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| **Committee:** | Southern Health and Disability Ethics Committee |
| **Meeting date:** | 12 November 2019 |
| **Meeting venue:** | Sudima Hotel, Christchurch Airport, 550 Memorial Drive, Christchurch |

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| **Time** | **Item of business** |
| 11:30am | Welcome |
| 11:35am | Confirmation of minutes of meeting of 8 October |
| 11:45am | New applications (see over for details) |
| 11:45 – 12:10pm  12:10 – 12:35  12:35 -1:00  1:00 – 1:25  1:25 – 1:50  1:50 – 2:15  2:15 – 2:40 | i 19/STH/184 (Jean/Dominic)  ii 19/STH/191 (Devonie/Pauline)  iii 19/STH/197 (Jean/Pauline)  iv 19/STH/198 (Devonie/Dominic)  v 19/STH/199 (Devonie/Sarah)  vi 19/STH/201 (Jean/Sarah)  vii 19/STH/202 (Jean/Pauline) |
|  | Substantial amendments (see over for details) |
| 2:40 – 3:05  3:05 – 3:30  3:30 – 3:55 | i 14/STH/132/AM03 (Devonie/Dominic)  ii 18/STH/183/AM03 (Jean/Pauline)  iii 17/STH/9/AM07 (Devonie/Sarah) |
|  | Second opinion on previously declined applications (see over for details) |
| 3:55 – 4:20 | i 19/NTB/100 (Devonie/Sarah) |
| 4:20pm | Meeting ends |

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| **Member Name** | **Member Category** | **Appointed** | **Term Expires** | **Apologies?** |
| Dr Sarah Gunningham | Lay (other) | 05/07/2019 | 05/07/2022 | Present |
| Dr Devonie Waaka | Non-lay (intervention studies) | 18/07/2016 | 18/07/2019 | Present |
| Assc Prof Mira Harrison-Woolrych | Non-lay (intervention studies) | 27/10/2015 | 27/10/2018 | Apologies |
| Dr Paul Chin | Non-lay (intervention studies) | 27/10/2018 | 27/10/2021 | Apologies |
| Professor Jean Hay-Smith | Non-lay (health/disability service provision) | 31/10/2018 | 31/10/2021 | Present |
| Mr Dominic Fitchett | Lay (the law) | 05/07/2019 | 05/07/2022 | Present |
| Dr Pauline Boyles | Lay (consumer/community perspectives) | 05/07/2019 | 05/07/2022 | Present |

## Welcome

The Chair opened the meeting at 11:45am and welcomed Committee members, noting that apologies had been received from Assc Prof Mira Harrison-Woolrych and Dr Paul Chin.

The Chair noted that the meeting was quorate.

The Committee noted and agreed the agenda for the meeting.

## Confirmation of previous minutes

The minutes of the meeting of 8 October were confirmed.

## New applications

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| **1** | **Ethics ref:** | **19/STH/184** |
|  | Title: | Transplanting HCV positive deceased donor kidneys in to HCV negative recipients |
|  | Principal Investigator: | Dr John Schollum |
|  | Sponsor: | National Renal Transplant Service |
|  | Clock Start Date: | 31 October 2019 |

Dr John Schollum was present by teleconference for discussion of this application.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this application.

Dr Devonie Waaka declared a potential conflict of interest, and the Committee decided to allow her to remain in the meeting room and take a full part in the discussion and decision relating to that item of business.

Summary of Study

1. This study is being conducted on behalf of the Ministry of Health renal transplant unit. With the new generation of highly effective treatments of hepatitis C, many countries around the world are transplanting kidneys from hepatitis C positive donors to patients without hepatitis C, and providing treatment for hepatitis C post-transplant. Almost 100% of those patients are infected with hepatitis C, and around 99% are effectively treated afterwards. In New Zealand the number of kidney donors is very low relative to the waiting list, and hepatitis C positive kidneys represent a chance to increase the number of donor kidneys.
2. This proposal to inform donors beforehand of the possibility to receive a hepatitis C kidney, at which point they would be placed on a hepatitis C kidney waiting list, and would later be asked to consent when a donor kidney becomes available.
3. The Committee asked whether this is a research study, to which the Researchers clarified that this is not a study but a new treatment protocol.

Summary of resolved ethical issues

The main ethical issues considered by the Committee and addressed by the Researcher are as follows.

1. The Committee clarified with the Researchers that the project is not being done for research, although the project does include an audit of results of standard care practice. On this basis, the Committee agreed that the project did not fall within the HDEC scope of review as it is an audit/related activity.

Although the Committee did not review the project on the basis of it being out of scope, it made the following recommendations for normal, ethical management of treatment:

1. Please state in the PIS that patient information will be collected as part of standard care, and as would be done were the patients not taking part in this alternative treatment plan.
2. Please make sure that patients are provided with the consumer medication guides for the proposed anti-HCV therapies.
3. Please make it mandatory to tell GPs whether the patient is receiving the HIPC Kidney.
4. Please remove the statement that participants may withdraw from the study.

Decision

This application was determined by consensus to be *out of scope for HDEC review*, as it describes an audit or related activity and does not involve the use, collection, or storage of human tissue without consent (*Standard Operating Procedures for Health and Disability Ethics Committees* para *33*).

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| **2** | **Ethics ref:** | **19/STH/191** |
|  | Title: | A clinical study of Δ133p53 expression in Ulcerative Colitis |
|  | Principal Investigator: | Professor Michael Schultz |
|  | Sponsor: |  |
|  | Clock Start Date: | 24 October 2019 |

Professor Michael Schultz and Dr Kunyu Li were present by teleconference for discussion of this application.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this application.

No potential conflicts of interest related to this application were declared by any member.

Summary of Study

1. The aim of this research is to investigate the association of genes and the immune system on mechanisms leading to Ulcerative Colitis (UC) disease — an uncommon cause of stomach pain and loose bowel.
2. Specifically, the research aims to determine if expression of the gene p53 isoform A133p53 is associated with the development and progression of Inflammatory Bowel Disease (IBD) and more specifically the disease called Ulcerative Colitis (UC). It is believed that the level of Al 33p53 could indicate the development and severity of IBD.
3. The findings of this research will provide significant new knowledge on whether the Al 33p53 isoform contributes to the development of IBD and whether it could predict IBD patients at risk of developing colorectal cancer. If this research produces promising results, it will allow A133p53 to be used as a biomarker to improve early diagnosis of IBD in patients who have bowel problems. It also has potential therapeutic implications by targeting A133p53 or associated pathways to provide better treatment interventions for IBD.
4. For participants, the study involves 6 additional biopsies during their colonoscopy appointment.

Summary of resolved ethical issues

The main ethical issues considered by the Committee and addressed by the Researcher are as follows.

