National Research Ethics Committee

NREC-CT Meeting

23rd October 2024

Attendance

Name	Role
Dr Cliona McGovern	Chairperson, NREC-CT B
Dr John Hayden	Deputy Chairperson, NREC CT-B
Colm O'Donnell	Deputy Chairperson, NREC-CT B
Ms Serena Bennett	Committee Member, NREC-CT B
Dr Åine de Róiste	Committee Member, NREC-CT B
Dr Karina Halley	Committee Member, NREC-CT B
Prof. Michaela Higgins	Committee Member, NREC-CT B
Ms Jasmine Joseph	Committee Member, NREC-CT B
Dr Ciaran Lee	Committee Member, NREC-CT B
Dr Andrew Lindsay	Committee Member, NREC-CT B
Dr Niall McGuinness	Committee Member, NREC-CT B
Prof. Seamus O'Reilly	Committee Member, NREC-CT B
Ms Evelyn O'Shea	Committee Member, NREC-CT B
Dr Jean Saunders	Committee Member, NREC-CT C
Dr Emily Vereker	Acting Head, National Office for RECs
Ms Patricia Kenny	Project Officer, National Office for RECs
Dr Jane Bryant	Project Officer, National Office for RECs
Dr Laura Mackey	Programme Officer, National Office for RECs
Dr Susan Quinn	Programme Manager, National Office for RECs
Ms Aileen Sheehy	Programme Manager, National Office for RECs

Mr Ciaran Horan*	Administrative Assistant, National Office for RECs

Apologies: Serena Bennett, Prof John Wells, Ann Twomey

Conflicts of Interest: Dr Michaela Higgins declared a Conflict of Interest with 2023-505650-17-00 study, and was not present at the meeting during the discussion for this study.

Quorum for decisions: Yes

Agenda

- Welcome & Apologies
- 2024-516440-25-00
- 2022-502282-24-00
- 2023-505766-28-00
- 2023-506269-78-00 SM-2
- 2022-500758-41-00 SM-17
- 2023-505650-17-00 SM-2
- 2022-501427-24-00 SM-8
- 2024-514180-25-00 SM-1
- 2023-505772-30-00 SM-1
- AOB

- The Chair welcomed the NREC-CT B.
  - The minutes from the previous NREC-CT B meeting on 25th September were approved.
  - The NREC Business Report was discussed and noted.

Applications

2024-516440-25-00

Institutions: Mater Misericordiae University Hospital

Study title: J5J-OX-JZZA: A Phase 1a/1b Trial of LY3962673 in Participants with KRAS G12D-Mutant Solid Tumors.

Dossiers Submitted: Part I & II

- **NREC-CT Decision:**

Request for Further Information

- **Additional Information Required RFI**

Part I Considerations (RFI) for addition to CTIS
Clinical

- Given that this is a first in human study, it is requested that additional granularity on how the safety review committee will operate on a practical basis, specifically:
    1. Whether the safety committees in each country will be integrated or operate separately when completing analyses, (and if integrated across sites and countries, how will that interaction work)
    2. Who will sit on the safety review committee other than the PI on the Irish site, and how many will be recruited
    3. What measures are in place to ensure safety monitoring continues seamlessly during PI absences (e.g., while on annual leave etc.)
    4. To provide a schedule for the safety monitoring committee, detailing activities for the duration of the study
- Additional clarity is requested on how members of the Independent Review Committee will be recruited.

Statistical Considerations

- Eligible participants will be randomised to a cohort based on Investigator discretion and in consultation with the sponsor, but this will also be dependent upon other factors including regional cohort availability and cohort prioritisation. The sponsor can elect to open, prioritise or close certain cohorts over others during the course of the trial and this has the potential to cause bias. Further information is required on how potential bias can be adjusted for in analyses.
- It is requested that the sponsor provides justification for undertaking subgroup analyses, given that such small samples may lead to imbalances or under-represented groups where statistically valid results are not possible.
- Biomarker analysis will be conducted according to local regulations is described in the protocol (p24). It is requested the sponsor provides additional detail regarding the purpose of this analysis.
- Although handling of missing, unused, and spurious data is addressed prospectively in the statistical methods described in the SAP, it is stated that adjustments to the planned analyses will be described in the final CSR (protocol, p100). It is requested that the sponsor provides further information on the scenarios where adjustments may be required, and to confirm how the integrity of the SAP will not be affected.

