National Research Ethics Committee

NREC-CT Meeting

24th April 2024

Attendance

Name	Role
Dr Cliona McGovern	Chairperson, NREC-CT B
Dr John Hayden	Deputy Chairperson, NREC CT-B
Prof. Colm O'Donnell	Deputy Chairperson, NREC-CT B
Ms Serena Bennett	Committee Member, NREC-CT B
Dr Katherine Benson	Committee Member, NREC-CT B
Prof. Michaela Higgins	Committee Member, NREC-CT B
Ms Jasmine Joseph	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
Prof. Abhay Pandit	Committee Member, NREC-CT B
Dr Emily Vereker	Head of Office, National Office for RECs
Ms Aileen Sheehy	Programme Manager, National Office for RECs
Dr Laura Mackey	Programme Officer, National Office for RECs
Dr Susan Quinn	Programme Manager, National Office for RECs
Ms Ella Davis	Student Intern, National Office for RECs
Ms Megan O'Neill*	Project Officer, National Office for RECs

*Drafted minutes

Apologies: Prof. John Wells, Ms Ann Twomey, Prof. Catherine Hayes

Quorum for decisions: Yes

Agenda

- Welcome & Apologies
- 2024-512477-27-00
- 2023-507268-37-00
- 2023-503765-37-00
- 22-NREC-CT-062_Mod-4
- 2023-505579-53-00 SM-1
- 2023-509429-37-00 SM 2
- 2023-504320-25-00 SM-1
- AOB

- The Chair welcomed the NREC-CT B.
- The minutes from the previous NREC-CT B meeting on 20th March 2024 were approved.
- The NREC Business Report was discussed and noted.

Applications

2024-512477-27-00

Institutions: Cork University Hospital, Mater Misericordiae University Hospital, University Hospital Galway, St James's Hospital

Study title: REFRaME-O1: A Phase 2/3 Open-label Study Evaluating the Efficacy and Safety of Luveltamab Tazevibulin (STRO-002) versus Investigator's Choice (IC) Chemotherapy in Women with Relapsed Platinum-resistant Epithelial Ovarian Cancer (Including Fallopian Tube or Primary Peritoneal Cancers) Expressing Folate Receptor Alpha (FOLR1)

- NREC-CT Decision:
- Request for further information

- Additional Information Required RFI

Part I Considerations (RFI) for addition to CTIS

1. Approximately 25 patients from Part 2 will participate in a PK substudy, as described on pg. 21 of the protocol, which will involve more intensive PK testing. Provide further information on how these participants are selected for the PK substudy, when they will be informed that they have been selected for the study and whether they will have the opportunity to opt out.
2. What is the process in place to change the Phase 3 dosing regimen based on the results from the Phase 2 aspect of the trial? Is the phase 2 part complete?

Part II Considerations

1. Financial arrangements

- The NREC-CT appreciated that reimbursement is available for the travel, accommodation and meals associated with a participant's trial activities, and requested that the Sponsor consider implementing similar reimbursement for carers travelling with the participant.
- The NREC-CT requested assurance that the reimbursement for expenses pertained to both the main study and the pre-screening aspect of the study. The NREC-CT requested that the Pre-Screening PISCF is updated accordingly to reflect this.

2. Subject information and informed consent form

- The NREC-CT noted that both the Main and Prescreening PISCF state that the study is reviewed by the Independent Ethics Committee (IEC) and requested that this is changed to the National Research Ethics Committee (NREC).
- The NREC-CT noted that informed consent can be obtained >21 days prior to the first dose to allow for additional screening time, as described in Section 8.1.1 of the protocol (pg. 75). The NREC-CT requested further details elucidating the upper limit of the timeframe for consent.
- The NREC-CT noted both "FOLR1" and "FRa" are used interchangably as acronyms of "folate receptor alpha" across the different participant-facing materials and PISCF. The NREC-CT requested that the acronyms are harmonised across these documents.
- The NREC-CT considered the following statement from the Prescreening PILCF (pg. 3); "If your tumour does not have the minimum level of FOLR1 expression needed for enrolment, you may be able to participate in a different research study. The investigator will present any other research opportunities to you using separate informed consent documents". The NREC-CT questions what these other research opportunities are. If this is not related to the clinical trials, the committee recommended that this statement is removed from the PISCF.
- The NREC-CT requested further information about what "de-identified health information" may be shared with other countries including China, as mentioned in the Main PISCF.

3. Suitability of the clinical trial sites facilities

- The NREC-CT noted that Site Suitability Form submitted by Mater Misericordiae University Hospital specified that exposure to ionising radiation is not above the standard of care. However, all other sites identified that exposure of ionising radiation related to trial procedures was above the standard of care levels. The NREC-CT requested further clarification as to why exposure to ionising radiation is deemed within standard of care at this site and above the standard of care at the other sites involved.

Study title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Crossover Study of Oral Deucrictibant Soft Capsule for On-Demand Treatment of Attacks in Adolescents and Adults with Hereditary Angioedema

- NREC-CT Decision:

- Request for further information

- Additional Information Required RFI

Part I Considerations (RFI) for addition to CTIS

1. The attack qualification will be conducted by the investigator or designee when the participant experiences a HAE attack, to determine whether it is non-laryngeal or laryngeal in nature, and thus the treatment plan. It should be clearly set out in the protocol who will complete attack assessment, whether it is solely the Investigator and how it will be ensured that they are contactable at all times in the event of a HAE attack outside typical business hours.
2. Further details are required on the safety implications of placebo treatment, and the potential consequences of delaying treatment of HAE attack when in placebo arm. This should be further elucidated in the study protocol.
3. Provide additional rationale for the pharmacokinetic studies only being conducted on adolescent participants.

Part II Considerations

1. Subject information and informed consent form

- The NREC-CT noted that the protocol indicates that attack qualification will be conducted by the Investigator or designee when the participant experiences a HAE attack, to determine whether it is non-laryngeal or laryngeal in nature, and thus the treatment plan, whilst the Main PISCF refers to the Study Doctor for this process. The NREC-CT requested that the protocol and PISCF are aligned to clearly set out who may complete attack qualification, whether it is an individual or members of the study team, and how it will be ensured that they are contactable at all times in the event of a HAE attack outside typical business hours.
- The NREC-CT requested that the Compensation for Trial Participants form and Main PISCF form are harmonized to clearly outline what expenses will be provided to participants. The NREC-CT requested that the monetary amounts for reimbursement are removed from the PISCF**.**
- The NREC-CT requests that further information around risk is included in the PISCF related to the potential of delayed treatment for participants on the placebo arm of the study.
- The Sponsor is requested to submit any participant-facing documentation that require updates as a result of the Part I Assessment.
- 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 as these documents are composed of images, rather than searchable text, and cannot be optimised for use with assistive software.

2. Suitability of the clinical trial sites facilities

- The NREC-CT queried the site suitability of St James' Hospital to conduct this clinical trial and the PK analysis on adolescents as this hospital does not treat

this cohort. The NREC-CT requested that it is explicitly set out whether the Applicant intends to enroll minors and if so, how this will be done (eg. Recruitment, phlebotomy etc). It should be noted by the Sponsor, that the inclusion of minors may require adapted patient materials, relevant assent and parental forms, the inclusion of a children's hospital site and relevant paediatric expertise.

2023-503765-37-00

Institutions: St James's Hospital

Study title: An Extension Study Assessing the Long-term Safety and Efficacy of Etranacogene Dezaparvovec (CSL222) Previously Administered to Adult Male Subjects with Hemophilia B

- NREC-CT Decision:

