Intervention Appendix:

Simvastatin

PANTHER:-
Precision medicine Adaptive Network platform Trial in Hypoxaemic acutE respiratory failuRe

Simvastatin Intervention Appendix Version V2.0 dated 11 JUN 2025

This Intervention Appendix applies to the following:-

Subphenotype	Hyperinflammatory	Hypoinflammatory
***Intervention**	Simvastatin Usual care	Simvastatin Usual care

**Note the patient may also be eligible for other interventions but this appendix covers the simvastatin intervention.*

PANTHER: Simvastatin intervention summary	
Intervention exclusion	1. Age < 18 years 2. Patient is known to be pregnant 3. Creatine kinase >10 times the upper limit of the normal range 4. Liver transaminases >8 times the upper limit of the normal range 5. Currently receiving ongoing treatment with any of the following: itraconazole, ketoconazole, HIV protease inhibitors, nefazodone, cyclosporine, amiodarone, verapamil, or diltiazem. 6. Severe renal impairment (eGFR < 30mL/min and not receiving renal replacement therapy). 7. Current or recent treatment (within 2 weeks) with statins 8. Physician decision that a statin is required for proven indication 9. Contraindication to enteral drug administration, e.g., patients with mechanical bowel obstruction. Patients with high gastric aspirates due to an ileus are not excluded. 10. Known hypersensitivity to simvastatin 11. Breast feeding 12. Any other medical condition or treatment that, at the clinical discretion of the investigator, is considered not in the participants best interest to start treatment with the IMP based on the approved version of the IMP SmPC.
Outcome measures	PANTHER primary endpoint:- the primary endpoint is defined in the master protocol PANTHER secondary endpoints:- the secondary endpoints are defined in the master protocol

ABBREVIATIONS

AE	Adverse Event
ARDS	Acute Respiratory Distress Syndrome
CI	Chief Investigator
CRF	Case Report Form
CTA	Clinical Trial Authorisation
DMC	Data Monitoring Committee
DSUR	Development Safety Update Report
EC	Ethics Committee
eCRF	Electronic Case Report Form
GMP	Good Manufacturing Practice
HRA	Health Research Authority
ICHNT	Imperial College Healthcare NHS Trust
ICMJE	International Committee of Medical Journal Editors
ICTU	Imperial Clinical Trials Unit
IMP	Investigational Medicinal Product
IND	Investigational New Drug
ITMG	International Trial Management Group
ITSC	International Trial Steering Committee
ITT	Intention to Treat
NIMP	Non- Investigational Medicinal Product
QA	Quality Assurance
QC	Quality Control
RSA	Region Specific Appendix
RSI	Reference Safety Information
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSAR	Suspected Serious Adverse Reaction
SUSAR	Suspected Unexpected Serious Adverse Reaction
CK	Creatine Kinase

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1. APPENDIX STRUCTURE

The PANTHER trial incorporates an adaptive trial design and the protocol is of a modular structure. For further details on the structure of protocol please see section 1 of the master protocol.

The master protocol contains information about the general conduct of the platform and as the interventions may change over time, an appendix is available for each intervention being studied within the PANTHER protocol. This appendix refers to simvastatin as part of the PANTHER protocol.

2. BACKGROUND

2.1 Intervention definition

This is to determine whether simvastatin improves 28-day organ free support days within the PANTHER trial.

2.2 Intervention-specific background

Simvastatin has pleiotropic effects that modify pathogenic mechanisms in ARDS (1). Data from a human model of lung inflammation induced by inhaled lipopolysaccharide (2), and a phase 2a RCT (3) supported the potential efficacy of simvastatin in ARDS. The EME-funded HARP-2 trial subsequently showed no benefit for simvastatin 80mg in an overall population of patients with ARDS (4). However, a secondary analysis of HARP-2, found that patients with the hyperinflammatory phenotype had improved 28-day survival when randomised to simvastatin (5). In ARDS due to COVID-19 simvastatin 80mg was associated with improved organ support-free days with a 95.9% posterior probability of superiority compared with control (6). The majority of patients with ARDS due to COVID-19 have the hypoinflammatory phenotype (7) suggesting the potential for benefit in that phenotype. The efficacy of simvastatin may relate to it being lipophilic. Together, these data support testing simvastatin in a phenotype-stratified trial.

