Medicines & Healthcare products Regulatory Agency

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02/03/2022

Dear Dr Pamela Sandu,

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

Our Reference:	CTA 24712/0060/001-0001
Eudract Number:	2021-006886-39
Product:	Noradrenaline (Norepinephrine), Plasma-Lyte® 148, Compound Sodium Lactate Solution for Infusion BP
Protocol number:	GN20AE342

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

I refer to your request for a clinical trial authorisation (CTA), received on 31/01/2022.

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:

1.-An amended protocol must be submitted to address the following points (a commitment to submit an amended protocol before dosing the first trial participant will not be acceptable). A tracked changes version as well as a clean version, ideally signed, are required:

1.1.-Pregnant participants must be excluded; therefore, this must be listed as exclusion criterion. A pregnancy test must be conducted and confirmed as negative before starting treatment with the investigational medicinal product (IMP) in this study.

1.2.-The following exclusion criteria must be added:

•Suspicious of other causes of shock different to sepsis (e.g. suspected cardiogenic shock, haemorrhagic shock, etc)

•History or evidence of any other medical, neurological or psychological condition that would expose the subject to an undue risk of a significant AE as determined by the clinical judgment of the investigator.

•Participation in other clinical trials of investigational medicinal products.

1.3.- Co-enrolment in an interventional Phase of other CTIMP is not agreed and must be removed from the protocol.

1.4.- The sponsor is required to provide in the protocol a detailed dose rationale to support the proposed starting and maximum doses of norepinephrine for peripheral intravenous administration. This must include an expanded discussion on safety aspects, dosing intervals and treatment duration.

1.5.-IMP treatment discontinuation criteria (e.g. due to toxicity) must be provided in the protocol.

1.6.-The protocol must be amended to clarify that the use of noradrenaline with volatile halogenated anaesthetic agents, monoamine oxidase inhibitors, linezolid, tricyclic antidepressants, adrenergic-serotoninergic drugs or any other cardiac sensitising agents is not recommended because severe, prolonged hypertension and possible arrhythmias may result.

1.7.-According to the protocol, “Only deaths that are assessed to be caused by the IMP will be reported to the sponsor. This report will be immediate – within 72 hours”. This is not fully acceptable, death assessed to be caused by the IMP must be reported to the sponsor as soon as possible and under no circumstances should this exceed 24 hours following knowledge of the serious adverse event. The protocol must be amended to make this clear.

1.8.-In the schedule of Assessment, the assessment of AEs is not conducted at the timepoints 6 and 12 hours. This is not acceptable. The schedule of assessments must be amended to reflect continuous AEs recording.

2.-The Independent Data Monitoring Committee (IDMC) must be declared in section E8-7 of the CTA Application form (Annex I).

3.- The sponsor is proposing the use of noradrenaline administered by a route of administration (peripheral venous infusion) that is not the licenced route of administration (via a central venous catheter), therefore, it is considered that any serious local reactions (e.g. peripheral ischaemia, including gangrene of the extremities or necrosis, considered related to the IMP), including life-threatening or fatal events, must be considered unexpected in this trial and reported as SUSAR. The document “RSI Form 55.005B v 1.0 noradrenaline” must be amended accordingly to make this clear and remove these events from the expected events.

*Remark:

Please, note that other changes to the protocol are not permitted.

If you require any clarification on these comments, please contact Dr Maria Urdaneta-Abate on Maria.UrdanetaAbate@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