Laboratory assessments	X	X	X	X		Clinical chemistry and haematology.
Ventilator settings	X[3]	X	X	X		Includes tidal volume, respiratory rates, static respiratory compliance, level of positive end expiratory pressure (PEEP), peak and plateau ventilator pressures, mean airway pressure and driving pressure. Measurements to be taken at intubation and at the time of each echocardiogram (± 30 mins)[2].
Lung function and blood gas measures	X[3]	X	X	X		Oxygen saturation (SaO_2) via pulse oximetry. Arterial Blood Gases (ABGs) measuring partial pressure of oxygen and carbon dioxide (PaO_2 and $PaCO_2$).[4] Oxygen requirement (FiO_2) should be documented at the same time point. pH, lactate and bicarbonate levels and base excess or deficit when available should also be documented when ABGs are assessed. Measurements to be taken at intubation and at the time of each echocardiogram (± 30 mins)[2].

Procedure	Study Period					Notes
	Screening[1]	Day 1	Day 2	Day 3	Up to day 28	
Electrical Impedance Tomography	X	X	X	X		Measurements to be taken at intubation and at the time of each echocardiogram when available (±2 hours)[2].
Serious Adverse Event (SAE) Review	<==========					SAEs will only be collected during the 3 day observation period or until participant withdrawal, whichever is sooner.
Concomitant medication review	<==========					Only specified prescription medication (name, start and end dates required) as described in Section 7.1 of the protocol. Vasopressor use to be documented for each time point of echocardiography.
Intensive Care Unit (ICU) length of stay		<==========				Will be recorded daily up to 28 days.
Ventilator free days		<==========				Will be recorded daily up to 28 days; however, follow up is not necessary beyond hospital discharge.
In hospital mortality		<==========				Will be recorded daily up to 28 days; however, follow up is not necessary beyond hospital discharge.
Biomarkers						
Blood sample for renin-angiotensin system (RAS) biomarkers		X	X	X		Blood samples to be taken at the same time as echocardiography (± 30 mins)[2].
Blood sample for biomarkers		X	X	X		Blood samples to be taken at the same time as echocardiography (± 30 mins)[2].

1. Screening may be considered part of Day 1.
2. When multiple measurements are to be taken at the same time in relation to echocardiography, blood sampling for RAS peptides should be given priority. Other measurements (e.g. ventilator settings) to be prioritized as per investigator for patient care.
3. Will be recorded at the time of intubation if available.
4. Where available, a blood sample is required for arterial blood gases (ABGs) for PaO_2/FiO_2 and oxygenation index. A FiO_2 measurement should be assessed at the same time point as ABGs are taken for PaO_2.

10.3. Appendix 3: Assessment Windows

10.3.1. Definitions of Assessment Windows for Analyses

Data management will maintain the allowable visit/sampling windows for study procedures. Calendar days will be used rather than 24 hour intervals from the start of the 1st echo measurement on Day 1, since it is unlikely study procedures will cross midnight. Both date and times are typically collected on the eCRF so if required elapsed times can be used.

10.4. Appendix 4: Study Phases and Treatment Emergent Adverse Events

10.4.1. Study Phases

10.4.1.1. Study Phases for Concomitant Medication

Study Phase	Definition
Prior	If medication end date is not missing and is before 4 days prior to screening visit
Concomitant	Any medication that is not a prior

NOTES:

- Please refer to Appendix 7: Reporting Standards for Missing Data for handling of missing and partial dates for concomitant medication. Use the rules in this table if concomitant medication date is completely missing.

10.5. Appendix 5: Data Display Standards & Handling Conventions

10.5.1. Reporting Process

Software	
• The currently supported versions of SAS software will be used. If required, the currently supported versions of R and STAN software may be used.	
Reporting Area	
HARP Server	: UK1SALX00175
HARP Compound	: GSK2586881
Analysis Datasets	
• Analysis datasets will be created according to Legacy GSK A&R dataset standards.	
Generation of RTF Files	
• RTF files will be generated for the final reporting effort.	

10.5.2. Reporting Standards

General

• The current GSK Integrated Data Standards Library (IDSL) will be applied for reporting, unless otherwise stated (IDSL Standards Location: https://spope.gsk.com/sites/IDSLLibrary/SitePages/Home.aspx):
  • 4.03 to 4.23: General Principles
  • 5.01 to 5.08: Principles Related to Data Listings
  • 6.01 to 6.11: Principles Related to Summary Tables
  • 7.01 to 7.13: Principles Related to Graphics
• Do not include participant level listings in the main body of the GSK Clinical Study Report. All participant level listings should be located in the modular appendices as ICH or non-ICH listings

Formats
• GSK IDSL Statistical Principles (5.03 & 6.06.3) for decimal places (DP's) will be adopted for reporting of data based on the raw data collected, unless otherwise stated. • Numeric data will be reported at the precision collected on the eCRF. • The reported precision from non eCRF sources will follow the IDSL statistical principles but may be adjusted to a clinically interpretable number of DP's.
Planned and Actual Time

• Reporting for tables, figures and formal statistical analyses:
  • Planned time relative to dosing will be used in figures, summaries, statistical analyses and calculation of any derived parameters, unless otherwise stated.
  • The impact of any major deviation from the planned assessment times and/or scheduled visit days on the analyses and interpretation of the results will be assessed as appropriate.
• Reporting for Data Listings:
  • Planned and actual time relative to study drug dosing will be shown in listings (Refer to IDSL Statistical Principle 5.05.1).
  • Unscheduled or unplanned readings will be presented within the participant's listings.

Unscheduled Visits
• Unscheduled will not be included in summary tables and/or figures.   • If unscheduled visits are included (decision on a case by case basis), the most appropriate method would be used (e.g. summaries displayed by slotting the unscheduled visits to analysis time points

as per Section 10.3.1)). • All unscheduled visits will be included in listings and figures (when they relate to individual participants – e.g. participant level response vs time profiles).	
Descriptive Summary Statistics	
Continuous Data	Refer to IDSL Statistical Principle 6.06.1
Categorical Data	N, n, frequency, %
Graphical Displays	
• Refer to IDSL Statistical Principals 7.01 to 7.13. • Where possible, use the same plotting symbol/linestyle/colour combination for a participant in all relevant Figures to facilitate easy cross comparison across different data types	

10.6. Appendix 6: Derived and Transformed Data

10.6.1. General

Multiple Measurements at One Analysis Time Point
• Mean of the measurements will be calculated and used in any derivation of summary statistics but if listed, all data will be presented. • If there are two values within a time window (as per Section 10.3.1) the value closest to the target day for that window will be used. If values are the same distance from the target, then the mean will be taken. • Participants having both High and Low values for Normal Ranges at any post-baseline visit for safety parameters will be counted in both the High and Low categories of "Any visit post-baseline" row of related summary tables. This will also be applicable to relevant Potential Clinical Importance summary tables.
Study Day

• Calculated as the number of days from First Echo Date:
  • Ref Date = Missing → Study Day = Missing
  • Ref Date < First Echo Date → Study Day = Ref Date – First Echo Date
  • Ref Data ≥ First Echo Date → Study Day = Ref Date – (First Echo Date) + 1

Study Date/Time (Time 0h)
• Calculated as the elapsed time since the date and time of the first echocardiogram • Used to align observations of different domains within an individual participant • Preference to derive using the same algorithm as the HARP standard helper macros and to display using an appropriate format to the range of values being displayed (e.g. xx days yy hours zz minutes or xx minutes and zz seconds)
•

10.6.2. Study Population

Age

• Age is approximated as only year of birth is captured:
  • Age = Calendar Year at Time of Informed Consent – Year of Birth
  • Age is sometimes referred to in this RAP as Age at Screening (but should be interpreted as Age at time of informed consent)

10.6.3. Pharmacodynamic / Biomarker

RAS Biomarkers
• Ang II/Ang(1-7) is calculated as the ratio of the value of Ang II to the corresponding (same-day) value of Ang(1-7). If either Ang II or Ang(1-7) is missing for a given Study Day then the ratio will also be derived as missing. • If required Ang II / Ang(1-5) (or any other ratio combination of the RAS peptides) would be derived and processed in an analogous way to the Ang II / Ang(1-7) ratio.

For the derivation of AngII / Ang(1-7) **ratios**, the following will apply:

Flags		Numerator (ANGII)			
		BLQ	**Data**	**ALQ**	**Missing**
Denominator (ANG1-7)	**BLQ**	(1/2 LLQ of ANGII) / (1/2 LLQ of Ang(1-7))	ANGII / (1/2 LLQ of Ang(1-7))	(ULQ of ANGII) / (1/2 LLQ of Ang(1-7))	Missing
	Data	(1/2 LLQ of ANGII) / Ang(1-7)	ANGII / Ang(1-7)	(ULQ of ANGII) / Ang(1-7)	Missing
	ALQ	(1/2 LLQ of ANGII) / (ULQ of Ang(1-7))	ANGII / (ULQ of Ang(1-7))	(ULQ of ANGII) / (ULQ of Ang(1-7))	Missing
	Missing	Missing	Missing	Missing	Missing
LLQ / ULQ = Lower / Upper Limit of Quantification, **BLQ / ALQ** = Below / Above Limit of Quantification					

Note: The status of the numerator and denominator / outcome should be sufficiently tracked to allow subsequent Summary Tables to display the amount of imputation necessary.

