Medicines & Healthcare products Regulatory Agency

MHRA

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Ms W van Bentum-Puijk
UNIVERSITY MEDICAL CENTRE UTRECHT
HEIDELBERGLAAN 100,
UTRECHT
NL-3584 CX
NETHERLANDS

15/12/2021

Dear Ms W van Bentum-Puijk,

NOTICE OF NON-ACCEPTANCE OF AMENDMENT

Our Reference:	CTA 30913/0006/001-0022
Eudract Number:	2015-002340-14
Product:	ceftriaxone, moxifloxacin, levofloxacin, piperacilin-tazobactam, ceftaroline, amoxicillin-clavulanate, azithromycin, clarithromycin, hydrocortisone, interferon beta-1a, anakinra, Lopinavir/Ritonavir Mylan, hydroxychloroquine, tocilizumab, Sarilumab, Heparin, Sarilumab unlicensed, Kaletra 80mg/20mg Oral Solution, Ascorbic Acid, simvastatin, Aspirin, Clopidogrel, Prasugrel, ticagrelor, Pascorbin, Ramipril, Lisinopril, perindopril, enalapril, captopril, losartan, valsartan, candesartan, irbesartan, Repagermanium, cysteamine bitartrate, TRV027, Casirivimab / imdevimab (Ronapreve)
Protocol number:	n/a
Substantial Amendment Code Number:	AM030

THE MEDICINES FOR HUMAN USE (CLINICAL TRIALS) REGULATIONS 2004 S.I. 1031

I refer to your notice of amendment received on 02/12/2021 concerning a proposed amendment to the terms of your request for a Clinical Trial Authorisation or to the particulars or documents that accompanied it. The Licensing Authority has carefully considered the proposed amendment but has decided, in accordance with regulation 24(5) of the Regulations, not to accept it on the following grounds.

Grounds for Non-Acceptance:
MEDICAL - Remarks: The present substantial amendment is refused. Should you wish to respond to this notice, a new substantial amendment should be submitted that addresses the following:

1. The investigator's brochure (IB) for TRV027 is unacceptable as it is lacking a dedicated reference safety information (RSI) section. The RSI is specific to expected serious adverse reactions (SARs) and should not contain information on other adverse events. All expected SARs must have occurred at least twice, and a statement is required that all fatal and life-threatening SARs will be considered unexpected for regulatory reporting purposes.

Guidance is provided in the Clinical Trials Facilitation Group document: http://www.hma.eu/fileadmin/dateien/Human_Medicines/01-About_HMA/Working_Groups/CTFG/2017_11_CTFG_Question_and_Answer_on_Reference_Safety_Information_2017.pdf.

The sponsor is reminded that the full application has been refused and any other documentation submitted in this application should be also re-submitted.

For further information on the above points, please contact Dr Juliet McColm: juliet.mccolm@mhra.gov.uk

The following comment is for future consideration / information only:

1. The immunoglobulin therapy domain-specific appendix is lacking an approval date, although the covering letter and saved document title declare the date as 24 November 2021. This should be addressed to ensure appropriate version control.

TOXICOLOGY - Remarks: The present substantial amendment is refused. Should you wish to respond to this notice, a new substantial amendment should be submitted that addresses the following regarding the IMP TRV027 :

1. Although the Sponsor has stated that the pivotal studies were conducted in accordance with GLP regulations, the Sponsor must confirm that the pivotal non-clinical toxicity studies were performed in a country that is a member of OECD Mutual Acceptance of Data (MAD) for GLP.

2. The Sponsor must supply a brief summary of the analytical assays, and their limits of quantification, used to characterise the nonclinical pharmacokinetics and toxicokinetics.

3. The Sponsor must provide a scientific rationale for the choice of the species used for the pivotal nonclinical studies.

4. In order to verify the suitability of the Ames study, the Sponsor must provide details of the bacterial strains used in this assay.

5. The Sponsor is required to provide an initial assessment of photoreactive potential of TRV027 as described in ICH guideline S10: Guidance on photosafety evaluation of pharmaceuticals. If no data is provided on phototoxicity, or a photosafety concern is identified, the Sponsor will be required to submit an amended protocol (complete, signed

document) to state that investigators advise patients take measures to minimise exposure to UV light for the duration of the study and for five half-lives after the last dose or provide justification that these measures will not be required.

If you believe it is possible to modify or adapt the proposed amendment to the protocol in order to address the concerns set out in the grounds for non-acceptance, you may respond, up to at least 14 days before the amendment is to be made, by giving written notice to the Authority and the relevant ethics committee in accordance with regulation 25(2). Any other modifications to the original notice of amendment that are required to address the grounds for non-acceptance will need to be submitted as a new valid notice of amendment.

Yours sincerely,

Clinical Trials Unit
MHRA