- Request for further information

- Additional Information Required RFI

Part II Considerations

1. **Compliance with use of biological samples**
   - The NREC-CT requested that the response provided to Section 4.1 of the Compliance with Member State applicable rules for the collection, storage and future use of human biological samples form, regarding the purpose of future use is modified to clearly set out what type of gene therapy research the samples may be used for. This information should also be captured in the PISCF.
2. **Financial arrangements**
   - The NREC-CT requested that the monetary value of reimbursement is not specified in the PISCF to avoid any undue influence on the Participant.
3. **Recruitment arrangements**
   - The NREC-CT requested an estimated number or expected proportion of participants due to participate in Ireland.
4. **Subject information and informed consent form**
   - The NREC-CT queried whether it was appropriate to include risks associated with the IMP in the PIL (pg. 3-4 and 12-15) as there is no administration of the IMP in this extension study, and therefore do not truly represent the risks associated with participation in this extension study.
   - The NREC-CT requests further information on the additional pathways of care, if any, that are available to participants who have identified issues in the questionnaires.
   - The NREC-CT requested that the PISCF is modified to inform participants of how unsolicited findings will be handled, as described in section 4.10 of the Compliance with Member State applicable rules for the collection, storage and future use of human biological samples form.
   - The NREC-CT considered the following statement on pg. 1 of the Optional Future Research PISCF. "If you consent, the samples will be stored and used to support potential future research for CSL222, gene therapy, and / or haemophilia B, until 5 years after the study has completed". The NREC-CT requested that this is modified to gene therapy relating to haemophilia B to remove any ambiguity, in

line with the Health Research Regulations (Data Protection Act 2018 (Section 36(2) (Health Research) Regulations 2018).

- The NREC-CT noted that the consent item seeking consent to the collection and storage of blood samples for "future research" in the Optional Informed Consent form for Blood Sampling (pg. 3) is not described 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: HSE National Policy for Consent in Health and Social Care Research (V1.1, 2023) https://hseresearch.ie/wp-content/uploads/2023/02/HSE-National-Policy-for-Consent-in-Health-and-Social-Care-Research-compressed.pdf
- The NREC-CT noted that the Optional Future Research Informed Consent Form to provide a liver tissue sample (pg. 7) makes reference to conducting "genetic testing" on the liver sample and requested that further details are provided in the Optional Future Research PISCF clarifying the type of genetic analysis that will be performed.
- The Sponsor is requested to submit any participant-facing documentation that require updates as a result of the Part I Assessment.
- 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 as these documents are composed of images, rather than searchable text, and cannot be optimised for use with assistive software.

22-NREC-CT-062_Mod-4

Institutions: Beaumont Hospital

Study title: A Phase 2 Trial of Adagrasib Monotherapy and in Combination with Pembrolizumab and a Phase 3 Trial of Adagrasib in Combination with Pembrolizumab versus Pembrolizumab in Patients with Advanced Non-Small Cell Lung Cancer with KRAS G12C Mutation

- NREC-CT Decision:

- Request for further information

- Additional Information Required RFI

    - The NREC-CT noted that reference to the Phase II study from the protocol (tracked changes pg. 6) and requested further clarity regarding the current status of the Phase

II study, including whether the Phase II study has now completed; have 220 participants already been recruited to the Phase II; and if the Phase II study has completed why reference to this study is continued throughout the documentation, including the study title, protocol and PISCFs.

- In line with the above consideration, the NRECT-CT queried why an amended PIL for Phase II had been supplied if detailed reference to Phase II is not included in protocol V8.0.
- The NREC-CT requested the rationale for the reduction in sample size from 700 to 550 participants for the Phase III study.
- The NREC-CT sought further clarity regarding the cohorts described in the protocol under the Original Phase 2 Study Design regarding interim analysis (tracked changes protocol, pg. 179-180). Noting that the arms in Phase II were 1A, 1B and 2, it is not clear what “Cohort A” is. The NREC-CT requested that this is described clearly, and that the number of participants to be recruited in Cohort A and B is given.
- The NREC-CT requested that the study documentation is revised to clearly set out what changes to the protocol and phase of the trial are being implemented with this substantial modification and what stage the participants are in.
- The NREC-CT requested clarity regarding the two amended Participant Dosing Diaries submitted for Phase III. It was not clear to the NREC-CT why the dosing diaries list 600mg of IMP as the dose in Phase III is 400mg (2 x 200mg tablets). Furthermore, the NREC-CT queried why both forms were required for this Phase III study, given that only one arm (Cohort 3) will receive the IMP.
- The NREC-CT queried the level of detail given in the GP letter about Phase II of the study, to then state that the patient is participating in the Phase III study only. The NREC-CT asked whether the GP needs to be informed about the Phase II study given it is closed, and requested that the document is reconsidered in line with the aforementioned changes to ensure it is clear to the GP which Phase of the trial the patient is participating in.
- The NREC-CT requested that the name given to the IMP is consistent throughout the GP letter, noting use of “MRTX849” on pg.2 of the letter despite title changes using “Adagrasib” throughout the rest of the letter, to ensure clarity for the GP.
- The NREC-CT considered the following consent item on pg. 67 of the Main Phase III PISCF, “I understand that my participation in the study will involve the collection, use and disclosure of information about me, my health and my participation in this study as described in the participant information sheet. I agree to this” and requested that this is modified to reflect that this “disclosure of information” will be anonymised/coded.
- The NREC-CT noted that aspects of the consent form in the Main Phase III PISCF seek blanket consent for future / additional use of samples / data, for unspecified purposes, without further consent. This type of consent is 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 requested that

future research is restricted to ‘specified health research, either in relation to a particular area or more generally in that area or a related area of health research, or part thereof’ and this is clearly stated in the main body and informed consent section of the PISCF.

- The NREC-CT noted the following consent item on pg. 67 of the Main Phase III PISCF, “I understand that the information held and maintained by the Health and Social Care Information Centre and other central bodies may be used to help contact me or provide information about my health status”. The NREC-CT requested that the Main PISCF is modified to provide information to participants, detailing what the Health and Social Care Information Centre is and what other central bodies this item refers to.
- The NREC-CT noted that the title of the trial and the first 28 pages of the Main Phase III PISCF use “pembrolizumab” consistently, but this is amended to KEYTRUDA from pg. 29 onwards. The NREC-CT requested the reasoning behind this change as it may cause confusion for a potential participant.
- The NREC-CT queried - under the assumption that the Phase II trial is still open as the PISCF has been modified for Phase II- whether is it ethically acceptable to recruit participants to the Phase II IB cohort of the study, with 600mg of investigational product and no pembrolizumab, taking into consideration that the dose in Phase III has been changed to 400mg BID and that pembrolizumab is standard treatment.
- The NREC-CT noted that the Main Phase III PISCF informs participants that the Phase II trial has closed and requested clarification as to why reference to the Phase II study remains in the Phase III PISCF, including in the title of the trial, and indicated that it could be removed from this document if the Phase II trial is indeed closed.
- The NREC-CT highlighted the use of both “Phase 2” and “Phase 3” in the titles of documents including the PISCFs and GP letter and the potential confusion this may cause a participant, GP or member of the research study team in determining which Phase a participant has consented to. The NREC-CT queried whether this raises an unnecessary risk for the participant and requested that these titles are reconsidered to lessen the risk posed by this ambiguity.
- The NREC-CT noted the modification to Cohort 4 comparator arm of the Phase III study from pembrolizumab plus chemotherapy to pembrolizumab alone. The NREC-CT requested the justification for the omission of chemotherapy, noting that the following statement has been removed from pg. 9 of the Main Phase III PISCF, “Pembrolizumab used by itself has not been approved for use as first treatment for patients with NSCLC whose tumour tests negative for PD-L1”.

2023-505579-53-00 SM-1

Institutions: Mater Misericordiae University Hospital, University Hospital Galway, Bon Secours Hospital Cork

Study title: A Phase 3, Single-Arm, Open-Label, Multicenter Study to Evaluate the Safety and Efficacy of Tafasitamab Plus Lenalidomide in Participants With Relapsed or Refractory Diffuse Large B-Cell Lymphoma

- NREC-CT Decision:

- Favourable

2023-509429-37-00 SM-2

Institutions: University College Cork, St Vincent's University Hospital, St Vincent's University Hospital, University Hospital Limerick

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

- NREC-CT Decision:

- Favourable

2023-504320-25-00 SM-1

Institutions: Merlin Park University Hospital, Connolly Hospital, Our Ladys Hospital Manorhamilton

Study title: A Phase 2, Multicenter, Randomized, Double-blind, Placebo-Controlled, Study to Evaluate the Efficacy and Safety of Afimetoran in Participants with Active Systemic Lupus Erythematosus

- NREC-CT Decision:

- Favourable

- AOB:
    - None