Health Research Authority
Yorkshire & The Humber - Leeds East Research Ethics Committee
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Please note: This is the favourable opinion of the REC only and does not allow you to start your study at NHS sites in England until you receive HRA Approval

13 May 2016

Dr Janet Brown
University of Sheffield
Weston Park Hospital, Whitham Road
Sheffield
S10 2SJ

Dear Dr Brown

Study title:	**The role of ZOLedronic acid and MENOpausal status on the tumour and bone microenvironment in patients with early breast cancer: a single centre, randomised, proof of concept clinical study.**
REC reference:	**16/YH/0151**
Protocol number:	**STH19171**
EudraCT number:	**2015-005713-67**
IRAS project ID:	**197918**

The Research Ethics Committee reviewed the above application at the meeting held on 03 May 2016. Thank you for attending with Ms Lindsey Frederick, Research Fellow, to discuss the application.

We plan to publish your research summary wording for the above study on the HRA website, together with your contact details. Publication will be no earlier than three months from the date of this favourable opinion letter. The expectation is that this information will be published for all studies that receive an ethical opinion but should you wish to provide a substitute contact point, wish to make a request to defer, or require further information, please contact the REC Manager Miss Kathryn Murray, nrescommittee.yorkandhumber-leedseast@nhs.net. Under very limited circumstances (e.g. for student research which has received an unfavourable opinion), it may be possible to grant an exemption to the publication of the study.

Ethical opinion

The members of the Committee present gave a favourable ethical opinion of the above research on the basis described in the application form, protocol and supporting documentation, subject to the conditions specified below.

Conditions of the favourable opinion

The REC favourable opinion is subject to the following conditions being met prior to the start of the study.

1. Submit a revised consent form to address the following issue:
   a. Replace the word 'patient' with 'participant'.
2. It was also recommended that the lay summary of the study (IRAS question A6-1) be revised to address the following points:
   a. Correct the error around the study duration (states 69 days, when this should be 65 days),
   b. Include additional detail around why the two groups have been selected (i.e. tumour/no tumour).

You should notify the REC once all conditions have been met (except for site approvals from host organisations) and provide copies of any revised documentation with updated version numbers. Revised documents should be submitted to the REC electronically from IRAS. The REC will acknowledge receipt and provide a final list of the approved documentation for the study, which you can make available to host organisations to facilitate their permission for the study. Failure to provide the final versions to the REC may cause delay in obtaining permissions.

Management permission must be obtained from each host organisation prior to the start of the study at the site concerned.

Management permission should be sought from all NHS organisations involved in the study in accordance with NHS research governance arrangements. Each NHS organisation must confirm through the signing of agreements and/or other documents that it has given permission for the research to proceed (except where explicitly specified otherwise).

Guidance on applying for HRA Approval (England)/ NHS permission for research is available in the Integrated Research Application System, at www.hra.nhs.uk or at http://www.rdforum.nhs.uk.

Where a NHS organisation's role in the study is limited to identifying and referring potential participants to research sites ("participant identification centre"), guidance should be sought from the R&D office on the information it requires to give permission for this activity.

For non-NHS sites, site management permission should be obtained in accordance with the procedures of the relevant host organisation.

Sponsors are not required to notify the Committee of management permissions from host organisations.

Registration of Clinical Trials

All clinical trials (defined as the first four categories on the IRAS filter page) must be registered on a publicly accessible database. This should be before the first participant is recruited but no later than 6 weeks after recruitment of the first participant.

There is no requirement to separately notify the REC but you should do so at the earliest opportunity e.g. when submitting an amendment. We will audit the registration details as part of the annual progress reporting process.

To ensure transparency in research, we strongly recommend that all research is registered but for non-clinical trials this is not currently mandatory.

If a sponsor wishes to request a deferral for study registration within the required timeframe, they should contact hra.studyregistration@nhs.net. The expectation is that all clinical trials will be registered, however, in exceptional circumstances non registration may be permissible with prior agreement from the HRA. Guidance on where to register is provided on the HRA website.

Clinical trial authorisation must be obtained from the Medicines and Healthcare products Regulatory Agency (MHRA).

The sponsor is asked to provide the Committee with a copy of the notice from the MHRA, either confirming clinical trial authorisation or giving grounds for non-acceptance, as soon as this is available.

It is the responsibility of the sponsor to ensure that all the conditions are complied with before the start of the study or its initiation at a particular site (as applicable).

Ethical review of research sites

NHS Sites

The favourable opinion applies to all NHS sites listed in the application taking part in the study, subject to management permission being obtained from the NHS/HSC R&D office prior to the start of the study (see "Conditions of the favourable opinion" below).