The use of simvastatin 80mg once daily enterally for up to 28 days is informed by previous trials in patients with ARDS and COVID (4, 6).

Simvastatin 80mg is generally safe and well tolerated in this patient population. In previous blinded trials investigating statins in critically ill patients (4,8) the incidence of elevated levels of creatine kinase (CK) and liver aminotransferases was reported to be similar to placebo. In the HARP-2 trial (4) concomitant use of drugs normally contraindicated with simvastatin use including macrolides, fucidin and amiodarone were allowed in the setting of regular CK and liver aminotransferases safety monitoring. In a recent open-label trial the incidence of elevated CK (0.7%) and liver aminotransferases (0.7%), while uncommon, was higher in the simvastatin 80mg group (6). This may in part be due to selective reporting of adverse events in the simvastatin group in an open-label design. Regardless, it is important to emphasis the maximum treatment period with simvastatin 80mg in this study is 28 days, with safety monitoring (CK and liver transaminases) to day 28. In COVID-19, statins were associated with reduced mortality and improved outcomes in meta-analyses.

2.3 Intervention Objectives

To test the efficacy of simvastatin to improve 28-day organ-support free days.

3. ENDPOINTS

3.1 Primary Endpoint

The primary endpoint of this intervention is defined in the PANTHER master protocol.

3.2 Secondary Endpoints

All secondary endpoints for this intervention are defined in the PANTHER master protocol

4. STUDY DESIGN

This intervention will be part of the PANTHER trial and treatment allocation will be adaptive as described in the master protocol.

5. PARTICIPANT ENTRY

5.1 Intervention-specific exclusion criteria

1. Age < 18 years
2. Patient is known to be pregnant
3. Creatine kinase >10 times the upper limit of the normal range
4. Liver transaminases >8 times the upper limit of the normal range
5. Currently receiving ongoing treatment with any of the following: itraconazole, ketoconazole, HIV protease inhibitors, nefazodone, cyclosporine, amiodarone, verapamil, or diltiazem.
6. Severe renal impairment (eGFR < 30mL/min and not receiving renal replacement therapy).
7. Current or recent treatment (within 2 weeks) with statins
8. Physician decision that a statin is required for proven indication
9. Contraindication to enteral drug administration, e.g., patients with mechanical bowel obstruction. Patients with high gastric aspirates due to an ileus are not excluded.
10. Known hypersensitivity to simvastatin
11. Breast feeding
12. Any other medical condition or treatment that, at the clinical discretion of the investigator, is considered not in the participants best interest to start treatment with the IMP based on the approved version of the IMP SmPC.

6. PROCEDURES AND MEASUREMENTS

6.1 Randomisation and Blinding

Simvastatin is provided as an open-label medication, whereby participants, the clinical team and study team will not be masked to the intervention.

6.2 Treatment

The treatment regimen will be followed as long as the patient is in the ICU for up to 28 days. If randomised to simvastatin, the treatment will be given to the patient for 28 days, if the patient is randomised to usual care, the patient must not receive simvastatin for 28 days. If the patient is discharged from ICU prior to day 28 the treatment will be discontinued.

6.3 Follow-up

Patients randomised to this intervention will be followed up as per the master protocol.

6.4 Laboratory Evaluations

Routinely collected clinical blood samples will be used to measure at least the following at day 7 (+/- 2), 14 (+/- 2), 21 (+/- 2) and 28 (+/- 2) while the patient continues to receive simvastatin in local clinical laboratories at the recruiting hospital.