- The sponsor is requested to confirm whether multiplicity considerations have been taken into account.

Part II Considerations

1. **Recruitment arrangements**

- The NREC-CT would like to commend the Sponsor on the quality of the documentation submitted for assessment.The NREC-CT requested further details on what steps will be taken to ensure the potential participant does not feel pressured to take part in the study (section 1.5, p1).
- The NREC-CT noted that in the Recruitment document (section 1.1, p1) that potential participants will be identified via databases at the site. Please clarify if this is the sole method for participant identification or if other recruitment methods, such as sharing study details with other Principal Investigators nationally will be used.

2. **Subject information and informed consent form**

- The Sponsor is requested to submit any Part 2 documentation that require updates as a result of the Part 1 Assessment.Please include detail of the Part 1 consideration that triggered the update to the Part 2 documentation.
- The National Office requests that all documentation provided in response to RFI is presented in an accessible and searchable format (Word or original PDF). We are unable to accept scanned documents (including documents modified using Optical Character Recognition) as these documents cannot be optimised for use with assistive software.

2022-502282-24-00

Institutions: Beaumont Hospital

Study title: A Multicenter, Open-label, Long-term, Safety, Tolerability, and Efficacy Study of XEN1101 in Subjects Diagnosed With Epilepsy (X-TOLE4)

Dossiers Submitted: Part I & II

- **NREC-CT Decision:**

Request for Further Information

- **Additional Information Required RFI**

Part II Considerations

1. **Financial arrangements**

- The NREC-CT requested the Compensation for trial Participants document Section 2 be updated to include accommodation expenses being offered to align with information provided in ICF.

2. **Subject information and informed consent form**

- The Sponsor is requested to submit any Part 2 documentation that require updates as a result of the Part 1 Assessment. Please include detail of the Part 1 consideration that triggered the update to the Part 2 documentation
- The National Office requests that all documentation provided in response to RFI is presented in an accessible and searchable format (Word or original PDF). We are unable to accept scanned documents (including documents modified using Optical Character Recognition) as these documents cannot be optimised for use with assistive software.
- The NREC-CT noted that the Protocol pg. 37 provides for referral by the investigator to mental health professional in the event the participant exhibits signs of depression or suicidal ideation. The Committee requested that the Main PIS-ICF pg. 10 be updated to clearly outline the care pathway in which the investigator may refer a participant to a mental health professional.
- The NREC-CT noted that there is an increased risk of suicide associated with seizure medications, and that in the Main PIS-ICF pg. 10 participants are directed to call the study doctor or the local emergency services if they are having suicidal thoughts or are in crisis. However, the study doctor may not be contactable at all times, and therefore, it is requested that further details about the care pathways and site resources for managing a participant in crisis are described. In addition, the sponsor may wish to include details regarding Irish national helplines, such as the Samaritans or Pieta House (https://www.samaritans.org/ireland/samaritans-ireland/ , https://www.pieta.ie/).
- The NREC-CT requested that the Main PIS-ICF pg. 10 bullet point regarding "Psychosis (disruptions to a person's thoughts and perceptions that make it difficult for them to recognize what is real and what isn't") be updated to include information that the participant should report this to the study doctor immediately.
- The NREC-CT requested that the Main PIS-ICF pg. 13 be updated to align with the Compensation for Trial participants' document.
- The NREC-CT requested the Main PIS-ICF pg 15 be updated to remove reference to "Research Ethics Committees" under who are authorised receipts of your personal data" as NREC will not have access to identifiable patient information.
- The NREC-CT requested the Main PIS-ICF consent form pg. 21 be updated to include a consent statement regarding referral to Mental Health Professional for example "I understand that in the event I'm referred to a Mental Health Professional during the course of the study that I will receive support and an appropriate pathway of care"
- The NREC-CT requested the Main PIS-ICF Risk section pg. 9-11 be updated to provide more description and reassuring detail about the risks/side effects along with the actions to take in the event of occurrence of these side effects. This may include the transient nature of some of the common adverse events.
- The NREC-CT requested the Main PIS-ICF Allergic Reactions pg. 10 be updated to provide advice on what the participant should do if they experience an allergic reaction.
- The NREC-CT noted that the pregnant partner and pregnancy follow-up PILs include results of non-clinical studies regarding the impact of the study drug in unborn rats. It is requested that this information is also included in the Main PIS-

ICF pg. 11 so that participants are aware of the potential side effects to a foetus prior to pregnancy occurring.

