National Research Ethics Committee

NREC-CT B

17th of August 2022

Attendance

Name	Role
Prof. John Faul	Chairperson, NREC-CT B
Dr Jean Saunders	Deputy Chairperson, NREC-CT B
Mr Philip Berman	Committee Member, NREC-CT B
Dr John Hayden	Committee Member, NREC-CT B
Mr Gavin Lawler	Committee Member, NREC-CT B
Prof. Colm O'Donnell	Committee Member, NREC-CT B
Ms Paula Prendeville	Committee Member, NREC-CT B
Prof Andrew Green	Committee Member, NREC-CT B
Ms Susan Kelly	Committee Member, NREC-CT B
Ms Deirdre MacLoughlin	Committee Member, NREC-CT B
Dr Mark Robinson	Committee Member, NREC-CT B
Dr Enda Dooley	Committee Member, NREC-CT B
Dr Christina Skourou	Committee Member, NREC-CT B
Dr Susan Quinn*	Programme Manager, National Office for RECs
Dr Emma Heffernan*	Project Officer, National Office for RECs
Ms Patricia Kenny	Project Officer, National Office for RECs
Ms Ayesha Carrim	Project Officer, National Office for RECs

*Drafted minutes

Apologies: Dr Cliona McGovern, Dr Lorna Fanning, Prof David Smith, Prof. Abhay Pandit, Ms Caoimhe Gleeson, Dr Mary McDonnell Naughton, Ms Serena Bennett, Dr Eimear McGlinchey, Ms Mandy Daly,

Quorum for decisions: Yes

Agenda

Welcome & Apologies

Application 22-NREC-CT-133

Application 22-NREC-CT-135

Application 22-NREC-CT-136

Application 21-NREC-CT-062_AMEND-5

Application 21-NREC-CT-079_AMEND-4

Application 22-NREC-CT-126_AMEND-1

Application 21-NREC-CT-021_AMEND-2

Application 22-NREC-CT-074_AMEND-2

Application 22-NREC-CT-003_AMEND-2

AOB

- The Chair welcomed the NREC-CT B.
    - The Minutes from the NREC-CT B meeting on 27 July 2022 were approved
    - The NREC Business Report was noted.
    - Declarations of interest: Dr Mark Robinson. (22-NREC-CT-003_AMEND-2). Dr Robinson left the meeting for the review of 22-NREC-CT-003_AMEND-2.

Applications

22-NREC-CT-133

Principal Investigator: Dr Richard Costello

Study title: CONNected Electronic Inhalers Asthma Control Trial 3 (“CONNECT 3”), a 24-Week Treatment, Multicenter, Open-Label, Randomized, Parallel Group Comparison Study of Standard of Care Treatment Versus the Budesonide/Formoterol Digihaler Digital System, to Optimize Outcomes in Adult Patients with Asthma

Lead institution: Beaumont Hospital

EudraCT No.: 2021-003951-41

- **NREC-CT comments:**

- The Committee noted this clinical trial application represents a 24-Week Treatment, Multicenter, Open-Label, Randomized, Parallel Group Comparison Study of Standard of Care Treatment Versus the Budesonide/Formoterol Digihaler Digital System, to Optimize Outcomes in Adult Patients with Asthma
- The Committee agreed that additional information was required to inform its deliberations and therefore, was not yet in a position to return a final ethics decision

- **NREC-CT Decision:**
  - Request for further information
- **Additional Information Required**

- The NREC-CT B queried the scientific justification for the study design whereby participants will be recruited from Standard of care on to the study drug. The NREC-CT B considered that a more robust study design would involve only recruiting participants who are currently on this drug and studying the effect of the Budesonide/formoterol electronic multidose dry powder inhaler (BF Digihaler) Digital System (DS) with 4 component devices. If this cannot be implemented, the NREC-CT B requested that the applicant please provide clear justification for the study design and format in this manner, particularly given the additional risks associated with this drug.
- The NREC-CT B noted that the Investigator Brochure states that during pregnancy, a fixed-dose combination therapy of budesonide and formoterol fumarate dihydrate should only be used when the benefits outweigh the potential risks. The NREC-CT B requested clarification as to how this risk/benefit will this be determined/quantified.
- The NREC-CT B noted that the Investigator Brochure states that patients should be tapered off this drug combination. The NREC-CT B requested clarification as to how this will be performed.
- The NREC-CT B queried whether it would be useful to have further monitoring visits at the start of the study to ensure tolerance to the study medicine
- The NREC-CT B requested further information regarding the role of a legal witness and a legal representative in the consent process, which are referred to in the NREC Application form.
- The NREC-CT B noted that the PIS/ICF references use/storage of samples. However, there is no mention of the method of collection of samples in the protocol or NREC application form and the NREC-CT B requested that this is included
- The NREC Application form refers to potential impact on participant insurance, the NREC-CT B requested that this information should also be included in the PIL/ICF
- The NREC-CT B requested that the dosage adjustment referenced in the IB should also be included in the PIL/ICF
- The PIS/ICF requires inclusion of a risk benefit analysis for pregnancy
- The NREC-CT B queried the necessity for the consent box to “follow the instructions given by the study doctor”.

- The CV of Prof Richard Costello does not include any GCP certification. The NREC-CT B request that the applicants please provide a revised CV, including GCP certification
- The NREC-CT B noted the site suitability form for St James' Hospital makes reference to reimbursement/vouchers for the Standard of Care group, whereas the PIL only references transport reimbursement. The NREC-CT B requested clarification on what reimbursements are available to each group.

22-NREC-CT-135

Principal Investigator: Dr Paula Calvert

Study title: A Randomized, Open-Label, Phase 3 Trial of Tisotumab Vedotin vs Investigator's Choice Chemotherapy in Second- or Third-Line Recurrent or Metastatic Cervical Cancer

Lead institution: University Hospital Waterford

EudraCT No.: 2019-001655-39

- **NREC-CT comments:**

- The Committee noted this clinical trial application represents an open label, randomised (1:1) global phase 3 study of tisotumab vedotin versus investigator's choice of chemotherapy (5 options in control arm, Topotecan, Vinorelbine, Gemcitabine, Irinotecan, Pemetrexed) in participants with cervical cancer who have received 1 or 2 prior lines of systemic therapy for their recurrent or metastatic disease
- The Committee agreed that additional information was required to inform its deliberations and therefore, was not yet in a position to return a final ethics decision

- **NREC-CT Decision:**
  - Request for further information
- **Additional Information Required:**

- The NREC-CT B noted there is reference to male and female participants in the radiation appendix and requested this is corrected/removed
- The NREC-CT B requested that references to UK sites are removed from the radiation appendix as they are not relevant in Irish context
- The NREC-CT had the following considerations regarding participant materials:
- The NREC-CT B considered the use of them term "a few tests" to be misleading (p3 PIC/ICF) and requested that this is amended
- The NREC-CT B considered the PIL to be comprehensive but lengthy and requests a plain English executive summary of the salient points of the study is included at the beginning of the PIL, outlining the aims of the study and the right to not participate.

- The NREC-CT B noted that the PIS/ICF introduction states that the purpose of the research is to study tisotumab vedotin to determine side effects and whether it works better than other available treatments. However, the NREC-CT B considered that the primary outcome of the study is survival, a more suitable phrasing would be “the purpose of this research is to find out whether tisotumab vedotin works better than other treatments available for cervical cancer. We will also find out whether it has side effects and what they are”
- The NREC-CT B requested that clarity is provided in the PIS/ICF 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-CT B requested correction of the minor typographical error: Page20, “… that your data will be transferred too and…” – should read “to”.
- The NREC-CT B requested that CVs must be provided for the investigators at the additional sites; Prof. Karen Cadoo, Dr Grzegorz Korpanty and Dr Dearbhaile Collins.
- The NREC-CT B noted the email address for the PI (paulacavert.referrals @whitefirldclinic.ie) in the NREC form appears to be incorrect; and further recommended not using an email address that is not specifically that of the PI or at an institution other than the study site.

