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IRAS Reference: 1008743

Study Title: Precision medicine Adaptive Network platform Trial in Hypoxemic acutE respiratory failuRe, the PANTHER Trial

Protocol number: 175151

Protocol Version: v2.0

Dear REC and MHRA

PANTHER Response to Grounds for Non-Acceptance

We are providing you with a response to the Notice of Grounds of Non-Acceptance and Right to amend request for the clinical trial entitled **Precision medicine Adaptive Network platform Trial in Hypoxemic acutE respiratory failuRe**, the **PANTHER** Trial. The **PANTHER** trial is a CTIMP and is a phase II trial with a Type A classification.

MHRA Clinical Grounds for Non-Acceptance

There were **18** points related to the Clinical GNA.

Points **1, 2, 3, 7, 9, 11, 12** and **13** have all been addressed following discussions with Dr Maria Urdaneta-Abate and Dr Andrea Manfrin from the MHRA. We have added additional text in the protocol to discuss the intended population, the close monitoring in place and lack of other treatment options to justify why these exclusion criteria may not be necessary, and a general exclusion criterion addressing the contraindications and other identified risk for the IMPs in the protocol. The 8 points are listed below:-

- 1.** The protocols exclusion criteria must be revised so that the threshold of absolute neutrophil count for eligibility is $\geq 1.5 \times 10^9/l$. A level below $1.5 \times 10^9/l$ indicates a substantial increase in infection risk. The benefit of the intervention has been marginal in a similar indication so the benefit risk balance is unknown. Participants should not be subjected to undue risk with a minimal chance of benefit. If the Sponsor intends to address a population with Duffy null phenotype (formerly "ethnic neutropenia" or "African heritage") this can only be implemented if the protocol is amended to clarify that the investigator has objectively confirmed the diagnosis of this condition at screening (e.g. genetic test to detect the normal variation in the atypical chemokine receptor 1 (ACKR1) gene and this must be adequately documented by the investigator during the screening.

Answer - As per first paragraph on page 1, we have addressed this point and have updated the protocol to v2.0. We will not consider the Duffy null phenotype

- 2.** The baricitinib protocol eligibility criteria must revise the age to < 65 years. The summary of

product characteristics (SmPC) indicates that the benefit risk balance is marginal for the main indication of rheumatoid arthritis, which has been extensively studied and determined to have a positive benefit risk balance only in patients “who have responded inadequately to, or who are intolerant to one or more disease-modifying anti- rheumatic drugs (DMARDs)”. In patients aged ≥ 65 years, the possible benefit is so marginal that the SmPC observes that in patients with rheumatoid arthritis baricitinib “should only be used if no suitable treatment alternatives are available in patients”. Therefore, for the indication in this trial, the population > 65 years is inappropriate at this stage of the trial. This is notwithstanding the statement in protocol section 2.2 that suggests this problem is only for “chronic use”. The Summary of Product Characteristics (SmPC) does not distinguish short-term from chronic use in the presentations that indicate a paucity of data for this population and marginal benefit and use as a drug of last resort. In this study there is no evidence of benefit, so the participants may only receive the toxicity. After efficacy is established in patients aged under 65 years the Sponsor can apply for an amendment to the protocol in which the data of benefit is presented and consideration of removing the age threshold can be made.

Answer - As per first paragraph on page 1, we have addressed this point and have updated the protocol to v2.0.

3. The previous point also applies to patients with a history of atherosclerotic cardiovascular disease or other cardiovascular risk factors (such as current or past long-time smokers), risk for venous thromboembolism or with malignancy risk factors (e.g. current malignancy or history of malignancy). This population also must be specified as excluded, as the SmPC indicates a general lack of positive benefit risk balance in patients with such risk factors WITHIN the authorised indications and baricitinib is considered a last line therapy in these patients. In this study there is no evidence of benefit. This is notwithstanding the statement in protocol section 2.2 that suggests this problem is only for “chronic use”. The Summary of Product Characteristics (SmPC) does not distinguish short-term from chronic use.

Answer - As per first paragraph on page 1, we have addressed this point and have updated the protocol to v2.0.

4. Patients with a history of herpes zoster virus infection must be specified as excluded because of the risk of re- activation with baricitinib.

Answer – This has been accepted and amended in an updated protocol v2.0.

- 5.** The protocol must be revised to indicate that infection with hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV) are excluded because of the risk of reactivation with baricitinib.
- 6.** Serology for HBV, HCV, HIV will be scheduled in the protocol at screening to ensure that infection with any of these is ruled out.

Answer – 5 and 6 are covered in the following change:- We will exclude patients with known herpes zoster virus, hepatitis B virus (HBV), hepatitis C virus (HCV) or human immunodeficiency virus (HIV) but not measure serology for HBV, HCV, HIV in all patients being screened. This has been amended in an updated protocol.

- 7.** In accordance with SmPC of baricitinib, the protocol must specify in eligibility criteria that receipt of live vaccine within four weeks prior to receipt of baricitinib is an exclusion criterion. The section on concomitant therapies must indicate that live vaccines are prohibited during the study and for three months after the last dose administration.

Answer - As per first paragraph on page 1, we have addressed this point and have updated the

protocol to v2.0

8. Patients with diverticular disease and patients chronically treated with concomitant medicinal products associated with an increased risk of diverticulitis: nonsteroidal anti-inflammatory drugs, corticosteroids, and opioids must be specified as excluded because of the risk of perforation with baricitinib.

Answer – In a previous response to Dr Steinberg, we had requested not to make this change based on the fact that our exclusion criteria aligns with that of other trials utilising Baricitinib. This has been accepted by Dr Steinberg.

9. Baricitinib and simvastatin are associated with elevations of liver transaminases. The protocols will reduce the exclusion criterion of liver transaminases from $> 8 \times$ upper limit of normal (ULN) to $> 2.5 \times$ ULN.

Answer - As per first paragraph on page 1, we have addressed this point in an updated protocol.

10. The Master protocol must be revised to indicate that participants who are breast feeding are excluded. The indication of an acute life-threatening condition is not a reason to omit this exclusion criterion to remind investigators to recognise that breast feeding would be a danger to the child.

Answer - In our previous response to Dr Steinberg we said will make this amendment. On reflection, we suggest we add this to each intervention specific appendix rather than the master protocol. We recognise certain populations such as participants who are breastfeeding are routinely excluded without considering the safety of the intervention. We want to ensure we conduct a trial which is inclusive where possible rather than automatically excluding all participants who are breast feeding in the master protocol but rather consider this on an intervention-by-intervention basis. If we were to study an intervention in future which was known to be safe in this population, this would mean we do not unnecessarily exclude these participants and allow the trial population to be inclusive and data generated to be more generalisable. This is similar to the approach we are taking with pregnant participants.

11. The simvastatin protocol must be revised to indicate that participants who receive concomitant administration of potent CYP3A4 inhibitors (agents that increase AUC approximately 5 fold or greater) (for examples, itraconazole, ketoconazole, posaconazole, voriconazole, HIV protease inhibitors (for example nelfinavir), boceprevir, telaprevir, erythromycin, clarithromycin, telithromycin, nefazodone and medicinal products containing cobicistat are excluded in accordance with the SmPC. The current exclusion criterion number 5 does not mention "CYP3A" and is considered inadequate in consideration of the use of the 80 mg dose of simvastatin, which has a substantially higher incidence of toxicity in comparison to lower doses. The exclusion criterion must be revised to indicate that the listed drugs ****are examples**** of CYP3A inhibitors and that the list is not exhaustive. It is preferred if a table listed another 10 or more examples of CYP3A inhibitors and that the exclusion criterion referred to the table, so that investigators could avoid the devastating toxicities of over-exposure to simvastatin through inadvertent concomitant prescribing.

Answer - As per first paragraph on page 1, we have addressed this point and have updated the protocol to v2.0

12. The simvastatin protocol must indicate that CYP3A inhibitors are prohibited for the duration of participation in the study. A reference to the table that lists CYP3A inhibitors

must be made. The discontinuation criteria must be revised to add that a need for a prohibited therapy listed in the exclusion criteria or list of prohibited therapies is a discontinuation criterion.

Answer - As per first paragraph on page 1, we have addressed this point and have updated the protocol to v2.0

- 13.** The simvastatin protocol must be revised to indicate that participants who receive concomitant administration of gemfibrozil, ciclosporin, or danazol are excluded in accordance with the SmPC.

Answer - As per first paragraph on page 1, we have addressed this point and have updated the protocol to v2.0

- 14.** The baricitinib SmPC indicates an association with hypoglycaemia. As participants with diabetes are not excluded, the protocol must specify that serum glucose is measured. The protocol section 6.4 statement: "There are no additional laboratory evaluations required in the baricitinib intervention, the standard laboratory evaluations that are required as per usual care should continue" does not address this requirement.

Answer - Our previous response proposed to Dr Steinberg was - Stress hyperglycaemic is common in the critically ill and therefore in this population regular glucose measurements are made as standard care and therefore request not to make this change – this was accepted by MHRA

- 15.** The baricitinib protocol must indicate that receipt of additional immunosuppressant therapy is prohibited for the duration of participation in the study. The discontinuation criteria in the protocol must be revised to add that a need for a prohibited therapy listed in the exclusion criteria or list of prohibited therapies is a discontinuation criterion.

Answer - Our previous response proposed to Dr Steinberg we said we will make this change, accepted by MHRA

- 16.** Protocol section 8.4 will be revised to delete the statement "In the case of discrepant views on causality between the investigator and others, all parties will discuss the case. In the event that no agreement is made, the regulatory authority will be informed of both points of view." A determination of related or unrelated must be recorded and the following are the rules: The investigator's determination of relatedness cannot be downgraded to unrelated. The Sponsor can upgrade a determination of unrelated to related. These decisions form the basis of reporting. It is acceptable for the Sponsor to present a dissenting opinion in the report.

Answer - Our previous response proposed to Dr Steinberg we said we will make this change, accepted by MHRA

- 17.** Figure 1 should be revised. The small size typeface and the contrast of black typeface on a red background result in text that is illegible, so the figure is more of a distraction than an enhancement of information provision.

Answer – The figure has now been updated in protocol v2.0

- 18.** Protocol section 8.6 uses the abbreviation "ISA" without providing a definition of the abbreviation. A document should always provide the definition of abbreviations that are not the most universally understood abbreviation not subject to contextual

misinterpretation. The use of abbreviations without provision of a definition distracts the reader and degrades the intelligibility of the document. Unintelligible documents are subject to rejection

Answer - Our previous response proposed to Dr Steinberg we said we will make this change, accepted by MHRA

Pharmaceutical Grounds for Non-Acceptance

1. Confirmation should be provided that a pharmacy dispensing label will be applied to the locally sourced simvastatin and baricitinib.

Answer – The following justification was provided to and accepted by Fiona Law (MHRA):-

As PANTHER is a Type A trial, the trial poses the potential risk of the IMPs used within the trial are considered no higher than standard medical care. We therefore propose that the IMP is dispensed in its marketed packaging and administered according to its marketing authorisation. These medicines are routinely used within critical care settings. Given the high-intensity nature of critical care units, introducing additional administration requirements may result in operational challenges, potential delays, and increased burden on NHS resources. A thorough risk assessment of the proposed process has been conducted, and we are confident that the critical care teams are fully equipped to manage the administration of these investigational medicinal products (IMPs) in the same manner as they would for standard-of-care treatments. The REMAP-CAP influenza domain for example uses of the proposed IMPs, baricitinib, in this manner. The rationale and Risk Assessment was requested by the MHRA in this response, the Risk Assessment is attached.

REC Conditions

1. Please submit the response to the peer review

*Answer - Apologies although this was submitted with the original application it may not have been clear this was the response to the peer review. It is attached again and named Attached – document named - **PANTHER Response to reviewer comments_final***

2. Please submit the PPI review

Answer - submitted, please see documents attached:-

PPI response on PIS

PPI feedback 3- PANTHER PIS Full V0.2 041024

PPI feedback 4-PANTHER PIS Full V0.2 041024

PPI feedback 5- PANTHER PIS Full V0.2 041024

3. Make the following changes to the appropriate Participant Information Sheets:
 - a) Clearly state that the study drugs will only be given for up to 10 days or up to 28 days respectively and that both medications will be discontinued upon discharge from the ICU.

Answer - this has been added to page 1 or 2 of each PIS form

- b) Ensure the document acknowledges and is relevant for participants who will be enrolled in the standard of care arm

Answer - Clarification has been added to page 2 and throughout all documents – see tracked changes

- c) Make clear under what circumstances a bronchoalveolar lavage will take place i.e., during ventilation/intubation

Answer - This has been added to page 3 of all documents

- d) Include contact detailed for the complaints team

Answer - This detail is available in the privacy notice, see updated document attached.

4. Include mention of PALS in the professional legal representative PIS and Post recovery participant PIS.

*Answer - The PIS (**PANTHER_PIS_V2.0_14042025**) is both Prospective and Retrospective PIS and contains the full study information including PALS information. This form is always provided in addition to any summary: PIS Summary, Personal Legal Representative Summary and Professional Legal Representative Summary and so all consenters will receive this information.*

HRA assessment queries:

1. Please add the HRA's recommended GDPR wording to the Participant Information Sheet. It can be found at

<https://www.hra.nhs.uk/planning-and-improving-research/policies-standards-legislation/data-protection-and-information-governance/gdpr-guidance/templates/transparency-wording-for-all-sponsors/>

Answer – this has been updated to include Imperial College wording that has been approved by the HRA for all for use in all of our Imperial College sponsored studies

2. Please include the definition of the end of study. In most cases this will be the date of the last visit of the last participant or the completion of any follow-up monitoring and data collection described in the protocol.

Answer – this has been updated.

The following documentation has updated and submitted as part of this response, tracked and clean versions are included in the submission: -

- PANTHER Protocols:-
 - PANTHER Master Protocol v2.0 11.06.2025_Clean
 - PANTHER Master Protocol v2.0 11.06.2025_TC
 - PANTHER Intervention Appendix_Simvastatin v2.0 11.06.2025_Clean
 - PANTHER Intervention Appendix_Simvastatin v2.0 11.06.2025_TC
 - PANTHER Intervention Appendix_Barticitinib v2.0 11.06.2025_Clean



- PANTHER Intervention Appendix_Barticitinib v2.0 11.06.2025_TC
- The following Participant Information Sheet and Informed Consent Forms
 - PANTHER PerLR Sum v2.0 14.04.2025_Clean
 - PANTHER PerLR Sum v2.0 14.04.2025_TC
 - PANTHER PIS ProLR Sum v2.0 14.04.2025_Clean
 - PANTHER PIS ProLR Sum v2.0 14.04.2025_TC
 - PANTHER PIS Sum v2.0 14.04.2025_Clean
 - PANTHER PIS Sum v2.0 14.04.2025_TC
 - PANTHER PIS v2.0 14.04.2025_Clean
 - PANTHER PIS v2.0 14.04.2025_TC
 - PANTHER Privacy Notice v2.0 14.04.2025_Clean
 - PANTHER Privacy Notice v2.0 14.04.2025_TC
- PANTHER Study Risk Assessment v3.0 12.06.2025
- PANTHER NIHR Peer Review 23.02.2024
- PANTHER Response to reviewer comments_final
- PPI response on PIS
- PPI feedback 3- PANTHER PIS Full V0.2 041024
- PPI feedback 4-PANTHER PIS Full V0.2 041024
- PPI feedback 5- PANTHER PIS Full V0.2 041024

Please do not hesitate to contact is if you require any further information.

Yours sincerely

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