Note: all other pharmacodynamic/biomarker endpoints derived from other items should be auto-calculated on the eCRF and therefore supplied in SI datasets.

In general, it is assumed that biomarker endpoints will require variance stabilising transformations, such as taking a $\log_e$ transformation prior to analysis (and that summary statistics appropriate to $\log_e$ normally distributed data will apply for all summaries; log base 10 may also be used in place of natural logarithms). However, this assumption will be considered for each endpoint individually prior to the generation of summary tables or statistical analysis, and if deemed more appropriate, a loge transformation will not be applied, or non-parametric methods may be employed.

If transformations are used then the results will be reported on the back-transformed scale unless otherwise stated.

Unless otherwise specified the following applies to the biomarkers

- Values below LLQ will be set as LLQ/2
- Values above the upper limit of quantification (ULQ) will be set as ULQ
- Imputed values will be used for the purposes of the computation of change from baseline and for summaries, plots and analysis, if deemed applicable.
- Number of data imputed will be highlighted in the summary tables & listings will report the values as below LLQ or above ULQ, alongside the imputed result used in statistical analyses.
- If multiple LLQ's and ULQ's are available per assay (i.e. multiple runs with different standard curves are utilised) then the LLQ and/or ULQ value used for the above purposes shall be the minimum of the available LLQs and/or the maximum of the BLQ's.

10.6.4. Reason for Intubation

The reason for intubation is captured in the eCRF using a free text field. To allow these items to be summarised succinctly each free text entry will be mapped to a common set of nomenclature. Upon receiving the data transfer associated with the planned data review (e.g. planned interim and/or end of study reporting) a list of the unique free text

entries from the reason for intubation field will be supplied to the medical monitor, who will assign each entry into one of the following categories (Note: each participant may only be assigned to a single category). Additional categories may be added based upon the observed data if deemed necessary by the medical monitor. Only categories that have terms mapped to them need to be displayed. A listing of unique free text terms and the mappings should also be produced (using similar design concepts to the Adverse Event shell AE2)

ID Number	Allowable mapping of free text (display in the order listed here)
0	Not Applicable (not intubated)
1	Sepsis
2	Pneumonia
3	Acute Respiratory Failure
4	Cardiac Cause
5	Neurologic event
6	Other reason for intubation
7	No reason for intubation supplied

10.6.5. Oxygenation Index (OI)

The derivation of Oxygenation Index was omitted from the protocol in error and has been documented in the RAP for completeness.

Oxygenation index (OI) (sometimes termed oxygenation factor) is another measure of gas exchange and pulmonary efficiency which factors in the mean airway pressure (Paw) term in the calculation step [El-Khatib, 2004].

It is calculated using Equation 1,

Equation 1 Oxygenation index

$$\text{Oxygenation Index (\%)} = \frac{\text{FiO2} * \text{Mean Airway Pressure}}{\text{PaO2}}$$

where Mean Airway Pressure and PaO2 are measured in mmHg and FiO2 is entered as a % and not a proportion

10.6.6. Echocardiogram (Choosing between TTE and TOE results for subsequent statistical analyses)

This section describes how to choose which result to select for subsequent statistical analyses when multiple options exist. They are based on the echocardiogram parameters after InForm Post Go Live 3.1 (implemented approx. Jan 2019). Table 2, Table 3, Table 4, Table 5, Table 6 and Table 7 enumerate the possible data combinations and which values to select for the planned echocardiogram endpoints.

Table 2 Selection algorithm (conditional on eCRF input) for the endpoints listed in Table 3

ID#	eCRF state for TTE (Transthoratic echocardiography)	eCRF state for TOE (Transesophageal echocardiography)	Selected value for statistical analyses	Text value to display in listings
1	<Blank>	<Blank>	Missing (".")	No result
2	<Blank>	Not Done	Missing (".")	No result
3	<Blank>	Numerical entry	<TOE value>	<TOE value>
4	Not Done	<Blank>	Missing (".")	No result
5	Not Done	Not Done	Missing (".")	No result
6	Not Done	Numerical entry	<TOE value>	<TOE value>
7	Numerical entry	<Blank>	<TTE value>	<TTE value>
8	Numerical entry	Not Done	<TTE value>	<TTE value>
9	Numerical entry	Numerical entry	<TTE value>	<TTE value>

Table 3 Endpoints to apply the Table 2 selection criteria to

CVTSTCD	Description
AK001	Ratio of RV to LV End-Diastolic Area
AK003	Systolic Eccentricity Index
AK006	Max Velocity S Wave at Tricuspid Annulus
AK007	Fractional Area Contraction
AK008	Acc Time of RV Ejection Flow (Tacc)
AK009	Mean Acc of RV Ejection Flow at End Exp
AK010	Mean Acc of RV Ejec Flow at End Exp-Insp
AK005	IVC Diameter at End Expiration
AK011	Respiratory Variations of RV VTI
TAPSE	Tricuspid Annular Plane Systol Excursion
AK012	Respiratory Variations of SVC Diameter
CARDOUT	Cardiac Output (CO)
LVEJ	Left Ventricular Ejection Fraction
AK013	LV Velocity (E') Tissue of Annulus
AK014	LV Early to Late Filling Velocities

Table 4 Selection algorithm for Paradoxical Septal Motion (CVTSTCD = AK002)

ID#	eCRF state for TTE (Transthoratic echocardiography)	eCRF state for TOE (Transesophageal echocardiography)	Selected value for statistical analyses	Text value to display in listings
1	ZZND (Not Done)	ZZND (Not Done)	Missing ("<blank>")	Not Done
2	ZZND (Not Done)	N (No)	N	No
3	ZZND (Not Done)	Y (Yes)	Y	Yes
4	N (No)	ZZND (Not Done)	N	No
5	N (No)	N (No)	N	No
6	N (No)	Y (Yes)	Y	Yes
7	Y (Yes)	ZZND (Not Done)	Y	Yes
8	Y (Yes)	N (No)	Y	Yes
9	Y (Yes)	Y (Yes)	Y	Yes
Note: If only one result is present (e.g. a TTE value only but no TOE value databased) then the selected text should be the value present (i.e. Yes, No or Not Done as appropriate to the available result).				

Table 5 Selection algorithm for TPG (Trans-tricuspid pressure gradient, CVTSTCD = AK004)

ID#	eCRF state for TTE (Transthoratic echocardiography)	eCRF state for TOE (Transesophageal echocardiography)	Selected value for statistical analyses	Text value to display in listings
1	<Blank>	<Blank>	Missing (".")	No result
2	<Blank>	Numerical entry	<TOE value>	<TOE value>
3	Numerical entry	<Blank>	<TTE value>	<TTE value>
4	Numerical entry	Numerical entry	<TTE value>	<TTE value>

Table 6 Selection algorithm for RAP (Right atrial pressure; Potential results could come from either ERATRIAP or AI001 CVTSTCD record but only possible to receive one of those codes for each participant/timepoint combination)

RAP "Estimated" or "Measured"	ID#	eCRF state for Measured (CVP)	eCRF state for TTE (Transthoratic echocardiography)	eCRF state for TOE (Transesophageal echocardiography)	Selected value for statistical analyses	Text value to display in listings
"Estimated" (i.e. only ERATRIAP record exists for that	1	N/A (No AI001 record)	<Blank>	<Blank>	Missing (".")	No result
	2		<Blank>	Numerical entry	<TOE value>	<TOE value>
	3		Numerical entry	<Blank>	<TTE value>	<TTE value>

RAP "Estimated" or "Measured"	ID#	eCRF state for Measured (CVP)	eCRF state for TTE (Transthoratic echocardiography)	eCRF state for TOE (Transesophageal echocardiography)	Selected value for statistical analyses	Text value to display in listings
participant / timepoint)	4		Numerical entry	Numerical entry	<TTE value>	<TTE value>
"Measured" (i.e. only AI001 record exists for that participant / timepoint)	5	<Blank>	N/A (No ERATRIAP record)	N/A (No ERATRIAP record)	Missing (".")	No result
	6	Numerical entry			<Measured value>	<Measured value>

Note: In the listing of Echocardiogram endpoints when the RAP is "measured" then the TTE and TOE columns should be populated with Not applicable and only the "Selected" column would be populated.

Table 7 Selection algorithm for PASP (Pulmonary artery systolic pressure, CVTSTCD = AH001CAL)

ID#	Selected TPG value (see Table 5)	Selected RAP value (See Table 6)	Selected value for statistical analyses	Text value to display in listings
1	Missing (".")	Missing (".")	Missing (".")	No result
2	Missing (".")	Numerical entry	Missing (".")	No result
3	Numerical entry	Missing (".")	Missing (".")	No result
4	Numerical entry	Numerical entry	<TPG + RAP>	<TGP + RAP>

Note: All PASP values in analysis and reporting datasets and consequent tables, listings and figures will be re-derived by stats and programming using the algorithms in Table 7.

PASP values are also automatically derived within the eCRF form and are supplied in the data management transfer of the CV dataset under the CVTSTCD of "AH001". However, it has been noted in test data transfers that the auto calculation does not always derive correct results due to the complexities of the data source combinations (e.g. Participant PPD Day 1 had a TPG from the TOE method but an estimated RAP from the TTE method but the eCRF autocalculation incorrectly supplied a missing PASP value).Therefore there is a need to programmatically re-drive PASP and as a consequence there will be additional records in ARDATA versions of the CV dataset compared to the SI version (CVTSTCD = AH001CAL).

