National Research Ethics Committee

NREC-CT A Meeting

20th October 2021

Attendance

Name	Role
Prof. Alistair Nichol	Chairperson, NREC CT-A
Dr Heike Felzmann	Deputy Chairperson, NREC-CT A
Prof. Mary Donnelly	Deputy Chairperson, NREC-CT A
Dr John O'Loughlin	Committee Member, NREC-CT A
Prof. Tina Hickey	Committee Member, NREC-CT A
Dr Dervla Kelly	Committee Member, NREC-CT A
Dr Darren Dahly	Committee Member, NREC-CT A
Dr Jimmy Devins	Committee Member, NREC-CT A
Mr Gerard Daly	Committee Member, NREC-CT A
Prof. Patrick Dillon	Committee Member, NREC-CT A
Ms Ann Twomey	Committee Member, NREC-CT A
Prof. Catherine Hayes	Committee Member, NREC-CT A
Ms Muireann O'Briain	Committee Member, NREC-CT A
Prof. David Brayden	Committee Member, NREC-CT A
Prof. John Wells	Committee Member, NREC-CT A
Prof. Mark Sherlock	Committee Member, NREC-CT A
Dr Geraldine Foley	Committee Member, NREC-CT A
Prof. Gene Dempsey	Committee Member, NREC-CT A
Ms Aileen Sheehy*	Programme Manager, National Office for RECs
Dr Laura Mackey*	Project Officer, National Office for RECs

*Drafted minutes

Apologies: none

Quorum for decisions: Yes

Agenda

- Welcome & Apologies
- Amendment 21-NREC-CT-092_AMEND-1
- Amendment 21-NREC-CT-093_AMEND-1
- Amendment 21-NREC-CT-057_AMEND-2
- Amendment 21-NREC-CT-098_AMEND-1
- Amendment 21-NREC-CT-099_AMEND-1
- Amendment 21-NREC-CT-062_AMEND-2
- Amendment 21-NREC-CT-104_AMEND-1
- Amendment 21-NREC-CT-107_AMEND-1
- Amendment 21-NREC-CT-105_AMEND-1
- Amendment 21-NREC-CT-103_AMEND-1
- AOB

- The Chair welcomed the NREC-CT A.
  - The minutes from the previous NREC-CT A meeting on 22nd September 2021 were approved.
  - A committee member queried a request for further information related to application 21-NREC-CT-086. This was noted by National Office staff and was included as a further clarification under a condition of a favourable opinion
  - A committee member noted that a previous submission (21-NREC-CT-083) had withdrawn their trial after review by the NREC-CT A. This trial will likely be resubmitted at a later date.
  - The NREC Business Report was discussed and noted.

Applications

21-NREC-CT-092_AMEND-1

Principal Investigator: Prof. Maeve Lowery

Study title: A Phase III, Randomized, Double-blind Trial Comparing Trastuzumab Plus Chemotherapy and Pembrolizumab With Trastuzumab Plus Chemotherapy and Placebo as First-line Treatment in Participants with HER2 Positive Advanced Gastric or Gastroesophageal Junction Adenocarcinoma (KEYNOTE 811)

Lead institution: St James's Hospital

- NREC-CT comments:

- The NREC-CT A noted that this application represents a substantial amendment to a Phase III, Randomized, Double-blind Trial Comparing Trastuzumab Plus Chemotherapy and Pembrolizumab With Trastuzumab Plus Chemotherapy and Placebo as First-line Treatment in Participants with HER2 Positive Advanced Gastric or Gastroesophageal Junction Adenocarcinoma.
- The NREC-CT A agreed that this substantial amendment application was well-prepared and the changes made to the protocol and participant information leaflets were reasonable.
- Based on the above, the NREC-CT A agreed that this substantial amendment application can be designated as favourable.

- NREC-CT Decision:

- Favourable

21-NREC-CT-093_AMEND-1

Principal Investigator: Dr Brian Casserly

Study title: A Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy in Subjects with Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Gating or Residual Function Mutation (F/G and F/RF Genotypes)

Lead institution: University Hospital Limerick

- NREC-CT comments:

- The NREC-CT A noted that this application represents a substantial amendment to a Phase 3, Open-label Study Evaluating the Long-term Safety and Efficacy of VX-445 Combination Therapy in Subjects with Cystic Fibrosis Who Are Heterozygous for the F508del Mutation and a Gating or Residual Function Mutation.

