National Research Ethics Committee

NREC-CT Meeting

24 March 2023

Attendance

Name	Role
Dr Cliona McGovern	Chairperson, NREC-CT
Dr Jean Saunders	Deputy Chairperson, NREC-CT
Dr Enda Dooley	Committee Member, NREC-CT
Ms Muireann O'Brien	Committee Member, NREC-CT
Dr John Hayden	Committee Member, NREC-CT
Dr Mary McDonnell Naughton	Committee Member, NREC-CT
Dr Heike Felzmann	Committee Member, NREC-CT
Mr Gerard Daly	Committee Member, NREC-CT
Ms Paula Prendeville	Committee Member, NREC-CT
Ms Deirdre MacLoughlin	Committee Member, NREC-CT
Prof Seamus O'Reilly	Committee Member, NREC-CT
Dr Susan Quinn	Programme Officer, National Office for RECs
Dr Emma Heffernan*	Project Officer, National Office for RECs
Dr Joan Devin	HRB Postdoctoral Intern, National Office for RECs
Bryony Milner	Administration Assistant, National Office for RECs

Apologies: None

Quorum for decisions: Yes

Agenda

- Welcome & Apologies

- 23-NREC-CT-018
- 23-NREC-CT-021
- 23-NREC-CT-022
- 23-NREC-CT-024
- 23-NREC-CT-020
- 23-NREC-CT-023
- 23-NREC-CT-025
- 23-NREC-CT-034
- 23-NREC-CT-019
- 23-NREC-CT-026
- AOB

- The Chair welcomed the NREC-CT

Applications

23-NREC-CT-018

Principal Investigator: Professor Laurence Egan

Study title: A Phase 2b Randomized, Double-blind, Active-and Placebo-controlled, Parallel-group, Multicenter Study to Evaluate the Efficacy and Safety of Induction and Maintenance Combination Therapy with Guselkumab and Golimumab in Participants with Moderately to Severely Active Crohn's Disease – DUET-CD

EudraCT: 2021-003314-39

Lead institution: University Hospital Galway

- NREC-CT comments:

- The NREC-CT 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 clarity on the following aspects of the NREC application form:
    - Discontinuation: Pg. 7 states that if participants are not responding to measures at 24 weeks, they will have the opportunity for increased levels, including the placebo group. However, on pg. 9 it states if they have not responded they will discontinue from further intervention. Please provide clarification.
    - Numbers participating: This application specifies that there will be 650 participants globally (Application Form), however in the ICF it states approximately 715 participants will be involved. Please provide clarification.
    - Clarification of monitoring for suicidality assessment: The NREC-CT requested clarity is provided regarding the reasons for this monitoring (Section C.14, page 13/14), whether it is a feature of having Crohn's disease, or a risk attaching to either or both of the study drugs, and how this risk is highlighted to participants.
- The NREC-CT queried whether participants receiving placebo be switched to the study drug at the end of the trial if this has proven effective (ICF p2, End of trial information sheet. P21)
- The NREC-CT queried whether data will be shared via the e-diary, and if so, that this should be specified in the PISCF.
- The NREC-CT noted that the PISCF was long and complex and requested that a plain English executive summary of the salient points of the study is made available for participants. Please see https://www.nrecoffice.ie/pil-summary-guidance/.
- The NREC-CT requested revisions to the following aspects of the Main ICF:
    - Pg. 2, heading "Why have I been invited" – For clarity, numbers of patients at each Irish site (and/or total participants at Irish sites) should be shown here.
    - Pg. 6, re Home Diary - Not all participants may be comfortable using an electronic device. An option of paper-based diary should be clearly outlined here also.
    - Pg. 19, 'Other medications' "…some medications that affect your immune system." Please list these medications, or the more commonly prescribed ones as examples, for completion.
    - Pg. 23 – Who will have access to your personal data". Please note the NREC has no access to personal data, this reference should be removed, also in any other sections of the applicant material where it is mentioned.

- The NREC-CT noted the section for Participant ID to be recorded on the PISCF (p29) and commented that the inclusion of this information would make the PISCF a linking sheet and would compromise pseudonymisation of the participant data. The Committee requested that the Participant ID number is removed (or redacted if applicable) on copies of the PISCF and confirmation is provided that the Participant ID number will only to be recorded on the site/master file PISCF copy. Specifically, the Participant ID should not be recorded (or else redacted) on the copy that is placed in the medical record file, to maintain pseudonymisation of trial data.
- Pregnant partner ICF:
    - The NREC-CT requested clarification as to whether participating partner will first be asked for written consent for their pregnant partner to be contacted.
    - The NREC-CT noted that there are references to non-Irish jurisdictions (United Kingdom) and requests that all participant materials be adapted for Irish audience/law/sites.
- The NREC-CT noted that there are references to non-Irish jurisdictions (United Kingdom) and requests that all participant materials be adapted for Irish audience/law/sites.
- 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 and will cover all sites.