1. The Committee noted that several of the answers given in the application form did not adequately address the questions. One answer says that the study will inform the establishment of a tissue bank. The Committee asked if they will use an existing tissue bank or whether they are establishing a new tissue bank. The Researchers responded that they would use an existing tissue bank, and the Committee noted that questions H and Mc in the application form were answered incorrectly.
2. With regard to the Researcher’s answers to questions r.5.4.1 and p.3.1, Committee stated that the *initial* approach to patients needs to come from someone in the patient’s clinical care team. It explained that the first approach can be brief, simply to gauge their interest, after which a researcher may approach the patient with a PIS. The Researchers agreed, and stated that Professor Schultz would make the first approach as the patients’ clinician.

Summary of outstanding ethical issues

The main ethical issues considered by the Committee and which require addressing by the Researcher are as follows.

1. The Committee noted that the answer to question r.3.3 indicates that all tissue will be collected from participants, however the answer to A.1.5 and the study protocol describe the study as also retrospectively using archive samples. The Researchers clarified that archival tissue samples were intended to be used for the retrospective part of the study.  
   The Committee stated that, because it was indicated at A.1.5 that no archival tissue will be used, other questions in the form have not been populated. It requested that the Researchers provide answers to the following questions:  
     
   r.3.4. How and from where will you obtain these existing stored human tissue samples?   
   r.3.5. Will any human tissue samples used in your study be imported from outside New Zealand? (Yes/No)   
   r.3.6. Will donors of existing stored human tissue samples used in your study be able to be identified by you or your research team? (Yes/No)   
   r.3.6.1. Please briefly explain why the use of existing stored human tissue samples in a form that may allow the donor(s) to be identified if necessary in your study.
2. With regard to question r.4.1 (about incidental findings to participants whose tissue is used in this study), the Committee stated that the most likely finding is that a participant has the A133p53 gene. It asked if there is any intent to inform participants of that finding. The Researchers clarified that they did not intend to inform participants, as the role of p53 is not clear, and the tests are exploratory. The Committee requested that this be made clear in the PIS.
3. The Committee asked about the consenting process (outlined at question p.2.1). It asked whether presenting participants with two forms when they go for their colonoscopy would give them enough time to consider tissue donation, and whether emailing the PIS with the patients’ booking email and standard care information might be a better process to ensure they have the time to become adequately informed about the study.  
   The Researchers agreed that the timespan given at present is short, and agreed to email the PIS beforehand.
4. The Committee asked if the archival samples collected retrospectively come from the tissue bank with consent for research. The Researchers stated that the samples will come from the Southern community lab, which is a clinical lab containing samples not consented for research, but which are anonymised. The Committee stated that consent is needed, and asked why the retrospective samples are being used in addition to the prospective samples.  
   The Researchers clarified that the retrospectively collected samples will help to give the prospective study a head-start in establishing the role of the p53 gene, and its results would determine if the prospective study is worth running.   
   As people have the right to determine what is to be done with their body parts, the Committee requested that either consent be sought for the use of that tissue, or a clear justification be provided for the use of tissue without consent.   
   The Committee recommended the Researchers refer to the HDEC guidelines on the use of tissue: <https://ethics.health.govt.nz/guides-templates-forms-0/human-tissue-use-%E2%80%93-guidance>.

The Committee requested the following changes to the Participant Information Sheet and Consent Form:

1. Please review all documents for typos/grammar mistakes.
2. Page 2: please explain in lay terms what genes are, as well as the p53 isoform A133p53.
3. Page 4 states “participants have the right to access information collected as part of the research”. Please make clear that their P53 results will not be shared, because they are exploratory.
4. The consent form states that the use of information up to the point at which the participant withdraws is optional – this is stated as *mandatory* in the PIS. Please make sure that these documents are consistent.
5. the PIS states that significantly abnormal results will be shared with the GP. As results will not be shared, please remove this.
6. The Committee noted that the Researchers were not seeking consent for FUR or to send tissue samples overseas for FUR. It suggested that it may be wise to add that option to the consent form in case there was a desire to conduct research using those samples in the future, as seeking consent at that time may not be practical.
7. Page 24: please remove the section titled “handling of genetic information”, as the treatment of this information is not apparently different to the treatment of any other study data.
8. Page 25: please make it clear that participants can request the results of screening and safety tests performed during the study. Please also state that participants can opt to receive a lay summary of study results.
9. FUR PISCF:
   * Page 2: please add “if you consent, residual tissue will be stored”.
   * Please explain ‘genes’.
   * Page 2: the Committee asked for clarification regarding the statement “you may be contacted in the future by the research team if there are new discoveries in your sample”. The Researchers explained that it is intended as a way to allow them to make contact with the participants once the role of P53 has been identified.  
     The Committee asked that this be made optional in the consent form, and that consent be confirmed with all participants who previously gave consent at the later date when the role of P53 is established. Please state in the PIS that they will be re-consented at a later date and ensure that there is a plan to support patients if the information may be upsetting to them.
   * Please add an optional tick-box for removing identifiers from samples.
   * Please state that participant data may be removed on withdrawal from the study in the PIS (all information in the consent form should be mentioned in the PIS).
   * The ‘What are my Rights’ section and ‘Privacy Protection’ section contain significant repetition. Please revise and remove repetitive sentences.
   * Page 5 para 4 contains an incomplete sentence. Please amend.
10. Please remove the ACC sheet at page 8.
11. Please add a clause to the CF (for both the main study and FUR) about understanding the arrangements for storage and destruction of samples.

Decision

This application was *declined* by consensus, as the Committee did not consider that the study would meet the following ethical standards:

* An application is only considered valid if all questions in the application form are answered in a manner that is likely to allow the Committee to make a final decision on the application the first time it is considered. As not all questions were answered correctly, the Committee did not have enough information to make a final decision on the application (*Standard Operating Procedures for HDECs* para *42.3*).
* The use, collection or storage of human tissue without informed consent constitutes a more than minimal risk activity, can only be justified if it is impossible, impractical or excessively costly to obtain consent, or that doing so would adversely affect the outcome of the research. Furthermore, the committee must be satisfied that:
  1. there is no harm to the person or interests of the donor or the donor’s extended family; and
  2. the research will be of significant potential public benefit; and
  3. the research is not being conducted principally for commercial gain

(*Collection and Use of Human Materials* para *3*).

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| **3** | **Ethics ref:** | **19/STH/197** |
|  | Title: | Effect of multi-target transcranial current stimulation on cognition and pain. |
|  | Principal Investigator: | Dr Divya Adhia |
|  | Sponsor: |  |
|  | Clock Start Date: | 31 October 2019 |

Dr Divya Adhia was present by teleconference for discussion of this application.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this application.

No potential conflicts of interest related to this application were declared by any member.

Summary of Study

1. The study investigates the immediate effect of multitarget transcranial stimulation on cognitive functioning and experimental pain measures in healthy middle-aged to older adults. It is believed that this will help to further evaluate the effect of multitarget transcranial stimulation in clinical populations at a later stage.

Summary of resolved ethical issues

The main ethical issues considered by the Committee and addressed by the Researcher are as follows.