To facilitate sensitivity analyses regarding the frequency/reason of "missing" PASP values an additional variable may be created in ARDATA datasets (as required) that tracks the inputs to the PASP calculation (see Table 8). This tracking variable would not need to be displayed in the listing of echocardiogram endpoints.

Table 8 Additional variable/result to track the derived PASP inputs (assigned a CVTSTCD = AH001src)

AH001src value	TPG source used in derivation of PASP (see Table 5)	RAP source used in derivation of PASP (See Table 6)
1	Missing (".")	Missing (".")
2	Missing (".")	TTE
3	Missing (".")	TOE
4	Missing (".")	Measured
5	TTE	Missing (".")
6	TTE	TTE
7	TTE	TOE
8	TTE	Measured
9	TOE	Missing (".")
10	TOE	TTE
11	TOE	TOE
12	TOE	Measured

10.6.7. Sequential Organ Failure Assessment (SOFA) score

The score will be calculated on a daily basis. Adrenergic agents that do not appear in Vincent, 1996 and for which a highest dose has been recorded, will be assigned a SOFA score of 2. Zero points are assigned if none of the points scoring criteria are met. If any of the information required to derive an individual SOFA component score is missing or cannot be obtained, then that component score will be set to a missing value.
The SOFA score will be calculated by summing the individual component scores (individual components derived as below). Note: Central Nervous System component will not be used in deriving the SOFA score in Study 205821:

SOFA Score / Variable (x)	0	1	2	3	4
Respiration: P_aO_2/F_iO_2 (mmHG)	$x \geq 400$	$300 \leq x < 400$	$200 \leq x < 300$	$100 \leq x < 200$	$x < 100$
				With Respiratory support (Note: if P_aO_2/F_iO_2 in these categories but subject not on respiratory support then a score of 2 should be assigned)	
Coagulation: Platelets (10^3 / mm^3)	$x \geq 150$	$100 \leq x < 150$	$50 \leq x < 100$	$20 \leq x < 50$	$x < 20$
Liver: Bilirubin (μmol/L)	$x < 20$	$20 \leq x < 33$	$33 \leq x < 102$	$102 \leq x < 204$	$x \geq 204$
Cardiovascular: Hypotension (Adrenergic agents administered for at least one hour; doses are in μg/kg/min)	Mean Arterial Pressure ≥ 70 mmHg	Mean Arterial Pressure < 70 mmHg	Dopamine≤5.0 (μg/kg/min) or any dose of: Dobutamine Or any dose of an adrenergic agent not listed here or in Vincent (1996)	Dopamine 5.1-15.0 (μg/kg/min) or Epinephrine≤0.1 or Norepinephrine≤0.1	Dopamine > 15.0 (μg/kg/min) or Epinephrine>0.1 or Norepinephrine>0.1
Central Nervous System: Glasgow Coma Score	$x \geq 15$	$13 \leq x \leq 14$	$10 \leq x \leq 12$	$6 \leq x \leq 9$	$x < 6$
Renal: Creatinine (μmol/L)	$x \leq 110$	$110 < x \leq 170$	$170 < x \leq 300$	$300 < x \leq 440$ [Or Urine output < 500 mL/day]	$x > 440$ [Or Urine output < 200 mL/day]
Note: Central Nervous System scoring algorithm has been included above for completeness but in Study 205821 it is not expected to form part of the overall SOFA total					

In the SI.CONMEDS record (for vasopressors) the units may have to be converted from μg/min to μg/kg/min dose by merging on the weight from the vital signs dataset (and other unit conversions may be required for the other SOFA components).

PaO2/FiO2 values from the eCRF form should be double checked for accuracy (e.g. visual inspection of raw datasets to determine if they in the expected ranges for the stated unit).

10.6.8. Oxygen Saturation

The oxygen saturation may be calculated from the provided ratio SaO2/FiO2 readout if the eCRF field for Oxygen Saturation (Vitals eCRF) is blank or missing.

10.6.9. Calculation of PaO2 / FiO2 and SpO2 / FiO2

If required (e.g. because the automatically calculated eCRF field is blank or the units used in the auto-derived field appear to be incorrect) and sufficient source data are available then:

- The PaO2/FiO2 endpoint can be calculated when patients are intubated and have an arterial line present. Prior to computing the ratio the PaO2 may need to be converted from kPa units to mmHg using the conversion rate 1/0.133. FiO2 should be expressed as a proportion and not a percentage when deriving the ratio.
- SpO2/ FiO2 will be calculated as a ratio of percentages.

10.6.10. Construction of ARDATA.ALLCVTS

Guidance on the structure of the master A&R dataset that will hold potential covariate variables (for use in model building) is contained in Table 9.

Table 9 Suggested Metadata for ARADTA.ALLCVTS (Modifications may be made if required, e.g. to add/remove variables based on questions arising from observed data – the HARP metadata form would capture the final specification used). SAS label text and units to be added as appropriate to the data item.

Type	Variable Name	Details	Suggestions for derivation / data source
Info	STUDYID	STUDYID	ARDATA.CV (Unique list of subjid, centreid and visitnum combinations where at least one PASP and/or RV Size Ratio result was evaluable in CMANALFL=1 records) VISITNUM 20.00 = DAY 1 VISITNUM 30.00 = DAY 2 VISITNUM 40.00 = DAY 3
Info	SUBJID	SUBJID	
Info	USUBJID	USUBJID	
Info	CENTREID	CENTREID	
Info	INVID	INVID	
Info	VISITNUM	VISITNUM	
Info	VISIT	VISIT	
Info	SUBJLEV	Extraction of set of subject level records	Only a single flag of 1 allowed per subject. Usually Day 1 record if present, day 2 (or 3) otherwise
Subject	AGE	Age at Screening	ARDATA.DEMO (AGE)
Subject	SEX	Sex	ARDATA.DEMO (SEX)
Subject	VSBMI	BMI at Screening	ARDATA.VITALS (VSBMI)
Subject	SAPSII	SAPS II at Screening	DMDATA.CC (Select CCORRSN where CCTESTCD=CC001)
Subject	RSINTU	Reason for Intubation at Screening (Categorical)	ARDATA.PR (Select the derived variable PRMIND which contains the mapping of the free text variable (PRINDC) for reason for intubation at screening visit (VISITNUM=10); see Section 10.6.4)
Time	INTUI	Intubated by Study Day (Binary Y/N)	ARDATA.PR (Where PRTREAT=INTUBATION & VISITNUM in (20,30,40)) For each subject and visitnum match: Set corresponding INTUI to Y if PROCCUR = Y for Day <i>; Set to N otherwise
Subject	ARDSX	ARDS Diagnosis at any time (Binary Y/N)	DMDATA.FACE (Where FCETSTCD=FCEBU001) Set to Y if Any of FCEORSCD = ZZY for a subject; Set to N otherwise

Type	Variable Name	Details	Suggestions for derivation / data source
Time	ARDSI	ARDS Diagnosis by Study Day (Binary Y/N)	DMDATA.FACE (Where FCETSTCD=FCEBU001) Treat any Screening results as being from Day 1 (use the worst case outcome as Day 1 result). For each subject and visitnum match: Set corresponding ARDSI to Y if FCEORSCD = ZZY for Day <i>; Set to N otherwise Note: Class any SCREENING result as DAY 1 record for the purposes of ARDS diagnosis
Subject	INOX	Inhaled Nitric Oxide at any time (Binary Y/N)	DMDATA.FACM (Where FCMTSTCD=FCMAX001) Set to Y if Any of FCMORSCD = ZZY for a subject; Set to N otherwise
Time	INOI	Inhaled Nitric Oxide by Study Day (Binary Y/N)	DMDATA.FACM (Where FCMTSTCD=FCMAX001) Treat any Screening results as being from Day 1 (use the worst case outcome as Day 1 result). For each subject and visitnum match: Set corresponding INOI to Y if FCMORSCD = ZZY for Day <i>; Set to N otherwise
Subject	VASOX	Vasopressor, Inotrope or other Vasoactive agent at any time (Binary Y/N)	DMDATA.FACM (Where FCMTSTCD=FCMAX002) Set to Y if Any of FCMORSCD = ZZY for a subject; Set to N otherwise
Time	VASOI	Vasopressor, Inotrope or other Vasoactive agent by Study Day (Binary Y/N)	DMDATA.FACM (Where FCMTSTCD=FCMAX002) Treat any Screening results as being from Day 1 (use the worst case outcome as Day 1 result). For each subject and visitnum match: Set corresponding VASOI to Y if FCMORSCD = ZZY for Day <i>; Set to N otherwise
Subject	PRONEX	Proned at any time (Binary Y/N)	ARDATA.PR (Where PRTREAT=MECHANICAL VENTILATION; exclude records with PRREFID=SOFA) Set to Y if Any of Subjects records have PRONE=Y

