National Research Ethics Committee

NREC-CT A Meeting

25 January 2023

Attendance

Name	Role
Prof. Alistair Nichol	Chairperson, NREC-CT A
Prof. Mary Donnelly	Deputy Chairperson, NREC-CT A
Prof. Tina Hickey	Committee Member, NREC-CT A
Dr Jimmy Devins	Committee Member, NREC-CT A
Prof. Catherine Hayes	Committee Member, NREC-CT A
Ms Muireann O'Briain	Committee Member, NREC-CT A
Prof. David Brayden	Committee Member, NREC-CT A
Dr Darren Dahly	Committee Member, NREC-CT A
Prof. Gene Dempsey	Committee Member, NREC-CT A
Prof. Donal Brennan	Committee Member, NREC-CT A
Prof. Austin Duffy	Committee Member, NREC-CT A
Mr Gerald Eastwood	Committee Member, NREC-CT A
Ms Evelyn O'Shea	Committee Member, NREC-CT A
Ms Ayesha Carrim	Project Officer, National Office for RECs
Dr Jane Bryant	Programme Officer, National Office for RECs
Dr Susan Quinn	Programme Manager, National Office for RECs
Dr Emma Heffernan*	Project Officer, National Office for RECs

*Drafted minutes

Apologies: Dr Heike Felzmann, Dr John O'Loughlin, Ms. Erica Bennett, Prof. Patrick Dillon, Mr Gerard Daly, Ms Ann Twomey, Dr Geraldine Foley, Dr Dervla Kelly & Prof. John Wells

Quorum for decisions: Yes

Agenda

- Welcome & Apologies
- 23-NREC-CT-008
- 23-NREC-CT-002
- 23-NREC-CT-003
- 23-NREC-CT-004
- 23-NREC-CT-005
- 23-NREC-CT-006
- AOB

- The Chair welcomed the NREC-CT A.
  - The minutes from the previous NREC-CT A meeting on 07 December 2022 were approved.
  - The NREC Business Report was discussed and noted.

Applications

23-NREC-CT-008

Principal Investigator: Prof Orla Hardiman

Study title: A multicenter, open-label extension study to investigate the long-term safety of FAB122 in patients with Amyotrophic Lateral Sclerosis ADOREXT (ALS trial with Daily ORal Edaravone EXTension) study

EudraCT: 2022-003050-32

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 more information

- **Additional Information Required**

- The NREC-CT requested further detail is provided to the committee regarding the safety data review of the parent study by the Data Safety Monitoring Board (DSMB)
- The NREC-CT requested that the GP letter is amended to advise GPs how they can manage side effects in participants.
- The NREC-CT requested further detail on how treatment of ALS impairments will be managed by the MDT.
- The NREC-CT noted that consent is listed as being recorded verbally, and requested assurance that the correct supports are in place to ensure the consent is witnessed and recorded, in accordance with best practice / regulations.
- The NREC- CT noted that the study insurance certificate provided does not cover the whole trial duration and requests assurance that the trial will be adequately insured for the whole duration.

23-NREC-CT-002

Principal Investigator: Prof Noel Gerard McElvaney

Study title: Phase 2, Open-label Study Evaluating Efficacy and Safety of VX-864 in Subjects With Alpha-1 Antitrypsin Deficiency Who Have the PiZZ Genotype, Over 48 Weeks

EudraCT: 2022-002746-40

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 more information

- **Additional Information Required**

- Overall, the NREC found the application to be substandard and requested that the entire application undergoes substantial review and revision before being resubmitted for review.

- The NREC-CT request that all study documents are proofread for accuracy and are aligned accordingly.
- The NREC Application Form contained multiple errors, including sections of text referring to an unrelated study drug / trial and requested that this is corrected.
- The NREC-CT noted that the justification provided for the study was not clear and requested the following:
    - Detail on how this study fits in to the broader parent study.
    - The rationale for the sample size.
    - The rationale for the differing cohort divisions.
    - Detail on how participants will be assigned to trial arms.
- The NREC-CT requested that standard of care treatment for patients with Alpha-1 Antitrypsin Deficiency who have the PiZZ Genotype is provided.
- The NREC-CT requested justification for the stopping of augmentation therapy.
- The NREC-CT requested further detail is provided on the justification and evidence base for asking participants not to use hormonal contraceptives during the study.
- The NREC-CT requested that the number of participants expected to participate in the trial is clarified.
- The NREC-CT requested that the GP letter is amended to include a list of medications they are permitted to prescribe in dealing with side effects.
- The NREC-CT noted that non-English speakers are excluded from the study and requested that this is reconsidered, and that provisions are put in place to allow non-English participants to participate.
- The NREC-CT requested further detail is provided regarding the washout period during screening of PiZZ genotype and level of antigenic AAT and requested the following information is provided:
    - What symptoms can participants expect to experience during a washout period?
    - What are the inclusion criteria regarding level of antigenic AAT?
    - Is it possible a participants AAT level would meet the required level to allow them to participate without undergoing washout period?
    - How likely is it that a participant would consent, undergo washout and then not be suitable to participate?
- The NREC-CT requested further details is provided on the qualifications / experience of the person carrying out interviews.
- The NREC-CT noted that the issue of capacity is not addressed and requested that this is addressed in line with regulations / best practice.
- The NREC-CT deemed the PISCF as inadequate, as it did not provide the required clear and accessible information to participants and requested the following:
    - The purpose of the trial needs to be explained to participants.

    - The PiZZ genotype needs to be explained to participants in plain English.
    - The potential side effects of the trial drug need to be explained in plain language.
    - A description of how participants would choose which arm of the trial they would be assigned to.
    - A description of why optional blood samples are being taken.
    - The washout period needs to be explained to participants.
    - Details of exclusion criteria must be included.
    - The potential harm in pregnancy needs to be explained to participants.
    - Liver biopsies need to be referenced in relation to samples used in the study, in relevant documents.
    - The requirement for a liver biopsy needs to be highlighted to participants.
    - The implication of results of the drug and alcohol tests needs to be explained to participants.
    - Explicit advice on contraception options suitable for participants should be included for both females and males.
- The NREC-CT noted that an addendum PISCF was included and requested that relevant information is also integrated into the main PISCF.
- The NREC-CT requested that a detailed account of previous clinical trial experience of PI and evidence of up-to-date ICH-GCP is provided.
- The NREC-CT requested that further detail is provided on the facilities and equipment available at the Beaumont Hospital site.
- The NREC-CT noted that the consent for future research was too broad and not in line with regulations / best practice and requested that this is amended - i) consent for future use of samples should be provided on a separate consent form and not bundled with general consent to data processing ii) it should be made optional, and iii) consent can only be obtained where future use of samples and data is defined such that participants are fully informed, and/or iv) that an option is provided to enable participants to consent to be contacted to provide fresh consent to future use is provided in a separate consent form
- The NREC-CT requested further detail is provided on the use of optional blood samples.
- The NREC-CT commended the applicant for compensating participants for their time.
- The NREC-CT requested the following in relation to participant renumeration:
    - Details of how the Greenfire payment process is adapted to the Beaumont site.
    - Options are provided to participants who do not wish to use the credit card, and that this option is elucidated in the PISCF.
    - Further clarification is provided regarding the card fees and noted that participants should not be out of pocket as a result of trial participation.

- The renumeration process is clearly explained to participants in the PISCF

23-NREC-CT-003

Principal Investigator: Prof Trevor Duffy

Study title: A Phase 2/3, Randomized, Double-Blinded, PlaceboControlled, Parallel-Group, 2-Arm, Multicenter, Operationally Seamless Study to Evaluate the Efficacy, Safety, Tolerability, Pharmacodynamics, Pharmacokinetics, and Immunogenicity of Efgartigimod PH20 SC in Participants Aged 18 Years and Older With Active Idiopathic Inflammatory Myopathy

EudraCT: 2021-001277-23

Lead institution: Connolly 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 more information

- **Additional Information Required**

- The NREC-CT noted a discrepancy between the number of sites (3), and the number of potential participants expected to be recruited (Application Form states that 4 participants are expected to be recruited at 4 sites) and requested that it is corrected.
- The NREC-CT noted that the SSA for Our Lady's Hospital states that 'Dr Whelans Research team will included a dedicated Research Coordinator and Sub-Investigators and members of the Specialist Rheumatology Nurse who will preform the unblinded position of joint count assessor in this study' and requested further clarification on this.
- The NREC-CT noted that potential participants are advised that they are not allowed to take a complex list of medications / therapies for various periods prior to the start of the study and queried whether this advice could be simplified.
- The NREC-CT requested that the optional testing for interferon signalling in Phase 3 should be included in at the end of the consent form.
- The NREC-CT noted that the final section on personal data in the consent form needs to be reworded in line with regulations, as it is currently open ended, stating that personal data can be used "for any additional scientific research".
- The NREC-CT notes that the patient diary tables on side effects and medication changes are not written in an accessible way for patients. Terms such as 'BID' and ''sub-lingual' should not be used and should be stated in plain English for participants.

- The NREC-CT deemed that the inclusion of advertising of sponsors 'patient care items' e.g., mugs and stress balls are not appropriate and should be removed.
- The NREC-CT requested justification for the large amount of non-essential patient materials which are heavily branded by the sponsor. They deemed that the 'Flip book' seems a reasonable summary, and the brochure is helpful. They queried whether the "Inspirational Workbook" is necessary, as the volume of documentation may be a burden to the participant.
- The NREC-CT requested justification for the number of participant questionnaires which must be completed during the study, as they had concerns regarding participant burden.
- Furthermore, the NREC requested justification as to why both SF36 and EQ5 DL being used and queried whether the shorter SF12 could be used in lieu of SF36.
- The NREC-CT noted the high participant burden in relation to completing questionnaires and requested that a clear estimate of the projected length of time required to complete questionnaires is included in the PIL.
- The NREC-CT noted a number of grammatical / punctuation errors in the application which may distort meaning and requested that all documents are proofread for accuracy.
- The NREC-CT requested a more detailed account of the PI, Dr Trevor Duffy's experience in clinical trial management is provided.
- The NREC-CT noted that the DPIA is excellent and commended the inclusion of IDMC and an independent committee to review eligibility based on previous biopsy data.
- The NREC-CT requested that it is made explicit in the PIL to the participant in addition to the consent form that their data may be transferred to a third country where data protection laws are less strict.
- The NREC-CT noted that details on study financing are not included in the submission and requested confirmation that the required funding is in place.

23-NREC-CT-004

Principal Investigator: Prof. Jarushka Naidoo

Study title: A Phase III, Open-label, Randomised, Multicentre Study of Ceralasertib Plus Durvalumab Versus Docetaxel in Patients With Advanced or Metastatic Non-Small Cell Lung Cancer Without Actionable Genomic Alterations, and Whose Disease Has Progressed On or After Prior Anti-PD-(L)1 Therapy and Platinum-based Chemotherapy: LATIFY

EudraCT: 2022-000493-26

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 more information

- **Additional Information Required**

- The NREC-CT noted that the protocol is clearly written.
- The NREC-CT requested that the GP letter is amended to include the side effects of Arm B and information regarding contraception requirements for participants.
- The NREC-CT requested that it is made clear to participants how many participants are expected to be recruited to Irish sites.
- The NREC-CT noted that aspects of the study are well described in the protocol but are not well described in the PISCF in order to inform participants, including:
    - Details regarding the end-of-study
    - The potential for screen failures. The NREC-CT requested that this is explained the PISCF, so participants can understand why they may be deemed ineligible to take part in the trial following screening.
- The NREC-CT noted that clinically stable patients may continue to receive either or both drugs in Arm A beyond disease progression if they benefit – it is not clear what happens to participants in Arm B. The NREC requested that this information is added to the PISCF.
- The optional genetic study is not well explained in the protocol p 116, 8.7 and is not clearly explained to the participant in the PISCF – the NREC requested that a clear explanation is provided in the PISCF and that participants are advised that any future use will require further ethical approval, in line with regulations.
    - The NREC-CT requested that a clear description and explanation of the optional blood sampling genomic test is also included.
- The NREC-CT noted that the PISCF states that 'if you agree, an optional tumour sample will be taken at disease progression…' and requested that it is made clear to participants that this is an optional genetic research study, and that additional consent is required.
- The NREC-CT noted that participants are required to fast for 3 hours twice per day, for 7 days, every 4 weeks and requested that this requirement is made clearer in the PISCF and that an explanation is provided to participants as to why they need to fast.
- The NREC-CT noted that the side effects of Arm B (docetaxel) are not described in the PISCF and request that this is amended.
- The NREC-CT requested that the term 'clubbing' is explained in the PISCF.
- The NREC-CT requested clarification as to the requirements for use of contraceptives:
    - The PISCF states that male participants must use contraception for 6 months after the last dose, but female participants only need to use contraception for 3 months in Group A – can this difference be explained?

    - Can an explanation be given as to why female participants on Arm A must use contraception for 3 months after the last dose, but female participants on Arm B must use contraception for 6 months?
    - The NREC-CT noted that the PISCF does not explain that female participants of childbearing potential are required to undertake a urine pregnancy test every cycle of treatment and requested that this is added to the PISCF.

- The NREC-CT noted the frequent (electronic) completion of PROs via questionnaires / surveys by the participant is potentially a huge burden for some participants and requested that this is explained in the PISCF, and an estimated length of time required to complete these questionnaires / surveys is included in the description.
- The NREC-CT noted that participants are required to complete an electronic diary and queried whether a paper-based option would also be made available to participants.
    - The NREC-CT requested further detail on the supports available to participant should they encounter any technical issues with their supplied devices.
- The NREC-CT requested that all references to UK based entities such as the NHS are removed and replaced with Irish references, where appropriate.
- The NREC-CT request that a lay summary PIL is made available for participants, highlighting the pertinent issues that trial participation will involve, such as the fasting requirements. This NREC guide may be useful: https://www.nrecoffice.ie/pil-summary-guidance/
- The NREC-CT noted that PISCF documents would benefit from a review by PPI representatives.
- The NREC-CT noted that pg. 5 of the Application Form noted that permission to carry out the trial has not been agreed in all sites and requested confirmation that all sites have agreed permission to conduct the trial.
- The NREC-CT noted that the PISCF states that ‘any additional data generated from your biosamples will be stored as long as necessary’ and requested that is it clearly stated in the PISCF the maximum length of time this data will be retained for and that this aligned with data retention periods outlined in the DPIA.
- The NREC-CT requested further detail is provided to participants regarding reimbursement, including:
    - the process involved in submitting receipts and claiming reimbursement.
    - the level of reimbursement permissible per day
    - whether all meals are included
    - whether overnight accommodation can be claimed.
- The NREC- noted that the study insurance certificate provided does not cover the whole trial duration and requested assurance that the trial will be adequately insured for the whole duration and will cover all sites

23-NREC-CT-005

Principal Investigator: Dr Dearbhaile Collins

Study title: A Phase 3, Randomized, Placebo-Controlled, Double-Blind,Multicenter Trial of Selinexor in Maintenance Therapy After Systemic Therapy for Patients With p53 Wild-Type, Advanced or Recurrent Endometrial Carcinoma

EudraCT: 2022-002540-42

Lead institution: Cork 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 more information

- **Additional Information Required**

- The NREC-CT requested justification for the placebo double blind, considering the possible harms to the placebo group through not receiving Selinexor in Maintenance Therapy if it proves to be efficacious.
- The NREC-CT requested that is it made clear to participants in the PISCF the potential implications of being randomised to the placebo group.
- The NREC-CT requested clarification as to whether there is a Data Monitoring Committee in place.
- The NREC-CT noted that samples will be sent to Foundation Medicine in the US for analysis and requested the following information is added to the PISCF:
- the role of Foundation Medicine in the trial.
- clarification as to how the 324 genes will be tested.
- information on what results will be made available to participants.
- clarification as to what would happen if test results indicated unexpected results or gene alterations not related to the trial.
- The NREC-CT requested that all acronyms are explained to participants in the PISCF, such as FDA.
- The NREC-CT noted that the PISCF was quite long and requested that a lay summary sheet is made available for participants.
- The NREC-CT noted that the PISCF suggests that participants will be able to access the results on the study online, whereas the Application Form suggests that participants will

not have access to study results and requested that this is clarified and aligned across all documentation.

- If the study results are not to be made available to participants, the NREC-CT requested justification for this.
- The NREC-CT noted that the Application Form states that data will be retained for 25 years and other documents state 15 years and requested that maximum data retention periods are clarified and aligned across all documentation.
- The NREC-CT noted that participants are advised that their data will be anonymised rather than pseudonymised and requested that this is corrected in the PISCF, in line with the DPIA.
- The NREC-CT noted that samples are being sent to the US and requested further information regarding the data protection arrangements in place and that this elucidated in the PISCF.
- The NREC-CT requested confirmation that study funding is in place.
- The NREC-CT noted that the financial arrangements regarding costs involved in trial participation are not well described in the PISCF and requested the following:
- clarification as to who is paying for the trial drug.
- clarification as what costs participants may be potentially exposed to and how these will be paid for.
- clarification as to what happens to participants who are public patients and do not have private medical insurance.

23-NREC-CT-006

Principal Investigator: Dr Ciara McDonnell

Study title: ApproaCH: A Phase 2b, Multicenter, Double-Blind, Randomized, Placebo-controlled Trial evaluating Efficacy and Safety of Subcutaneous Doses of TransCon CNP Administered Once Weekly for 52 Weeks in Children with Achondroplasia followed by an Open Label Extension period

EudraCT: 2022-002954-25

Lead institution: Children's Health Ireland at Temple Street

- **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 more information

- **Additional Information Required**

- The NREC-CT noted variability between the protocol and the PISCF in reference to pregnancy testing (The PISCF states that females who can have children will be tested, the protocol states investigator discretion will be applied). The NREC requested the information is clarified and aligned.
- The NREC-CT requested that the term CNP is explained in the GP letter.
- The NREC-CT noted that recruitment procedures are not well described in the SSA and requested this is amended.
- The NREC-CT requested justification for the use of excipients in the placebo.
- The NREC-CT noted that the assent forms and passport were well written documents.
- The NREC-CT deemed that the PISCF for parent is relatively comprehensive. However, a number of clarifications are required:
- The detail re the constituents of the placebo is not clearly outlined and it does not explicitly state that they will receive the excipients and requested that this is explained to parents.
- An approximation of the volume to be administered should be included, and suggested a range based on volume could be helpful.
- The burden of the placebo must be very clearly explained to parents, particularly as they will be providing their child with regular injections, which may be placebo. This should also be explained to children.
- The NREC-CT noted that there is advice to children of ‘childbearing age’ and advised that investigator discretion should be applied, and this aspect discussed with parents where appropriate, with adequate support.
- The NREC-CT noted that the PISCF states that participants ‘may be compensated’ and requested that this is changed to ‘will be compensated’.

- AOB: