MHRA
151 Buckingham Palace Road
London SW1W 9SZ
United Kingdom

mhra.gov.uk

Prof M Parmar
UNIVERSITY COLLEGE LONDON
MEDICAL RESEARCH COUNCIL CLINICAL TRIALS UNIT
90 HIGH HOLBORN
LONDON
WC1V 6LJ
UNITED KINGDOM

08/11/2017

Dear Prof M Parmar

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 2004/1031 (as amended)(the 'Regulations')

Our Reference:	20363/0380/001-0001
Eudract Number:	2017-002329-39
Product:	Durvalumab
Protocol number:	RE06

NOTICE OF GROUNDS FOR NON-ACCEPTANCE AND RIGHT TO AMEND REQUEST

I refer to your request for a clinical trial authorisation (CTA), received on 18/10/2017. The Licensing Authority has carefully considered your request in accordance with regulations 18-20 of the Regulations, but has decided that it is not acceptable at this point on the following grounds:

Grounds for Non-Acceptance
Medical Points
* An amended protocol (clean, ideally signed document) should be submitted to address the following (a commitment to submit an amended protocol before dosing the first trial participant will not be acceptable):
1) The Sponsor is required to amend the exclusion criteria for QT interval and exclude patients whose QT interval corrected using Fridericia's formula (QTcF) > 450 msec or a rationale must be provided why a QT interval of 470 msec should be considered acceptable both in male and female patients.
2) The Sponsor is required to amend the protocol and clarify that a serum pregnancy test will be performed to exclude pregnancy at screening. Urine pregnancy test is acceptable after contraception has been established. In case of doubt a urine pregnancy test must always be followed by a serum pregnancy test.
3) The following statement cannot be considered acceptable: "Not engaging in sexual activity for the total duration of the trial and the drug washout period is an acceptable practice". As stated in the CTFG guidance about contraception "the reliability of sexual abstinence needs to be evaluated in relation to the duration of the clinical trial and the preferred and usual lifestyle of the subject". Considering the long duration of the treatment and washout phases, abstinence for the duration of the trial and the drug washout period is not deemed acceptable. The Sponsor is required to amend the protocol and state that contraceptive measures will apply to all male participants and to women of

childbearing potential. The protocol must state that abstinence is acceptable only if it is the preferred and usual lifestyle of the subject.
4) The Sponsor is required to provide a strong rationale to support inclusion of adult patients whose body weight is 30 kg or the body weight inclusion criterion must be amended as appropriate.
5) It is not acceptable that the trial toxicity management guidelines are not included in the trial protocol, but provided separately. The Sponsor is required to amend the protocol and include in the protocol the toxicity management guidelines for all treatment arms.
6) The Sponsor is required to extend the AEs/SAEs collection to at least 105 days after the last study drug administration or a rationale must be provided to support a 90-day duration of safety follow-up.
For clarification on the above points, please contact Dr Maria Beatrice Panico on 020 3080 6825.
Remark concerning the durvalumab Investigator Brochure (IB): the Sponsor is reminded that a serious adverse reaction which occurred once cannot usually be considered expected, unless there is a very strong plausibility of a causal relationship with the IMP and a robust justification based on medical judgement is provided. In the case of this IB single occurrences have to be considered unexpected due to the absence of a strong justification to support their expectedness. The Sponsor is required to acknowledge this remark and commit reporting single occurrences as SUSARs. The Sponsor is also reminded that in future medical concepts will not be allowed.
Remark concerning Tremelimumab IB: If non-serious adverse reactions are included in the Reference Safety Information (RSI) table the sponsor is reminded that should a serious event occur for any term which has only ever previously been seen as non-serious this should be considered unexpected and therefore reported as a SUSAR. Single occurrences are unexpected.
Remark concerning addition of future arms: the Sponsor is advised to contact the MHRA (please send an email to clintrialhelpline@mhra.gov.uk) before submitting an amendment adding additional arms. The Sponsor is reminded that the only changes that can be implemented at the time of the GNA response are the ones required to address the grounds of non-acceptance (GNAs) raised by the MHRA.

Pharmaceutical Points
* The QP declaration provided does not refer to the proposed trial. An updated declaration should be provided.
* The full supply chain to be used in this trial for both IMPs should be confirmed (and all necessary supporting document for these sites submitted (MIA(IMP) or QP declaration).
For further information on the above points, please contact Dr Graham McNaughton on 020 3080 6148.

You may respond to the grounds identified in this letter within the timescales set out in regulations 18-20 [14 days for regulations 18 and 20; 30 days for regulation 19 (advanced therapy medicinal products or products containing genetically modified organisms)], otherwise your application will be deemed to

have been refused. This amended request should cover all the issues raised in this letter, and only these issues.

Yours sincerely,

Clinical Trials Unit
MHRA