National Research Ethics Committee

NREC-CT A Meeting

05 October 2022

Attendance

Name	Role
Prof. Alistair Nichol	Chairperson, NREC-CT A
Prof. Tina Hickey	Committee Member, NREC-CT A
Prof. John Wells	Committee Member, NREC-CT A
Prof. Mary Donnelly	Committee Member, NREC-CT A
Ms Muireann O'Briain	Committee Member, NREC-CT A
Ms. Erica Bennett,	Committee Member, NREC-CT A
Ms Evelyn O'Shea	Committee Member, NREC-CT A
Ms Ann Twomey	Committee Member, NREC-CT A
Prof. Donal Brennan	Committee Member, NREC-CT A
Prof. Austin Duffy	Committee Member, NREC-CT A
Dr John O'Loughlin	Committee Member, NREC-CT A
Mr Gerard Daly	Committee Member, NREC-CT A
Prof. David Brayden	Committee Member, NREC-CT A
Prof. Gene Dempsey	Committee Member, NREC-CT A
Dr Geraldine Foley	Committee Member, NREC-CT A
Dr Dervla Kelly	Committee Member, NREC-CT A
Dr Emily Vereker	Head, National Office for RECs
Ms Patricia Kenny	Project Officer, National Office for RECs
Dr Susan Quinn	Programme Manager, National Office for RECs
Dr Jane Bryant	Programme Officer, National Office for RECs
Ms Rachel McDermott	Programme Administrator, National Office for RECs
Dr Emma Heffernan*	Project Officer, National Office for RECs

*Drafted minutes

Apologies: Dr Heike Felzmann, Prof. Patrick Dillon, Dr John O'Loughlin, Mr Gerald Eastwood, Dr Jimmy Devins, Dr Darren Dahly, Prof. Catherine Hayes

Quorum for decisions: Yes

Agenda

Welcome & Apologies

- 22-NREC-CT-153
- 22-NREC-CT-154
- 22-NREC-CT-155
- 22-NREC-CT-156
- 2022-500587-35-00

AOB

The Chair welcomed the NREC-CT A.

The minutes from the previous NREC-CT A meeting on 7th September 2022 were approved.

The NREC Business Report was discussed and noted.

Applications

22-NREC-CT-153

Principal Investigator: Prof Orla Hardiman

Study title: RANDOMISED DOUBLE-BLIND PLACEBO-CONTROLLED PHASE 3 TRIAL OF TRIUMEQ IN AMYOTROPHIC LATERAL SCLEROSIS

EudraCT: 2020-005069-15

Lead institution: Beaumont Hospital

- **NREC-CT comments:**

- The NREC-CT A agreed that additional information was required to inform its deliberations before a final ethics position could be returned.

- **NREC-CT Decision:**

Request for Further Information

- **Further Information Requested:**

- The NREC-CT A requested details as to the current standard of care (SoC) for participants in Ireland, and confirmation that this treatment is not used off label as SoC in Ireland. The NREC noted the protocol states patients can continue standard of care medications (p21), but it is unclear if they can start additional therapies after screening.
- The NREC-CT A noted that patients are permitted to join the study if they are on a stable dose of Riluzole or have stopped Riluzole 30 days prior to the study commencement. For the 2-year study period, it is not clear to the NREC if patients are allowed to commence Riluzole or start other standard of care treatments that are available if they were not taking these at baseline. Please provide further details.
- Regarding eligibility, the NREC-CT A queried whether participants not on a stable dose of this medication could be given the opportunity to stabilise on this treatment, before enrolling in the study.
- The NREC-CT A noted one third of participants will be on placebo and requested that this is very clearly explained to participants in the Patient Information leaflet, as it may influence their decision whether to participate.
- The NREC-CT A noted the inclusion of the CSSR suicide study, and request confirmation regarding the pathway of referral, and the mental health support available, given the current waiting periods in Ireland.
- For the Patient self-reported assessment EQ-5D-5L, the NREC queried as to the process whereby the participant may be unable to write or to complete themselves, will a member of the study team fill this out or should the patient complete with a family member?
- The NREC-CT A noted that Page 5 of the PIL lists very common side effects and page 18 (Appendix E) lists common and uncommon side effects. The NREC suggest that all adverse events are listed together and not separated on different sections of the PIL, to ensure accessibility. Furthermore, as the PIL states patients are to report serious side effects to the investigator, the emergency contact information should be provided on the same page as this statement.
- The NREC-CT A requested that the consent for use of data should be separated out from the reset of the consent section, in line with best practice and the Data Protection Act 2018 (Section 36(2)) (Health Research) Regulations 2018). Alternatively, there should be a statement clarifying that the patient can still participate in the study if they answer “no” to the future use of their samples.
- The NREC-CT A noted that participants will be recompensed for travel and incidental expenses (including hotel, if relevant). However, the limit is €25 per visit, which would not be adequate for an overnight stay, or for travel. The NREC-CT A request confirmation that all relevant trial related expenses incurred by participants will be reimbursed and this is elucidated in the PISCF.