23-NREC-CT-021

Principal Investigator: Prof Kenneth McDonald

Study title: The impact of Empagliflozin on Left atrIal Volume and the feasibility of using Fitbit and mHealth to prescribe Exercise in non-diabetic Pre- Heart Failure

EudraCT: 2022-002650-48

Lead institution: University College Dublin

- NREC-CT comments:

- The NREC-CT 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 a 'thank you' event will be held for participants and requested that due to the potential impact on participant privacy and confidentiality, this event is reconsidered.
- The NREC-CT noted that the second last sentence in the GP letter is incomplete and requested that this is amended.
- The NREC-CT noted that participants will be provided with a Fitbit and will need to access smart phone during the trial and requested clarification as to if participants do not own a smartphone / tablet, will they be provided with one?
- The NREC-CT Noted that section C12 of the NREC Application Form states that *'. Some patients may feel claustrophobic during the scan which could lead to the inability to complete the test'* and requested clarification as to what would happen should a participant be unable to undertake an MRI scan.
- The NREC-CT noted that pg. 3 of the PISCF states that participants are to undergo genetic testing and requested that clarity is provided in the PIS/ICF regarding genetic testing:
    - The genetic testing requested must be restricted and defined.
    - The type of genetic testing to be undertaken must be clearly explained to participant,
    - Explicit consent for genetic testing should be obtained in an optional genetic PISCF.
- The NREC-CT noted that pg. 8 of the PISCF states that the study drug has a minor influence on the ability to drive and operate machines and requested that participants should be given more detailed information on potential symptoms that would impair their ability to drive or operate machinery. The NREC-CT requested that if participants experience these symptoms, they should be advised to report it to their study doctor who will assess their safety and ability to drive or use machinery.
- The NREC-CT requested that SSAs are provided for The Conway Institute at UCD, St Vincent's Private Hospital and St Vincent's University Hospital
- The NREC-CT noted that the CV for Prof Keith McDonald is lacking in detail and requested a more comprehensive CV outlining previous clinical trial experience is provided for review.
    - The NREC-CT requested that evidence of up-to-date ICH-GCP certification is provided for Prof Keith McDonald
- The NREC-CT requested that CVs are provided for Dr Bethany Wong and Prof Mark Ledwidge outlining details of previous clinical trial experience and evidence of up-to-date ICH-GCP certification.

- The NREC-CT noted that data will be transferred between St Michael's Hospital and the Conway Institute at UCD and requested further detail provided on how this data will be transferred.
- The NREC-CT noted that the PI Institutional address is listed as The Heartbeat Trust and requested clarification as to the role of The Heartbeat Trust in the trial.
- The NREC-CT noted that the PISCF is seeking blanket consent for future use of samples / data, for unspecified purposes, without further consent. This type of consent not in line with best practice, the Declaration of Taipei 2016 and not in compliance with the Data Protection Act 2018 (Section 36(2) (Health Research) Regulations 2018), where informed participant consent is a mandatory safeguard. The NREC-CT requests i) that consent for future use of samples is provided on a separate consent form and not bundled ii) is 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 is provided in a separate consent form.
    - The NREC-CT request confirmation that subsequent research ethics review will be sought for specific research once clearly defined.
- The NREC-CT noted the references is made to NREC being able to access participants biological material and requested that that this is removed from the Application Form and PISCF
- The NREC-CT requested that the maximum length data will be retained is clearly stated across and aligned across all documentation.
- The NREC-CT noted that the study insurance certificate provided does not cover the whole trial duration and requested that the insurance policy is updated to provide cover for the full duration of the study.
- The NREC-CT deemed that the maximum stated compensation for each trial visit is €20 which seems very low in an Irish context and may leave participants out of pocket. The NREC-CT requested confirmation that participants will be reimbursed for all reasonable out of pocket expense.
    - 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 travel and meals are included, whether overnight accommodation can be claimed.

23-NREC-CT-022

Principal Investigator: Dr Jarushka Naidoo

Study title: A multicentre, single-arm phase II trial of adagrasib in patients with KRASG12C-mutant NSCLC, including the elderly (?70 years) or patients with poor performance status

EudraCT: 2022-002736-31

Lead institution: Beaumont Hospital

- NREC-CT comments:

