NORTHERN TERRITORY GOVERNMENT | NT HEALTH

menzies school of health research

20 August 2024

Ethics Administration Office
File Reference Number: HREC-2024-4911
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Dr Joshua Morigi
Clinical Director of Molecular Imaging Unit
Royal Darwin Hospital
Joshua.morigi@nt.gov.au
CC: michail.charakidis@nt.gov.au;
aries.balino@nt.gov.au
Via Email

Dear Dr Morigi,

NT HREC Reference Number: 2024-4911
Project Title: *Fibroblast Activation protein imaging research SPECT/CT (FIRST-NT): Assessing the safety and tolerability of 99mTc-3BP4971 SPECT/CT*

Thank you for submitting the above research project for ethical review. This project was considered by the Human Research Ethics Committee of Northern Territory Health and Menzies School of Health Research (NT HREC) in accordance with the NHMRC *National Statement on Ethical Conduct in Human Research 2007 (Updated 2018) at* its meeting held on the 24 July 2024.

The NT HREC has granted **Conditional Ethical Approval** of this research project.

The HREC can see the benefits of this submission, but the risks are not clear, and we are unable to come to a clear decision on risk versus benefit for participants. Our role is to protect participants and as you can understand this is of utmost importance for phase 1 clinical trials that are first in human studies of investigational products. The comments of the HREC below are to further understand the risk-benefit balance for potential participants

Please note: Research should not commence until you have received a letter of Full Ethical Approval.

Approval is conditional upon the following issues of concern being addressed:

1. TGA reporting is required. Please submit a CTA to the TGA. *National Statement on Ethical Conduct in Human Research (N.S) (2007) (updated 2018) s3.1.7.*
2. The risks to participants of this research have not been presented clearly. Please elaborate to include but not limited to an explanation of first in human trial risk. *N.S 2007 (updated 2018) Chapter 2.1.*
3. Please clarify the extent of involvement of 3B Pharmaceuticals. *N.S 2007 (updated 2018) s3.1.10, 5.2.11.*
4. Q7, Please provide data that supports that 99mTc-3BP-4961 is not influenced by fasting. *N.S 2007 (updated 2018) s3.1.4 - 3.1.5.*
5. Q14, *'The sample size does not allow for statistical power considerations, but it is expected that the data from the 10 patients will provide sufficient data to assess for the safety and tolerability of the IV administration of the IP.'* On what is this sample size based? *N.S 2007 (updated 2018) s1.1b, 3.1.2.*
6. Q12: Please comment on the selection criterion for female patients who may have childbearing potential. Please also comment on the participant's dosimetry level (or permissible threshold) as a selection criterion. *N.S 2007 (updated 2018) s1.1b, 3.1.12-3.1.22.*
7. Q12: Why are cancer patients chosen for this study to determine safety and tolerability? Others have recruited healthy young adults to determine safety: Dubash et al. 2020, https://link.springer.com/article/10.1007/s00259-020-04724-y *N.S 2007 (updated 2018) s1.1b, 3.1.12-3.1.22.*
8. Q12: The purpose of the Phase 2 is unclear. The authors have agreed that a small number of recruitments is unlikely to have any statistical significance (hence, there is little quality of evidence

for clinical relevance). Please comment/advise how the Phase 1 data will be used to improve the optimal time for imaging in this phase. *N.S 2007 (updated 2018) s1.1b.*