22-NREC-CT-154

Principal Investigator: Prof Sean Gaine

Study title: IMPAHCT: A Phase 2b/3, Randomized, Double-Blind, Placebo-Controlled, 24 Week Dose Ranging and Confirmatory Study to Evaluate the Safety and Efficacy of AV-101 in Patients with Pulmonary Arterial Hypertension (PAH)

EudraCT: 2021-001910-13

Lead institution: Mater Misericordiae University Hospital

- **NREC-CT comments:**

- The NREC-CT A agreed that additional information was required to inform its deliberations before a final ethics position could be returned.

- **NREC-CT Decision:**

Request for Further Information

- **Further Information Requested:**

- The NREC-CT A requested confirmation is provided that participation in this study will not affect Standard of Care treatment in Ireland
- The NREC-CT A requested justification for the upper age limit to participate in the trial being set at 75 years.
- The NREC-CT A noted that the PIL is generally informative but very lengthy and dense, and considered a summary PIL would be helpful for participants. The Committee noted that the introduction to the PIL is very clear and could be used/incorporated into a summary PIL
- The NREC-CT A requested that the risks associated with the cardiac catheterization procedure are clearly stated for participants, so they can make a fully informed decision about participating in the trial
- The NREC- CT A requested that a separate consent form is used for future research.
- The NREC-CT A requested that the PIL is updated to provide contraceptive advice for male participants and male partners of female participants
- The NREC-CT A noted the inclusion of a PIL Withdrawal Form and determined that that language used in this form could be considered coercive and requested that the form is amended so participants who wish to leave the trial do not feel pressurized to remain.
    - Furthermore, the NREC-CT A noted that withdrawal procedures described in the NREC Application Form differ from those described in the PIL and requested that these are aligned.
- The NREC-CT A requested that the following are amended in the PIL
    - Pg. 3, provide clarification to participants that they will be enrolled in one part of the overall study only.

    - Details on the number of Irish site and number of potential recruits
    - Pg.19 – ‘who has reviewed this study’ - This should be changed to the correct title, the National Research Ethics Committee
    - Pg. 5 correct the typo ‘right heart catheterisation’.
- The NREC-CT A noted in the inclusion of a Quality-of-Life Questionnaire and requested the following details:
    - Acknowledgement in the PIL/ICF that completion of this assessment may cause distress
    - Clarification as to the psychological supports available and referral pathway for participants who may experience distress / anxiety when completing this assessment
- The NREC-CT A noted that number of fields in the application form appeared to be completed incorrectly/ incompletely, e.g. A2 (dates do not align with study duration), C1, C2, C10, G3, F5. The Committee requested that the form is reviewed in detail and any inconsistencies amended.
- The NREC-CT A requested that NREC Appendix Form Clinical trials of investigational medicinal production in combination with exposure to radiation is reviewed and signed by a radiologist to provide reassurance that any exposure to radiation is under the supervision and justification of a radiologist and that the studies will be reviewed and reported by a competent radiologist.
- The NREC-CT A requested justification is provided for the storage of data for 50 years.
- The NREC-CT A requested that contact details for the data controller are provided in the DPIA
- Furthermore, the NREC-CT A requested that reference to the Irish Data Protection Commission is included in the DPIA.