1. The Committee noted that the Researcher’s answer to question r.4.6 of the application form had been answered in terms of a participant withdrawing from the study, rather than for the study as a whole, and asked if there were any broad criteria for terminating the study as a whole. The Researcher explained that there were not any such criteria, as the technique is very safe, the Researchers are very experienced with the technique, and only healthy participants will be recruited.
2. The Committee stated, with regard to the applicant’s answer to question b.1.4, that the study is not a therapeutic study.
3. The Committee asked whether the study staff are trained/experienced in the management of SAEs, and where the study would take place. The Researcher explained that the study procedures will be done in a hospital laboratory, that a CI will be present as well as medical staff and research staff who are first aid trained.
4. The Committee noted that participants are asked not to eat for 2 hours before testing, and that testing will last for 3 hours, and asked if food would be available on sight. The Researcher confirmed that food would be available, and also clarified that participants are only restricted from eating heavy meals beforehand (which would be explained over the phone).

Summary of outstanding ethical issues

The main ethical issues considered by the Committee and which require addressing by the Researcher are as follows.

1. The Committee noted that the study’s exclusion criteria excludes those that are unable to read English. However, the consent form states: “I have read or had read to me in my first language…”. The Researcher explained that this sentence is merely intended to ensure that the reader has understood the form. The Committee asked for “in my first language” to be removed.
2. The Committee queried the Researcher’s answer to question b.4.4 of the application form, which stated that data generated in the study will be used for FUR. It noted that no information regarding the future use of information was given in the PIS. The Researcher explained that while no future research is planned, they intended to keep the option for future use of data open, and would only share the information in a de-identified form. The Committee stated that participants should be informed of how their data may be used in the PIS.
3. The Committee asked why there is a DSMC. The Researcher responded that the DSMC will only be established in case a participant has violated the protocol, e.g. drinking alcohol, and if they had a SAE. The Committee asked about the makeup of DSMC, to which the Researcher stated that the members will be from the study team.  
   The Committee stated that the members cannot be part of the research team for the DSMC to be independent, and that a charter is required, including guidance under what circumstances the committee will meet. The Researcher explained that the committee is an academic research committee, and would meet only if there had been an adverse event (which would most likely be a seizure). Furthermore, they stated that if a participant had a seizure the study would be halted, and the research committee and the HDEC would be notified before re-commencing.  
   The Committee asked for this and all relevant information about the Committee’s operating procedures to be formally written into the protocol.
4. The Committee asked how potential participants will be recruited. The Researcher explained that participants will be voluntarily recruited from a university staff email, as well as through advertisements in newspapers and on social media.  
   The Committee suggested that to meet the recruitment targets the advertisements would need to make the study look attractive, and recommended outlining the future benefits so that those with a social conscience might be motivated to enrol. The future benefits are not made clear in the PIS (although it is also important to make clear that there is no benefit to the participants themselves).
5. The Committee asked whether the screening procedure was sufficient enough to ensure that any health issues are identified in participants, as some questions are technical and participants may or may not know the answers to the questions. The Researcher explained that they will also seek consent to contact the participant’s GP if they are unsure of any answers. The Committee asked that access to the GP contact details should be mandatory, and that both participants and GPs should be notified if any diagnosable condition is recorded.
6. The Committee suggested to make previous research available to participants.
7. In response to question r.1.7 the Researcher had indicated that no participants will receive treatment at the direction of a medical health professional. However, The Committee noted that transcranial stimulation is a treatment. Consequently, the following questions were not populated in the form, which require answering by the researcher:
   * r.1.7.1. Will any of these participants have given written consent to participate? (Yes/No)
   * r.1.7.1.1. Does your intervention study involve trialling a medicine or item? (Yes/No)
   * r.1.7.1.2. Having regard to the following questions, will your study be carried out principally for the benefit of the manufacturer or distributor of the medicine or item being trialled?
     1. Who is initiating the study?
     2. Who is designing and planning the research questions that the study will ask?
     3. Will the PI or other investigators receive remuneration from the manufacturer or distributor?
     4. Is the manufacturer or distributor putting any unreasonable restrictions or delays on the timely publication of the results of the study?
     5. Is the manufacturer or distributor providing any funding and/or materials for the study?

(**Yes**, my study will be carried out principally for the benefit of the manufacturer or distributor of the medicine or item in question; **No**, my study will not be carried out principally for the benefit of the manufacturer or distributor of the medicine or item in question)

The Committee requested the following changes to the Participant Information Sheet and Consent Form:

1. Page 3: “it will be best to be prepared to be in either group”. This implies that the participant has some choice as to which group they are part of. Please amend to “please be prepared to be in either group”.
2. Please re-write in lay terms “blinding is to eliminate a placebo-effective stimulation”.
3. Please state that the participant’s research data might be made available to other researchers who are not connected with the study, and explain what future unspecified research data may be used for and in what form it would be shared (how it will be de-identified).
4. In the section on brainwave testing and putting the cap on the head, please add a statement about the cultural issue for Māori of touching the head.
5. Please describe how the study may benefit future patients.
6. Consent form:
   * Please remove the yes/no tick boxes from the consent form for all statements that aren’t truly optional, i.e. those where a participant could select ‘no’ and still participate in the study.
   * Please make it mandatory to be able to contact the participant’s GP (and mention this in the PIS).

Decision

This application was *provisionally approved* by consensus, subject to the following information being received:

* Please include a section in the protocol detailing the procedures of the research committee in relation to this study.
* Please upload a cover letter, and include your answers to the questions from the application form listed above.
* Please amend the information sheet and consent forms, taking into account the suggestions made by the committee

After receipt of the information requested by the Committee, a final decision on the application will be made by Professor Jean Hay-Smith and Dr Pauline Boyles.

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| **4** | **Ethics ref:** | **19/STH/198** |
|  | Title: | ION-682884 for the treatment of Hereditary Transthyretin-Mediated Amyloid Polyneuropathy |
|  | Principal Investigator: | Prof Ed Gane |
|  | Sponsor: | Pharmaceutical Research Associates Ltd (NZ) |
|  | Clock Start Date: | 31 October 2019 |

Sarah Coates, Genevieve and Leigh Cunningham were present by teleconference for discussion of this application.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this application.

No potential conflicts of interest related to this application were declared by any member.

Summary of Study

1. The study is testing a new treatment for patients with Transthyretin-Mediated Amyloid Polyneuropathy. It will involve randomising patients 6:1, with 6 being the investigational product and 1 being the standard of care drug currently available in America but not in NZ. As a result, participants will receive 1 of 2 drugs not currently available in NZ. The investigational product is given 4 times per week, whereas the standard of care medication is given weekly. As there will be many study visits, the sponsor is offering home-care nurses to visit participants at their own home, and to teach them how to do their own injections if they want to. All participants will get one of the two treatments until week 55, at which point the SOC arm will cross over to the IP and carry on until week 85 post-randomization. Approximately 85 participants will be recruited in NZ.
2. There is an optional PK sub-study for 3 days, 6 hours post drug administration.
3. The present study will also follow with an optional open-label study (pending separate HDEC and regulatory approval) at the very end of the protocol.

Summary of resolved ethical issues

The main ethical issues considered by the Committee and addressed by the Researcher are as follows.

