20 August 2018

Professor Peter Wark
Department of Respiratory Medicine
John Hunter Hospital

Dear Professor Wark,

Re: Choosing Between Biological Agents for Severe Allergic Eosinophilic Asthma (18/08/15/3.01)

HNEHREC Reference No: 18/08/15/3.01
NSW HREC Reference No: HREC/18/HNE/206

Thank you for submitting the above protocol for single ethical review. This project was first considered by the Hunter New England Human Research Ethics Committee at its meeting held on **15 August 2018.** This Human Research Ethics Committee is constituted and operates in accordance with the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research (2007)* (National Statement) and the *CPMP/ICH Note for Guidance on Good Clinical Practice*. Further, this Committee has been accredited by the NSW Ministry of Health as a lead HREC under the model for single ethical and scientific review. The Committee's Terms of Reference are available from the Hunter New England Local Health District website: http://www.hnehealth.nsw.gov.au/ethics/Pages-Research-Ethics-and-Governance-Unit.aspx

As part of the procedure for ethical approval of research involving humans in the Hunter New England Local Health District the above protocol has reviewed by the Clinical Trials Sub-Committee, an advisory group of the Hunter New England Human Research Ethics Committee.

The Hunter New England Human Research Ethics Committee has resolved that the above protocol will be approved subject to a satisfactory response being received to the following concerns:

- In accordance with section 1.1.b of *the National statement on Ethical Conduct in Human Research, 2007 (updated 2018),* Research has Merit when it is "designed or developed using methods appropriate for achieving the aims of the proposal." However, the above protocol is designed as a non-inferiority study, although the protocol states that neither investigational product is established as a benchmark. Is this an ethical use of non-inferiority and should the study be configured as a head-to-head superiority study? A critical design issue for non-inferiority studies is adequate sample size calculation, as an underpowered study may deliver the appearance of non-inferiority by design. Therefore, the sample size calculation needs review and if possible independently reviewed;
- How is acceptable medication adherence being measured;
- Can potential participants be included if they are currently on or have previously used one of these agents? If they have not responded to one of these agents previously, can they be included in the study;

Hunter New England Research Ethics & Governance Office
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- Will participants be able to access the drug after the end of the trial, section 3.1.38(c) of *the National Statement on Ethical Conduct in Human Research 2007 (updated 2018) r*equired that potential participants be informed as whether they will have access after completion of the project or active treatment phase of the project to the intervention, treatment or information that they have received, and if so, with what limitations, if any;
- No justification has been given for the numbers in the sub-studies (40 in each arm plus the non-responders); and
- On page eight of the Participant Information Statement under "What happens if I fail to respond to the treatment I am given?" paragraph two, there is a reference to "the next trial" is there an associated trial to this one?

Please note: All Tax Invoices are raised by our Centralised Billing Service, so if there are any special conditions required by the Organisation re. the payment of accounts, please ensure you provide the details so we can enter these instructions on the Request to Raise the Tax Invoice.

Note: each of the above concerns should be responded to in a letter - **DO NOT amend the Ethics Application or any part thereof but where necessary the protocol should be revised with tracked changes.**

In addition, in accordance with Section 3.3.12 of the National Health and Medical Research Council's *National Statement on Ethical Conduct in Human Research (2007)* Prior to commencing the study, it should be registered in a publicly accessible register. The Committee recommends the Australian New Zealand Clinical Trials Registry (ANZCTR) at www.anzctr.org.au/default.aspx

With regard to the recruitment documentation:

- in accordance with the requirements of s. 2.2.6 of the *National Statement on Ethical Conduct in Human Research (2007)* relating to informed consent the following changes should be made to the Participant Information Statement:
  - Page two, under "Which treatment will I receive if I agree to be in the study?" line one, "making and informal choice about" should be changed to "choosing";
  - Page three, the table of study visits needs to be made more meaningful for the participants with the different tests or measures explained (in a legend below the table is acceptable);
  - Page five, under "What are the possible risks and disadvantages of taking part?" the side effects of the drugs should be included;
  - Page six, the table representing the timing of the optional sample collection or the explanations of the sub study are not in layterms and so should be rewritten and simplified;
  - Page seven, the section on "Residual samples" should specify what type of research the samples may be used for and where they will be stored;
  - Page nine, the heading "Part 2 How is the research study being conducted?" should be deleted; and
  - Page eleven, a further line should be added to the table for HREC Contact

Please quote:	Reference No: 18/08/15/3.01

All revised documents must have an updated version number and date in the footer of the document. *For ease of review please track the requested changes to the revised documentation.*

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If this application is for multicentre research please submit both Master and Site Specific recruitment documentation. The version numbers and dates should be sequential for each type of documents. Please note that the Site specific documentation will usually be version 1 regardless of the version number of the Master documentation.

Please note that all responses should be from the Chief Investigator or where the research involves a postgraduate student, the students Principal Supervisor.

In order to facilitate the further review of your application, please provide the requested information as soon as possible. Your response should be emailed to the Manager, Research Ethics & Governance: HNELHD-HREC@hnehealth.nsw.gov.au **Please note only an electronic copy is required do NOT sent a hard copy.**

Please note that if a response to this letter is not received within 3 months or two meetings (whichever occurs sooner), the project will be dismissed and you will be required to re-submit the project at a later date. You may request additional time to respond.

Please quote **18/08/15/3.01** in all electronic correspondence.

You are reminded that it is a condition of the *National Statement on Ethical Conduct in Human Research (2007)* that your Research may not commence until you have received an approval letter.

Yours Sincerely,

Dr Nicole Gerrand
Executive Officer
Hunter New England Human Research Ethics Committee

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