Type	Variable Name	Details	Suggestions for derivation / data source
Time	PRONEI	Proned by Study Day (Binary Y/N)	ARDATA.PR (Where PRTREAT=MECHANICAL VENTILATION & VISITNUM in (20,30,40); exclude records with PRREFID=SOFA) For each subject and visitnum match: Set corresponding PRONEI to Y if PRONE = Y for Day <i>; Set to N otherwise
Subject	ECMOX	ECMO at any time (Binary Y/N)	ARDATA.PR (Where PRTREAT= EXTRACORPOREAL MEMBRANE OXYGENATION) Set to Y if Any of Subjects records have PROCCUR=Y
Time	ECMOI	ECMO by Study Day (Binary Y/N)	ARDATA.PR (Where PRTREAT= EXTRACORPOREAL MEMBRANE OXYGENATION & VISITNUM in (20,30,40)) For each subject and visitnum match: Set corresponding ECMOI to Y if PROCCUR = Y for Day <i>; Set to N otherwise
Subject	ECCO2RX	ECCO2R at any time (Binary Y/N)	ARDATA.PR (Where PRTREAT= EXTRACORPOREAL CO2 REMOVAL) Set to Y if Any of Subjects records have PROCCUR=Y
Time	ECCO2RI	ECCO2R by Study Day (Binary Y/N)	ARDATA.PR (Where PRTREAT= EXTRACORPOREAL CO2 REMOVAL & VISITNUM in (20,30,40)) For each subject and visitnum match: Set corresponding ECCO2RI to Y if PROCCUR = Y for Day <i>; Set to N otherwise
Subject	LCONDT	Last Contact Date (Date)	ARDATA.DS (Where DSSCATCD=4 & VISITNUM=0) Select DSSTDT
Subject	LCONDY	Last Contact Study Day (Continuous)	ARDATA.DS (Where DSSCATCD=4 & VISITNUM=0) Select DSSTDY
Subject	FUDT	Date of Follow Up Visit (Date)	DMDATA.VISIT (Where VISITNUM=50) Select VISITDT

Type	Variable Name	Details	Suggestions for derivation / data source
Subject	DTHHOSP	In hospital mortality (Categorical Y/N/U)	DMDATA.SS (Where VISITNUM=50 & SSTESTCD=AD009) Set to Y if SSORRSCD=ZZY; to N if SSORRSCD=ZZN and to U if SSORRSCD=ZZUNK
Subject	DERDTHDT	Derived Death Date (Date)	Set to the earliest of the dates obtained from… DMDATA.DTH (match on SUBJID and select DDDT) Or LCONDT variable if DTHHOSP = Y Or If no dates located above but subject has DMDATA.STATUS DTHBWIND=Y then set to a derived date corresponding to day 3 (relative to that subjects date of 1st echo) Otherwise set to missing
Subject	DERDTHDY	Derived Death Study Day (Continuous)	The study day of the DERDTHDT (relative to time zero – the date of 1st echo) Set to missing if DERDTHDT = missing
Subject	DTH28	Death by Day 28 (Categorical Y/N/U)	Set to Y if DERDTHDY not missing & $\leq$ 28 Set to N if [DERDTHDY = missing & LCONDY $\geq$ 28] or [DERDTHDY $\geq$ 28] Set to U otherwise
Subject	SURVIND	Survival Censoring Indicator (Categorical)	Set to 0 if DERDTHDT not missing Set to 1 (censored time) otherwise <Note: Indicator variable should be used in conjunction with LCONDY in any time to event analyses>
Subject	ICUDY	Length of stay (days) in ICU (Continuous)	DMDATA.HRU (Where HUCLVCD=4) Select HUNDYCAR
Subject	HOSPDY	Length of stay (days) in Hospital (Continuous)	DMDATA.HRU (Where HUCLVCD=8) Select HUNDYCAR

Type	Variable Name	Details	Suggestions for derivation / data source
Subject	DYWOVNT	Ventilation Free Days (1 to 28) (Continuous)	DMDATA.HRU (Where HUSCATCD=3) Select DYWOVNT
Subject	SGX1TO3	Any Surgery between Day 1 and Day 3 (Binary Y/N)	DMDATA.SURGERY (Where VISITNUM=50) Select SPYN
Time	RVDYSI	Single variable capturing RV Dysfunction Status by Study Day (Categorical: 1=No PCD 2=Moderate PCD (not severe enough to qualify as ACP) 3 = Non-severe ACP 4 = Severe ACP)	ARDATA.CV (Where CVANALFL=1 & CVTSTCD in (AK015, AK016)) For each subject and visitnum match Set to: • 1 if CVTSTCD=AK015 & CVORRSCD=N • 2 if [CVTSTCD=AK015 & CVORRSCD=Y] & [CVTSTCD=AK016 & CVORRSCD=51] • 3 if [CVTSTCD=AK015 & CVORRSCD=Y] & [CVTSTCD=AK016 & CVORRSCD=52] • 4 if [CVTSTCD=AK015 & CVORRSCD=Y] & [CVTSTCD=AK016 & CVORRSCD=53]
Subject	RVDYSX	Single variable capturing Worst observed RV Dysfunction Status at any time (Categorical)	MAX of RVDYSI variable (group by SUBJID)
Subject	PCDACPX	Any PCD or ACP at any time in study (Binary Y/N)	Set to Y if RVDYSX in (2,3,4) Set to N otherwise
Time	PCDACPI	Any PCD or ACP by Study Day (Binary Y/N)	Set to Y if RVDYSI in (2,3,4) Set to N otherwise
Subject	NORVDYSX	Did not have PCD or ACP at any time in study (Binary Y/N)	Set to Y if RVDYSX = 1 Set to N otherwise
Time	NORVDYSI	Did not have PCD or ACP on Study Day (Binary Y/N)	Set to Y if RVDYSI = 1 Set to N otherwise
Subject	PCDX	Worst case was PCD at any time in study (Binary Y/N)	Set to Y if RVDYSX = 2 Set to N otherwise
Time	PCDI	PCD on Study Day (Binary Y/N)	Set to Y if RVDYSI = 2 Set to N otherwise

Type	Variable Name	Details	Suggestions for derivation / data source
Subject	ACPX	Worst case was ACP at any time in study (Binary Y/N)	Set to Y if RVDYSX = 3 Set to N otherwise
Time	ACPI	ACP on Study Day (Binary Y/N)	Set to Y if RVDYSI = 3 Set to N otherwise
Subject	SEVACPX	Worst case was Severe ACP at any time in study (Binary Y/N)	Set to Y if RVDYSX = 4 Set to N otherwise
Time	SEVACPI	Severe ACP on Study Day (Binary Y/N)	Set to Y if RVDYSI = 4 Set to N otherwise
Subject	ARDNOX	ARDS but no PCD or ACP at any time in study (Binary Y/N)	Set to Y if [ARDSX=Y & NORVDYSX=Y] Set to N otherwise
Subject	ARDPCDX	ARDS and worst case PCD at any time in study (Binary Y/N)	Set to Y if [ARDSX=Y & PCDX =Y] Set to N otherwise
Subject	ARDACPX	ARDS and worst case ACP at any time in study (Binary Y/N)	Set to Y if [ARDSX=Y & ACPX =Y] Set to N otherwise
Subject	ARDSACPX	ARDS and worst case Severe ACP at any time in study (Binary Y/N)	Set to Y if [ARDSX=Y & SEVACPX =Y] Set to N otherwise
Time	GII	Global Inhomogeneity Index (Continuous)	DMDATA.CC (Select CCORRSN where CCTESTCD=BY001 & VISITNUM in (20,30,40))

Type	Variable Name	Details	Suggestions for derivation / data source
Time	<Various Vital Signs> SYSBP DIABP HEART TEMP RESP VSPO2BLD VSMAP VSPPV	Take names/properties directly from dataset (Continuous)	DMDATA.VITALS (Where VISITNUM in (20,30,40) & VSREFID ^= SOFA) Select (use same name) SYSBP DIABP HEART TEMP RESP VSPO2BLD VSMAP VSPPV Match on subjid and visitnum
Time	OI	Oxygenation Index (Continuous)	DMDATA.RE (Where VISITNUM in (20,30,40) & RETESTCD=AC002) Select REORRSN Match on subjid and visitnum
Time	PAO2	Partial pressure of arterial O2 (mmHg) (Continuous)	DMDATA.LAB (Where VISITNUM in (10,20,30,40) & LBREFID ^=SOFA & LBTESTCD=PAO2_BLP) For each subject select the most recent non-missing value from visitnum 10,20 (and set result to have visitnum=20) prior to merging by subject and visitnum Select LBORRESN
Time	PAO2DM	DateTime of PAO2 Sample (DateTime)	DMDATA.LAB (Where VISITNUM in (10,20,30,40) & LBREFID ^=SOFA & LBTESTCD=PAO2_BLP) For each subject select the most recent non-missing LBORRESN value from visitnum 10,20 (and set result to have visitnum=20) prior to merging by subject and visitnum Combine LBDT and LBACTTM into a single datetime formatted variable