22-NREC-CT-136

Principal Investigator: Prof Elizabeth Vandenberghe

Study title: A Multicenter, Open-label, Phase 2 Basket Study to Evaluate the Safety and Efficacy of MK-2140 as a Monotherapy and in Combination in Participants with Aggressive and Indolent B-cell Malignancies

Lead institution: St James's Hospital

EudraCT No.: 2021-004450-36

- **NREC-CT comments:**

- The Committee noted this clinical trial application represents a Multicenter, Open-label, Phase 2 Basket Study to Evaluate the Safety and Efficacy of MK-2140 as a Monotherapy and in Combination in Participants with Aggressive and Indolent B-cell Malignancies
- The Committee agreed that additional information was required to inform its deliberations and therefore, was not yet in a position to return a final ethics decision

- **NREC-CT Decision:**
  - Request for further information
- **Additional Information Required:**

- The NREC-CT B noted that a 'CTIMP in Combination with Exposure to Radiation Form' was not submitted as part of the application and requested that this form is submitted for review and is signed by both a medical physicist and radiologist/radiation oncologist.
- The NREC-CT noted the inclusion of a QoL questionnaire (QLQ-C30 and EQ-5D-5L) and requested details of provisions in place to support participants, should the questionnaire indicate a mental health issue.
- The NREC-CT B noted that the potential risks associated with radiation exposure is well described in the NREC Application Form, but not in the PIS/CF, and requested that potential risks associated with exposure to radiation are elucidated in the PIS/CF, in line with those described in the NREC Application Form.
- The NREC-CT B noted that recruitment materials were not available for review as part of the submission and noted that these will need to be submitted for review as a Substantial Amendment, when available.
- Furthermore, the NREC-CT B requested that any Substantial Amendment submission will reference how these materials will be used with potential participants.
- The NREC-CT B noted that the consent for Future Biomedical Research is not in line with explicit consent regulations. The area of 'B cell malignancies' was deemed too broad, and the NREC-CT B requested that participants are given options as to how their samples will be used in the future, and this is amended in the FBR PIS/CF.
- Furthermore, the NREC-CT B deemed that the reference to 'Whole genome sequencing' was too broad and requested that genomic sequencing be confined to genes involved in the disease being treated and /or genes involved in the metabolism of the medicines being used in the trial. Furthermore, the NREC-CT B requested clarification is provided on the mechanism for anonymisation, storage and security and transfer of genetic material and its associated data.
- The NREC-CT noted that participants will be asked to complete a QoL questionnaire (QLQ-C30 and EQ-5D-5L) and requested that a more detailed explanation of the questionnaire is elucidated in the PIS/CF, including information on provisions in place to support participants, should the questionnaire indicate a mental health issue.
- Furthermore, the NREC-CT B requested clarification as to how this questionnaire will be administered, such at what stage during the trial and by whom.
- The NREC-CT B noted a discrepancy between the data retention periods stated in the DPIA and PIS/CF – pg5 of the DPIA states that *"The Sponsor may retain the data for longer up to the life of associated medicinal products plus 35 years',* whereas pg15 of the PIS/CF indicates the period to be at least 25 years. The NREC-CT B requested clarification is provided on how long data will be retained for, and that this is aligned in both the PIS/CF and the DPIA.

- The NREC-CT B noted that QoL data will be collected by Medidata and requests clarification on the role of Medidata in the collection of this data – including details about the ownership of the data, data collection, data processing, data retention, participant confidentiality and potential risks involved. The NREC-CT B requests that all relevant information regarding Medidata is incorporated into the DPIA.
- The NREC-CT B noted that the Insurance Certificate expires on 29th July 2023 and requested confirmation that insurance cover is valid for the duration of the trial

21-NREC-CT-062_AMEND-5

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

EudraCT No.: 2018-004117-40

- **NREC-CT comments:**

- The NREC-CT B noted this clinical trial application represents 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)
- Based on the above, the Committee agreed that this substantial amendment application be designated as favourable

- **NREC-CT Decision:**
  - Favourable
- **Additional Information Required:**
- The NREC-CT B commented that a summary PIL would be helpful for participants.