9. (Page 2 of 182 and) Page 25 of 182: On page 2 of the application, the authors state that the patients will undergo three SPECT scans at specific time points, but this is not reflected in the ethics application on Page 25. There is an inconsistency of methods on Page 2 and Page 25. Further, given SPECT is ionizing radiation, can the authors please justify the multiple SPECT scans? A recent study by Nakaigawa et al. 2024 examined [89Zr]Zr-DFOgirentuximab as a radiotracer but did not do multiple imaging. *N.S 2007 (updated 2018) s1.1b.*
10. The management (destruction or storage) of blood samples is not provided. *N.S 2007 (updated 2018) Chapter 3.1, element 4.*
11. 1200 MBq is a fairly high dose, will there be any dosimetry calculations, and will previous exposure be considered? *N.S 2007 (updated 2018) s1.1b, 3.1.4 - 3.1.6.*
12. As the study involves the administration of 1 extra test using a radioactive isotope, can the PI please provide a radiation physics report on the extra radiation dose and explain that in lay terms in the PICF. Please include in the PICF a comment about the additional radiation exposure. *N.S 2007 (updated 2018) s3.1.4 - 3.1.6.*
13. Page 7 of the Investigator Brochure summarizes non-clinical (animal) studies and conclude the compound to be presumably well binding and non-toxic. The Bellberry review (IB17/26) has asked for a justification why the respective studies did not adhere to GLP. There does not appear to be any mention of GLP in the document, it would therefore be good if the investigators could clarify this. If the trial was not done according to GLP the investigators need to clarify which components did not adhere to GLP and how this could impact on the observed non-toxicity in the worst case. *N.S 2007 (updated 2018) s3.1.4 - 3.1.6.*
14. Q27: Can the investigators commit to a publication of results even if the outcome is not as expected? The application suggests that this is at the discretion of the PI but I believe that clinicaltrials.gov, where the study will be registered, and according to the National Statement that it requires publication/dissemination at study end. *N.S 2007 (updated 2018) s1.3d, 3.1.63 – 3.1.72.*
15. Page 1 of the Participant information sheet: *'Your decision will not affect your ability to receive treatment and you will not lose any benefits to which you are entitled.'* There is no further information regarding benefits. *N.S 2007 (updated 2018) s1.7b, 2.1.2, 3.1.4 – 3.1.6.*
16. Participant Information Sheet: language needs to be simpler e.g. 'tracer' is used and not explained. *N.S 2007 (updated 2018) s2.2.2 - 2.2.4.*
17. Researchers have not justified the inclusion criteria of "suspected to have cancer" appropriately, as the group who do not have cancer will receive an additional dose without any prospect of benefit. *N.S 2007 (updated 2018) s1.1b, 3.1.12-3.1.22.*
18. The PI has not led any trials before. the PI may have been involved in early phase trials, but has not provided a track record of their involvement and level of support in previous institutions beyond a list of roles. The HREC suggests the addition of an experienced clinical trials researcher. *s1.1e, 3.1.9.*
19. The sponsor appears to not be a mature sponsor, and has no track record in safe provision of scientific quality or clinically safe care as a sponsor. Please comment. *N.S 2007 (updated 2018) s3.1.9.*
20. There are no institutional support structures capable of supervising research, no independent or pseudo independent people in the institution who are able to provide oversight of the work. Please include a Data Safety Monitoring Board (DSMB). *N.S 2007 (updated 2018) s5.5.3.*
21. The current adverse event reporting mechanism is not sufficient for clinical trials. Please provide a detailed safety monitoring and reporting schedule in line with the NHMRC and Australian clinical trials reporting guidleines. *N.S 2007 (updated 2018) s5.5.3.*
    1)_ *(https://www.nhmrc.gov.au/about-us/publications/safety-monitoring-and-reporting-clinical-trials-involving-therapeutic-goods#block-views-block-file-attachments-content-block-1)* and the Therapeutic Goods Administration
    2)*(https://www.tga.gov.au/sites/default/files/australian-clinical-trial-handbook.pdf)*
22. The team has not conducted Phase 1 trials here. Have the team conducted Phase 2 trials here? *N.S 2007 (updated 2018) s1.1e, 5.1.2b.*
23. It is essential when conducting a Phase 1 Clinical Trial that the researchers have adequate experience in their implementation.The PI has not led any trials before. The PI may have been involved in early phase trials, but has not provided a track record of their involvement and level of support in previous institutions beyond a list of roles. Please include a researcher on the team with

adequate experience and expertise in conducting a Phase 1 Clinical Trial. *N.S 2007 (updated 2018) s1.1e, 5.1.2b.*

24. Literature review – please include a more in depth literature review that includes background information with references. *N.S 2007 (updated 2018) s1.1c, 3.1.1c.*
25. Please include more information in both the HREC application and protocol on the products safety testing history, for example, where it was tested, what it was tested on, and the results of these tests. *N.S 2007 (updated 2018) s1.1e, 5.1.2b.*
26. Significance and merit – please elaborate on the significance of the study and how it demonstrates research merit. *N.S 2007 (updated 2018) s1.1.*
27. Selection criteria – please justify why renal patients are being excluded from the study, given they are the most likely potential beneficiaries. What level of kidney disease would be considered for either recruitment or exclusion? *N.S 2007 (updated 2018) s1.1b, 3.1.12-3.1.22.*
28. Q14 Sampling size – " Up to 10 patients": Please clarify the exact sample size. *N.S 2007 (updated 2018) s1.1b, 3.1.12-3.1.22.*
29. Please clarify the name of the the proposed investigational product as both (IP) 99mTc-3BP-4961 and (IP) 99mTc-3BP-4971 are referred too throughout the application. *N.S 2007 (updated 2018) s1.1b.*
30. Q9, Justification: "Previous studies based on molecules similar to the IP have demonstrated equal if not superior performance of this molecule in identifying sites of possible malignancy." Please provide evidence. *N.S 2007 (updated 2018) s1.1b.*
31. Assessing effectiveness: Please provide detailed information on how safety, tolerability, pharmacokinetics and biodistribution will measured and assessed. *N.S 2007 (updated 2018) s1.1b, 3.1.1.*
32. Q25 Data storage/security & Q26 – please provide specific information regarding data storage. For example, the data will be stored on a password protected server within the NT Health IT system as this is not currently explicit. *N.S 2007 (updated 2018) s3.1.44 – 3.1.46.*
33. PICF – please explicitly state that withdrawal will not have an impact on a participants standard care. *N.S 2007 (updated 2018) s3.1.30.*
34. Please provide information on how the performance and efficacy agreement between the proposed investigational product (IP) 99mTc-3BP-4961 and the currently used molecule fluoro-deoxiglucose (FDG) will be calculated/assessed. *N.S 2007 (updated 2018) s1.1b.*
35. Q31 Risk: Please discuss the potential risks associated with the use of an investigational product the first time in humans. This trial is high risk and cannot be considered higher than low risk given it is a trial of an investigational product for the first time in humans. Please expand on this section. *N.S 2007 (updated 2018) s2.1, 3.1.4, 3.1.6.*
36. Q33; Please also expand on this section – particularly relating the issue of risks related to the product being administered for the first time in humans. *N.S 2007 (updated 2018) s2.1, 3.1.4, 3.1.6.*
37. Please comment on the role of the 3BP in the trial. *N.S 2007 (updated 2018) s3.1.10, 5.2.11.*
38. Q36, reciprocity: "The data collected over time will be beneficial for all patients." Please emphasise that there will be no direct benefit to the patients taking part in this trial. *N.S 2007 (updated 2018) s1.7b, 3.1.4, 3.1.6.*
39. Participant information sheet (PIS): Please include a pictorial flip chart in addition to the PIS to ensure fully informed consent is achieved. *N.S 2007 (updated 2018) s2.2.3, 5.2.17.*
40. Q12: "Maximum 28 days for screening, planning and obtaining consent…" Screening a patient can only occur once consent has been obtained. There is some ambiguity in the application regarding screening and consent. *N.S 2007 (updated 2018) s1.1b.*
41. PICF 1/5: "Although the diagnosis of cancer will still rely on the findings of the FDG PET scan, or "usual scan", our doctors will also examine data from the new scan." To avoid risk of coercion please amend to read: "Your diagnosis and assessment will rely on the findings of the FDG PET scan (usual scan). Although doctors will also examine data from the new experimental scan, this will not be used in your clinical management. The experimental scan is only being performed to investigate its safety and tolerability." *N.S 2007 (updated 2018) s2.1, 3.1.23 -3.1.38.*
42. PICF 1/5: "The goal is to determine if this new scan could potentially replace the usual one in the future. It's important to note that this trial marks the first time the 99Tc-3BP-4961 tracer is being used in humans. However, its safety and toxicity levels have been tested on animals and researchers have confirmed it is safe." Please amend this section to read "The safety and tolerability of 99Tc-3BP-4961 SPECT/CT in humans is unknown, the purpose of this investigation is to determine

whether it is safe and determine whether there are any adverse effects". *N.S 2007 (updated 2018) s2.1, 3.1.23 -3.1.38.*

Notes:

- Q 27. 'Participants in the study will be offered to provide feedback and the summary of the project outcomes.' Is this not meant to say that participants will be provided with feedback and the summary of outcomes?
- Can the PI provide details when the last GCP course was completed?
- For clarification, only phase 1 is covered and further HREC approval will be required for Phase 2.

You are requested to respond to the Committee's concerns in a letter with each issue used as a heading with your response outlined below. Please also include any relevant or requested attachments with both track changes and clean versions with your response, merged into a single file.

Approval has been delegated for full **HREC Committee** review.

A letter confirming approval will be sent to you once the above matters have been addressed satisfactorily and approved by the HREC. The research may commence only on receipt of the Full Ethical Approval letter.

If your response is not received within three months from the date of this letter, or the researcher has failed to make contact, the project will be considered withdrawn. Once withdrawn, you will be required to resubmit the application with full documentation.

Should you wish to discuss the above research project further, please contact the Ethics Administrators via email: NTHREC@menzies.edu.au

Yours sincerely,

Dr David Carroll
Deputy Chair
Human Research Ethics Committee
of NT Health and Menzies School of Health Research
http://www.menzies.edu.au/ethics

NT HREC is registered and certified with the Australian National Health and Medical Research Council (NHMRC) and operates in accordance with the NHMRC *National Statement on Ethical Conduct in Human Research (2007)*. NHMRC Reg no. EC00153