Pharmacy Manual

Version 1.0

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TABLE OF CONTENTS

ASSOCIATED DOCUMENTS AND FORMS

1.	SmPC for Simvastatin
2.	SmPC for Baricitinib
3.	PANTHER Intervention Appendix_Simvastatin
4.	PANTHER Intervention Appendix_Baricitinib

1 INTRODUCTION

The purpose of this document is to describe the procedures involved in all aspects of Investigational Medicinal Product (IMP) management by the staff at the investigational site for the PANTHER trial. This includes the receipt, storage, documentation, dispensing, replacement, destruction and unblinding, where applicable, of the IMP at the site.

2 SCOPE

As PANTHER is a platform trial, interventions may be removed and added throughout the trial. This document will be amended periodically throughout the trial. This document covers all aspects of IMP handling from Sponsor authorisation of the site to the archiving of documentation at the site.

3 ABBREVIATIONS

CI	Chief Investigator
eCRF	electronic Case Report Form
EDC	Electronic Data Capture
IB	Investigator Brochure
IMP	Investigational Medicinal Product
ISF	Investigator Site File
MDR	Medicines Defect Report
PF	Pharmacy File
PI	Principal Investigator
QP	Quality Person
SmPC	Summary of Product Characteristics

4 RESPONSIBILITES

Chief Investigator (CI)	❖ All roles delegated to the Study Manager / Monitor, as described below and in the text, can be performed by the CI. ❖ Oversight of compliant IMP management
Principal Investigator (PI)	❖ Take overall responsibility for the trial at the site. ❖ Ensure facilities, staff resources and education are appropriate to carry out the trial.

	❖ Delegate tasks responsibly and ensure they are documented on the Site Staff Signature and Delegation of Duties Log. ❖ Be available to give advice, support and to sign off documents as required. ❖ Responsible for the accountability of all IMP at the site.
Pharmacy staff	❖ Meet all regulatory and trial-specific requirements for IMP accountability including ordering, receipt, storage, temperature monitoring, dispensing, return of used/unused IMP, destruction and documentation.
Local Research Nurse / Local Research Coordinator (or equivalent)	❖ Perform duties delegated by the PI (documented on the Delegation of Duties Log). ❖ Assist in collecting, collating and processing documentation. ❖ Responsible for receipt, storage, dispensing, return of used/unused IMP and documentation in the ICU.
Study Manager/ Monitor	❖ Authorise participating sites and release of IMP (where applicable) ❖ Oversee site ordering and supply procedure (where applicable) ❖ Review security and conditions of IMP storage.

5 PROCEDURES

5.1 Description of IMP(s)

The IMPs involved in this trial are Simvastatin and Baricitinib as shown in Table 1.

Simvastatin is a statin which inhibits 3-hydoroxy-3-methylglutaryl coenzyme A (HMG-CoA) reductase. Simvastatin has pleiotropic effects that modify pathogenic mechanisms in ARDS. Baricitinib is an oral selective JAK1/2 inhibitor.

Table 1: IMPs

Name	Active component
Simvastatin	Simvastatin
Baricitinib	Baricitinib

5.2 IMP Packaging and Labelling

- **Simvastatin**

Where simvastatin is obtained via hospital stock, the stock will be commercial, licensed stock and will be labelled and packaged in accordance with the marketing authorisation. If simvastatin is provided by the Sponsor or manufacturer and is commercial licensed stock, the above applies. If provided by the Sponsor or manufacturer and is clinical trial stock then specific clinical trial labelling and packaging may apply and will comply with all applicable country regulations, please see section 10 of the region specific appendix for more detail. This manual will be updated with more detail if specific clinical trial labelling and packaging is required.

- **Baricitinib**

Where baricitinib is obtained via hospital stock, the stock will be commercial, licensed stock and will be labelled and packaged in accordance with the marketing authorisation. If baricitnib is provided by the Sponsor or manufacturer and is commercial, licensed stock the above applies. If provided by the Sponsor or manufacturer and is clinical trial stock then specific clinical trial labelling and packaging may apply and will comply with all applicable country regulations, please see section 10 of the region specific appendix for more detail. This manual will be updated with more detail if specific clinical trial labelling and packaging is required.

5.3 IMP Shipment and Storage

- **Simvastatin**

If simvastatin is obtained via hospital stock, the site will be responsible for IMP ordering, shipment and storage in transit. If simvastatin is provided by the Sponsor or manufacturer additional information will be provided, simvastatin will be stored as per SmPC requirements, typically in tablet form and usually at room temperature.

▪ Baricitinib

If baricitinib is obtained via hospital stock, the site will be responsible for IMP ordering, shipment and storage in transit. If baricitinib is provided by the Sponsor or manufacturer additional information will be provided, baricitinib will be stored as per SmPC requirements, typically in tablet form and usually at room temperature.

5.4 IMP Site Supply and Stock

▪ Simvastatin

- Where possible simvastatin will be provided from local hospital stock. If not from local hospital stock, details of how the stock is provided by country is available in the region-specific appendix.
- Sites should follow local processes for ensuring that stock is available for the trial.
- It is the responsibility of the site team (pharmacy and ICU teams) to ensure there are adequate stock levels of the IMP available at the time of randomisation (which may be outside normal office hours).

▪ Baricitinib

- Where possible baricitinib will be provided from local hospital stock. Details of how the stock is provided by country is available in the region-specific appendix.
- Sites should follow local processes for ensuring that stock is available for the trial.
- It is the responsibility of the site team (pharmacy and ICU teams) to ensure there are adequate stock levels of the IMP available at the time of randomisation (which may be outside normal office hours).

5.5 IMP Storage in Pharmacy and ICU

- Storage conditions for the IMP should be as per the Summary of Product Characteristics (SmPC) for that product and via the Pharmacy Manual if stock is provided by the Sponsor or manufacturer. IMP must only be accessed by appropriate staff on the delegation log or the clinical personnel who will be administering the IMP.
- Storage monitoring requirements may vary by country depending on the source of the IMP. Temperature monitoring will be as per local site practice unless stated otherwise. If simvastatin or baricitinib are provided by the Sponsor, further details on storage and temperature monitoring may be provided.

▪ Simvastatin

- Simvastatin is available in tablet form. No reporting of temperature excursions to the Sponsor are required if hospital stock is used.

▪ Baricitinib

- Baricitinib is available in tablet form. No reporting of temperature excursions to the Sponsor are required if hospital stock is used.

5.6 IMP Randomisation/Allocation

Randomisation will be performed using the electronic data capture (EDC) in this case OpenClinica via Sealed Envelope. The patient must receive the IMP for the required duration unless deemed a permitted omission, a protocol deviation will be entered on the eCRF. Permitted omissions include if the patient develops a mechanical bowel obstruction and the treatment is temporarily or permanently discontinued, or if the clinician following randomisation believes it is no longer in the patient's best interest to continue. For further details on the randomisation process, please see the PANTHER eCRF data completion guidelines.

▪ Simvastatin

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

▪ Baricitinib

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

5.7 IMP Prescription/Dispensing

▪ Simvastatin

If simvastatin is provided via hospital stock, the study does not mandate a study drug prescription template, however the dose, route of administration and duration should be documented in the patients' medical notes. If simvastatin is provided by the Sponsor or manufacturer additional accountability information may be required and this manual will be updated with this detail.

- **Baricitinib**

If baricitinib is provided via hospital stock, the study does not mandate a study drug prescription template, however the dose, route of administration and duration should be documented in the patients' medical notes. If baricitinib is provided by the Sponsor or manufacturer additional accountability information may be required and this manual will be updated with this detail.

5.8 IMP Preparation/Administration

- **Simvastatin Preparation & Administration**

Simvastatin 80mg - The treatment should commence as soon as possible after the participant is randomised. Specifically, within 4 hours of randomisation for the initial dose. 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. The treatment will only be provided while the patient is in the ICU and will be provided and administered by local clinical staff.

Warnings

For those preparing to administer simvastatin, ensure the tablet is not crushed or dispersed if you are pregnant.

Dosing

Simvastatin will be prescribed via the participants' in-patient drug administration chart (or equivalent) and administered to the participant by appropriately trained clinical staff in accordance with local practice. Simvastatin will be administered at a dose of 80 mg once daily by the enteral route for up to 28 days. It will be considered a protocol deviation if during the 28-day course two or more doses of simvastatin are missed.

For Patients who are able to Swallow

Preferred method of administration is tablets swallowed whole.

For Patients with swallowing difficulties

For patients who are unable to swallow whole tablets and do not have a gastric tube in situ:

1. Crush the tablet with a mortar and pestle or a tablet crusher
2. Add 10 to 20mL of sterile water and mix well

3. Draw the mixture into an oral dispenser/syringe

4. Rinse the crushing device with 10mL of sterile water, then repeat with another 10mL (total of 20mL) and draw into the oral dispenser/syringe, to ensure that all of the medicine is removed

5. Give the mixture immediately

6. Rinse the oral dispenser/syringe with a further 10mL of sterile water and give to the patient, to ensure the entire dose is given If the person cannot swallow thin fluids (i.e. is at risk of aspiration), crush the tablet and mix with a spoonful of yoghurt or fruit puree.

For patients with gastric tubes

For patients with nasogastric, orogastric, percutaneous enterogastric (PEG), or percutaneous enterojejunal (PEJ) tube in situ:

1. If relevant, stop the continuous feed

2. Flush the tube with 30mL of sterile water

3. Crush the tablet to a fine powder using a mortar and pestle or a tablet crusher

4. Add 10mL of sterile water to the powder and mix well (the tablet does not disperse easily)

5. Draw the mixture into the enteral syringe

6. Rinse the crushing device with 10mL of sterile water, then repeat with another 10mL (total of 20mL) and draw into the enteral syringe, to ensure that all of the medicine is removed

7. Give the mixture (~30mL) immediately into the enteral feeding tube

8. Rinse the enteral syringe with a further 20mL of sterile water to ensure the entire dose is given

9. If other medicines are given, flush the tube with at least 5 mL of sterile water between each medicine

10. After the final medicine is given, flush the tube with 30mL of sterile water

11. Restart the continuous feed immediately after dosing, if relevant

Dose adjustment in renal and liver impairment

Severe renal impairment not receiving renal replacement therapy is an exclusion for this intervention. 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.

The first dose of the study drug will be administered as soon as possible after randomisation, ideally within four hours of randomisation and 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. The treatment will only be provided while the patients are in the ICU and will be provided and administered by local clinical staff.

- ## Baricitinib Preparation and Administration

Baricitinib 4mg* should commence as soon as possible after the participant is randomised. Specifically, within 4 hours of randomisation for the initial dose. 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. The treatment will only be provided while the patients are in the ICU and will be provided and administered by local clinical staff.

*depending on the most recent GFR, see dosing table below for more information

Warnings

Staff should wear a mask and gloves when dispersing Baricitinib. Do not prepare or disperse Baricitinib tablets if pregnant.

If 1 mg tablets are not available, a 2 mg tablet can be split using a tablet splitter that has a razor blade to administer half a 2 mg tablet once daily. Alternatively, 2 mg of baricitinib can be given every second day.

Dosing

Baricitinib will be prescribed on the participants' in-patient drug administration chart (or equivalent) and administered to the participant by appropriately trained clinical staff in accordance with local practice. Baricitinib will be administered (usually via tablet) at a dose of 4mg once daily by the enteral route for up to 10 days. The dosing regimen below will be used in the setting of renal impairment. It will be considered a protocol deviation if during the 10-day course two or more doses of baricitinib are missed.

eGRF	**Baricitinib Dose**
30 to <60 mL/min 2mg	30 to <60 mL/min 2mg
15 to <30 mL/min 1mg	15 to <30 mL/min 1mg
<15 mL/min (or receiving RRT) withheld	<15 mL/min (or receiving RRT) withheld

For patients who are able to swallow

The preferred method of administration is tablets swallowed whole.

For patients with swallowing difficulties

For patients who are unable to swallow whole tablets and have an enteral feeding tube in situ:

1. Place the tablet(s) in sterile water in an enteral syringe.

a. Use 15mL of water for a gastrostomy tube, or 30mL of water for a nasogastric tube

2. Swirl gently until completely dispersed and an even suspension is formed. The tablet may take 5 minutes to completely disperse.

3. Administer the solution via the tube soon after preparation.

4. Rinse the enteral syringe with 15mL of water to ensure the entire dose is given

Note that this solution may block tubes that are smaller than size 12 French.

For patients with gastric tubes

For patients with nasogastric, orogastric, percutaneous enterogastric (PEG), or percutaneous enterojejunal (PEJ) tube in situ:

1. If relevant, stop the continuous feed

2. Flush the tube with 30mL of sterile water

3. Crush the tablet to a fine powder using a mortar and pestle or a tablet crusher

4. Add 10mL of sterile water to the powder and mix well (the tablet does not disperse easily)

5. Draw the mixture into the enteral syringe

6. Rinse the crushing device with 10mL of sterile water, then repeat with another 10mL (total of 20mL) and draw into the enteral syringe, to ensure that all of the medicine is removed

7. Give the mixture (~30mL) immediately into the enteral feeding tube

8. Rinse the enteral syringe with a further 20mL of sterile water to ensure the entire dose is given

9. If other medicines are given, flush the tube with at least 5 mL of sterile water between each medicine

10. After the final medicine is given, flush the tube with 30mL of sterile water

11. Restart the continuous feed immediately after dosing, if relevant

Dosing adjustment in renal and liver impairment

Baricitinib dose is adjusted for renal function in the dosing table above. If the patient is receiving renal replacement therapy baricitinib must be withheld. There is no adjustment for liver impairment.

- ### Stopping IMP

Discontinuation of IMP may occur in certain circumstances, such as due to a serious adverse event or the clinician believes the treatment is no longer in the patient's best interest. These reasons are detailed in the intervention appendix.

5.9 IMP Returns and Destruction

- ### Simvastatin

If provided by hospital stock, please follow local procedures for the return and destruction of hospital stock. If provided by the Sponsor or manufacturer specific destruction requirements may apply.

- **Baricitinib**

If provided by hospital stock, please follow local procedures for the return and destruction of hospital stock. If provided by the Sponsor or manufacturer specific destruction requirements may apply.

5.10 IMP Transfer

- **Simvastatin**

If provided by hospital stock IMP transfer across sites is not applicable. If provided by the Sponsor or manufacturer any IMP transfer must be approved by the Sponsor or regional co-ordinating centre. Further detail can be found in the region specific appendix.

- **Baricitinib**

If provided by hospital stock IMP transfer across sites is not applicable. If provided by the Sponsor or manufacturer any IMP transfer must be approved by the Sponsor or regional co-ordinating centre. Further detail can be found in the region specific appendix.

5.11 IMP Quarantine and Reclaim

If the IMP is provided by the Sponsor or manufacturer and temperature monitoring is required, IMP should be quarantined under the following circumstances by the Pharmacy department (or equivalent) at participating sites:

- Temperature excursion during shipment transit
- Temperature excursion during storage at Pharmacy or equivalent
- Violation of other required conditions i.e. protection from light, either during shipment transit or during storage at Pharmacy or equivalent
- Damage of IMP packaging that may affect the IMP i.e. mould, breakage of vials
- Inadequate labelling or incorrectly labelled IMP packaging
- IMP has reached expiry date
- The Trial Manager, Sponsor or manufacturer/supplier has instructed to do so
- The study has finished

Where IMP stock provided by the Sponsor/manufacturer has expired or the trial is completed, IMP must be quarantined immediately to avoid possibility of dispensing the expired IMP/remaining IMP in error.

5.1 IMP Recall

There may be an IMP defect, whereby the IMP at participating sites must be quarantined and will be collected or required to be sent back to the manufacturer/supplier for investigation/destruction.

5.1 Identifying defective IMP

A defective IMP may be identified by :

- A healthcare professional at a participating site, observing clinical symptoms/events that may indicate a defective product has been used (Note: this can be an adverse drug reaction or lack of efficacy)
- A healthcare professional, pharmacist or member of the research team recognising that the product is defective, prior to use i.e. incorrect packaging, unusual colour of product etc.
- The IMP manufacturer and/or packager, before or after production/packaging or shipping to participating sites
- The regulatory authority, upon inspection, or R&D/other auditing bodies

The following actions should be taken at all participating sites following identification of a potential defective IMP:

- Prevent use if possible
- Retain/preserve evidence if possible
- Prevent interference with the product if possible
- Note as much information as possible regarding any clinical incidents, where the health of a participant has been affected either due to an adverse drug reaction of lack of efficacy

Notification of a defect in an IMP can be issued from:

- The manufacturer
- The regulator
- The Trial Sponsor or delegate (i.e. Trial coordinating team)

5.1 Reporting procedures

Participating sites must notify the Study Manager/Monitor at the trial coordinating centre immediately after identifying an IMP defect, by telephone or email.

Regulatory reporting requirements may vary by country and details can be found in the region specific appendix.

For commercially available IMPs used within clinical trials, a drug recall or alert is usually cascaded via the site Pharmacy departments who have an appropriate system in place to cascade this information to healthcare professionals/research staff on site.

For IMPs without a marketing authorisation, a recall or drug alert may be received by the CI, whose responsibility it will be to contact/notify site PIs and their pharmacy departments, or to delegate this to a member of the study team i.e. Trial Manager. This should be done within 24 hours.

If a research member becomes aware of a recall or drug alert first, they must inform the CI and cascade the information as above.

5.1 Replacing defective IMP stock

The CI/PI or delegate will order new stock for participating sites, as required. The CI is responsible for communicating any further actions, as a result of the recall, to all participating sites i.e. additional participant monitoring/study visits that may be required.

Where the stock is supplied by the local hospital, the site will be responsible for replacing stock.

6 Version History

Version	Date Effective	Reason for Update
V1.0	17 Feb 2025	First version