- The NREC-CT A acknowledged that this substantial amendment application was clearly presented for the most part.
- The NREC-CT A agreed that additional clarification was required to inform its deliberations and was not in a position to return a final ethics opinion.

  - NREC-CT Decision:

- Request for Further Information

  - Further Information Requested:

- The NREC-CT A requested that the following sentence is re-added to the PIL: '*Only the researchers or others who are doing their jobs will be able to see the information about you from this research study* '.
- The NREC-CT A noted that those not participating in the study or those who withdraw from the study will not get access to the treatment. The NREC-CT A requested clarity around how those not participating in the trial can gain access the treatment in Ireland outside of the trial and that this information also be included in the PIL.

21-NREC-CT-057_AMEND-2

Principal Investigator: Prof. Catherine Kelly

Study title: A Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Pembrolizumab Versus Treatment of Physician's Choice in Participants with Advanced Endometrial Cancer

Lead institution: Mater Misericordiae University Hospital

  - NREC-CT comments:

- The NREC-CT A noted that this application represents a substantial amendment to a Multicenter, Open-label, Randomized, Phase 3 Trial to Compare the Efficacy and Safety of Lenvatinib in Combination with Pembrolizumab Versus Treatment of Physician's Choice in Participants with Advanced Endometrial Cancer.
- The NREC-CT A agreed that the changes outlined in the Investigator Brochure were clearly outlined.
- Based on the above, the NREC-CT A agreed that this substantial amendment application can be designated as favourable.

  - NREC-CT Decision:

- Favourable

21-NREC-CT-098_AMEND-1

Principal Investigator: Dr Paul McNally

Study title: A Phase 3, Open-label Study Evaluating the Long-term Safety of VX445 Combination Therapy in Subjects with Cystic Fibrosis

Lead institution: Children's Health Ireland, Crumlin

- NREC-CT comments:

- The NREC-CT A noted that this application represents a substantial amendment to a Phase 3, Open-label Study Evaluating the Long-term Safety of VX445 Combination Therapy in Subjects with Cystic Fibrosis.
- The NREC-CT A agreed that the substantial amendments made to this study were clearly presented and reasonable.
- Based on the above, the NREC-CT A agreed that this substantial amendment application can be designated as favourable.

- NREC-CT Decision:

- Favourable

21-NREC-CT-099_AMEND-1

Principal Investigator: Dr Richard Bambury

- Study title: A phase III, randomized, double-blind,placebo controlled,Multicenter trial testing Ipatasertib plus abiraterone plus Prednisone/prednisolone, relative to Placebo plus abiraterone plus Prednisone/prednisolone in adult male Patients with asymptomatic or mildly Symptomatic, previously untreated, Metastatic castrate-resistant prostate Cancer

Lead institution: Cork University Hospital

- NREC-CT comments:

- The NREC-CT A noted that this application represents a substantial amendment to a phase III, randomized, double-blind,placebo controlled,Multicenter trial testing Ipatasertib plus abiraterone plus Prednisone/prednisolone, relative to Placebo plus abiraterone plus Prednisone/prednisolone in adult male Patients with asymptomatic or mildly Symptomatic, previously untreated, Metastatic castrate-resistant prostate Cancer.
- The NREC-CT A highlighted that while the updates made to the Investigator Brochure were clear, additional clarification as to whether this impacted other documentation was required.

- Given these inconsistencies the NREC-CT A agreed that it was not in a position to return a final ethics opinion and further information is required to inform its deliberations.

  - NREC-CT Decision:

- Request for Further Information

  - Further Information Requested:

- The NREC-CT A requested further information on how the changes related to the safety information have not warranted changes to the participant materials.
- The NREC-CT A requested further information on how existing participants and new participants will be made aware of the updated safety information.
- The NREC-CT A requested a copy of the of latest version of the Participant Information Leaflet.