- The NREC-CT requested the Main PIS-ICF pg. 14 reference to 'personal insurance' be updated to provide clarity as to what type of insurance is being referred to here i.e. health, life etc.
- The NREC-CT requested the Main PIS-ICF pg. 9 reference to not driving while getting used to medication be updated to provide context with requirement to be seizure free.
- The NREC-CT requests the sentence in the Main PIS-ICF pg. 9 i.e., 'you will be asked not to drive' is changed to include the side effect first, e.g., 'due to the sedative effects of the study drug, you will be asked not to operate complex machinery such as driving, until you have gotten used to the study medication'.
- The NREC-CT noted that the Protocol pg 31 states that participants should not drive, operate complex machinery etc., until they have become accustomed to the potential sedative effects of the study drug. However, in the Main PIS-ICF, this is described as 'calming effects' which the NREC-CT considered inappropriate/unacceptable and requested it is updated to better reflect the description in the Protocol.
- The NREC-CT noted that alcohol consumption is not permitted, as described in the Main PIS-ICF pg. 9, yet in Protocol pg. 31, alcohol is limited to 2 standard units per day. It is requested that information regarding alcohol consumption in the Main PIS-ICF and Protocol are aligned.

2023-505766-28-00

Institutions: St James's Hospital

Study title: A Phase II/III, Extension Study of Orally Administered PHA-022121 for Acute Treatment of Angioedema Attacks in Patients with Hereditary Angioedema due to C1-Inhibitor Deficiency (Type I or Type II)

Dossiers Submitted: Part I & II

- **NREC-CT Decision:**

Request for Further Information

- **Additional Information Required RFI**

Part II Considerations

1. Financial arrangements

- The NREC-CT requested that the Compensation for trial participants document be updated to include more detail on the monetary payment to participants including if compensation is proposed for the full duration of the study.

2. Subject information and informed consent form

1. The NREC-CT noted that the Protocol pg 3 states that 'Part B is planned to continue until the availability of commercial supply of Deucrictibant' which is to be commended. The Sponsor is requested that the PISCF is updated to clarify if participants will be expected to continue to submit data through ePRO over a long

period until there is an availability of commercial supply. The burden of this should be clearly outlined in the PISCF

- The NREC-CT noted that the protocol states 'Part B is planned to continue until the availability of commercial supply of deucrictibant'. It was requested that this is added to the PISCF and confirm whether this is related to commercial supply in Ireland or elsewhere.

2023-506269-78-00 SM-2

Institutions: Cork University Hospital, Children's Health Ireland

Study title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Fixed-Dose, Multicenter Study to Examine the Efficacy and Safety of ZX008 in Subjects with CDKL5 Deficiency Disorder Followed by an Open-Label Extension

Dossiers Submitted: Part I & II

- **NREC-CT Decision:**

- Request for Further Information

- **Additional Information Required RFI**

Part II Considerations

1. **Recruitment arrangements**

- The NREC-CT noted the consent for participation and data processing for 16/17-year-olds on Informed Consent Form for Participant 12-17 years old. The Committee wish to advise of a recent national policy change informed by discussions at a national level with relevant authorities: participants aged 16yrs+ may consent to both participation in a regulated study and associated data processing - https://www.nrecoffice.ie/guidance-on-age-of-consent-for-regulated-research-in-ireland/
- The NREC-CT requested confirmation that participants will be reconsented using the Adult Informed Consent Form for trial participation and future use of data once they turn 16 years of age.