Type	Variable Name	Details	Suggestions for derivation / data source
Time	PACO2	Carbon dioxide partial pressure (mmHg) (Continuous)	DMDATA.LAB (Where VISITNUM in (10,20,30,40) & LBREFID ^=SOFA & LBTESTCD=PCO2_BLP) For each subject select the most recent non-missing value from visitnum 10,20 (and set result to have visitnum=20) prior to merging by subject and visitnum Select LBORRESN
Time	LACT	Serum Lactate (mmol/L) (Continuous)	DMDATA.LAB (Where VISITNUM in (10,20,30,40) & LBREFID ^=SOFA & LBTESTCD=LACT_PLC) For each subject select the most recent non-missing value from visitnum 10,20 (and set result to have visitnum=20) prior to merging by subject and visitnum Select LBORRESN
Time	HC03	Serum Bicarbonate (mEq/L) (Continuous)	DMDATA.LAB (Where VISITNUM in (10,20,30,40) & LBREFID ^=SOFA & LBTESTCD=HC03_PLC) For each subject select the most recent non-missing value from visitnum 10,20 (and set result to have visitnum=20) prior to merging by subject and visitnum Select LBORRESN
Time	PH	Blood pH (Continuous)	DMDATA.LAB (Where VISITNUM in (10,20,30,40) & LBREFID ^=SOFA & LBTESTCD=PH_BLG) For each subject select the most recent non-missing value from visitnum 10,20 (and set result to have visitnum=20) prior to merging by subject and visitnum Select LBORRESN
Time	BASEXA	Base excess (arterial whole blood) (mEq/L) (Continuous)	DMDATA.LAB (Where VISITNUM in (10,20,30,40) & LBREFID ^=SOFA & LBTESTCD=BASEXA_BLC) For each subject select the most recent non-missing value from visitnum 10,20 (and set result to have visitnum=20) prior to merging by subject and visitnum Select LBORRESN

Type	Variable Name	Details	Suggestions for derivation / data source
Time	BDEFA	Base deficit (arterial whole blood) (mEq/L) (Continuous)	DMDATA.LAB (Where VISITNUM in (10,20,30,40) & LBREFID ^=SOFA & LBTESTCD=BDEFA_BLC) For each subject select the most recent non-missing value from visitnum 10,20 (and set result to have visitnum=20) prior to merging by subject and visitnum Select LBORRESN
Time	TROPI	Troponin I (UG/L) (Continuous)	DMDATA.LAB (Where VISITNUM in (10,20,30,40) & LBREFID ^=SOFA & LBTESTCD=TROPI_PLC) For each subject select the most recent non-missing value from visitnum 10,20 (and set result to have visitnum=20) prior to merging by subject and visitnum Select LBORRESN
Time	TROPT	Troponin T (UG/L) (Continuous)	DMDATA.LAB (Where VISITNUM in (10,20,30,40) & LBREFID ^=SOFA & LBTESTCD=TROPT_PLC) For each subject select the most recent non-missing value from visitnum 10,20 (and set result to have visitnum=20) prior to merging by subject and visitnum Select LBORRESN
Time	PFSOFA	PaO2/FiO2 entered onto SOFA form (Continuous)	DMDATA.LAB (Where VISITNUM in (10,20,30,40) & LBREFID =SOFA & LBTESTCD=PAO2FI_BLQ) For each subject select the most recent non-missing value from visitnum 10,20 (and set result to have visitnum=20) prior to merging by subject and visitnum Select LBORRESN
Time	FIO2	Fraction of Inspired Oxygen (%) (Continuous)	DMDATA.FAPR (Where VISITNUM in (20,30,40) & FPRTSTCD=FPRAW005) Select FPRORSN. Match on subjid and visitnum

Type	Variable Name	Details	Suggestions for derivation / data source
Time	FIO2DM	DateTime of FIO2 Sample (DateTime)	DMDATA.FAPR (Where VISITNUM in (20,30,40) & FPRTSTCD=FPRAW005) Combine FPRDT and FPRTM into a single datetime formatted variable Match on subjid and visitnum
Time	PFDIFF	Difference between PaO2 and FiO2 Sampling occasions (mins)	(PAO2DM - FIO2DM) converted into minutes
Time	PFECRF	PaO2/FiO2 derived (Continuous)	PAO2 / (FIO2 / 100)
Time	PFECRF30	PaO2/FiO2 (sampling within ±30 mins) (Continuous)	Select PFECRF if ABS(PFDIFF) ≤ 30; set to missing otherwise
Time	FPRBH001	Static Respiratory System Compliance (mL/cm H2O) (Continuous)	DMDATA.FAPR (Where VISITNUM in (20,30,40) & FPRTSTCD= FPRBH001) Select FPRORSN. Match on subjid and visitnum
Time	FPRBH003	Pressure Support Ventilation (Binary Y/N)	DMDATA.FAPR (Where VISITNUM in (20,30,40) & FPRTSTCD= FPRBH003) Match on subjid and visitnum Set Y if FPRORSCD=ZZY Set N otherwise
Time	FPRAB001	Tidal Volume (mL) (Continuous)	DMDATA.FAPR (Where VISITNUM in (20,30,40) & FPRTSTCD= FPRAB001) Select FPRORSN. Match on subjid and visitnum
Time	FPRAB002	Positive End Expiratory Pressure PEEP (cm H2O) (Continuous)	DMDATA.FAPR (Where VISITNUM in (20,30,40) & FPRTSTCD= FPRAB002) Select FPRORSN. Match on subjid and visitnum
Time	FPRAB003	Peak Ventilatory Pressure (cm H2O) (Continuous)	DMDATA.FAPR (Where VISITNUM in (20,30,40) & FPRTSTCD= FPRAB003) Select FPRORSN. Match on subjid and visitnum
Time	FPRAB008	Plateau Ventilatory Pressure (cm H2O) (Continuous)	DMDATA.FAPR (Where VISITNUM in (20,30,40) & FPRTSTCD= FPRAB008) Select FPRORSN. Match on subjid and visitnum

Type	Variable Name	Details	Suggestions for derivation / data source
Time	FPRBH004	Mean Airway Pressure (cm H2O) (Continuous)	DMDATA.FAPR (Where VISITNUM in (20,30,40) & FPRTSTCD= FPRBH004) Select FPRORSN. Match on subjid and visitnum
Time	FPRBH005	Driving Pressure (cm H2O) (Continuous)	DMDATA.FAPR (Where VISITNUM in (20,30,40) & FPRTSTCD= FPRBH005) Select FPRORSN. Match on subjid and visitnum
Time	<Various Echo endpoints and the key RAS peptides>	Take from source dataset	ARDATA.STATSCAT (drop STUDYID, CENTREID, INVID, INVNAME, AGE, SEX, RACE, RACECD, ATRTCD, ATRTGRP, TRTCD, TRTGRP, USUBJID, VISIT, AH001AC, AK015, AK016 variables) Select remaining variables and match on subjid and visitnum

10.7. Appendix 7: Reporting Standards for Missing Data

10.7.1. Premature Withdrawals

Element	Reporting Detail
General	• Subject study completion (i.e. as specified in the protocol) was defined as having completed the Day 3 assessments as shown in the SoA. • Withdrawn subjects may be replaced in the study. • All available data from participants who were withdrawn from the study will be listed and all available planned data will be included in summary tables and figures, unless otherwise specified (e.g. because they withdrew consent as detailed in the study protocol). • Withdrawal visits will be slotted as per Appendix 3: Assessment Windows or will be summarised as withdrawal visits.

10.7.2. Handling of Missing Data

Element	Reporting Detail

General	• Missing data occurs when any requested data is not provided, leading to blank fields on the collection instrument:
	  ○ These data will be indicated by the use of a "blank" in participant listing displays. Unless all data for a specific visit are missing in which case the data is excluded from the table.
	  ○ Answers such as "Not applicable" and "Not evaluable" are not considered to be missing data and should be displayed as such.

Outliers	• Any participants excluded from the summaries and/or statistical analyses will be documented along with the reason for exclusion in the clinical study report.

Missing Categorical Covariates	• In the statistical models of RAS peptides as predictors of measures of RV function (and other associated models), a number of categorical covariates (e.g. sex, prior history of RAS modulators, type of echocardiogram, use of vasopressors, proning status, use of nitric oxide) may be required. The following rules should be applied to variables that are to be included in the final statistical model:
	• In the unlikely event that sex is not recorded for a participant, then data from that participant will not be included.
	• For prior history of RAS modulators, a participant is assumed not to have had such a history unless explicitly reported otherwise.
	• For the other variables listed above, which are recorded on each study day, the following imputation algorithm should be applied for missing values:
	  ○ If the same variable is not missing on a previous study day (including screening, if applicable), impute the most recent known value.
	  ○ Otherwise, if the same variable is not missing on a subsequent study day, impute the value from the nearest time point after the missing one.
	• Otherwise, keep the value as missing and exclude the participant from the analysis

10.7.2.1. Handling of Missing and Partial Dates/Times

Element	Reporting Detail
General	• Partial dates will be displayed as captured in participant listing displays.
Adverse	• The eCRF allows for the possibility of partial dates (i.e., only month and year) to be

Element	Reporting Detail
Events	recorded for AE start and end dates; that is, the day of the month may be missing. In such a case, the following conventions will be applied for calculating the time to onset and the duration of the event: ○ Missing Start Day: First of the month will be used unless this is before the start date of study treatment; in this case the study treatment start date will be used and hence the event is considered On-treatment as per Appendix 4: Study Phases and Treatment Emergent Adverse Events. ○ Missing Stop Day: Last day of the month will be used, unless this is after the stop date of study treatment; in this case the study treatment stop date will be used. • Completely missing start or end dates will remain missing, with no imputation applied. Consequently, time to onset and duration of such events will be missing.
Concomitant Medications/ Medical History	• Partial dates for any concomitant medications recorded in the CRF will be imputed using the following convention: ○ If the partial date is a start date, a '01' will be used for the day and 'Jan' will be used for the month ○ If the partial date is a stop date, a '28/29/30/31' will be used for the day (dependent on the month and year) and 'Dec' will be used for the month. • The recorded partial date will be displayed in listings.

10.8. Appendix 8: Values of Potential Clinical Importance

10.8.1. Laboratory Values

Note: Due to usage of local labs, care should be taken to ensure each supplied unit has been converted into the units given below before applying the PCI criteria (if applicable – any multipliers of LLN / ULN do not require units).

PCI values have been taken from Study ACE114622 (mild to moderate ARDS). Since no investigational product is being administered in this study any PCI flags will act more as an awareness for the study team when interpreting the RAS peptides / other clinical outcomes for those individuals. Any lab tests which the medical monitor has not specified PCI ranges for are denoted as "NA" but will still be reviewed as part of the Min/Max variables in the Summary tables.

Haematology				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (Relative – Multipliers of LLN)	**High Flag (Relative – Multipliers of ULN)**
Platelet Count			0.4	NA
Red Blood Cell (RBC) Count			NA	NA
While Blood Cell (WBC) Count (absolute)			0.67	1.82
Haemoglobin		Male	0.67	1.03
		Female	0.67	1.13
Hematocrit	Ratio of 1	Male	0.3	0.54
		Female	0.3	0.54
(Total) Neutrophils			NA	NA
Lymphocytes			NA	NA
Monocytes			NA	NA
Eosinophils			NA	NA
Basophils			NA	NA

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag (Relative – Multipliers of LLN)	**High Flag (Relative – Multipliers of ULN)**
Urea / BUN			NA	NA
Chloride			NA	NA
Creatinine			NA	2
Potassium			0.86	1.10
Sodium			NA	NA
Total CO_2			NA	NA
Total Bilirubin			NA	NA

Clinical Chemistry				
Laboratory Parameter	**Units**	**Category**	**Clinical Concern Range**	
			Low Flag	**High Flag**
Troponin I (Note: Has been spelt as Troponon in Protocol)	ng/mL		NA	> 0.04
Troponin T (Note: Has been spelt as Troponon in Protocol)	ng/mL		NA	> 0.10

10.8.2. Vital Signs

Vital Sign Parameter (Absolute)	**Units**	**Clinical Concern Range**	
		Lower	**Upper**
Systolic Blood Pressure	mmHg	<85	>160
Diastolic Blood Pressure	mmHg	<45	>100
Heart Rate	bpm	<40	>110

10.9. Appendix 9: Abbreviations & Trade Marks

10.9.1. Abbreviations

Abbreviation	Description
ADaM	Analysis Data Model
AE	Adverse Event
AIC	Akaike's Information Criteria
A&R	Analysis and Reporting
BLQ	Below Limit of Quantification
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CPMS	Clinical Pharmacology Modelling & Simulation
CPSR	Clinical Pharmacology Study Report (interchangeable with the CSR abbreviation)
CS	Clinical Statistics
CSR	Clinical Study Report
CTR	Clinical Trial Register
CV_b / CV_w	Coefficient of Variation (Between) / Coefficient of Variation (Within)
DBF	Database Freeze
DBR	Database Release
DIC	Deviance Information Criteria
DOB	Date of Birth
DP	Decimal Places
eCRF	Electronic Case Record Form
EMA	European Medicines Agency
FDA	Food and Drug Administration
FDAAA	Food and Drug Administration Clinical Results Disclosure Requirements
GSK	GlaxoSmithKline
IA	Interim Analysis
ICH	International Conference on Harmonization
IDMC	Independent Data Monitoring Committee
IDSL	Integrated Data Standards Library
IMMS	International Modules Management System
IP	Investigational Product
ITT	Intent-To-Treat
LAR	Legally Acceptable Representative
LLN	Lower Limit of Normal
MMRM	Mixed Model Repeated Measures
PCI	Potential Clinical Importance
PD	Pharmacodynamic
PDMP	Protocol Deviation Management Plan
PK	Pharmacokinetic
PP	Per Protocol
PopPK	Population PK
QC	Quality Control

Abbreviation	Description
QTcF	Frederica's QT Interval Corrected for Heart Rate
QTcB	Bazett's QT Interval Corrected for Heart Rate
RAP	Reporting & Analysis Plan
RAMOS	Randomization & Medication Ordering System
SAC	Statistical Analysis Complete
SDSP	Study Data Standardization Plan
SDTM	Study Data Tabulation Model
SoA	Schedule of Assessments (also known as Time and Events table)
SOP	Standard Operation Procedure
TA	Therapeutic Area
TBC	To Be Confirmed
TFL	Tables, Figures & Listings
ULN	Upper Limit of Normal
ULQ	Upper Limit of Quantification

10.9.2. Trademarks

Trademarks of the GlaxoSmithKline Group of Companies
NONE

Trademarks not owned by the GlaxoSmithKline Group of Companies
SAS

10.10. Appendix 10: List of Data Displays

10.10.1. Data Display Numbering

The following numbering will be applied for RAP generated displays:

Section	Tables	Figures
Study Population	1.1 to 1.n	1.1 to 1.n
Safety	2.1 to 2.n	2.1 to 2.n
Pharmacodynamic and / or Biomarker	3.1 to 3.n	3.1 to 3.n
Participant Status and / or Other Clinical Assessments	4.1 to 4.n	4.1 to 4.n
Statistical Modelling	5.1 to 5.n	5.1 to 5.n
Section	**Listings**	
ICH Listings	1 to x	
Other Listings	y to z	

10.10.2. Mock Example Shell Referencing

Non IDSL specifications will be referenced as indicated and if required example mock-up displays provided in Appendix 11: Example Mock Shells for Data Displays.

Section	Figure	Table	Listing
Study Population	POP_Fn	POP_Tn	POP_Ln
Safety	SAFE_Fn	SAFE_Tn	SAFE_Ln
Pharmacodynamic and / or Biomarker	PD_Fn	PD_Tn	PD_Ln
Participant Status and / or Other Clinical Assessments	OCA_Fn	OCA_Tn	OCA_Ln
Statistical Modelling	SM_Fn	SM _Tn	SM _Ln

NOTES:

- Non-Standard displays are indicated in the 'IDSL / Example Shell' or 'Programming Notes' column as '[Non-Standard] + Reference.'

10.10.3. Deliverables

Delivery Priority [1]	Description
SAC X	Final Statistical Analysis Complete

NOTES:

1. Indicates priority (i.e. order) in which displays will be generated for the reporting effort

10.10.4. Study Population Tables

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.1.	Enrolled	ES1	Summary of Subject Disposition for the Subject Conclusion Record	ICH E3, FDAAA, EudraCT, CONSORT	SAC 1
1.2.	Screened	ES6	Summary of Screening Status and Reasons for Screen Failure	Journal Requirements	SAC 1
1.3.	Safety	NS1	Summary of Number of Subjects by Country and Site ID	EudraCT/Clinical Operations	SAC 1
Protocol Deviations					
1.4.	Safety	DV1	Summary of Important Protocol Deviations	ICH E3	SAC 1
Population Analysed					
1.5.	Enrolled	SP1A	Summary of Study Populations	IDSL	SAC 1
1.6.	Enrolled	SP2A	Summary of Exclusions from the Safety/Evaluable/Completed/At Risk Populations	IDSL If possible separate page for each population (this may require non-standard wrapper macro to call the standard macro separately for each population) If the Evaluable with prohibited conmed population is different to evaluable add it in (otherwise footnote the evaluable table to indicate they are the same)	SAC 1

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Demographic and Baseline Characteristics					
1.7.	Safety	DM1	Summary of Demographic Characteristics by PCD/ACP status	ICH E3, FDAAA, EudraCT Instead of the set of treatment variables (columns) please use “No PCD/ACP” and “Any PCD/ACP” and “All Participants” as columns to group the subjects As well as the standard set of demography items (Sex, Age, Age Group, Height, Weight, BMI) please also include the following Disease specific baseline variables (with units if applicable) to facilitate manuscript publication (mixture of continuous and categorical variables) Baseline should be the **earliest** non-missing value from SCREENING or DAY 1 visits. Do not display values from Days 2 or 3 (if multiple timepoints are available for an item) SAPSII, SOFA, PaO2/FiO2 (from SOFA form), PaO2, FiO2, PaCO2, Oxygenation Index, Reason for Intubation (use the mapped variable not free text results), Proned, Receiving Inhaled Nitric Oxide, “Managed with Vasopressors, inotropes or other vasoactive agents”, ECMO, ECCO2R, Global Inhomogeneity Index, SpO2, Serum Lactate, Serum Bicarbonate, pH, Base excess (arterial whole blood), Base deficit (arterial whole blood), Central Venous Pressure, Static respiratory system compliance, Respiratory rate (not from vitals but from FAPR), Pressure support (Y/N), Tidal Volume, PEEP, Peak Pressure, Plateau Pressure, Mean Airway Pressure, Driving Pressure, In-hospital Mortality (Y/N/Unkown) Note: Summarise with n, Median, Lower and Upper quartiles, Min and Max: Length of stay in ICU, Length of stay in hospital, Ventilation free days	SAC 2

Study Population Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
1.8.	Safety	DM11	Summary of Age Ranges	EudraCT	SAC 2
Prior and Concomitant Medications					
1.9.	Safety	MH4	Summary of Current Medical Conditions	ICH E3	SAC 2
1.10.	Safety	MH4	Summary of Past Medical Conditions	ICH E3	SAC 2
1.11.	Safety	CM1	Summary of Concomitant Medications	ICH E3 Exclude the SOFA related records	SAC 2