21-NREC-CT-062_AMEND-2

Principal Investigator: Prof. Ray McDermott

Study title: A Phase 3, Randomized, Double-blind Trial of Pembrolizumab (MK-3475) Plus Enzalutamide Versus Placebo Plus Enzalutamide in Participants with Metastatic Castration-Resistant Prostate Cancer (mCRPC) (KEYNOTE-641)

Lead institution: St Vincent's University Hospital

  - NREC-CT comments:

- The NREC-CT A noted that this application represents a substantial amendment to a Phase 3, Randomized, Double-blind Trial of Pembrolizumab (MK-3475) Plus Enzalutamide Versus Placebo Plus Enzalutamide in Participants with Metastatic Castration-Resistant Prostate Cancer.
- The NREC-CT A acknowledged that the substantial amendments made to the Investigator Brochure and Participant Information Leaflet were clear and reasonable.
- Based on the above, the NREC-CT A agreed that this substantial amendment application can be designated as favourable.

  - NREC-CT Decision:

- Favourable
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21-NREC-CT-104_AMEND-1

Principal Investigator: Dr Ciara McDonnell

Study title: ACcomplisH: A Phase 2, multicenter, double-blind, randomized, placebo-controlled, dose escalation trial evaluating safety, efficacy, and pharmacokinetics of subcutaneous doses of TransCon CNP administered once weekly for 52 weeks in prepubertal children with achondroplasia followed by an Open-Label Extension Period

Lead institution: Temple Street Hospital

- NREC-CT comments:

- The NREC-CT A noted that this application represents a substantial amendment to a Phase 2, multicenter, double-blind, randomized, placebo-controlled, dose escalation trial evaluating safety, efficacy, and pharmacokinetics of subcutaneous doses of TransCon CNP administered once weekly for 52 weeks in prepubertal children with achondroplasia followed by an Open-Label Extension Period.
- The NREC-CT A agreed that while some clarifications across the documentation were required, this application can be designated as Favourable with Conditions.

- NREC-CT Decision:

- Favourable with Conditions

- Associated Conditions:

- The NREC-CT A requested further information on how the changes related to the protocol and investigator brochure have not warranted changes to the participant materials.
- The NREC-CT A requested a copy of the of latest version of the Participant Information Leaflet.

21-NREC-CT-107_AMEND-1

Principal Investigator: Dr Declan O'Rourke

Study title: A Double-Blind, Placebo-Controlled, Multicenter Study with an Open-Label Extension to Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients with Duchenne Muscular Dystrophy

Lead institution: Temple Street Hospital

- NREC-CT comments:

- The NREC-CT A noted that this application represents a substantial amendment to a Double-Blind, Placebo-Controlled, Multicenter Study with an Open-Label Extension to

Evaluate the Efficacy and Safety of SRP-4045 and SRP-4053 in Patients with Duchenne Muscular Dystrophy.

- The NREC-CT A highlighted that updates to a number of documents have been included in this substantial amendment.
- The NREC-CT A acknowledged what while most changes are reasonable, some inconsistencies regarding the changes made in the protocol and IB are not clearly reflected in the Participant Information Leaflets.
- Given these inconsistencies the NREC-CT A was not in a position to return a final ethics opinion and required further information to inform its deliberations.

  - NREC-CT Decision:

- Request for Further Information

  - Further Information Requested:

- The NREC-CT A requested that the PIL and the Consent Form are reviewed for accuracy throughout particularly with reference to the length of extension period, frequency of biopsy.
- The NREC-CT A requested that the Assent Forms for different age groups are checked for inconsistencies regarding, e.g. representation of adverse events, statement regarding missing school which currently appears only in the form for youngest children etc.
- The NREC-CT A noted inconsistency in inclusion/exclusion of placebo numbers in statements regarding numbers who have received the drug and requested that all participant materials are revised to ensure that placebo numbers are excluded in the statements regarding the numbers who have previously received the drug.
- The NREC-CT A requested that that the recordings of online transmitted tests being held for 15 years are de-identified.
- The NREC-CT A noted that the text in the ICF refers to ‘low rates of treatment-related serious (17.5%) or severe (21.3%) adverse events’. As these figures are relatively high, the NREC-CT A requested that the language around serious or severe adverse events is amended.
- The NREC-CT A requested the following changes to the participant materials:
    - The word ‘optional’ has been changed to ‘elective’ in one of the Adolescent Assent forms, though retained for an older age-group. The NREC-CT A considers that the term ‘optional’ is more accessible and should be used in all of the Adolescent materials.
    - The Main ICF has an amendment which states ‘“I agree to have my functional assessments transmitter via an online streaming…”. This should be corrected to ‘my child’s…’.
    - A more accessible font should be used in the Assent for Under 8 Years rather than Italic cursive, more like the kind of font used in early readers.