Non NHS sites

The Committee has not yet completed any site-specific assessment(s) (SSA) for the non-NHS research site(s) taking part in this study. The favourable opinion does not therefore apply to any non-NHS site at present. I will write to you again as soon as an SSA application(s) has been reviewed. In the meantime no study procedures should be initiated at non-NHS sites.

Summary of discussion at the meeting

All other issues noted in preliminary discussion were raised with the researcher or noted in correspondence.

Social or scientific value; scientific design and conduct of the study

Members discussed the primary and secondary endpoints detailed for the study and it was agreed that the study was powered to achieve the primary outcome measures. It was discussed whether the 40mls blood sample was a sufficient draw to carry out testing relevant to the secondary endpoints.

You confirmed that the 40ml samples which would be collated across the five study time points were sufficient to carry out all of the testing required in relation to the primary and secondary endpoints. You added that whilst there were many assays this had been accurately calculated to ensure the sample was sufficient. You clarified that you used to work

in Clinical Science, specifically genetics, and had your own laboratory. You confirmed you fully understood this work and what would be a priority if it was not possible to draw the full sample size required. You also advised that the calculations and measurements had taken into account of what volume would remain after the sample had spun down in the centrifuge.

Ms Frederick further advised that the calculations had also allowed for a margin of error and requirement to repeat tests.

The REC queried whether there was sufficient power to the sample size calculations to allow achievement of both the primary and secondary objectives.

You confirmed that the study was powered to achieve the primary research objectives as these were the main trial purposes; however, you confirmed that you were happy that the study was also sufficiently powered to achieve meaningful results for the secondary objectives. You added that the exploratory endpoints were included as a springboard for further research following the close of this trial.

Members discussed the optional additional bone marrow sample and it was queried whether there was potential for so few participants to consent to this additional sub-study that the applicants were unable to gather enough information.

You explained that the research team had debated around whether to make the additional bone marrow sample a mandatory element to trial participation; however, it was agreed that this was inappropriate. You advised that as the Research Fellow was so heavily involved in the trial, this made for better uptake of the optional elements, as the participants would develop a relationship with the individual members of the research team. You anticipated that uptake on the additional bone marrow sample would be around 50%, which was made easier as single-site study, where all members of the research team were working closely with the participants. You admitted that this may seem optimistic; however, the team believed that this level of recruitment would be possible.

Favourable risk benefit ratio; anticipated benefit/risks for research participants (present and future)

The Committee commented that it was known that post-menopausal women benefitted from taking zoledronic acid when diagnosed with early stage breast cancer. It was queried whether the participants in this cohort were disadvantaged from the delayed administration or removal of the repeated dosing of the drug.

You explained that in the existing trials participants had a grace period of a couple of months to begin taking the zoledronic acid. You clarified that it was the meta-analysis, rather than the trials, which had highlighted the benefits of taking zoledronic acid. You further advised that the standard of care was changing to include this provision and this would be implemented by the end of the trial, meaning the patient participants would receive a five year prescription for the drug as part of their cancer care management.

Members noted that the study duration was 65 days and it was queried whether this was an acceptable interval to postpone administration of the zoledronic acid.

You confirmed that the delay was acceptable and the drug would be received within the correct timeframe, as qualified by the previous trial.

The REC queried whether there was the potential for participants to be excluded from forthcoming CTIMP trials directly linked to their breast cancer due to their prior involvement with this study.

You explained that as this trial was directly linked to the breast cancer surgery and its follow-up, you did not think this would interfere with future CTIMP participation. You added that you had spoken with the surgical MDT who confirmed that they were not anticipating any CTIMP enrolment in the near future and they had also confirmed that this trial was to be prioritised as the benefit of zoledronic acid administration had been seen.

It was further queries whether participants would be eligible for enrolment in a CTIMP study as soon as they had completed the follow-up for this trial.

You confirmed that this was the case – you explained that whilst CTIMP studies often had rigid criteria around the wash-out period from previous studies prior to recruitment; you didn't think this study would cause issue.

The Committee discussed the administration of the trial drug via IV, which presented further safety issues and it was queried whether there was an alternative oral bisphosphonate which could be used.

You explained that the trial had been designed in order to mirror the likely way this would be assimilated into standard of care treatment. You explained that early chemotherapy was often administered via an IV drip, before patients are asked if they would like to change to an alternative and less restrictive method. You confirmed that zoledronic acid had been extensively used in current clinical practice in this manner of administration. You advised that an American study had focussed on the use of a variety of bisphosphonates; however, the trial had not included any control arm against which to measure the results, so it was difficult to say whether there was an alternative. You confirmed that administration of zoledronic acid via IV was likely to be the standard care pathway moving forward.

Members queried whether zoledronic acid was available for oral administration.