10.10.5. Safety Tables

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Serious Adverse Events					
2.1.	Safety	AE16	Summary of Serious Adverse Events by System Organ Class and Preferred Term (Number of Participants and Occurrences)	FDAAA, EudraCT Conditional output: a listing on its own may be sufficient if there are few events. Display lines showing “Drug-related SAE” and “Drug-related Fatal SAE” should be omitted as there is no study drug involved.	SAC 2
Laboratory					
2.2.	Safety	LB1	Summary of Clinical Chemistry Values by Timepoint	ICH E3 Exclude the SOFA related records There is no baseline in this study as there is no treatment being administered. Therefore the only data that can be presented is raw values rather than changes from baseline.	SAC 2

Safety: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
2.3.	Safety	LB1	Summary of Haematology Values by Timepoint	ICH E3 Exclude the SOFA related records There is no baseline in this study as there is no treatment being administered. Therefore the only data that can be presented is raw values rather than changes from baseline.	SAC 2
Vital Signs					
2.4.	Safety	VS1	Summary of Vital Signs by Timepoint	ICH E3 Exclude the SOFA related records There is no baseline in this study as there is no treatment being administered. Therefore the only data that can be presented is raw values rather than changes from baseline.	SAC 2

10.10.6. Pharmacodynamic and Biomarker Tables

Pharmacodynamic and Biomarker: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Echocardiography					
3.1.	Evaluable	PD_T1 (ECHO)	Summary of Echocardiogram Measurements by Timepoint	Two separate statistics tables: 1) for continuous, 2) for qualitative echo measurements.	SAC 1
3.2.	Evaluable	SM_T1 (ECHO)	Within- and Between-Subject Variability of Continuous Echocardiogram Measurements		SAC 1
RAS Biomarkers					
3.3.	Evaluable	PD_T2 (RAS)	Summary of RAS Biomarker Measurements by Timepoint	Present results for levels and log transformed in two separate tables.	SAC 1
3.4.	Evaluable	SM_T1 (RAS)	Within- and Between-Subject Variability of RAS Biomarker Measurements		SAC 1

Participant Status and Other Clinical Assessments: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Disease Diagnosis Status					
4.1.	At risk	OCA_T1 (DISEASE_INCIDENCE)	Summary of ARDS, PCD and ACP Incidence Rates by Timepoint and Study	Create two tables: 1) summarizing of number of the cases, where patient may contribute multiple times and 2) with overall incidence rates including the joint categories. Note: Shell does not contain all items to be displayed	SAC 1

10.10.7. Pharmacodynamic and Biomarker Figures

Pharmacodynamic and Biomarker: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Echocardiography					
3.1.	Evaluable	PD_F2 (SCAT3D_YN)	Scatterplot of PASP vs RV Size Ratio marked by Paradoxical Septal Motion Status	Scatterplot of (x-axis) PASP vs (y-axis) RV size ratio. Paradoxical Septal Motion Status is marked by black(Y)-grey(N) colour. For Not Done PSM status leave blank (i.e. do not plot a coloured circle within the data point)	SAC 1
RAS Biomarkers					
3.2.	Evaluable	PD_F1 (SCAT2D)	Scatterplots of Ang II, Ang(1-7) and Ang(1-5) combinations	Display with a Log10-transformed x and y axis scales. Separate page/plot for each combination. Present Ang II Vs Ang(1-7), Ang II Vs Ang(1-5) and Ang(1-7) Vs Ang(1-5) in listed order	SAC 1
3.3.	Evaluable	PD_F4 (SERIES1D)	Individual Line Plots of RAS Biomarkers by Timepoint	On separate pages, time series plots for RAS biomarker readouts: Ang II, Ang(1-7), Ang(1-5), Ang II/Ang(1-7) ratio per visit (use log10 scale for y-axis). If the number of subject is too large omit the legend.	SAC 1

Pharmacodynamic and Biomarker: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
3.4.	Evaluable	PD_F2 (SCAT3D_YN)	Scatterplots of Selected Echocardiography Endpoints Vs selected RAS biomarkers by Paradoxical Septal Motion Status	On separate pages, scatterplots of (x-axis) RAS biomarker readouts: Ang II, Ang(1-7), Ang(1-5), Ang II/ Ang(1-7) ratio (using log10 axis scale), vs (y-axis) PASP and RV size ratio readouts. Paradoxical Septal Motion Status is marked by black(Y)-grey(N) colour. For Not Done PSM status leave blank (i.e. do not plot a coloured circle within the data point)	SAC 1
3.5.	Evaluable	PD_F3 (SCAT3D_CONT)	Scatterplots of PASP vs. RV Size Ratio marked by RAS biomarker levels	On separate pages, scatterplots for (x-axis) PASP vs (Y-axis) RV size ratio coloured by RAS biomarker readouts: Ang II, Ang(1-7), ANG II/ Ang(1-7) ratio and Ang(1-5) on rainbow colour scale (no log-transformation). For each RAS biomarker scatterplot without and with visit marks provided.	SAC 1

10.10.8. Statistical Modelling Tables

Statistical Modelling: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Preparatory Analysis					
5.1.	Evaluable	SM_T2 (BICORR_PHARM)	Bivariate Correlations of RAS Biomarkers with Pharmacodynamic Endpoints	Consider three different measures of correlation:1) derived from the bivariate mixed effect model and its between-marker Sigma vcov matrix 2) Pearson correlation 3) Spearman correlation A version of this output should be produced as soon as possible after the interim or final analysis has been triggered in order to enable the team to decide a) which covariates to include in the models and b) which of the conditional outputs (if any) to produce. List of continuous covariates to be provided at run time by statistician	SAC 1

Statistical Modelling: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.2.	Evaluable	SM_T2 (BICORR_CONT)	Bivariate Correlations of Ang II, Ang(1-7), PASP and RV Size Ratio with Continuous Covariates	Consider three different measures of correlation:1) derived from the bivariate mixed effect model and its between-marker Sigma vcov matrix 2) Pearson correlation 3) Spearman correlation A version of this output should be produced as soon as possible after the interim or final analysis has been triggered in order to enable the team to decide which covariates to include in the primary and secondary models. List of continuous covariates to be provided at run time by statistician	SAC 1
5.3.	Evaluable	SM_T3 (ECHO_RAS_ CAT)	Summary Statistics of RAS biomarkers and Echocardiogram Endpoints by Categorical Covariates	A version of this output should be produced as soon as possible after the interim or final analysis has been triggered in order to enable the team to decide which covariates to include in the primary and secondary models. List of categorical covariates will be provided by statistician at time of analysis	SAC 1

Statistical Modelling: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Statistical Modelling					
5.4.	Evaluable	SM_T4 (MODEL1)	Summary of Primary Model Results: Ang II as a Predictor of PASP and RV Size Ratio	On separate pages: **Table 1)** subtitle: Model Parameters Values with Statistics **Table 2)** subtitle: PASP and RV Model Predictions for Reference Ang II Values: Pre-dose <Ang_II_level> (pg/mL) and Post-dose <Ang_II _level> (pg/mL) **Table 3)** subtitle: Probability of RV Disfunction Given Reference Ang II Values: Pre-dose <Ang_II_level> (pg/mL) and Post-dose <Ang_II _level> (pg/mL) Add any sensitivity reference value results onto separate pages. For clear separation the subtitles start with 'SENSITIVITY:'	SAC 1

Statistical Modelling: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.5.	Evaluable	SM_T4 (MODEL2)	Summary of Secondary Model Results: Ang(1-7) as a Predictor of PASP and RV Size Ratio	On separate pages: **Table 1)** subtitle: Model Parameters Values with Statistics **Table 2)** subtitle: PASP and RV Model Predictions for Reference Ang(1-7) Values: Pre-dose < Ang(1-7)_level> (pg/mL) and Post-dose < Ang(1-7)_level> (pg/mL) **Table 3)** subtitle: Probability of RV Disfunction Given Reference Ang(1-7) Values: Pre-dose < Ang(1-7)_level> (pg/mL) and Post-dose < Ang(1-7)_level> (pg/mL) Add any sensitivity reference value results onto separate pages. For clear separation the subtitles start with 'SENSITIVITY:'	SAC 1

Statistical Modelling: Tables					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
5.6.	Evaluable	SM_T4 (MODEL3)	Summary of Secondary Model Results: Ang(1-5) as a Predictor of PASP and RV Size Ratio	[conditional output] On separate pages: **Table 1)** subtitle: Model Parameters Values with Statistics **Table 2)** subtitle: PASP and RV Model Predictions for Reference Ang(1-5) Values: Pre-dose < Ang(1-5)_level> (pg/mL) and Post-dose < Ang(1-5)_level> (pg/mL) **Table 3)** subtitle: Probability of RV Disfunction Given Reference Ang(1-5) Values: Pre-dose < Ang(1-5)_level> (pg/mL) and Post-dose < Ang(1-5)_level> (pg/mL) Only analysis would be the sensitivity reference value, but still start the subtitles with 'SENSITIVITY:'	SAC 1
5.7.	Evaluable	SM_T4 (MODEL4)	Summary of Secondary Model Results: Ang II and Ang(1-7) as Joint Predictors of PASP and RV Size Ratio	[conditional output] Model only run if data permit	SAC 1