- In the Assent Age 8-12, Page 3 states biopsy ‘done after about a year or two years”. Is this accurate if the biopsy at week 48 has been dropped?
- In the Assent Age 12-14, Page 3 states ‘to start taking new medicine’. The NREC-CT A requests that this is amended as many of the participants will receive a placebo.

21-NREC-CT-105_AMEND-1

Principal Investigator: Prof. John Crown

Study title: A Randomized, Double-blind, Placebo-controlled, Phase 3 Study of Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy for the Treatment of Chemotherapy-Candidate Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2- Negative (HR+/HER2-) Locally Recurrent Inoperable or Metastatic Breast Cancer (KEYNOTE-B49)

Lead institution: St Vincent’s University Hospital

- NREC-CT comments:

- The NREC-CT A noted that this application represents a substantial amendment to a Randomized, Double-blind, Placebo-controlled, Phase 3 Study of Pembrolizumab Plus Chemotherapy Versus Placebo Plus Chemotherapy for the Treatment of Chemotherapy-Candidate Hormone Receptor-Positive, Human Epidermal Growth Factor Receptor 2-Negative Locally Recurrent Inoperable or Metastatic Breast Cancer.
- The NREC-CT A commented positively on a number of documents in this substantial amendment application, in particular, the future use of biological samples consent form.
- The NREC-CT A agreed that additional clarification was required on certain elements of the documentation to inform its deliberations and was not in a position to return a final ethics opinion.

- NREC-CT Decision:

- Request for Further Information

- Further Information Requested:

- The NREC-CT A requested that the term ‘leftover tumour tissue’ is amended to a more appropriate term such as ‘tumour tissue remaining after the study’.
- The NREC-CT A requested clarity on whether participants will be able to access new treatments if they become available over the duration of the trial. If so, the NREC-CT recommended that this is included in the Participant Information Leaflet.
- The NREC-CT A noted that the CV of the Principal Investigator was submitted with the amendment documentation but considered that some of the information provided was

limited. The NREC-CT A requested that a more comprehensive CV is submitted for review.

21-NREC-CT-103_AMEND-1

Principal Investigator: Dr Helen Ann (Eibhlin) Conneally

Study title: A Phase 3, multicenter, open-label, randomized study to evaluate the efficacy and safety of fedratinib compared to best available therapy in subjects with DIPSS - intermediate or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis and previously treated with ruxolitinib (The "FREEDOM-2" trial)

Lead institution: St James's University Hospital

- NREC-CT comments:

- The NREC-CT A noted that this application represents a substantial amendment to a Phase 3, multicenter, open-label, randomized study to evaluate the efficacy and safety of fedratinib compared to best available therapy in subjects with DIPSS -intermediate or high-risk primary myelofibrosis, post-polycythemia vera myelofibrosis, or post-essential thrombocythemia myelofibrosis and previously treated with ruxolitinib.
- The NREC-CT A acknowledged that all changes described in this substantial amendment application was in line with FDA requirements.
- The NREC-CT A noted a minor inconsistency regarding medication administration and was not in a position to return a final ethics opinion. Further information was required to inform its deliberations.

- NREC-CT Decision:

- Request for Further Information

- Further Information Requested:

- The NREC-CT A noted that the FDA follow-up in the documentation for thiamine was 90 days, however the follow-up for this study is 30 days. The NREC-CT A requested clarity around the 30 day follow-up and whether this is based on the 2013 FDA review of studies.

- AOB:

  - The NREC-CT A requested further information regarding the implementation of the CTR in early 2022 and how this will impact current committee processes.

- The Chair closed the meeting.