You advised that it was not – you confirmed that if the method of administration was to be changed, as different bisphosphonate would be offered. You further added that it took a longer time for practices to be assimilated to standard of care, which was why the research team did not want to delay the start to this study.

The response was received and no further issues were raised.

Other ethical issues were raised and resolved in preliminary discussion before your attendance at the meeting.

Approved documents

The documents reviewed and approved at the meeting were:

Document	*Version*	*Date*
GP/consultant information sheets or letters [GP Letter Group A]	1.0	11 March 2016
IRAS Checklist XML [Checklist_30032016]		30 March 2016
Other [GP Letter Group B]	1.0	11 March 2016
Other [Student CV]		28 January 2016
Participant consent form [ZOLMENO Consent Form]	1.0	11 March 2016
Participant information sheet (PIS) [ZOLMENO Participant Information Sheet]	1.0	11 March 2016
REC Application Form [REC_Form_21032016]		21 March 2016
Research protocol or project proposal [ZOLMENO protocol]	1.0	11 March 2016

Summary CV for Chief Investigator (CI) [Chief Investigator CV (JEB)]	1.0	11 March 2016
Summary of product characteristics (SmPC) [SPC Zoledronic Acid]	1.0	11 March 2016

Membership of the Committee

The members of the Ethics Committee who were present at the meeting are listed on the attached sheet.

Statement of compliance

This Committee is recognised by the United Kingdom Ethics Committee Authority under the Medicines for Human Use (Clinical Trials) Regulations 2004, and is authorised to carry out the ethical review of clinical trials of investigational medicinal products.

The Committee is fully compliant with the Regulations as they relate to ethics committees and the conditions and principles of good clinical practice.

The Committee is constituted in accordance with the Governance Arrangements for Research Ethics Committees and complies fully with the Standard Operating Procedures for Research Ethics Committees in the UK.

After ethical review

Reporting requirements

The attached document "After ethical review – guidance for researchers" gives detailed guidance on reporting requirements for studies with a favourable opinion, including:

- Notifying substantial amendments
- Adding new sites and investigators
- Notification of serious breaches of the protocol
- Progress and safety reports
- Notifying the end of the study

The HRA website also provides guidance on these topics, which is updated in the light of changes in reporting requirements or procedures.

User Feedback

The Health Research Authority is continually striving to provide a high quality service to all applicants and sponsors. You are invited to give your view of the service you have received and the application procedure. If you wish to make your views known please use the feedback form available on the HRA website: http://www.hra.nhs.uk/about-the-hra/governance/quality-assurance/

HRA Training

We are pleased to welcome researchers and R&D staff at our training days – see details at http://www.hra.nhs.uk/hra-training/

With the Committee's best wishes for the success of this project.

Yours sincerely

pp.
Dr Rhona Bratt
Chair

E-mail: nrescommittee.yorkandhumber-leedseast@nhs.net

Enclosures: *List of names and professions of members who were present at the meeting and those who submitted written comments*

"After ethical review – guidance for researchers" [*SL-AR1 for CTIMPs]*

Copy to: *Dr Erica Wallis, Sheffield Teaching Hospitals NHS Foundation Trust*

Yorkshire & The Humber - Leeds East Research Ethics Committee

Attendance at Committee meeting on 03 May 2016

Committee Members:

Name	*Profession*	*Present*	*Notes*
Miss Jennifer Blaikie	Senior Research Ethics Administrator	Yes	
Dr Rhona Bratt (Chair)	Retired Multimedia Project Manager	Yes	
Professor Kenneth Brodlie	Retired Professor of Visualization	Yes	
Dr Alexandros Chatziagorakis	ACF ST in General Adult Psychiatry	No	
Dr Deborah Jane Fox	Senior Lecturer in Nursing	Yes	
Mrs Ann Kay	Retired Special Needs Coordinator	Yes	
Dr Nicolas Orsi	Senior Research Fellow	Yes	
Dr Andrew Pollard	Consultant Anaesthetist	Yes	
Dr Anna Rees	Core Medical Trainee (year 2)	No	
Mr Satti Saggu	Senior Associate for Research	No	
Mr Roly Squire	Consultant Paediatric Surgeon	Yes	
Mr Karl Ward	Senior Research Nurse	Yes	
Mr Tom Wilson	Consultant ENT Surgeon	Yes	
Miss Kate Woodrow	Assistant Chief Pharmacist	Yes	

Also in attendance:

Name	*Position (or reason for attending)*
Dr Ian Max Huxham	Observer – Retired Scientist
Dr Nicky Kime	Observer – Senior Research Fellow
Miss Kathryn Murray	Covering REC Manager
Dr Janet Brown	Chief Investigator
Ms Lindsey Frederick	Research Fellow