1. The Committee stated that answers to questions in the application form should be given in plain English. For future applications please write the responses in lay language.
   * Question b.1.1 asked about the objectives of the study: this is to see how effective this drug is as opposed to inotersen.
   * Question b.1.2 asked about the scientific basis of the study: the answer given does not describe what has happened leading up to this study, and it was not immediately clear that inotersen is a precursor/parent drug to the investigational product being tested now.
   * Question b.2.1 asks for a summary and justification of the study design: however, no justification was given.
   * Question r.1.1 asks about the risks associated with the study procedures: the principle risk to participants is the study drug itself, however this was not stated. The adverse effects of inotersen should also be noted.
2. The Committee noted, for clarification, that it is against NZ law to stop a therapeutic study for commercial interests.
3. The Committee asked for confirmation that no sponsor or CRO staff would be given access to information for participants who are pre-screened but do not consent to participate. This was confirmed by the Researchers.
4. The Committee stated that the Researchers’ answer to question p.2.8 (will you inform participants of the results of your study?) is not acceptable, as it is a right of participants to receive a lay summary of the study results. The Researchers expressed that this was an oversight.

Summary of outstanding ethical issues

The main ethical issues considered by the Committee and which require addressing by the Researcher are as follows.

1. The Researchers’ answer to question b.4.4.1 states that partially de-identified data will be given to researchers outside the present study. The Committee asked for clarification regarding how/to what level the data will be de-identified.
2. The Committee asked that the Researchers ensure that clinical trial registration is completed before the study commences.
3. The Committee asked for the Researchers’ rationale for requiring blood and urine samples to be retained for 15 years. It further noted that the answer to r.3.12 (“If participants decide to stop taking part in the study, but do not request withdrawal of their samples, the Sponsor and its authorised representatives may continue to use their samples for research and testing for future side effects or to explore other findings or research related to ION-682884 or hATTR-PN until the end of the storage period.”) allows for mandatory future research on those samples. It requested that participants be explicitly asked for consent on withdrawal, and that this option should be in the consent form as a separate tick box.
4. The Committee asked if the third-party vendor will be used to provide participants with compensation, as was stated in the PIS. The Researchers explained that they would not be using the third-party vendor at their site, but that other sites may want to use it.  
   The Committee stated that the vendor is not well suited to the New Zealand context and raises a lot of issues. The Researchers agreed that it would be simpler to remove it from the PIS. If a third-party vendor is intended to be used by one or more New Zealand sites, the following questions require clarification:

- How quickly are participants reimbursed?

- The email discussed only US dollar and euros – will participants be paid in USD?

- The reimbursement policy does not refer to unscheduled visits (for example assessment of AEs outside of scheduled visits); how will this be dealt with?

- Can a participant opt out of using the 3rd party vendor and deal directly with the site?

1. The Committee asked about the possibility of at-home visits, and the Researchers explained that a third-party company is being employed who will do the at-home-visits. The Committee requested that a safety protocol be retrieved from that company.

The Committee requested the following changes to the Participant Information Sheet and Consent Form:

1. Please detail how/to what level study data used for FUR will be de-identified.
2. Please make clear that no genetic testing will be done on samples kept for FUR.
3. If you are using the third-party vendor, please make the information about it clearer.
4. The confidentiality section is long and confusing. Please split it into sections about identifiable health information and coded health information. ‘Authorisation to use and share medical information’ includes information about the confidentiality measures again, and does not distinguish between what is identifiable and what is not. Please amend for clarity.
5. Page 7 refers to vitamin A. Please say that those are tablets.
6. At the top of page 3 there is a long paragraph: please amend and separate sentences.
7. Some paragraphs bleed into the footers, and there are some ‘orphan headings’ – please proofread and amend accordingly.
8. In the section on pregnancy and reproductive risks for sexually active men the content is mixed-up, e.g. egg donation in the section on male reproductive risk. Please proofread and amend accordingly.
9. Consent form: please add the option for the continued use of samples for future research in the case that the participant withdraws from the study.
10. Pregnant partner form needs to be amended to also address pregnant participants: please state “you/your partner”
    * Please re-order the section about confidentiality so that paragraph 6 follows paragraph 3.
    * Please remove any repetition in the consent clauses.
    * The phrase “because your male partner (the father of your biological child)” is unnecessary, please remove.
    * Please remove the duplicate clause “I’ve had an opportunity to discuss”/“I’ve had questions answered to my satisfaction”.
11. PK sub-study: please remind participants in the consent form that their blood samples are going overseas.

Decision

This application was *provisionally approved* by consensus, subject to the following information being received:

* Please upload a cover letter providing clarification regarding how/to what level data used for FUR will be de-identified.
* Either remove information about the third-party vendor from the compensation section of the PIS, or answer the questions listed in the ‘outstanding ethical issues’ section above.
* Please upload a safety protocol for the at-home study visits.
* Please amend the information sheet and consent forms, taking into account the suggestions made by the committee

After receipt of the information requested by the Committee, a final decision on the application will be made by Dr Sarah Gunningham and Dr Devonie Waaka.

Given the number of conditions attached to this provisional approval, it is encouraged that the Researchers contact the secretariat for clarification on any points if needed.

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| **5** | **Ethics ref:** | **19/STH/199** |
|  | Title: | Atezolizumab Plus Bevacizumab in Patients with Hepatocellular Carcinoma After Surgical Resection or Ablation |
|  | Principal Investigator: | Prof Ed Gane |
|  | Sponsor: | Roche Products (New Zealand) Limited |
|  | Clock Start Date: | 31 October 2019 |

Sarah Coates, Merika, Genevieve and Stephen Duffy were present by teleconference for discussion of this application.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this application.

No potential conflicts of interest related to this application were declared by any member.

Summary of Study

1. Background: Atezolizumab is an antibody (a protein similar to the ones produced by your body's immune system) that blocks the programmed death-ligand 1 (PD-L1) pathway. The PD‑L1 pathway is involved in regulating the body's natural immune response, but tumors can take advantage of this regulation to partially resist or evade the immune system. By blocking the PD-L1 pathway, atezolizumab may help the immune system stop or reverse the growth of tumors. Atezolizumab is approved by the U.S. Food and Drug Administration (FDA) for the treatment of bladder cancer, lung cancer, and triple‑negative breast cancer. Bevacizumab is an antibody that slows the growth of new blood vessels and may help the body stop the growth of tumors. It has been approved for treating certain advanced cancers such as colorectal and nonsmall cell lung cancer.
2. The purpose of this phase-3 study is to compare the effects of atezolizumab plus bevacizumab versus active surveillance (not receiving any treatment) on patients with completely resected or ablated HCC who are at high risk for disease recurrence. Participants will be randomized to either atezolizumab plus bevacizumab or no treatment. The active surveillance arm is effectively equivalent to current standard of care.
3. Genome and FUR testing is optional.

Summary of resolved ethical issues

The main ethical issues considered by the Committee and addressed by the Researcher are as follows.

1. The Committee asked for application answers to be given in plain English (most notably for question a.1.5).
2. The Committee noted that the primary contact was listed as “team liver research”, and requested that the Secretariat update this to Sarah Coates, and that the Researchers list a specific person in future applications.
3. In response to the Researchers’ answer to b.1.1, the Committee asked for a plain English description of what the study will test. The Researchers stated that it will test whether the combination treatment in comparison to surveillance will prolong the time to disease for these patients once they’ve had a definitive treatment.
4. With regards to the Researchers’ answer to r.3.10, the Committee asked what genomic analysis will be mandatory for the study. The Researchers clarified that only PD-L1 is a mandatory test.
5. With regards to the Researchers’ answer to question p.3.1, the Committee stated for clarification that the initial approach to patients must be made by a member of their clinical care team. It further asked if the Researchers intended to do any advertising, to which they clarified that they would not.
6. The Committee expressed concern regarding the questionnaires, which say that the interviewer must “keep to the script” of the phone interview, although some of the questions could lead to concerns for the wellbeing of interviewees. It asked how those interviewees would be supported. The Researchers explained that the research nurse conducting the interview is sufficiently qualified to offer support to the participant over the phone, and would then raise that concern with the research team.

Summary of outstanding ethical issues

The main ethical issues considered by the Committee and which require addressing by the Researcher are as follows.

1. The Committee asked for clarification about the de-identification of study data used for FUR. The Researchers responded that study data will be partially de-identified as defined by the HDEC guidelines (“coded with abbreviated identifiers (e.g., initials, date of birth, sex)”). The Committee asked for the data to be as de-identified as possible. Please remove the date of birth; study codes may still be used.
2. In response to r.2.1.1, the Committee stated that no personal or health information from individuals may be shared with the sponsor prior to individuals having given consent.
3. The Committee asked for new evidence of independent peer review, as the Australian ethics review letter does not include the minutes of the review or written comments from the reviewers.

The Committee requested the following changes to the Participant Information Sheet and Consent Form:

1. Please proofread for typos and repetition (e.g. most notable in pages 9-13, including repeat headings).
2. Page 21: the Committee discussed the wording on the mandatory use of tissue, which it noted was very broad. The Researchers stated that biomarker analyses are in their nature exploratory; that they are part of the development of treatment, but they are not established. The Committee asked for the scope of the mandatory biomarker analysis to be more restricted and specific to the present study.
3. The Committee further noted that samples taken during screening will still be used, and could be stored for 5 years if the participant does not take part in the study. The Researchers confirmed this, and explained that those who are ineligible or decide not to enrol in the study must explicitly withdraw consent for their samples. The Committee asked that this be made very clear to participants, and that when participants withdraw consent, or are informed of study ineligibility, they are specifically asked if they give consent for their samples to be retained for biomarker research.
4. Similarly, the Committee felt that the language on genomic testing was too broad and went beyond what is necessary for the main study. Please remove the paragraph regarding genome testing on page 21 from the main study PIS, as it relates to the FUR PIS.
5. Pregnancy PISCF:
   1. the Committee noted that the expiry date for data collection is 15 years. It is unclear whether this relates to the expiration of consent, or the timeframe for data collection. Please clarify.
   2. The consent clause includes information about notifying the pregnant partner’s GP about study results and study participation. However, as no tests will be undertaken for the pregnant partner and no study information will be produced, the Committee asked for this to be removed.
6. Please clarify in the PIS that you are only collecting information up to the birth of the child, and that no data will be collected on the infant. This includes any postnatal assessments, such as APGAR scores etc.
7. FUR tissue PIS:
   1. please remove repetition in the “what are my rights” section.
   2. Page 5 paragraph 4 please remove the incomplete sentence.
   3. Please delete the section which states that the results would only be disclosed to an employer if required by law, as this does not apply in NZ.
8. Genome sequencing PIS/CF:
   1. the ‘risks’ section includes the risks of taking blood. Please delete this if no additional blood will be sampled for this sub-study.
   2. Page 3: please delete the section which states that the results would only be disclosed to an employer if required by law, if this does not apply in NZ.
9. Questionnaires: please outline the steps an interviewer will take if a participant states they feel 'extremely anxious or depressed' during the telephone interview. What will be done if the response is recorded in a written questionnaire?

Decision

This application was *provisionally approved* by consensus, subject to the following information being received:

* Please upload an updated version of the protocol, stating that data used in FUR will be de-identified with date of birth removed, and that study data from individuals collected before they consent will not be shared with the sponsor.
* Please confirm that data shared with other researchers not connected with the current study will at most be identified by subject number; and that all other identifiers (initials, date of birth etc) are removed.
* Please confirm that no health or personal information from individuals will be shared with the Sponsor, prior to their consent for study participation.
* Please provide new evidence of independent peer review with either minutes or comments from the reviewers.
* Please amend the information sheet and consent forms, taking into account the suggestions made by the committee

After receipt of the information requested by the Committee, a final decision on the application will be made by Dr Sarah Gunningham and Dr Devonie Waaka.

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| **6** | **Ethics ref:** | **19/STH/201** |
|  | Title: | ctDNA for early cancer detection |
|  | Principal Investigator: | Dr Dianne Sika-Paotonu |
|  | Sponsor: | University of Otago Wellington |
|  | Clock Start Date: | 31 October 2019 |

Dr Dianne Sika-Paotonu was present by teleconference for discussion of this application.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this application.

Professor Jean Hay-Smith member declared a potential conflict of interest and the Committee decided to allow her to remain in the meeting room and take a full part in the discussion and decision relating to that item of business.

Summary of Study

1. This study is part of a wider project aiming to develop a new way of detecting cancer earlier. The method to be tested is currently used in NZ to monitor patients receiving cancer treatment. It allows the clinician to look at how a tumour is behaving by identifying tumour pieces in the blood stream, which allows for more timely decision-making. This blood test could be applied in screening to pick up the presence of cancers earlier. The project so far has involved discussions with interested parties in the pacific to gather their initial perspectives on developing a blood test to pick up cancer earlier, and the feedback so far is positive.
2. This present study will expand on that engagement/consultation by setting up focus groups to gather patient’s/whanau perspectives on dealing with cancer, and their thoughts on developing this blood test to pick up cancer earlier.
3. It will aim to involve participants across groups of Tongan, Samoan and Cook Island populations. These are further divided into three groups: children 10-18 years old; 18-50 years; and thirdly 50+ years old; as well as Health professionals.

Summary of resolved ethical issues

The main ethical issues considered by the Committee and addressed by the Researcher are as follows.

1. The Committee asked if separate ethics approval will be sought in Tonga, Samoa and The Cook Islands, which the Researcher confirmed. The Committee stated that its approval will only apply to activities conducted in NZ.
2. The Committee asked how many participants will be expected to understand CTDNA. The Researcher explained that some information about CTDNA will be explained to participants beforehand.
3. The Committee enquired about the primary purpose of the study: whether it is that participants can talk about their experience of living with cancer/living with family members with cancer, as well as their feelings about ways of diagnosing cancer with early detection, or more primarily to talk about this particular treatment. The Committee noted that the potential value of the treatment seemed clear.  
   The Researcher confirmed that the purpose is mainly to allow participants to talk about their experiences of cancer and to discuss this specific blood test. They furthermore would like to use it as an opportunity to connect with specific communities.
4. The Committee noted the risk of biasing participants in providing information on ctDNA. The Researcher explained that the information provided would be brief, and only a description of the blood tests and the invasive nature of extracting blood.
5. The Committee asked whether all interviews and materials will be in English, which the Researcher confirmed, as most Pacific Islanders living in New Zealand can speak English, but that translation will be made if necessary.
6. The Committee asked why the Researcher is seeking access to the medical records of the participants. The Researcher explained that only the type of cancer will be accessed for confirmation in case the participants are unsure. If they are a relative or whanau, then only what they describe will be used. The Committee asked for this to be made clear in the PIS.
7. Regarding the Researcher’s answer to question b.4.4 on the application form, the Committee asked what kinds of future unspecified research the data might be used for. The Researcher clarified that the data may be needed to guide the development of ctDNA technology. The data would stay within the study team, but the results might be communicated outside of the team.
8. The Committee asked how the focus groups will be recorded and how data will be kept secure and unidentifiable. The Researcher explained that the groups will be audio recorded to ensure that they are accurately recorded, transcribed and then de-identified.
9. The Committee asked how privacy among members of the focus groups will be ensured. The Researcher explained that rules about privacy will be described at the start, but also that cultural norms should ensure that participants are respectful.

Summary of outstanding ethical issues

The main ethical issues considered by the Committee and which require addressing by the Researcher are as follows.

1. The Committee stated its concern that the study question is unclear. While this does not require addressing, the following should be considered:
   1. Firstly, it is not clear what it would mean if the participants do not support the new blood test, and what if there are mixed views.
   2. Secondly, the Committee noted that the study involves two quite distinct questions: an analysis of specific population’s experiences with cancer, and their views of the new blood test.
2. The Committee requested the peer review comments by the HRC, or alternatively comments from another independent reviewer.

The Committee requested the following changes to the Participant Information Sheet and Consent Form:

1. Please add a statement in the PIS stating that the group sessions are a closed meeting and that others’ details should not be shared.
2. The Committee stated that those under 16 may be able to provide consent as well if they are deemed competent. Please amend the assent form to enable the researcher to declare whether they believe that the participant is competent to give informed consent.

Decision

This application was *provisionally approved* by consensus, subject to the following information being received:

* Please provide the peer review comments by HRC, or otherwise comments from another independent reviewer.
* Please amend the information sheet and consent forms, taking into account the suggestions made by the committee

After receipt of the information requested by the Committee, a final decision on the application will be made by Professor Jean Hay-Smith and Dr Sarah Gunningham.

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| **7** | **Ethics ref:** | **19/STH/202** |
|  | Title: | Neonatal Nutritional Interventions Early School-age Outcomes Studies |
|  | Principal Investigator: | Dr Chris McKinlay |
|  | Sponsor: | University of Auckland |
|  | Clock Start Date: | 31 October 2019 |

Dr Chris McKinlay and Prof Jane Harding were present by teleconference for discussion of this application.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this application.

No potential conflicts of interest related to this application were declared by any member.

Summary of Study

1. This study is a follow-up of two previous clinical trials, and investigates the later health, growth and development of children at 6 to 7 years of age who received nutritional interventions as babies. Interventions around the time of birth can have consequences for life-long health, with potential for both beneficial and unintended adverse effects. It is therefore critical that neonatal trials undertake high-quality long-term follow-up to fully assess the overall impact of early-life interventions on health and wellbeing. Using the same comprehensive, multidimensional assessment, this study aims to see children who participated in either the hPOD or ProVide studies as babies, at 6-7 years’ corrected age either at school or at home. This is the earliest age at which life-course trajectories of cognition, learning and cardiometabolic health can be reliably determined. This study is funded solely by a Health Research Council of New Zealand Programme Grant.

Summary of resolved ethical issues

The main ethical issues considered by the Committee and addressed by the Researcher are as follows.

1. As one of the prior studies was done in NZ as well as overseas, the Committee asked for confirmation that children enrolled in other countries would not be included in this study, which the Researchers confirmed.
2. With regards to the Researchers’ answer to question b.1.1, the Committee noted that although the study question was about neurocognitive function at 6-7 years, consent was being sought for access to data on cognitive function up to 16 years.  
   The Researchers explained that they are primarily interested in evaluating the 6-7 years age group, but are aware that there can be potential trade-offs across various measures that may only be present later. Often there are questions that are important and can be answered with access to routinely collected data, but it is difficult to go back and seek consent for that.
3. A secondary purpose of this study is to look at new ways to obtain consent.  
   The Committee noted that this secondary study question was not mentioned in the PIS, which the Researchers explained was intentional so as not to bias the results. They further noted that no additional information was being sought, and that it did not pose any increased risk.  
   The Committee suggested a simple general statement about this aim, however the Researchers stated that even a general statement could prompt participants to ask about it, leading to bias. In light of this the Committee was sufficiently satisfied that the benefits of not seeking consent outweighed the risks.
4. The Committee asked what sort of future research data will be used for, and how it will be de-identified. The Researchers explained that they have a standard approved protocol for data-sharing, that they do not make data publicly available, but can share it in a coded but otherwise anonymous form. Data will only be provided to researchers for ethically approved protocols.
5. The Committee asked about the whanau engagement research mentioned in the PIS. The Researchers explained that that will be a separate study seeking separate ethical review.
6. The Committee asked whether the Researchers thought that there might be a risk of creating stigma by pulling children out of class for this study. The Researchers said that their experience with similar studies was that children did not feel stigmatised, and that the parents and school will be notified in advance to ensure the children know why they are there.
7. With regards to question p.1.7, the Committee asked if the Researchers thought that some children under the age of 16 may be able to give informed consent on the collection/use of IDI data. The Researchers noted that access to medical records is similar to medical procedures, where children are typically do not provide consent until they turn 16. They further stated that data linkage is quite complex, and that it would be difficult to explain it to a child in a short period of time, or to go back later to seek consent. However, they confirmed that were a child to ask to withdraw consent then they would do so.
8. The Researcher clarified that information on data-linkage is not in the PIS as that is being done at separate time points: there is a separate data linkage PIS.

Summary of outstanding ethical issues

The main ethical issues considered by the Committee and which require addressing by the Researcher are as follows.

1. With regard to question r.1.1 on procedures in the study, the Committee noted that teachers of the children will be asked to fill out a questionnaire about the child, and asked whether the teachers should be considered participants and whether they should be provided with a concise PIS. The Researchers agreed to do this and provide the Committee with a teacher PIS.

The Committee requested the following changes to the Participant Information Sheet and Consent Form:

1. Please proofread the PIS, in particular correcting use of the word ‘provide’.
2. Please check that there is information in the PIS that teachers are also being asked for consent.
3. Please check that there is information about accessing medical and school records in the PIS.

Decision

This application was *approved* by consensus, subject to the following non-standard conditions:

* Please amend the information sheet and consent forms, taking into account the suggestions made by the committee.