22-NREC-CT-155

Principal Investigator: Prof. Edward McKone

Study title: A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-121 Combination Therapy in Subjects With Cystic Fibrosis

EudraCT: 2021-000713-17

Lead institution: St Vincent's University Hospital

- **NREC-CT comments:**

- The NREC-CT A agreed that additional information was required to inform its deliberations before a final ethics position could be returned.

- **NREC-CT Decision:**

Request for Further Information

- **Further Information Requested**:

- The NREC-CT A requested confirmation that this drug combination has been approved by the HPRA
- The NREC-CT A were not assured that participants would be aware that the study is a safety study, and requested that this is made clear in the PIL
- The NREC-CT A noted that the GP letter lists the potential side effects of the trial drug, the NREC-CT A requested a) that clarification is included regarding whether participants will be able contact the study doctor between visits to help manage side effects, and b) that some advice be included in the GP letter as to how they can help to manage common side effects in participants, recognising that GPs may be more accessible to (some) participants between study visits, or that participants may wish to consult their usual doctor about the more common side effects.
- The NREC-CT A noted that samples will be taken for future biomedical research and requested that participants are given the option of opting out of future biomedical research and that this is elucidated in the PISCF.
- The NREC-CT A noted that Section E16 of the NREC Application Form states that '*Participants will sign the main adult consent form when they reach the age of legal competence'* and requested reassurance that participants when they reach the legal age of competence, will be given the opportunity to read the PISCF and invited to sign the relevant consent form should they wish to continue participating in the trial.
- The NREC-CT A noted the advice given against pregnancy in participants, particularly regarding participating children between the ages of 12-16. The NREC-CT A requested that female participants under the age of 16, who have not already discussed pregnancy, and the implications of pregnancy in CF prior to participation in the study, have the opportunity to do so with their study doctor, in combination with discussion of the PIL. Furthermore, the NREC sought further information regarding the guidance and supports that will be provided to parents and children regarding conducting pregnancy tests in this age group, and that it is clearly highlighted to parents that this is a component of taking part in the study.
- The NREC-CT A requested that the risks associated with pregnancy in CF patients are elucidated in the parent / guardian PISCF
- The NREC-CT requested that male participants are also reminded at each study visit of the requirement to avoid conceiving a child while participating in the trial.
- The NREC-CT A requested that further details are provided in the parent / guardian PISCF regarding the contraceptives permitted / recommended to participants while participating in the trial and this is elucidated in the PISCF
- The NREC-CT A requested that the sponsor confirm if participation in the trial will affect the private medical insurance of children taking part in the trial.

- The NREC-CT A noted that the adult and parent / guardian PISCF prohibits discussion of trial participation on social media and requested assurance that children and teenagers taking part in the trial are not penalised for such use of social media
- The NREC-CT A requested that a more explicit account of the reimbursement process is described in the parent / guardian PISCF, including
    - When and how reimbursements are made, including a brief explanation of the role of Greenphire in this process and in travel arrangements, and
    - a brief explanation of how reimbursements will be managed on the Clincard System
    - Inclusion of contact details of a contact person for parents / guardians should they have any queries regarding reimbursement
- Furthermore, The NREC-CT A noted the language used in the description of remuneration for participants is more suited to the US context and requested that this is clarified for an Irish audience
- The NREC-CT A noted the use of the study name 'Skyline 104' on the study factsheet and requests that this is replicated across the patient facing documents to ensure clarity and consistency.

22-NREC-CT-156

Principal Investigator: Dr Nina Orfali

Study title: A Phase 1/2, Multi-center, Open-label Study of IMGN632 Monotherapy Administered Intravenously in Patients with CD123-positive Acute Myeloid Leukemia and Other CD123-positive Hematologic Malignancies

EudraCT: 2018-003210-40

Lead institution: St James's Hospital

- **NREC-CT comments:**

- The NREC-CT A agreed that additional information was required to inform its deliberations before a final ethics position could be returned.