2022-500758-41-00 SM-17

Institutions: St James's Hospital

Study title: A Multi-Center, Randomized, Double-Blind, Placebo-Controlled Multiple Ascending Dose Study to Evaluate the Safety and Tolerability of QRL-201 in Amyotrophic Lateral Sclerosis

Dossiers Submitted: Part I & II

- **NREC-CT Decision:**

Request for Further Information

- **Additional Information Required RFI**

Part II Considerations

1. **Subject information and informed consent form**

- The NREC-CT noted that the language used in the sentence on Pg. 19 of the PISCF 'If your health worsens and you die while in the study drug administration period or follow-up period' is insensitive and may cause undue distress. The Committee requested that this statement is rewritten using more appropriate language.
- The NREC-CT requested that the optional consent items on Pg. 22 of the PISCF are moved to a separate page of the PISCF with a separate signature line to ensure that they are not conflated with general trial participation.
- The Sponsor is requested to submit any Part 2 documentation that require updates as a result of the Part 1 Assessment. Please include detail of the Part 1 consideration that triggered the update to the Part 2 documentation
- The National Office requests that all documentation provided in response to RFI is presented in an accessible and searchable format (Word or original PDF). We are unable to accept scanned documents (including documents modified using Optical Character Recognition) as these documents cannot be optimised for use with assistive software.

2023-505650-17-00 SM-2

Institutions: Children's Health Ireland

Study title: A Randomized, Double-blind, Placebo-controlled Clinical Study to Evaluate Mavacamten in Adolescents (age 12 years to < 18 years) with Symptomatic Obstructive Hypertrophic Cardiomyopathy

Dossiers Submitted: Part I & II

- **NREC-CT Decision:**

Request for Further Information

- **Additional Information Required RFI**

Part I Considerations

1. **Protocol**

- It was noted that the study's primary and secondary endpoints were determined at 28 weeks. The Protocol only states that the purpose of the extension study 'to collect additional safety and efficacy data'. It is queried whether additional endpoints should be captured in the protocol related to the extension study. Please provide rationale for their omission.
- It was noted that participants on the placebo arm will now be offered the study drug as part of the open label extension. Are these patients at a higher risk of having an undetected or delay in the detection of adverse events due to the

reduction in the monitoring from 24 visits in the first 56 weeks to visits happening every 12 weeks in the OLE?

Part II Considerations

1. Recruitment arrangements

- Brochures, K2_Recruitment material_Patient Assent Guide & K2_Recruitment material_Parent Information Brochure, intended for the 12-17 cohort were noted by the NREC-CT to have a number of inconsistencies and omissions e.g. study duration captured as 56 weeks rather than the 200 weeks stated elsewhere. These documents also lack any comprehensive information around the open-label LTE period and the follow-up period. The Committee requested that these documents are revised to address these omissions and inconsistencies.
- The NREC-CT requested that the brochure material provided (Recruitment material_Patient Assent Guide & K2_Recruitment material_Parent Information Brochure) is amended to make it explicitly clear to potential participants that all participants will receive the study drug under the open-label extension study.

2. Subject information and informed consent form

- The NREC-CT noted a number of discrepancies around the duration of the study across the documentation. Pg. 2 of the Protocol Synopsis states 229 weeks from the date of consent to the last visit, Pg. 19 of the Protocol states 223 weeks, the main ICF states 229 weeks. The Committee requested that the relevant documents are amended to reflect the correct duration.
- The NREC-CT requested that further information around the process for weight-based dosing is included in the PIS-ICF and Assent forms.
- The NREC-CT noted in the protocol that there will be an increase in dose of the study drug under the open-label extension. If this increase could potentially lead to an increase in adverse events, the Committee requests that this information is expanded upon in the PIS-ICF, including any impact from the reduced monitoring in the open label extension.
- The Sponsor is requested to submit any Part 2 documentation that require updates as a result of the Part 1 Assessment. Please include detail of the Part 1 consideration that triggered the update to the Part 2 documentation
- The National Office requests that all documentation provided in response to RFI is presented in an accessible and searchable format (Word or original PDF). We are unable to accept scanned documents (including documents modified using Optical Character Recognition) as these documents cannot be optimised for use with assistive software.

2022-501427-24-00 SM-8

Institutions: Cork University Hospital, St James's Hospital

Study title: (Summit) A Multi-Part, Randomized, Double-Blind, Placebo-Controlled Phase 2 Clinical Study of the Safety and Efficacy of CGT9486 in Subjects with NonAdvanced Systemic Mastocytosis

Dossiers Submitted: Part I & II

- **NREC-CT Decision:**

- Request for Further Information

- **Additional Information Required RFI**

Part II Considerations

1. Compliance with use of biological samples

- It was noted that the extension study is extended from 2 to 5 years. However, endpoints of the extension study take place at year 1 and year. Please provide rationale for no endpoints being specified for year 5 of the extension study.

Part II Considerations

2. Subject information and informed consent form

- The NREC-CT requested that the details related to dose selection in Part 2 of the study is better elucidated in the PISCF as per the amendments included in the study protocol.
- The NREC-CT requested that Page 4 is amended to further explain what Formulation A and B are.
- The NREC-CT noted the removal of text related to entry and exit interviews from the PISCF, however this information is included in Pg. 87 of the Protocol. The Committee requests clarification whether entry and exit interviews will take place for Irish participants.
- The NREC-CT noted a discrepancy regarding the collection of buccal swabs in the Informed Consent Form (ICF) and the compliance biological sample form. The collection of Buccal swabs has been removed from the ICF. In the "Treatment Period" section of the ICF on page 7, it states that a blood sample will be collected to test for DNA traits associated with tryptase. However, the "Compliance Biological Sample" section, page 3, mentions that either blood or buccal swabs will be collected for HAT and section 1.3 specifies that up to three buccal swab samples will be collected. The NREC-CT requested further clarification to resolve this discrepancy.
- The NREC-CT requested that further information is included in the PISCF around the potential for dose interruptions and dose reductions as specified in the Protocol.
- The NREC-CT requested clarification why the wording in the Drug Diary has been amended to “each day or every other day” when the PIL states ‘daily dose’.
- The NREC-CT noted that the Drug Diary states the drug is taken at least 1 hours before or 2 hours after a meal, but the following has been added to the PISCF “ you will be instructed to either take your study drug with food and water, or … empty stomach”. The Committee requested that this discrepancy is amended.

- The NREC-CT noted that the Drug Diary states that " you will take ____tablets of study drug", however the number of tablets to be taken is clearly not explained in the Drug Diary or PISCF. The Committee requested that both documents are amended to better explain the number of tablets needed to be taken.
- The Sponsor is requested to submit any Part 2 documentation that require updates as a result of the Part 1 Assessment. Please include detail of the Part 1 consideration that triggered the update to the Part 2 documentation
- The National Office requests that all documentation provided in response to RFI is presented in an accessible and searchable format (Word or original PDF). We are unable to accept scanned documents (including documents modified using Optical Character Recognition) as these documents cannot be optimised for use with assistive software.

2024-514180-25-00 SM-1

Institutions: Cork University Hospital, St Vincent's University Hospital, Mater Private Hospital, University Hospital Waterford, Mater Misericordiae University Hospital, Beaumont Hospital, Bon Secours Hospital Cork

Study title: An Open-label Randomized Phase 3 Study of Tucatinib in Combination with Trastuzumab and mFOLFOX6 versus mFOLFOX6 given with or without either Cetuximab or Bevacizumab as First-line Treatment for Subjects with HER2+ Metastatic Colorectal Cancer

Dossiers Submitted: Part I & II

- **NREC-CT Decision:**

- Favourable

2023-505772-30-00 SM-1

Institutions: St James's Hospital, St Vincent's University Hospital, University Hospital Galway, Cork University Hospital

Study title: A Phase 3 Trial of Fianlimab (REGN3767, Anti-Lag-3) + Cemiplimab versus Pembrolizumab in Patients with Previously Untreated Unresectable Locally Advanced or Metastatic Melanoma

Dossiers Submitted: Part I & II

- **NREC-CT Decision:**

  Request for Further Information

- **Additional Information Required RFI**

Part II Considerations

1. **Subject information and informed consent form**

- Although not part of the substantial modification presented, the NREC-CT noted that Future Biomedical Research Sub-study Informed Consent Form does not describe the future use of samples in line with regulations and best practice. The Committee requested that future use of samples is sufficiently explained so as to constitute broad informed consent, as required under the Health Research Regulations (Data Protection Act 2018 (Section 36(2) (Health Research) Regulations 2018). Furthermore, it should be confined to the disease or drug under study in this trial. Consent can only be obtained where future use of samples and data is defined such that participants are fully informed,
  and/or: that an option is provided to enable participants to consent to be contacted in the future about other research studies.
  The PISCF should also make it clear to participants that subsequent research ethics review will be sought for specific research once clearly defined.
  For further guidance, please see: NREC Guidance on Use of biological samples and associated data - https://www.nrecoffice.ie/guidance-on-use-of-biological-samples-and-associated-data/

- AOB: