Medicines & Healthcare products Regulatory Agency

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Dr P Bath
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13/05/2021

Dear Dr P Bath,

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

Our Reference:	CTA 03057/0073/001-0001
Eudract Number:	2021-000185-15
Product:	Ciclesonide, Niclosamide Ethanolamine
Protocol number:	21001

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

I refer to your request for a clinical trial authorisation (CTA), received on 28/04/2021.

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 - GNA Remarks: Clinical grounds for Non-Acceptance.
* An amended protocol/IB should be submitted to address the following points. A tracked changes version as well as a clean version, ideally signed, are required. A commitment to submit an amended protocol before dosing the first trial participant will not be acceptable.
1. A scientific rationale for the inclusion of Ciclesonide and Niclosamide as IMP's in this trial must be provided.
2. There are no eligibility criteria specific to previous receipt of a COVID vaccine. Whilst the latter is acceptable in principle, the Sponsor is asked to stratify for the fact that some trial participants may have been previously vaccinated (otherwise if it looks like one arm works as prophylaxis it could be because all those in that arm had the vaccine, rather than secondary to the new intervention).
3. The IMP Appendices must be clearly linked to the core protocol version and date, i.e. they must reference the core document that they relate to.
4. The IB provided is version 1.0, dated the 26th August 2020. The MHRA have approved a more recent version of the IB for UNI911 (Niclosamide Ethanolamine), Version 2.0, dated the 23rd September 2020. The most up to date IB must be provided.

5. Individual treatment withdrawal criteria based on safety must be provided.
6. There is no benefit:risk assessment in the protocol, the protocol must be modified accordingly, with particular attention given to the fact trial participants are likely to have 'significant' co-morbidities and be on multiple medications as a result.
7. There is a paucity of safety monitoring planned. The protocol should address the known side-effect profile of the IMP's and how any risks will be mitigated for in this trial where the trial population are elderly, likely to be frail, with co-morbidities and on multiple medications.
For further information email lisa.campbell@mhra.gov.uk
PHARMACEUTICAL - GNA Remarks: Pharmaceutical Grounds for Non-Acceptance:
1. The stability data presented do not support the proposed shelf life of 36 months for the ciclesonide drug product. Significant increases in impurity RRT 1.12 are observed in the 60 dose inhalers, when stored inverted, at 18/24 month time points, with out of specification results observed. Unknown and total impurities are also out of specification at 18/24 month time points for some batches. Further justification is required and/or a reduction in the shelf life should be proposed.
For further information on the above point, please contact Dr Graham McNaughton on 020 3080 6148 or graham.mcnaughton@mhra.gov.uk.

You are reminded that any changes to a document other than those requested in this letter to address the grounds of non-acceptance (GNAs) are not permitted. Any other additional changes should be addressed via an appropriate amendment following MHRA authorisation, if granted.

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.

Yours sincerely,

Clinical Trials Unit
MHRA