Intervention Appendix:

Baricitinib

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

Baricitinib Intervention Appendix Version V2.0 dated 11 JUN 2025

This Intervention Appendix applies to the following:-

Subphenotype	Hyperinflammatory	Hypoinflammatory
***Intervention**	Baricitinib Usual Care	Baricitinib Usual Care

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

PANTHER: Baricitinib intervention summary	
Intervention exclusion	1. Age <18 years 2. Patient is known to be pregnant 3. Absolute neutrophil count less than $0.5x10^9$/L 4. Liver transaminases >8 times the upper limit of the normal range 5. Currently receiving ongoing immunosuppressants (high-dose corticosteroids, T-cell-targeted or B-cell-targeted therapies, interferon, or JAK inhibitors) 6. Severe renal impairment (eGFR < 15mL/min) or receiving renal replacement therapy 7. Known active tuberculosis infection or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines. 8. Known hypersensitivity to baricitinib 9. Breast feeding 10. Known herpes zoster virus, hepatitis B virus, hepatitis C virus or human immunodeficiency virus (HIV) 11. 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
HIV	Human Immunodeficiency Virus
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
RRT	Renal Replacement Therapy
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 baricitinib as part of the PANTHER protocol.

2. BACKGROUND

2.1 Intervention definition

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

2.2 Intervention-specific background

Baricitinib is an oral selective JAK1/2 inhibitor widely used for autoimmune diseases. Baricitinib reduces mortality in patients with ARDS due to COVID-19 in multiple clinical trials (1-3). Despite concerns about immunosuppression, the incidence of serious infections and as well as thrombosis was not significantly increased compared to placebo, particularly in the short-term setting of acute illness.
Given the majority of patients with ARDS due to COVID-19 have the hypoinflammatory phenotype (4), this suggests potential benefit in that phenotype. However, data in ARDS due to COVID-19 also indicate baricitinib reduces secretion of pro-neutrophilic mediators in the lungs (5) which drive the hyperinflammatory phenotype (6) indicating a role in the hyperinflammatory phenotype. Baricitinib was prioritised over other immunomodulators based on existing proof of concept in ARDS due to COVID, and its broader spectrum activity compared with single cytokine blockade. For example, by inhibiting JAK1/2, baricitinib inhibits not only IL-6, but also the other cytokines in the IL-6 superfamily, the pro-inflammatory cytokines IL-12 and IL-23, and type I /II interferons (7), all of which have been implicated in the pathogenesis of ARDS.
The dose regimen chosen is the same as with COVID-19, 4mg enterally daily for 10 days with adjustment for renal dysfunction (1).
Baricitinib has a favourable safety profile (1, 8). In addition the short half-life avoids potential sustained immunosuppression after ARDS resolution. While it has been recommended that chronic use should be avoided in patients aged 65 years or older, in patients who are long-time smokers, and in patients with risk factors for venous thromboembolism, cardiovascular disease or risk factors for malignancy, in this setting treatment is only for up to 10 days and this dose regimen was well tolerated in a similar population of patients with COVID-19.

2.3 Intervention Objectives

To test the efficacy of baricitinib 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. Absolute neutrophil count less than $0.5x10^9$/L
4. Liver transaminases >8 times the upper limit of the normal range
5. Currently receiving ongoing immunosuppressants (high-dose corticosteroids, T-cell-targeted or B-cell-targeted therapies, interferon, or JAK inhibitors)
6. Severe renal impairment (eGFR < 15mL/min) or receiving renal replacement therapy
7. Known active tuberculosis infection or, if known, latent TB treated for less than 4 weeks with appropriate anti-tuberculosis therapy per local guidelines.
8. Known hypersensitivity to baricitinib
9. Breast feeding
10. Known herpes zoster virus, hepatitis B virus, hepatitis C virus or human immunodeficiency virus (HIV)
11. 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

Baricitinib 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 baricitinib, the treatment will be given to the patient for 10 days, if the patient

is randomised to usual care, the patient must not receive baricitinib for 28 days. If the patient is discharged from ICU prior to day 10 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

There are no additional laboratory evaluations required in the baricitinib intervention, the standard laboratory evaluations that are required as per usual care should continue.

7. TREATMENTS

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

- Baricitinib 4mg*
- Usual care

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

7.1 Investigational Medicinal Product Details

Baricitinib 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 baricitinib.

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

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

7.3 Storage and Dispensing

Where possible baricitinib will be provided from local hospital stock. If baricitinib 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.

Baricitinib is available in tablet form. Storage conditions for baricitinib should be as per Summary of Product Characteristics (SmPC). If baricitinib 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 baricitinib is provided direct from the manufacturer or Sponsor, then storage and temperature monitoring may be required. Details of these 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 baricitinib. After randomisation, once the allocation is revealed as 'usual care' the patient must not receive any baricitinib 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 Baricitinib intervention

Baricitinib will be administered at a dose of 4 mg once daily by the enteral route for up to 10 days. Baricitinib 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 dosing regimen below will be used in the setting of renal impairment.

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

The first dose of baricitinib will be administered as soon as possible after the patient 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 10-30ml 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 10-day course two or more doses of baricitinib are missed.

7.4.3 Dose adjustment

The dose of baricitinib will be adjusted depending on the eGFR, see table in the section above for more detail. If the patient is receiving renal replacement therapy baricitinib must be withheld.

7.5 Accountability

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

Baricitinib 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 baricitinib; high-dose corticosteroids (>200mg hydrocortisone or equivalent), T-cell-targeted or B-cell-targeted therapies, interferon, or JAK inhibitors.

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 baricitinib 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 baricitinib

Baricitinib 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 baricitinib.

8.1 Potential intervention specific Serious Adverse Events (SAE)

There are no intervention specific SAEs. All other 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 17:16:35 +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 2.2 Background – detail added