21-NREC-CT-079_AMEND-4

Principal Investigator: Prof Ray McDermott

Study title: A Randomized Phase 3 Study Evaluating Cystectomy with Perioperative Pembrolizumab and Cystectomy with Perioperative Enfortumab Vedotin and Pembrolizumab versus Cystectomy Alone in Cisplatin-Ineligible Participants with Muscle-Invasive Bladder Cancer (KEYNOTE-905/EV-303)

Lead institution: Tallaght University Hospital

EudraCT No.: 2018-003809-26

- **NREC-CT comments:**

- The NREC-CT B noted this clinical trial application represents a Randomized Phase 3 Study Evaluating Cystectomy with Perioperative Pembrolizumab and Cystectomy with Perioperative Enfortumab Vedotin and Pembrolizumab versus Cystectomy Alone in Cisplatin-Ineligible Participants with Muscle-Invasive Bladder Cancer (KEYNOTE-905/EV-303)
- The NREC-CT B agreed that additional information was required to inform its deliberations and therefore, was not yet in a position to return a final ethics decision on this Substantial Amendment.

- **NREC-CT Decision:**
  - Request for further information
- **Additional Information Required:**

- The NREC-CT B noted that the PIL does not mention that the trial recruitment has been halted for new participants over safety concerns and would request that this be updated to include this information for current and future participants.
- The NREC-CT B queried that there is no mention of the mechanism of how participants will be given the new participant card, have the old card removed, and what explanations will be given to them about the updated card and requested clarification of same.
- The NREC-CT B requested information on whether the HPRA have approved the restart of recruitment and what measures have they taken to address the safety concerns raised by HPRA. There is not enough information in the PIL – transparency is required for future participants.

22-NREC-CT-126_AMEND-1

Principal Investigator: Prof Ray McDermott

Study title: A PROSPECTIVE RANDOMISED PHASE III STUDY OF ANDROGEN DEPRIVATION THERAPY WITH OR WITHOUT DOCETAXEL WITH OR WITHOUT LOCAL RADIOTHERAPY WITH OR WITHOUT ABIRATERONE ACETATE AND PREDNISONE IN PATIENTS WITH METASTATIC HORMONE-NAÏVE PROSTATE CANCER

Lead institution: Tallaght University Hospital

EudraCT No.: 2012-000142-35

- **NREC-CT comments:**

- The NREC-CT B noted this clinical trial application represents a prospective randomised phase III study of androgen deprivation therapy with or without docetaxel with or without local radiotherapy with or without abiraterone acetate and prednisone in patients with metastatic hormone-naïve prostate cancer.

- The NREC-CT B agreed that additional information was required to inform its deliberations and therefore, was not yet in a position to return a final ethics decision on this Substantial Amendment

- **NREC-CT Decision:**
- Request for further information
- **Additional Information Required:**

- The NREC-CT B advised that they are unable to approve the letter to participants summarising the outcome of the study in its current format. The NREC-CT B commented that the letter is complex/technical and would benefit from PPI involvement to simplify the syntax and language for a vulnerable non-technical audience.
- The NREC-CT B noted that the second element of the letter is to state that participants data will be used further however there is no mention if the participant has already consented to this or what the participant has agreed to in the first place. The NREC-CT B requested that the letter be updated to include this information as it wasn't clear. Please note that an opt out approach is not considered appropriate.
- The NREC-CT B also noted that the possibility of withdrawing consent is raised, however it indicates that if withdrawal of data interferes with the trial objectives, then the company can refuse to allow participants to exercise their rights. The NREC-CT B would comment that this would be a breach of data protection regulations. The NREC-CT B raised concerns with consent procedures for on-going use of data & request clarification on this.

21-NREC-CT-021_AMEND-2

Principal Investigator: Prof Douglas Veale

Study title: A phase 3, Randomised, Double-Blind, Placebo-controlled study to evaluate the efficacy and safety of Deucravacitinib in participants with active Psoriatic Arthritis who are Naive to Biologic Disease-modifying Anti-rheumatic drugs

Lead institution: St. Vincent's University Hospital

EudraCT No.: 2020-005097-10

- **NREC-CT comments:**

- The NREC-CT B noted this clinical trial application represents a phase 3, Randomised, Double-Blind, Placebo-controlled study to evaluate the efficacy and safety of Deucravacitinib in participants with active Psoriatic Arthritis who are Naive to Biologic Disease-modifying Anti-rheumatic drugs
- Based on the above, the NREC-CT B agreed that this substantial amendment application be designated as favourable with conditions

- **NREC-CT Decision:**
- Favourable with conditions

- **Conditions of Approval:**

- The NREC-CT B requested that the Participant ID Card be updated to include an explanation for PK and to give a lay language explanation for greater than or equal to symbol – for example ‘at least 10 hours’.
- The NREC-CT B Committee noted the following on the Pregnancy Test Instructions. The same information appears on both pages. Please clarify if this is an error and provide an updated instruction for review.
- The NREC-CT B noted that the scanned image of the test apparatus needs to be improved as the position ‘S’ as identified in the ‘How to use the kit’ instructions is not discernible in the image. The NREC-CT B suggested that adding a highlighter to it would improve for participants

22-NREC-CT-074_AMEND-2

Principal Investigator: Prof Brian Kirby

Study title: A Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study Evaluating the Efficacy and Safety of Bimekizumab in Study Participants With Moderate to Severe Hidradenitis Suppurativa

Lead institution: St. Vincent's University Hospital

EudraCT No.: 2019-002551-42

- **NREC-CT comments:**
- The NREC-CT B noted this clinical trial application represents a Phase 3, Randomized, Double-Blind, Placebo-Controlled, Multicenter Study Evaluating the Efficacy and Safety of Bimekizumab in Study Participants With Moderate to Severe Hidradenitis Suppurativa.
- The Committee agreed that additional information was required to inform its deliberations and therefore, was not yet in a position to return a final ethics decision on this Substantial Amendment.

- **NREC-CT Decision:**
- Request for further information
- **Additional Information Required:**

- The NREC-CT B requested that the Thank You Letter be updated as while it is thorough and informative the language in it could be considered coercive. The language is too saccharine & could be interpreted as patronising by patients so should be amended. The NREC-CT advised the applicants consider adding that participation remains voluntary and they may withdraw at any time.

22-NREC-CT-003_AMEND-2

Principal Investigator: Prof Suzanne Norris

Study title: A Phase 2, Double-Blind, Randomized, Parallel Group Study Evaluating the Efficacy, Safety, and Tolerability of Obeticholic Acid Administered in Combination with Bezafibrate in Subjects with Primary Biliary Cholangitis Who Had an Inadequate Response or Who Were Unable to Tolerate Ursodeoxycholic Acid

Lead institution: St James's Hospital, Dublin 8, Ireland

EudraCT No.: 2018-002575-17

- **NREC-CT comments:**
- The Committee noted this clinical trial application represents a Phase 2, Double-Blind, Randomized, Parallel Group Study Evaluating the Efficacy, Safety, and Tolerability of Obeticholic Acid Administered in Combination with Bezafibrate in Subjects with Primary Biliary Cholangitis Who Had an Inadequate Response or Who Were Unable to Tolerate Ursodeoxycholic Acid
- Based on the above, the Committee agreed that this substantial amendment application be designated as favourable.
- **NREC-CT Decision:**
- Favourable

- AOB:

The Chair closed the meeting.