- The NREC-CT 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 contraception use is required for 6 months after the trial end, and requested clarity and justification is provided for this requirement.
- The NREC-CT noted that there is inconsistency in the number of patients due to be recruited in Ireland, the NREC application form states 8 on 6 sites, however the PIL states 12 patients. Please clarify the number of patients being recruited.
- The NREC-CT requested clarification as to why the pregnancy in a trial participant's partner is not considered an SAE.
- The NREC-CT requested that clear information is provided upfront to male study participants to advise them to inform their partner immediately regarding their participation in the trial, the requirement for contraception, and the potential risks.
- The NREC-CT requested that the PIL at page 10 'Information for women taking part in the ADEPPT Study' be adjusted, so that the statement 'The study treatment could reduce fertility' moves from the end of the section to the end of the first bullet point of the section.
    - The NREC-CT also requested that the Pregnant Partner be advised to seek advice from her own doctor in the light of the details provided.
- The NREC-CT requested that further information /a short summary regarding the details of the trial should be included in the Pregnant Partner ICF.
- The NREC-CT considered the layout of the consent section in the form 'Withdrawal of IC', (Page 2, top of page), to be unclear (3 consent boxes for 4 options) and request that this should be revised, including improvement to spacing, for participant clarity.
- The NREC-CT noted that the information provided under 'Data Protection in genetic research' is potentially confusing with the present wording appearing to conflate 'data

loss' and 'data disclosure' and requested that the wording is reviewed so the intended meaning is clear to the participant.

- The NREC-CT requested further clarity/explanation is provided to participants regarding the statement “In addition, results from genetic examinations must be disclosed under certain conditions before a life insurance policy is taken out.” (PISCF Master, page 12 of 21).
- The NREC-CT noted that participants will not be reimbursed for trial participation. The NREC-CT requested that to ensure equitable access to clinical trials across all socio-economic groups that trial participants are reimbursed for reasonable out-of-pocket expenses. The NREC-CT requested the following:
    - A detailed description of the trial related expenses participants are permitted to claim (such as travel, parking, refreshments, etc) is provided in the PIL, so participants are reassured that trial participation will not leave them out-of-pocket.
    - Details on the process involved in claiming expenses and how and when they will be reimbursed.
    - Additionally, the NREC-CT requests that a participant should be permitted to bring a companion for these visits, and that this companion should also be eligible for reimbursement.

23-NREC-CT-024

Principal Investigator: Prof John Crown

Study title: A Phase 1/1b Open-Label, Multicenter Study to Investigate the Safety, Tolerability, Pharmacokinetics, and Antitumor Activity of KIN-2787 in Participantswith BRAF and/or NRAS Mutation-positive Solid Tumors

EudraCT: 2021-005389-16

Lead institution: St Vincent's University Hospital

- NREC-CT comments:

- The NREC-CT 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 that the terms and conditions (charter) of the drug review committee was not included in the application and requested that this is provided for review by the committee.
- The NREC-CT noted that this study will take place in SVUH and requested that the sponsor considers reaching out to the oncology community around the country to alert them to this study and ensure equity in access.
- The NREC-CT noted that a number of superfluous documents were submitted for review, such as out of date UK GMP certificates, documents in French and German and requested clarification as to why these were included in the submission for NREC review. The NREC-CT requested the documentation submitted is thoroughly checked by appropriate personnel before submission for review.
- The NREC-CT noted that the PISCF is seeking blanket consent for future use of samples / data, for unspecified purposes, without further consent. This type of consent not in line with best practice, the Declaration of Taipei 2016 and not in compliance with the Data Protection Act 2018 (Section 36(2) (Health Research) Regulations 2018), where informed participant consent is a mandatory safeguard. The NREC-CT requests i) that consent for future use of samples is provided on a separate consent form and not bundled ii) is 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 is provided in a separate consent form.
    - The NREC-CT request confirmation that subsequent research ethics review will be sought for specific research once clearly defined.
- The NREC-CT noted that pg. 14 of the PISCF states that participants are to undergo genetic testing and requested that clarity is provided in the PIS/ICF regarding genetic testing:
    - The genetic testing requested must be restricted and defined.
    - The type of genetic testing to be undertaken must be clearly explained to participant,
    - Explicit consent for genetic testing should be obtained in an optional genetic PISCF.
- The NREC-CT noted that the consent material layout is not in line with best practice and requests that the applicant provides participants with a layered approach to consent. Please see HSE National Policy for Consent in Health and Social Care Research, (2022) https://hseresearch.ie/publications/

- The NREC-CT noted that the PISCF states that participants ‘may’ be reimbursed for reasonable trial related expenses and requested that this is amended to ‘will’ be reimbursed.
- The NREC-CT noted that details of renumeration available to participants for trial related expenses is not well described in the PISCF and requested further detail is provided to participants regarding reimbursement, including:
    - the level of reimbursement permissible per day,
    - the process involved in submitting receipts and claiming reimbursement,
    - whether all meals are included,
    - whether overnight accommodation can be claimed
    - whether a companion’s expenses can also be claimed.