## Substantial amendments

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| **1** | **Ethics ref:** | **14/STH/132/AM03** |
|  | Title: | Optimising mechanical ventilation in ICU |
|  | Principal Investigator: | Associate Professor Geoffrey Shaw |
|  | Sponsor: |  |
|  | Clock Start Date: | 27 August 2019 |

Assoc Prof Geoff Shaw was present in person for discussion of this amendment.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this amendment.

No potential conflicts of interest related to this application were declared by any member.

Summary of Study

1. This study is a randomized controlled trial, aiming to improve care of mechanically ventilated patients in the Intensive Care Unit (ICU) by providing clinicians with clear information about the condition of a patient's lung. Currently clinicians use "rules of thumb" when selecting ventilator settings. The primary objective is to recommend the best ventilator settings to maximise lung volume. This information is not available on any modern ventilator. It is intended to model the lungs using mathematical methods to better inform intensive care clinicians about the lung condition, and how this evolves over time, so ventilation can be optimised.
2. This study has been held up, as a related study found a harm associated with the intervention. Although the DSMB subsequently approved that study to go ahead, the steering committee closed the study and published their results. Due to that incident a higher level of expert review has been required to indicate that this present study is safer and different to the related study. After some review there have been agreed changes to the protocol.
3. Additionally, a new data protocol is now required due to new ventilators and monitoring equipment in the facility
4. The changes are as follows:
   1. The inclusion criteria: P/F ratio ≤ 200 mmHg on an FiO2 of ≥ 50%. Patients with a P/F ratio >200 but ≤300 on >5 cm PEEP will be retested on PEEP = 5 cmH2O and an FiO2 =50%.
   2. Patients who have previously participated in CURE RCT are not eligible for re-enrolment. Patients re-ventilated within 10 days of enrolment date will return to their previous assigned ventilation arm and continue in the trial. Patients will return to standard management after 10 days of enrolment.
   3. All participants will be ventilated using a pressure-controlled mode During a staircase recruitment manoeuvre (SRM), synchronised intermittent mandatory ventilation (SIMV) with pressure control will be used.
   4. The maximum peak inspiratory pressure (Pi) is now 43 cmH2O and maximum PEEP is 28 cmH2O. The PEEP adjustment and monitoring procedure (PUMP) manoeuvre will be performed ±4 cmH2O of the current PEEP. The criteria for before initiating an SRM in the control arm are now defined; the decision to initiate this is still based on clinical judgement.
   5. If an (urgent) SRM is felt to be in the patient's ‘best interests’, they will be randomised and undergo the assigned protocol using 'presumed consent'. Delayed proxy consent will be sought as soon as possible. For all other participants, proxy consent will be sought before enrolment. If family or whanau decline participation in the study, the patients will be managed according to standard practice. We will seek agreement to use any data already collected, but if this is also not agreed to, the data will be deleted.
   6. All recruitment and PEEP titration manoeuvres are carried out during normal working hours (0600-1800h) 7. A basic weaning guideline is defined to help transition patient to assisted spontaneous breathing (ASB).

The Committee requested the following changes to the Participant Information Sheet and Consent Form:

1. The Committee stated that there were no significant ethical issues with the amendment itself, but that over the course of the study the PIS had become outdated and required amendment. At the moment it references ‘proxy’ consent from family/whanau. The current NEAC guidelines require that, where an adult participant is unable to give informed consent, family/whanau provide an opinion on whether the treatment meets the participants’ best interests, however they cannot consent on the participants’ behalf.

They do not need to sign to express those views, but they may do so to formalise it.

For example, in addition to amending the pre-existing consent clauses the following may be added:

*I believe that \_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_\_ (participant’s name) would wish to participate in this study if he/she had been able to understand the information that I have received and understood.*

Decision

This amendment was *provisionally approved* by consensus, subject to the following information being received:

* Please upload an updated PIS/CF with the change suggested above.

After receipt of the information requested by the Committee, a final decision on the amendment will be made by Dr Devonie Waaka and Mr Dominic Fitchett.

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| **3** | **Ethics ref:** | **17/STH/9/AM07** |
|  | Title: | GDM Registry |
|  | Principal Investigator: | Dr John Baker |
|  | Sponsor: |  |
|  | Clock Start Date: | 04 October 2019 |

Dr Carl Eagleton was present by teleconference for discussion of this amendment.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this amendment.

No potential conflicts of interest related to this application were declared by any member.

Summary of Study

1. The purpose of the GDM study is to establish a diabetes in pregnancy registry that will improve diabetes screening post-pregnancy and help us understand more about how commonly women develop type II diabetes and the impact of this on your future health. The information from this research also aims to improve care by better predicting peoples’ risk of type II diabetes and identifying gaps in current treatment.
2. Approval was previously granted for the study as an opt-in registry for diabetes in pregnant women. Over 1000 women have been consented into the diabetes registry, and only 5 of those invited have not consented. However, a significant proportion of women are missed from the registry.
3. For this reason, the Researchers feel that it would be reasonable to have an opt-out consenting process rather than opt-in.

Summary of resolved ethical issues

The main ethical issues considered by the Committee and addressed by the Researcher are as follows.

1. The Committee asked if the new phase of this project should no longer be considered research, but rather be considered as standard care. The Researcher agreed with this, and stated that the registry has been shown to be useful: it has improved the screening of diabetes at 3 months, and shown that 45% of Pacifica women who had gestational diabetes only have pre-diabetes at 3 months, and 6% have type 2 diabetes by 3 months. As the research has shown that it is important and worthwhile, the registry should continue to be used as part of standard of care with an opt-out consent model.
2. The Committee noted that it was not within the scope of HDEC to review standard of care activities, and that the collection of data would also be out of scope as an audit/related activity. They stated that if the Researchers were to use this data for research purposes, they would need to seek ethics review, as the data is not consented for research.

Summary of outstanding ethical issues

The main ethical issues considered by the Committee and which require addressing by the Researcher are as follows.

1. The Committee stated that as the previous study is now concluded, a notification of conclusion of study should be submitted along with a final report.

Decision

This application was determined by consensus to be *out of scope for HDEC review*, as it describes an audit or related activity and does not involve the use, collection, or storage of human tissue without consent (*Standard Operating Procedures for Health and Disability Ethics Committees* para *33*).

## Review of approved studies

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| **1** | **Ethics ref:** | **19/NTB/100** |
|  | Title: | 0170 - Phase 3 Clinical Effect Durability of TD-9855 for Treating snOH in Subjects with Primary Autonomic Failure |
|  | Principal Investigator: | Prof Tim Anderson |
|  | Sponsor: | Theravance Biopharma Ireland Ltd |
|  | Clock Start Date: | 20 June 2019 |

No member of the study team was present for discussion of this application.

Potential conflicts of interest

The Chair asked members to declare any potential conflicts of interest related to this application.

No potential conflicts of interest related to this application were declared by any member.