1) Creatine Kinase
2) Alanine Transaminase and/or Aspartate Transaminase

7. TREATMENTS

Patients will be randomly assigned to one of the two treatment interventions:-

- Simvastatin 80mg
- Usual care

7.1 Investigational Medicinal Product Details

Simvastatin is a licensed IMP and will be obtained via hospital stock from each participating site where possible, although this may vary by country (please see relevant country Region Specific Appendix (RSA) and the study Pharmacy Manual for more detail). The current Summary of Product Characteristics (SmPC) will be used and the need to update will be reviewed yearly on the anniversary of the study approval date.

7.2 Labelling and Packaging

Depending on the IMP risk classification in each country, the following labelling and packaging requirements will apply to simvastatin.

If the risk is deemed no higher than standard medical care, then no specific labelling or packaging is required for simvastatin. If the risk is deemed higher than standard of care, then labelling requirements may apply.

As the risk may vary by country, please see the relevant country RSA for more detail.

7.3 Storage and Dispensing

Where possible simvastatin will be provided from local hospital stock. If simvastatin is not available from hospital stock, then stock may be provided by alternative means such as via the Sponsor or sourced from the manufacturer, details of supply is available in the Pharmacy Manual. Any country specific differences of stock supply is detailed in the RSA.

Simvastatin is available in tablet form. Storage conditions for simvastatin should be as per Summary of Product Characteristics (SmPC). If simvastatin is provided from local hospital stock, storage monitoring requirements are risk adapted and temperature monitoring will be as per local site practice. As stock is off the shelf it is usual to follow local practice for dealing with temperature excursions in drug storage areas. If simvastatin is provided direct from the manufacturer or Sponsor, then storage and temperature monitoring may be required. Details

of any requirements are available in the pharmacy manual. No reporting of temperature excursions to the Sponsor is required.

Any country specific differences in storage monitoring will be detailed in the RSA

7.4 Dosage, Duration and Compliance

7.4.1 Usual care

Patients randomised to the 'usual care' group will not receive simvastatin. After randomisation, once the allocation is revealed as 'usual care' the patient must not receive any simvastatin for a duration of 28 days. Any administration will be considered a protocol deviation, unless started for a proven indication which develops after randomisation.

7.4.2 Simvastatin intervention

Simvastatin will be administered at a dose of 80 mg once daily by the enteral route for up to 28 days. Simvastatin will be prescribed on the participants' in-patient drug administration chart (or equivalent) and administered to the participant by appropriately trained clinical staff with appropriate competencies in accordance with local practice. These staff do not need to be on the study delegation log.

The first dose of simvastatin will be administered as soon as possible after the participant is randomised, ideally within four hours of randomisation. Subsequent doses will be given each morning starting on the following calendar day. If for any reason a dose is not administered at the intended time, it should be administered subsequently but not more than 12 hours after the intended time of administration.

If after randomisation the patient is not able to receive enteral drug administration, e.g., patients with mechanical bowel obstruction the treatment may be temporarily or permanently discontinued. Any omission of study drug will be recorded in the Case Report Form (CRF) to monitor treatment compliance. Permitted omissions of study drug will not be reported as a protocol violation. For more details on discontinuation of interventions and missed doses please refer to the Pharmacy Manual.

If the patient has a nasogastric, orogastric, percutaneous enterogastric (PEG), or percutaneous enterojejunal (PEJ) tube, IMP can be crushed and mixed with 15-30ml water and flushed down the tube. To ensure that the feeding tube is not blocked it can be flushed with a further 10-30 ml water following IMP administration. IMP administration details can be found in the Pharmacy manual.

All doses given will be recorded on the chart and reasons for a dose being missed will be documented as per routine practice. The timing of each dose and compliance will be recorded in the trial database. It will be considered a protocol deviation if during the 28-day course two or more doses of simvastatin are missed.

7.4.3 Dose adjustment

There is no simvastatin dose adjustment for renal failure or during renal replacement therapy but simvastatin must be stopped if there is renal failure that is caused or contributed to by rhabdomyolysis.

In addition simvastatin will be stopped if

1) Creatine Kinase is elevated more than 10 times the upper limit of normal or
2) Alanine Transaminase or Aspartate Transaminase or both are elevated more than 8 times the upper limit of normal

If a single dose of amiodarone (single intravenous bolus or any enteral dose) is administered no change is required for the simvastatin dose. However, if a patient receives more than a single dose of amiodarone, simvastatin dose should be reduced to 20mg daily.