23-NREC-CT-020

Principal Investigator: Dr Niall Patrick Conlon

Study title: A Phase II, Double-blind, Placebo-controlled, Randomized, Dose-ranging, Parallel Group Study to Evaluate the Safety and Efficacy of PHA-022121 Administered Orally for Prophylaxis Against Angioedema Attacks in Patients with Hereditary Angioedema due to C1-Inhibitor Deficiency (Type I or Type II)

EudraCT: 2021-000227-13

Lead institution: St. James’s Hospital

- NREC-CT comments:

- The NREC-CT 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 clarity on the placebo-controlled design. The justification provided is the lack of oral route alternatives for blinding (NREC application form C.9), but the application also mentions an oral medicine Orladeyo is licensed (e.g. NREC application form C.6), The NREC-CT requested that the applicant clarify this comment in relation to the placebo justification.

    - Regarding informing participants of same, the NREC-CT noted that Orladeyo is also only briefly listed once on the PIL and primary attention is given to medications that are administered in other ways. Given that the stated rationale for the study is the need for an oral prophylactic, provision of additional information on Orladeyo would also be merited in the PIL. It should be made explicit for participants whether using Orladeyo is a potential alternative to study medication, and what its risks consist in (outlined for other medication on p.7 of the PIL).
- Study duration: The trial duration is stated as 6 months from May to November, in DPIA approval document (document 7982), but this does not align with the protocol description of minimum 48 weeks (12 Weeks (stage 1) + “at least” 24 Weeks (stage 2), plus potentially 8 weeks screening and 4-week follow-up, described as 48 weeks total) per patient. The NREC-CT requested that the applicant please clarify.
- The NREC-CT queried how patients who are on pre-existing prophylaxis therapy are discontinued from that treatment. The NREC-CT noted that patient facing materials inform patients they must be willing to stop these medications to partake, but all the HCP facing referral materials assume the patient has already discontinued these medications. The NREC-CT requested that the applicant please clarify arrangements to support patients with this decision and harmonise all documentation. The PI should encourage a dialogue with the primary carer about this decision, rather than a patient isolated decision. Further references are provided below for context:
    - PIL (p3/19) language assumes patient has already stopped taking prophylaxis medication and can’t participate if they currently are on prophylaxis medication- however the protocol says those that are dissatisfied with current prophylaxis therapy can partake (after a washout period).
    - Patient invitation letter/recruitment brochure says eligible participants must ’be willing to stop taking any current medications for HAE prevention’.
    - PI to physician letter says they must already have ceased prophylaxis medications,
    - The HCP brochure for recruitment describes patients who have already ceased prophylaxis medications due to adverse events or lack of efficacy as eligible (but doesn’t mention those that are willing to give up existing treatment, and how they should be supported)
- The NREC-CT deemed that overall sufficient and clearly presented information is provided to the participant. The participant’s understanding is supported by the provision

of well-developed additional information materials, such as ICF summary (1.3c) and ICF tool (1.16b).

- The NREC-CT requested that all branding is removed from participant materials including tote bags as this may impact on participation confidentiality by identifying them as a participant in this study.
- The NREC-CT noted that the last table on p.19 PIL/ICF is not shown in full and requested that this is amended.

23-NREC-CT-023

Principal Investigator: Dr Jarushka Naidoo

Study title: A Phase 3 Study to Evaluate Zimberelimab (AB122) Combined with Domvanalimab (AB154) Compared to Pembrolizumab in Front-Line, PD-L1-High, Locally Advanced or Metastatic Non-Small Cell Lung Cancer

EudraCT: 2020-003562-39

Lead institution: Beaumont Hospital

- NREC-CT comments:

- The NREC-CT 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 PISCF was long and complex and requested that a plain English executive summary of the salient points of the study is made available for participants. Please see https://www.nrecoffice.ie/pil-summary-guidance/
- The NREC-CT noted that some of the language used across the four submitted PISCFs is overly complex and dense and requested that the PISCFs are revised to be more patient-friendly and simplified into plain language for a lay audience with medical terminology explained or simplified.
- The NREC-CT requested that NREC having access to coded data, is removed from the PISCF.
- The NREC-CT requested that the reference to the US FDA is removed from Section 1.1, page 1 of the Main PISCF and replaced with Irish / EU references, where appropriate.