10.10.9. Statistical Modelling Figures

Statistical Modelling: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Statistical Modelling Figures					
5.1.	Evaluable	SM_F1	Scatterplot of PASP vs RV Size Ratio, Coloured by Ang II Value, with Posterior Prediction Regions for RV Function Measurements for Protocol-Defined Reference Values of Ang II	On separate pages: **Figure 1)** the scatterplot version with no visit marks and subtitle: Pre-dose <Ang_II_level> (pg/mL) and Post-dose <Ang_II _level> (pg/mL) Ang II **Figure 2)** the scatterplot version with visit marks and subtitle: Pre-dose <Ang_II_level> (pg/mL) and Post-dose <Ang_II _level> (pg/mL) Ang II **Figure 3)** subtitle: PASP Median and 95% Equal-Tailed Credibility Intervals for Pre-dose <Ang_II_level> (pg/mL) and Post-dose <Ang_II _level> (pg/mL) Ang II **Figure 4)** subtitle: RV size Median and 95% Equal-Tailed Credibility Intervals for Pre-dose <Ang_II_level> (pg/mL) and Post-dose <Ang_II _level> (pg/mL) Ang II **Figure 5)** subtitle: Prediction Regions for RV Function Measurements for Pre-dose <Ang_II_level> (pg/mL) and Post-dose <Ang_II _level> (pg/mL) Ang IIAdd any sensitivity reference value results onto separate pages. For clear separation the subtitles start	SAC 1

Statistical Modelling: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
				with 'SENSITIVITY:'	
5.2.	Evaluable	SM_F1	Scatterplot of PASP vs RV Size Ratio, Coloured by Ang(1-7) Value, with Posterior Prediction Regions for RV Function Measurements for Protocol-Defined Reference Values of Ang(1-7)	On separate pages: **Figure 1)** the scatterplot version with no visit marks and subtitle: Pre-dose <Ang(1-7)_level> (pg/mL) and Post-dose <Ang(1-7) _level> (pg/mL) Ang(1-7) **Figure 2)** the scatterplot version with visit marks and subtitle: Pre-dose <Ang(1-7)_level> (pg/mL) and Post-dose <Ang(1-7) _level> (pg/mL) Ang(1-7) **Figure 3)** subtitle: PASP Median and 95% Equal-Tailed Credibility Intervals for Pre-dose <Ang(1-7)_level> (pg/mL) and Post-dose <Ang(1-7) _level> (pg/mL) Ang(1-7) **Figure 4)** subtitle: RV size Median and 95% Equal-Tailed Credibility Intervals for Pre-dose <Ang(1-7)_level> (pg/mL) and Post-dose <Ang(1-7) _level> (pg/mL) Ang(1-7) **Figure 5)** subtitle: Prediction Regions	SAC 1

Statistical Modelling: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
				for RV Function Measurements for Pre-dose <Ang(1-7)_level> (pg/mL) and Post-dose <Ang(1-7) _level> (pg/mL) Ang(1-7) Add any sensitivity reference value results onto separate pages. For clear separation the subtitles start with 'SENSITIVITY:'	
5.3.	Evaluable	SM_F1	Scatterplot of PASP vs RV Size Ratio, Coloured by Ang(1-5) Value, with Posterior Prediction Regions for RV Function Measurements for Protocol-Defined Reference Values of Ang(1-5)	[conditional output] On separate pages: **Figure 1)** the scatterplot version with no visit marks and subtitle: Pre-dose <Ang(1-5)_level> (pg/mL) and Post-dose <Ang(1-5) _level> (pg/mL) Ang(1-5) **Figure 2)** the scatterplot version with visit marks and subtitle: Pre-dose <Ang(1-5)_level> (pg/mL) and Post-dose <Ang(1-5) _level> (pg/mL) Ang(1-5) **Figure 3)** subtitle: PASP Median and 95% Equal-Tailed Credibility Intervals for Pre-dose <Ang(1-5)_level> (pg/mL) and Post-dose <Ang(1-5) _level> (pg/mL) Ang(1-5) **Figure 4)** subtitle: RV size Median and 95% Equal-Tailed Credibility Intervals for Pre-dose <Ang(1-5)_level> (pg/mL) and Post-dose <Ang(1-5) _level> (pg/mL) Ang(1-5) **Figure 5)** subtitle: Prediction Regions	SAC 1

Statistical Modelling: Figures					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
				for RV Function Measurements for Pre-dose <Ang(1-5)_level> (pg/mL) and Post-dose <Ang(1-5) _level> (pg/mL) Ang(1-5) Only analysis would be the sensitivity reference value, but still start the subtitles with 'SENSITIVITY:'	
5.4.	Evaluable	SM_F2	Boxplots of Ang II, Ang(1-7), Ang(1-5), PASP and RV Size Ratio by Categorical Covariates. Auxiliary output for Table 5.3	[conditional output]	SAC [1]

10.10.10. ICH Listings

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Subject Disposition					
1.	Screened	ES7	Listing of Reasons for Screen Failure	Journal Guidelines	SAC 1
2.	Enrolled	ES2	Listing of Reasons for Study Withdrawal	ICH E3	SAC 1
Protocol Deviations					
3.	Safety	DV2	Listing of Important Protocol Deviations	ICH E3	SAC 1
4.	Enrolled	IE3	Listing of Subjects with Inclusion/Exclusion Criteria Deviations	ICH E3	SAC 1
Populations Analysed					
5.	Enrolled	SP3a	Listing of Subjects Excluded from Any Population	ICH E3	SAC 1
Demographic and Baseline Characteristics					
6.	Safety	DM2	Listing of Demographic Characteristics	ICH E3 Use same set of variables as the corresponding summary table	SAC 2
Prior and Concomitant Medications					
7.	Safety	CP_CM3	Listing of Concomitant Medications	IDSL Exclude the SOFA related records	SAC 2
Adverse Events Section is not applicable as non-serious AEs are not being databased					
Serious and Other Significant Adverse Events					
8.	Safety	AE8CPa	Listing of Serious Adverse Events	ICH E3	SAC 2
9.	Safety	AE14	Listing of Reasons for Considering as a Serious Adverse Event	ICH E3	SAC 2
10.	Safety	AECP8	Listing of Serious Adverse Events Leading to Withdrawal from Study	ICH E3	SAC 2

ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
All Laboratory					
11.	Safety	LB5	Listing of All Laboratory Data for Participants with Any Value of Potential Clinical Importance	ICH E3 Exclude the SOFA related records	SAC 2
Vital Signs					
12.	Safety	VS4	Listing of All Vital Signs Data for Participants with Any Value of Potential Clinical Importance	IDSL Exclude the SOFA related records	SAC 2

10.10.11. Non-ICH Listings

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Pharmacodynamic and Biomarker Listings					
13.	Evaluable	PD_L1	Listing of Echocardiograph Measurements	Include all echo measures except the original eCRF PASP (AH001), AH001src, the programmatically derived variable containing the combined RAP (RAP), AK015 and AK016 which concern the ACP/PCD and its severity (those are displayed in Listing 19). Keep the order as in Section 5.5. Except for Estimated and Measured RAP have blank records if no result obtained for a test to maintain consistency of output for each subject and visit combination	SAC 1
14.	Evaluable	PD_L2	Listing of RAS Biomarker Values	Listing on non-transformed levels. Include Ang II / Ang(1-7) ratio and ANG(1-5)	SAC 1
Participant Status and Other Clinical Assessments Listings					
15.	At Risk	OCA_L5	Listing of Disease Diagnosis Status	Match to items in Table 4.1	SAC 1
16.	Safety	AE2 (Modified)	Listing of Relationship between Reasons for Intubations and Verbatim Text	Display the Mapped categories (in place of System Organ Class – in the order implied in Section 10.6.4) and all of the free text reasons within each mapping (in place of Verbatim text) and omit the Preferred Term column (from the AE2 shell)	SAC 1

Non-ICH: Listings					
No.	**Population**	**IDSL / Example Shell**	**Title**	**Programming Notes**	**Deliverable [Priority]**
Statistical Modelling Listings					
17.	Evaluable	SM_L1	Listing of Primary Statistical Model Output: Ang II as a Predictor of PASP and RV Size Ratio	Start with Gelman-Rubin diagnostics for model parameters convergence given different starting points. Mark considered burn-in period. Further, include model printouts from PROC MCMC for parameter estimates and PASP and RV Size Ratio predictions given Ang II reference values.	SAC 1
18.	Evaluable	SM_L1	Listing of Secondary Model Results: Ang(1-7) as a Predictor of PASP and RV Size Ratio	Start with Gelman-Rubin diagnostics for model parameters convergence given different starting points. Mark considered burn-in period. Further include model printouts from PROC MCMC for parameter estimates and PASP and RV Size Ratio predictions given Ang(1-7) reference values.	SAC 1
19.	Evaluable	SM_L1	Listing of Secondary Model Results: Ang(1-5) as a Predictor of PASP and RV Size Ratio	[conditional output] Start with Gelman-Rubin diagnostics for model parameters convergence given different starting points. Mark considered burn-in period. Further include model printouts from PROC MCMC for parameter estimates and PASP and RV Size Ratio predictions given Ang(1-5) reference values.	SAC 1
20.	Evaluable	SM_L1 (Modified for model structure / parameters)	Listing of Secondary Model Results: Ang II and Ang(1-7) as Joint Predictors of PASP and RV Size Ratio	[conditional output]	SAC 1

10.11. Appendix 11: Example Mock Shells for Data Displays

Data Display Specification will be made available on Request