- **NREC-CT Decision:**

Request for Further Information

- **Further Information Requested:**

- The NREC-CT A requested that the GP letter includes specific contraception advice for female and male participants and female partners of male participants.
- The NREC-CT A noted that pg. 6 section 4.1 of the NREC Appendix Form Clinical trials of investigational medicinal production in combination with exposure to radiation is

amended, so that the 'yes' box is ticked – indicating that participants are receiving an additional 11mSv of radionuclides compared to non-trial patients

- The NREC-CT A noted the high participant burden in relation to clinical visits and requested that a clear estimate of the projected length of time of each visit, as well as the total time taken for all visits over the course of the study is included in the PIL. Additionally:
    - It needs to be clearly stated why additional visits may be required.
    - It needs to be clearly stated to participants their expected duration in the trial
- The NREC-CT A noted discrepancies between the length of time infusions take in the protocol and PIL and requested that this is clarified and that the description in the protocol and PIL are aligned, so participants are fully informed about the length of time infusions are likely to take.
- The NREC-CT A noted that the application for consent of further use of biological samples is not in line with national regulations on 'explicit consent' and requested the following:
    - A separate consent form for future research is used
    - Participants should be given options to future data use, such as limiting future use to a specific disease area.
    - Confirmation that any further research using participant samples or data from this study, will undergo full ethics review
- The NREC-CT A noted that pg. 2 of the PIL states *'This research study tests IMGN632, a new study drug that shows activity against BPDCN, and has been tested in about 148 human cancer patients'* and requested clarification as to whether the '148 cancer patients' had BPDCN or other types of cancer, and this is clearly stated in the PIL
- Pg 2 of the PIL *'Why is this study being done'* is unclear and is potentially confusing for participants. The NREC-CT A requested that a clear description of the specific study participants are being enrolled in, with associated studies also described.
- The NREC-CT A requested that a sub-title be added to the PISCF title to reflect/describe the expansion study that BPDNC are being asked to consent to.
- Pg 2 of the PIL states that '*up to 252 participants are expected to take part in this study'.* This is potentially misleading, and the NREC-CT A requested it is made clear to participants how many participants are expected to take part in this specific trial globally and in Ireland.
- Furthermore, the NREC-CT A requested that the procedure for inclusion of study participants is clarified in the PIL.
- Pg 2 of the PIL *'what happens if I decide to particate'* needs to include a clear description of the screening process that takes place before patients are deemed eligible to participant in the trial, clearly detailing the process involved in screening, the various tests that will be conducted, the potential outcomes of screening and the length of time screening takes, so participants can make an informed decision about participating in the trial and understand that they may be deemed ineligible after screening.

- The NREC-CT A requested that the relevant contact details including names, phone numbers, including an out-of-hours phone number, are added to the participant subject card
- The NREC-CT requested the following is amended in the PISCF documents:
    - Pg 3 - the term *'intrathecal'* is explained in plain language to participants in the PIL.
    - Pg 6 - the term *'PK'* is explained in plain language to participants in the PIL.
    - Pg 8 - the term *'febrile neutropenia'* is explained in plain language to participants in the PIL.
    - P4 of the PIL notes that participants will undergo blood sampling. The NREC-CT A requested that is made clear to participants how often blood samples will be taken over the course of screening and also when participating in the trial.
    - Pg 6 of the PIL notes that participants will undergo a lumbar puncture. The NREC-CT A requested that a more detailed description of this procedure, including why this procedure is required, is explained in plain language to participants in the PIL
- Furthermore, pg. 6 notes that the lumbar puncture may include injection of chemotherapy if tests are positive for cancerous cells. The NREC-CT A requested clarification as to:
    - When these test results will be available
    - Whether participants are required to undergo a second lumbar puncture should their tests indicate a positive result requiring administration of chemotherapy and that this is clearly explained in the PIL.
    - Clarification as to whether the chemotherapy administered during lumbar puncture is part of the trial.
- The NREC-CT A noted that participants are required to undergo a PET scan and requested that participants are advised to refrain from contact with pregnant people, babies and small children for 6 hours post scan and this is explained in the PIL.
- P12 of the PIL states that side effects may lead to dose reduction or cessation of the trial drug. The NREC-CT A requested clarification is provided to participants as to whether patients that require the study drug to be stopped will be removed from the trial, and that this is elucidated in the PIL
- The NREC-CT noted that is the description of the potential side effects is lacking in detail and requested the PIL is amended to include the following:
    - Pg 8 febrile neutropenia states that *'severe events have been reported'* - further detail is required to explain these severe events including, the severity, duration and consequences in terms of potential treatments available and potential removal from the trial for these severe events
    - Furthermore, the NREC-CT A requested that further detail is provided in each case where *'events have been reported'* is listed in the potential side effects, including, the severity, duration and consequences in terms of

potential treatments available and potential removal from the trial for these events

- The NREC-CT A noted that P10 of the PIL highlights the risks associated with imaging – and requested that the last line of text is reworded to be more sensitive.
- The NREC-CT A requested that it is elucidated in the PIL that participants will be monitored for potential infusion reactions and that they should seek immediate medical treatment should they experience symptoms after discharge from the clinic as well as notify the investigator / clinic.
    - Furthermore, it should be explained in the PIL that if participants experience a life -threatening infusion reaction that they will be withdrawn from the trial.
- Pg 11 of the PIL *"what happens if I have side effects"* – the NREC-CT A requested that participants are advised to seek emergency medical treatment if required for potential side effects, in addition to informing the study doctor of same.
- The NREC-CT A requested a detailed description of the previous experience of carrying out phase 1/2 trials at the Clinical Research Facility in St. James's Hospital
- The NREC-CT A requested details of Dr Orfali's previous experience in managing phase 1/2 trials
- In relation to renumeration outlined in the Patient and Caregiver Meals and Incidentals Report document, The NREC-CT A requested the following:
    - The NREC-CT A noted that expenses must be submitted after each visit and within 7 days of the visit and consider this an unreasonable requirement, considering participants may be ill, or experience side effects as a result of participating in the trial and requested reassurance that all trial related expenses incurred by the participant will be reimbursed, regardless of when reimbursement requests are submitted.
    - The NREC-CT A requested reassurance that all reasonable expenses for participants requiring unscheduled visits or admission to hospital should they experience side effects due to trial participation will be reimbursed.
    - The NREC-CT A requested clarification as to whether participants will be able to submit expenses to the study site coordinator at SJH if they wish, as they may find it burdensome to upload documents to the online portal. If this is the case, then it needs to be explained in the PIL with contact details of the relevant person in SJH included.
    - The NREC-CT A requested confirmation that all trial participants will be reimbursed for trial related expenses at all stages of the trial including consenting, screening and clinic visits
    - Furthermore, the NREC-CT A requested that participants who do not pass screening will also be reimbursed for trial related expenses.
    - The NREC-CT A noted US centric terms such as *'ground transport'* requested the language in this document is adapted to an Irish audience.

- The NREC-CT A requested that details of reimbursement of trial related expenses are included in the PIL, so participants are reassured that trial participation will not leave them out of pocket.

2022-500587-35-00

Principal Investigator: N/A Part 1

Study title: Tranexamic acid for hyperacute spontaneous IntraCerebral Haemorrhage (TICH-3)

Lead institution: N/A Part 1

- **NREC-CT comments:**

- The NREC-CT A agreed that additional information was required to inform its deliberations before a final ethics position could be returned.

- **NREC-CT Decision:**

Request for Further Information

- **Further Information Requested:**

- The The NREC-CT A requested clarification on the minimum age of enrolment, and if adolescents of 17 years old will be included.
- The NREC-CT A requested that specific detail is provided as to how all emergency consent procedures undertaken in Ireland comply with each of the conditions set out in Art. 35(1) of Regulation (EU) No. 536/2014 on clinical trials on medicinal products for human use.
- The NREC-CT A requested clarification on the nature and grade of the independent doctor proposed to be consulted for enrolment of a participant, where the participant lacks capacity or a legal representative, and the process by which this doctor will be identified in an emergency situation.
- The NREC-CT A requested clarification as to how the term ‘without undue delay’ is defined, what time is indicated, and request a justification of this time provided.
- The NREC-CT A requested further justification for the omission of pregnancy tests for participants, and further detail on the process where a participant is obviously pregnant, or where the treating doctor has been informed that the participant is pregnant.
- The NREC-CT A requested further detail on the parameters that will inform decision making in the DSMC, including stopping criteria.
- The NREC-CT A requested that the definition of a legal representative is set out as per Irish legislation.

AOB:

The Chair closed the meeting.