Summary of Study

1. This study will look at whether the investigational drug TD-9855 works and how safe it is when taken over a period of time to treat symptomatic neurogenic orthostatic hypotension (snOH) in people with Parkinson’s disease (PD), multiple system atrophy (MSA), or pure autonomic failure (PAF). It will also look at the effects of TD-9855 on general well-being and whether it can improve symptoms of neurogenic OH (nOH).
2. TD-9855 has being developed for a range of medical treatments, including for snOH.
3. If someone has orthostatic hypotension (OH), it means that they get low blood pressure when they stand up. If someone has neurogenic OH (nOH), it means that the OH is caused by an impairment of the autonomic nervous system. The autonomic system is responsible for automatic body functions such as blood pressure control. In people with nOH due to PD, MSA, or PAF, nerve cells do not release enough norepinephrine, which is the chemical involved in blood pressure. Extra norepinephrine that is not used by the body can be taken back up by nerve cells or broken down by the body. The study drug has been designed to prevent norepinephrine from being taken back up by nerve cells, thereby increasing the amount of norepinephrine available. It is hoped that this might reduce the symptoms of nOH.
4. In this study, participants will be people who have completed a previous study taking either TD -9855 or placebo for 4 weeks. In this study, they will receive treatment for 22 weeks, split into two periods: a 16-week open-label period followed by a 6-week double-blind period. In the 16-week open-label period, all participants will first receive the study drug (10 mg per day) for 4 weeks. After 4 weeks if the participant’s score in Orthostatic Hypotension Symptom Assessment Question 1 (OHSA#1) demonstrates a reduction of at least 2 points compared to baseline, they will then continue to receive the study drug for another 12 weeks. Following completion of the 16-week open-label period, participant will enter the 6- week double-blind withdrawal period where they will be randomised to receive either study drug or placebo.

Summary of resolved ethical issues

The main ethical issues considered by the Committee and addressed by the Researcher are as follows.

1. The Committee disagreed with the Northern B HDEC regarding outstanding ethical issue 1:  
     
   *“The Sponsor presented no plans to define any minimum improvement criteria before a participant is moved through from the 4-week RCT (19/NTB/97) to this 22-week study. Participants simply need to meet the PI’s judgement that it is worth them continuing, and half of them will be on placebo. The Committee did not feel that it is fair to enrol participants into a second longer study without them having met specified improvement criteria. Given that this is a multicentre study, and given the concerns with safety monitoring/reporting outlined below, the Committee did not feel that participants’ best interests are served by having each investigator making a qualitative decision in isolation, to put people from one study into the next, without some knowledge of efficacy and safety throughout the first study.”*Since most of the patients will come from outside the study, the Committee did not believe it was important that the previous study 19/NTB/9 had to have proven benefit for those people. The Committee noted that a participant’s continued participation from that study into the present study would be based on a conversation between the investigator and the participant, their interest to continue and the investigator’s judgement. Furthermore, the Committee noted that participants who had received placebo would not be able to meet any pre-defined improvement criteria.
2. The Committee disagreed with the Northern B HDEC regarding whether outstanding ethical issue 2 was sufficient to justify a decline:  
     
   *“In response to the Committee’s request for a safety protocol, the Researcher explained that there is a "cross-functional Safety Review Team" and an IDMC. However, neither were mentioned in the protocol so that roles, composition, meeting frequencies and so forth are all unknown. According to the Protocol, 7.4.3, adverse event reporting goes through to a general reporting service for the company rather than to a committee dedicated to this trial. (To report an SAE or AESI, complete and send the SAE/AESI Report Form to the following: 1. Theravance Biopharma Clinical Safety 2. Fax: (650) 808-3786 3. Email: 0170\_Safety@theravance.com)  
   This response provided the Committee with insufficient information regarding how the safety oversight for this trial works. The Committee expects to see more detail laid out in the protocol. This is a multisite study, so integration of safety reporting is important.”*The Committee observed that the IDMC is noted in the study protocol, and that Northern B HDEC could have requested the IDMC charter in their first review.

Summary of outstanding ethical issues

The main ethical issues considered by the Committee and which require addressing by the Researcher are as follows.

1. The Committee agreed with the Northern B HDEC regarding outstanding ethical issue 3, although stated that it was not on its own sufficient to decline the application:  
     
   *“The sponsor’s comments about everyone knowing that this sort of participant is a burden to their caregivers is a claim that the Committee felt was unsupported… while the Committee acknowledges that this is an exploratory outcome and not compulsory for a caregiver to complete in order for a participant to be enrolled, the sponsor has not offered any mitigation strategy to limit harm to participants from seeing their loved one answer this questionnaire.”*  
     
   The Committee noted that “caregiver burden”, although not an ideal title, was standard for such documents in clinical practice. However, the Committee observed that some participants may place a very high burden on family/whanau, and it was important that the Researchers take responsibility to mitigate harm caused should a participant become distressed by the concept that they were imposing such a ‘burden’ on his / her caregiver. They agreed that the Researchers had not addressed this issue in their provisional response, although stated that, if all other issues relating to the study were addressed, this could be addressed as a non-standard condition of approval.
2. The Committee agreed with the Northern B HDEC regarding outstanding ethical issue 4:  
     
   *“The issue of having a sponsor’s representative present during tilt table testing is the same as with 19/NTB/97. The Researchers should be trained to do the tilt table testing accurately before the study begins, otherwise they should not be doing it. Tilt table testing is not a new investigation, some cardiologists do this in clinical practice on a regular basis to investigate suspected autonomic dysfunction. The "sponsors rep" could be anyone with or without qualifications to be giving advice in a clinical situation - this is not acceptable.”*The Committee stated that the Researchers had not addressed this issue in their provisional approval response, and specifically did not answer why, if the medical professionals have the expertise, it was appropriate to have representatives of the sponsor present.

The Committee noted that the Ethical Guidelines referenced by the Northern B HDEC did not match the primary moral issue on this point, which may have caused some confusion in the Response to Provisional Approval.

1. The Committee further noted that the above two issues are not fundamental problems with the project, and could be addressed by the Researchers in a resubmission: the previous decision to decline appears to be due to the fact that after a provisional approval the committee may only fully approve or decline the application, and not all of the issues raised on provisional approval had been adequately addressed by the researcher.

Decision

This application was *declined* by consensus, as the Committee did not consider that the study would meet the following ethical standards:

* The Guidelines state that investigator’s commitment to the advancement of knowledge entails a duty to accept responsibility for her or his activities in relation to research participants and communities. The Committee felt that by not showing how they would mitigate harm if a participant were to become expressed by the implication that they are burdening their family/whanau, the Researchers had not demonstrated their willingness to take responsibility for the impacts of their actions (*Ethical Guidelines for Interventional Studies* para *4.15*)

## General business

1. The Committee noted the content of the “noting section” of the agenda.
2. The Chair reminded the Committee of the date and time of its next scheduled meeting, namely:

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| --- | --- |
| **Meeting date:** | 10 December 2019 |
| **Meeting venue:** | Christchurch Clinical Studies Trust Limited |

The following members tendered apologies for this meeting.

* Dr Pauline Boyles

1. **Problem with Last Minutes**

The minutes of the previous meeting were agreed and signed by the Chair and Co-ordinator as a true record.

The meeting closed at 3:30pm.