7.5 Accountability

If simvastatin is provided from local hospital stock, accountability will be risk adapted and in line with standard care, and there is no requirement for trial specific accountability. Each site hospital pharmacy should plan to supply drug stock according to their local practices.

If simvastatin is provided by the Sponsor or manufacturer accountability may be required. Clarification of accountability requirements can be found in the Pharmacy Manual.

Simvastatin will only be administered to participants while they are in-patients in ICU and the IMP will not be returned to site pharmacies. Site pharmacies should follow their local practice / policies for drug destruction and documentation. No approval from the Sponsor is required.

7.6 Drug interactions / Precautions / Contraindications

The following medications are considered contraindications to simvastatin: - itraconazole, ketoconazole, HIV protease inhibitors, nefazodone, cyclosporine, amiodarone, verapamil, or diltiazem.

All other interventions will be allowed as per the clinical team. Interactions with other medicinal products are contained in the SmPC.

7.7 Overdose of IMP

As simvastatin is administered by appropriate clinical staff, who are trained and experienced in administering medicinal products, overdose is extremely unlikely. No antidote is available so in the case of an overdose symptomatic treatment should be administered as per local policy.

7.8 Discontinuation of simvastatin

Simvastatin should be discontinued for the following reasons:-

- At the request of the participant or their personal/professional legal representative
- Adverse Event/ Serious Adverse Event
- Allergic reaction to IMP

- If the investigator considers that a participant's health will be compromised due to adverse events or concomitant illness that develop after entering the study.

8. PHARMACOVIGILANCE

Definitions of safety outcomes and adverse event reporting can be found in the master protocol. This section details safety specific information relating to simvastatin.

8.1 Potential intervention specific Serious Adverse Events (SAE)

There are no intervention specific SAEs. All SAEs should be reported regardless of randomisation allocation. Specific safety outcomes are collected as secondary endpoints, and these are detailed in the master protocol.

There may be cases where SAE reporting may vary by country and this will be detailed in the RSA.

9. STATISTICAL CONSIDERATIONS

9.1 Intervention specific stopping rules

Information on when interventions will be stopped can be found in the master protocol and the statistical analysis plan.

9.2 Subphenotypes

Detail of the subphenotypes are provided in the subphenotype appendix.

10. REGULATORY AND ETHICAL ISSUES

The master protocol does not contain detail about interventions used within the PANTHER trial. This because interventions will change over time. Information about these interventions are contained in each intervention appendix. These appendices will also change over time, such as additional IMPs added. The original intervention appendix and any subsequent adaptations will be submitted to the relevant ethics committee for review and approval before implementation.

10.1 Intervention specific Consent issues

As detailed in the master protocol, participants eligible for this intervention in the PANTHER trial will be critically ill. They may be receiving ICU level care including sedation; therefore, participants may not have capacity to provide informed consent at the time of eligibility. In these situations to ensure rapid treatment of the condition deferred consent, and the use of legal representatives will be available as per approval of the appropriate ethical review body.

Details of the consent process approved by country can be found in the RSA.

10.2 End of Trial

Please see the master protocol for the definition of the end of trial.

10.3 Risk Assessment

The risk assessment of this intervention will be performed in accordance with the risk assessment of the trial overall. The risk of the intervention will be assessed before any participant is randomised to this intervention. The risk assessment may be updated throughout the trial. Further detail on the risk assessment process can be found in the master protocol.

Chief Investigator

Danny McAuley Digitally signed by Danny McAuley Date: 2025.07.02 17:15:27 +01'00' 02.07.2025

Prof Danny McAuley Signed and Dated

11. REFERENCES

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12. REVISION HISTORY

Version	Date	Summary of changes
1.0	03 MAR 2025	First version
2.0	11 JUN 2025	Exclusion criteria updated Section 2.2 background updated