- The NREC-CT noted that section 5.1, page 14 of the Main PISCF states that if a participant's test results are positive for HIV or Hepatitis, that the researchers must report this to the government by law and requested that this is corrected to the Director of Public Health/Medical Officer of Health for the area of residence of the participant.
- The NREC-CT requested removal of the term 'general research' from Section 12.1 Biological Sample Research, page 10 of the Pre-screening PISCF as it is too broad.
- The NREC-CT noted that the Optional Consent for Additional Research states that 'The specific nature of the research will vary and is not known at this time but may include looking for biomarkers to better understand your disease, to understand how the study drug(s) work(s) or for general research. This additional research may also include genetic or genomic testing, which may involve sequencing of your genetic information' and requested that an option is provided to enable participants to consent to be contacted in the future once the research is defined.
    - The NREC requested confirmation that subsequent research ethics review will be sought for specific research once clearly defined.
- The NREC-CT requested removal of all references to trial arms no longer recruiting, are removed from the Treatment Beyond Progression PISCF.
- The NREC-CT noted that a 'legally authorised representative's' (LAR) signature is included in all four submitted PISCFs. As there was no reference to participants that lack-decision making capacity in the application form, the NREC-CT queried under what circumstances would legally acceptable/authorised representative sign the PISCF's. The sponsor should ensure that any involvement of a representative or proxy individual in the consent protocol, is in accordance with all applicable legislative frameworks. Specifically, under Irish data protection law, a legally authorised representative cannot lawfully consent on behalf of another individual for the processing/use of personal data for health research but can provide assent as a safeguard. The sponsor should give consideration to
    - procedures that can be implemented to seek assent from the legally designated individual, or a proxy individual who understands the will and preference of the participant.
    - the HSE-National-Policy-for-Consent-in-Health-and-Social-Care-Research
    - the Health Research Regulations
- The NREC-CT noted the inclusion of an impartial witness signature on the ICF and requested that a statement is added to clarify that the impartial witness is not consenting on the participant's behalf, and that signed participant consent is still required, where possible. Where a participant cannot sign for themselves, the statement should further clarify that the impartial witness is documenting the participants consent on their behalf.

- The NREC-CT noted that section F.3, pages 34 and 35 of the NREC Application Form state that a wide range of service providers and affiliated companies are permitted to access the healthcare records and personally identifying data of participants. This is in contradiction with page 18 of the Main PISCF, which states that only 'The Study Site and the principal investigator(s) and/or sub-investigator(s) will have access to your personal data (un-coded)'. The NREC-CT requested confirmation that access to personally identifiable data is restricted to the Study Site and investigators, and that 3rd party companies have limited access to coded data only.
- The NREC-CT noted that section 11.1, of the PISCF states that while participants may be reimbursed for their costs, 'prior written approval from the Sponsor' is required'. The NREC-CT considers this is an unduly burdensome process for a participant and requested clarification of the overall reimbursement process.
    - The NREC-CT requested further detail is provided to participants regarding reimbursement, including:
    - the level of reimbursement permissible per day
    - the process involved in submitting receipts and claiming reimbursement.
    - whether all meals are included
    - whether overnight accommodation can be claimed
    - whether a companion's expenses can also be claimed.

23-NREC-CT-025

Principal Investigator: Prof Orla Hardiman

Study title: A Phase 1-3 Study to Evaluate the Efficacy, Safety, Pharmacokinetics and Pharmacodynamics of Intrathecally Administered ION363 in Amyotrophic Lateral Sclerosis Patients with Fused in Sarcoma Mutations (FUS-ALS)

EudraCT: 2020-005522-28

Lead institution: St James's Hospital

- NREC-CT comments:

- The NREC-CT 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 have concerns in relation to the design of Part 1 of this study for the placebo group, given the risks associated with repeated lumbar punctures and intrathecal drug administration.
    - The NREC-CT requested additional justification for the double-blind study design, and why an open-label design was not considered appropriate for this part.
    - The NREC-CT requested clarification on whether Patient and Public Involvement (PPI) was sought at any point. It is the view of the NREC-CT that it would be helpful to understand the view of the Amyotrophic Lateral Sclerosis (ALS) community on the study procedures and overall trial design.
- The NREC-CT requested clarification as to feasibility of a participant taking part the trial when using a ventilator and have concerns in relation to the ventilator diary for placebo participants, and requested clarification as to why an unwell ventilated participant would continue to receive a placebo via lumbar puncture.
- The NREC-CT requested that the consenting process for 16- to 18-year-olds is carried out in accordance with policy and best practice, with assent / consent forms amended accordingly. Specifically, research participant aged 16 years or older can legally consent to their own participation in the clinical trial but can only provide assent the processing of their personal data if they are aged under 18 years. Please see HSE-National-Policy-for-Consent-in-Health-and-Social-Care-Research.
- The NREC-CT noted that a 'legally authorised representative' signature is included on the main PISCF on behalf of a person that lacks decision-making capacity. As there was no reference in the application form to participants that lack-decision making capacity, the NREC-CT queried under what circumstances would legally acceptable/authorised representative sign the PISCF's. The sponsor should ensure that any involvement of a representative or proxy individual in the consent protocol, is in accordance with all applicable legislative frameworks. Specifically, under Irish data protection law, a legally authorised representative cannot lawfully consent on behalf of another individual for the processing/use of personal data for health research but can provide assent as a safeguard. The sponsor should give consideration to:
    - procedures that can be implemented to seek assent from the legally designated individual, or a proxy individual who understands the will and preference of the participant.
    - the HSE-National-Policy-for-Consent-in-Health-and-Social-Care-Research.
    - the Health Research Regulations

- The NREC-CT considered the Main PISCF to be comprehensive but lengthy and requested that a lay summary PIL is made available for participants. This NREC guide may be useful: https://www.nrecoffice.ie/pil-summary-guidance
- The NREC-CT noted that section 6 of the Main PISCF describe the risks related to a lumbar puncture procedure for participants and requested inclusion of the risk that the lumbar puncture may be unsuccessful.
- The NREC-CT requested that any risks related to the frequency of the lumbar punctures are explained in the PISCF.
- The NREC-CT noted the inclusion of a C-SSRS and requested the following:
    - details of provisions in place to support participants, should the questionnaire indicate a mental health issue.
    - Acknowledgement in the PIL/ICF that completion of this assessment may cause distress, and clarification as to the pathway of care and referral offered to participants displaying a mental health issue.
- The NREC-CT noted that future use of samples is not sufficiently explained in the PISCF (main and assent) and not constitute broad informed consent, as required under the Health Research Regulations. The NREC-CT request that this is amended as follows: - 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 request confirmation that subsequent research ethics review will be sought for specific research once clearly defined.
- The NREC-CT noted that section 4.4, page 11 of the Main PISCF states that the participant may request that all saved blood and CSF samples be destroyed, with no optional further testing. The NREC-CT requested clarification on what happens to these samples and related participant data in the event of a participant's death during the study.

23-NREC-CT-034

Principal Investigator: Prof Orla Hardiman

Study title: A Phase 2, Multicenter, Randomized, Double-Blind, Placebo-Controlled Study Evaluating Safety and Efficacy of CORT113176 (Dazucorilant) in Patients with Amyotrophic Lateral Sclerosis (DAZALS)

EudraCT: 2021-005611-31

Lead institution: Beaumont Hospital

- NREC-CT Decision:

Favourable with conditions

- Conditions of Approval

- An additional statement in the PISCFs advising participants that their data will be transferred outside the EU (to the United Kingdom).
- Confirmation as to the maximum length of time samples /data will be retained for and that this is aligned across all documentation.
- Details of the sub-study (not being conducted in Ireland) is removed from the PISCF.
- That the cover letter is signed

23-NREC-CT-019

Principal Investigator: Prof Sean Kennelly

Study title: A multicentre, randomized, double-blind, placebo-controlled, parallel- group phase 3 study to evaluate the safety and efficacy of masitinib as add-on therapy in patients with mild to moderate Alzheimer's disease, treated with standard of care: cholinesterase inhibitors, memantine

EudraCT: 2021-002179-21

Lead institution: St James's Hospital

- NREC-CT comments:

- The NREC-CT B 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 this submission was of extremely poor quality with multiple inconsistencies across documents, syntax and spelling errors in the NREC Application Form, and a poor PISCF. The NREC-CT requested that all documentation is thoroughly proofread and revised accordingly.

- The NREC-CT noted multiple syntax and spelling errors in the NREC Application Form and requested that this document is proofread for accuracy and errors corrected.
- The NREC-CT noted conflicting information provide in the NREC Application Form (E7 & E10) regarding non-English speakers and requested that this is corrected and details as to the provisions in place for inclusion of non-English speakers is clearly stated.
- The NREC-CT requested that D8 of the NREC Application Form regarding inclusion women of childbearing potential in the trial is corrected.
- The NREC-CT noted that pg. 4 of the PISCF refers to urinary cytology at weeks 48 and 96 and considering the stated length of the trial is 48 weeks requested that this is clarified in the PISCF.
    - Furthermore pg. 7 of the PISCF states that urinary cytology samples will be taken at screening and week 24, contradicting pg. 4 of the PISCF and requested that this is clarified in the PISCF.
- The NREC-CT noted that participants lacking decision making capacity will be included in the trial and requested clarity regarding the consent process. Specifically, a 'legally authorised representative' cannot lawfully consent for the processing of personal data for health research, on behalf of a participant who lacks decision-making capacity to consent but can provide assent as a safeguard. The applicant must therefore specify whether a consent declaration from the HRCDC will be applied for to ensure compliance with the Regulations, or rationale as to why a consent declaration is not required.
- The NREC-CT noted that section E13 of the NREC Application Form states that the identification of a legal representative would be carried out 'by the legal team in the hospital' and requested clarification regarding this statement and how this is determined in line with Regulations.
- The Committee queried under what circumstances would legally acceptable/authorised representative sign the PISCFs. The sponsor should ensure that any involvement of a representative or proxy individual in the consent protocol, is in accordance with all applicable legislative frameworks. The sponsor should give consideration to
    - procedures that can be implemented to seek assent from the legally designated individual, or a proxy individual who understands the will and preference of the participant.
    - the HSE-National-Policy-for-Consent-in-Health-and-Social-Care-Research.
    - the Health Research Regulations
- The NREC-CT noted that the PISCF is of poor quality and requested the following:
    - the PISCF is thoroughly revised to be more patient-friendly and simplified into plain language for a lay audience.
    - the study drug side effects be clearly laid out in the PISCF and the NREC Application Form.
    - medical terminology, such as 'menarche' and 'concomitant' are described in plain English.

- The NREC-CT requested that a plain English executive summary of the salient points of the study is made available for participants. Please see https://www.nrecoffice.ie/pil-summary-guidance/
- The NREC-CT noted that the consent material layout is not in line with best practice and requests that the applicant provides participants with a layered approach to consent. Please see HSE National Policy for Consent in Health and Social Care Research, (2022) https://hseresearch.ie/publications/
- The NREC-CT noted that a pregnant partner consent form was not included in the application and requested that this is provided for committee review.
- The NREC-CT noted that the GP letter asks GPs to inform study staff should the participant become pregnant and requested that consent to their GP sharing information about them is listed in the ICF.
- The NREC-CT noted that the participants caregiver is asked to sign the consent form and requested clarification as to why a person's care giver is signing the consent form (If caregivers are participating in the trial, they will need to complete a separate PISCF, which will need to be provided for NREC review).
- The NREC-CT noted that the PISCF is seeking blanket consent for future use of samples / data, for unspecified purposes, without further consent. This type of consent not in line with best practice, the Declaration of Taipei 2016 and not in compliance with the Data Protection Act 2018 (Section 36(2) (Health Research) Regulations 2018), where informed participant consent is a mandatory safeguard. The NREC-CT requests i) that consent for future use of samples is provided on a separate consent form and not bundled ii) is 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 is provided in a separate consent form.
    - The NREC-CT request confirmation that subsequent research ethics review will be sought for specific research once clearly defined.
- The NREC-CT noted that participants are advised to contact NREC regarding additional study information and requested that this is removed.
- The NREC-CT noted the section for Participant ID to be recorded on the PISCF and commented that the inclusion of this information would make the PISCF a linking sheet and would compromise pseudonymisation of the participant data. The Committee requested that the Participant ID number is removed (or redacted if applicable) on copies of the PISCF and confirmation is provided that the Participant ID number will only to be recorded on the site/master file PISCF copy. Specifically, the Participant ID should not be recorded (or else redacted) on the copy that is placed in the medical record file, to maintain pseudonymisation of trial data.
- The NREC-CT requested that a CV is provided for Prof Leroi detailing relevant clinical trial experience and evidence of up-to-date ICH-GCP certification.
- The NREC-CT requested clarification of the role of 'Alexion' in the trial.
- The NREC-CT noted that details of remuneration available to participants for trial related expenses is not well described in the PISCF and requested further detail is provided to participants regarding reimbursement, including:

- the level of reimbursement permissible per day,
- the process involved in submitting receipts and claiming reimbursement,
- whether all meals are included,
- whether overnight accommodation can be claimed
- details as to the compensation arrangement in place for the study partner

23-NREC-CT-026

Principal Investigator: Prof Orla Hardiman

Study title: A Multicenter, Open-label Extension (OLE) Study to Evaluate the Safety, Pharmacodynamics, and Clinical Effects of WVE-004 in Patients with C9orf72-associated Amyotrophic Lateral Sclerosis (ALS) and/or Frontotemporal Dementia (FTD)

EudraCT: 2022?002267?29

Lead institution: St James's Hospital

- NREC-CT comments:

- The NREC-CT 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 participants lacking decision-making capacity will be included in the trial and requested clarity regarding the consent process. Specifically, a ‘legally authorised representative’ cannot lawfully consent for the processing of personal data for health research, on behalf of a participant who lacks decision-making capacity to consent but can provide assent as a safeguard. The applicant must therefore specify whether a consent declaration from the HRCDC will be applied for to ensure compliance with the Regulations, or rationale as to why a consent declaration is not required.
- The sponsor should ensure that any involvement of a representative or proxy individual in the consent protocol, is in accordance with all applicable legislative frameworks. The sponsor should give consideration to:
    - procedures that can be implemented to seek assent from the legally designated individual, or a proxy individual who understands the will and preference of the participant.

    - the HSE-National-Policy-for-Consent-in-Health-and-Social-Care-Research.
    - the Health Research Regulations
- The NREC-CT noted that section E11 of the application form states that the investigator would be responsible for assessing capacity, annually.
    - The NREC-CT request that the decision-making capacity should be assessed by a qualified individual who is independent of the study team.
    - The NREC-CT request confirmation that decision-making capacity will be assessed more regularly than once a year, as proposed.

- The NREC-CT noted that pg. 21 of the PISCF states that 'In some cases, genetic research may give rise to statutory or contractual obligations which require you to disclose the results of your genetic analysis to third parties (such as insurance companies or employers). However, you will not be contacted by the Sponsor or any future researchers with the results of any analysis. There are laws to protect against your future requests for insurance being affected by providing your consent to the future use of your samples and Coded Data as set out in this consent form' and requested that
    - clarification is provided to participants as to the statutory or contractual obligations which require disclosure of results of their genetic analysis to third parties.
    - clarification as to which 3rd parties this information will be disclosed to
    - justification as to why participants will not be themselves provided with this information, as it could impact their health care needs.
- The NREC-CT noted the inclusion of a C-SSRS and requested the following:
    - details of provisions in place to support participants, should the questionnaire indicate a mental health issue.
    - Acknowledgement in the PIL/ICF that completion of this assessment may cause distress, and clarification as to the pathway of care and referral offered to participants displaying a mental health issue.
- The NREC-CT noted that the PISCF was long and complex and requested that a plain English executive summary of the salient points of the study is made available for participants. Please see https://www.nrecoffice.ie/pil-summary-guidance/.
- The NREC-CT noted the use of medical terminology and acronyms 'Antisense Oligonucleotide', 'Intrathecal', 'Dynamometry', 'Immunogenicity' in the PISCF and requested that medical terminology / acronyms are explained to participants using plain English.

- The NREC-CT noted that pg. 20 of the PISCF is seeking blanket consent for future use of samples / data, for unspecified purposes, without further consent. This type of consent not in line with best practice, the Declaration of Taipei 2016 and not in compliance with the Data Protection Act 2018 (Section 36(2) (Health Research) Regulations 2018), where informed participant consent is a mandatory safeguard.
    - The NREC-CT requests that consent for future use of samples is i) provided on a separate consent form and not bundled and ii) 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 is provided in a separate consent form.
    - The NREC request confirmation that subsequent research ethics review will be sought for specific research once clearly defined.
- The NREC-CT requested that clarity is provided in the PISICF regarding genetic testing. The genetic testing requested must be restricted and defined, explained clearly to the participant, with explicit consent obtained for genetic testing requested in the ICF.
    - The NREC requested confirmation that subsequent research ethics review will be sought for specific research once clearly defined.
- The NREC-CT noted that healthy volunteers taking part in the MRI dummy run scan will be followed up should their MRI reveal any unexpected finding and requested that the healthy volunteers GP is also informed of same, and that this is clearly explained in the PISCF.
- The NREC-CT noted the section for Participant ID to be recorded on the PISCF and commented that the inclusion of this information would make the PISCF a linking sheet and would compromise pseudonymisation of the participant data. The Committee requested that the Participant ID number is removed (or redacted if applicable) on copies of the PISCF and confirmation is provided that the Participant ID number will only to be recorded on the site/master file PISCF copy. Specifically, the Participant ID should not be recorded (or else redacted) on the copy that is placed in the medical record file, to maintain pseudonymisation of trial data.
- The NREC-CT noted that pg. 16 of the PISCF and pg. 3 of the Study Partner ICF – What will happen if you change your mind: states that “It may be helpful if you could explain your reasons” and requested that this is amended. As per the HSE National Policy for Consent in Health and Social Care Research (Section 2.2.6) participants must have the right to withdraw consent at any time without needing to provide a reason, and this right must be set out in an unambiguous and unconditional manner.

- The NREC-CT requested that it is explained to study partners in the study partner PISCF the impact on the study participant, should they prematurely withdraw from their consent.
- The NREC-CT requested that further detail on the standard of care for patients with C9orf72-associated Amyotrophic Lateral Sclerosis (ALS) and/or Frontotemporal Dementia (FTD) is provided in the PISCF.
- The NREC-CT noted that the Pregnant partner PISCF states that data will be retained for 25 years and requested details of the processes in place for obtaining the consent of the child, on reaching the age of 18 years, for the processing/retention of their personal data.
- The NREC-CT noted that pg.1 of the Pregnant partner PISCF states that 'with regard to the data for your child after the delivery, both parents make the decision together as custodians'. Note: Under Irish law, where the biological parents are not married, the mother is the legal guardian of the child. The NREC-CT requested that the PISCF should state that paternal consent is required where the biological parents are unmarried. Please see the HSE-National-Policy-for-Consent-in-Health-and-Social-Care-Research.
- The NREC-CT noted that pg. 28 of NREC Application Form states that 'The insurance will not cover damage due to a risk which participants were informed in the Participant Information Sheet' and requested that this is clarified.
- The NREC-CT noted that provisions are in place to provide compensation to participants and their carer/partner for travel and requested that participants are also compensated for reasonable out of pocket expenses, such as meals or overnight accommodation should it be required, and that this is elucidated in the relevant PISCFs.
- The NREC-CT requested clarification as to how the study partner will be reimbursed i.e. will they be reimbursed directly or through the trial participant and that this is clarified in the PISCF. If Scout Clinical require personal information from the study partner, then this needs to be elucidated in the study partner PISCF.
-

- AOB: