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**30/11/21**

**Re: Study Title: Randomized, Embedded, Multi-factorial, Adaptive Platform Trial for community - Acquired Pneumonia**

**REC reference: 18/Io/0660**

**EudraCT number: 2015-002340-14**

**IRAS project ID: 237150**

**Substantial amendment 30 (AM030) Expedited Approval**

I am submitting substantial amendment AM030 for the REMAP-CAP study.

**This involves:**

**The addition of a new intervention, TRV027 into the ACE2 RAS domain**

**The reopening of the immunoglobulin domain with new interventions**

**The addition of the Monoclonal Antibody Domain**

**The addition of a new intervention, TRV027 into the ACE2 RAS domain**

We are adding TRV027 to the ACE2 RAS domain, this will be part of the *ACEi in combination with TRV-027, an angiotensin (1,7) analogue (ACEi + TRV-027)* arm within the domain.

TRV027 is a similar peptide to angiotensin1-7 but selectively recruits  $\beta$ -arrestin to AT1. This translates into unique downstream signalling. This recruitment of  $\beta$ -arrestin stimulates the activation of endothelial cell nitric oxide synthase and prostacyclin production which may contribute to its in vivo vasodilatory properties.

TRV027 IMP stock comes with clinical trial labelling (provided as part of this substantial amendment).

**The addition of the Monoclonal Antibody Domain**

Monoclonal Antibody Therapy (additional samples)

Casirivimab and Imdevimab are neutralising monoclonal antibodies that have been shown to bind to SARS-CoV2 virus, blocking its entry into the body's cells, reducing the virus' effects.

The interventions available are:

1.2g casirivimab / 1.2g imdevimab (low dose)

4g casirivimab / 4g imdevimab (high dose)

This study is taking into account evidence derived from other clinical trials, and a UK wide policy that recommends the use of low dose casirivimab /imdevimab for use in patients hospitalised due to COVID-19 and have blood tests that show, they do not have antibodies against SARS-CoV-2. We are comparing the effects of low dose compared to a higher dose. Additional samples will be collected

as part of this domain. These samples will be transported to a central laboratory for testing. All samples collected under this study will be used within this study or in other ethically approved studies. The 1st sample will be taken with 24 hours of the treatment being completed, one sample between days 3 and 7 and one sample between days 7 and 14. We will take a final sample between days 14 and 28 if the participant is still in hospital. Each blood sample will take up to 6mls (2 teaspoons or less).

### **The reopening of the immunoglobulin domain with new interventions**

Immunoglobulin; Convalescent Plasma Therapy (additional samples)

COVID-19 immunoglobulin therapy is a blood-based treatment, giving patients antibodies to help fight infection. Antibodies are found in plasma, which is the liquid part of blood. It contains a mixture of proteins including antibodies, clotting factors, and natural anticoagulants. Convalescent plasma is plasma collected from volunteers who have recovered from COVID-19, which contains antibodies to help fight COVID-19.

The interventions available are:

No Immunoglobulin Therapy (no placebo)

High Titre Convalescent Plasma

This study is taking into account evidence derived from the results from the 1st stage of this domain in REMAP-CAP, as well as other clinical trials. There are a significant number of patients with an impaired immune system who would be eligible to be included within this trial and may benefit from this intervention. This population of patients are potentially also less likely to respond to COVID-19 vaccinations and are therefore more at risk of COVID-19 disease. Additional samples will be collected as part of this domain. These samples will be transported to a central laboratory for testing. All samples collected under this study will be used within this study or in other ethically approved studies. We will take blood and respiratory samples from participants on entering the study and then a single respiratory sample each week until hospital discharge. The blood sample will take up to 15mls (3 teaspoons or less).

Patients would only be randomised to these treatments if participants have acute illness due to confirmed COVID-19 and are immunosuppressed at the time of eligibility.

### **I have also made the below changes to the MHRA CTA.**

TRV027

casirivimab / imdevimab (Ronapreve)

I have also updated the participant information sheets to add the new interventions and domains

### **Documents submitted as part of Substantial amendment AM030:**

REMAP-CAP - ACE2 RAS DSA - V2 - 14 Oct 2021

REMAP-CAP - ACE2 RAS DSA - V2 - 14 Oct 2021\_TC

Summary of changes to ACE2 RAS Domain-Specific Appendix V1.0 - 16 Nov 2021

REMAP-CAP - Monoclonal Antibody DSA V1 - 22 November 2021

REMAP-CAP COVID-19 Immunoglobulin Therapy Domain-Specific Appendix V3 - 24 November 2021

REMAP-CAP COVID-19 Immunoglobulin Therapy Domain-Specific Appendix V3 - 24 November 2021\_TC from V1.01

Amendment\_Tool\_AM30\_20211201

revised-gb-spc-ronapreve-clean-120mg-ml12aug2021docx

TRV027 Vial Carton Label version3 REMAP-CAP 19Jul21

TRV027 IMPD V4.0 26August2021

TRV027 IMPD V4 Signature page  
TRV027 IB Ed 7 30Nov2021

Brief REMAPCAP ProLR\_IS summary v5 261121 TC  
Brief REMAPCAP ProLR\_IS summary v5 261121 CLEAN  
UK REMAP CAP COVID19 PerLR ICF V1.9 2021.11.26 Scotland TC  
UK REMAP CAP COVID19 PerLR ICF V1.9 2021.11.26 Scotland CLEAN  
UK REMAP CAP COVID19 PerLRIS ICF v1.10 2021.11.26 NI TC  
UK REMAP CAP COVID19 PerLRIS ICF v1.10 2021.11.26 NI CLEAN  
UK REMAP CAP COVID19 PerLRIS ICF v1.11 2021.11.26 TC  
UK REMAP CAP COVID19 PerLRIS ICF v1.11 2021.11.26 CLEAN  
UK REMAP CAP COVID19 PIS ICF V1.9 2021.11.26 Scotland TC  
UK REMAP CAP COVID19 PIS ICF V1.9 2021.11.26 Scotland CLEAN  
UK REMAP CAP COVID19 PIS ICF V1.10 2021.11.26 NI TC  
UK REMAP CAP COVID19 PIS ICF V1.10 2021.11.26 NI CLEAN  
UK REMAP CAP COVID19 PIS v1.11 TC  
UK REMAP CAP COVID19 PIS v1.11 CLEAN  
UK REMAP CAP COVID19 Retro PIS ICF V1.9 2021.11.26 Scotland TC  
UK REMAP CAP COVID19 Retro PIS ICF V1.9 2021.11.26 Scotland CLEAN  
UK REMAP CAP COVID19 Retro PIS ICF V1.10 2021.11.26 NI TC  
UK REMAP CAP COVID19 Retro PIS ICF V1.10 2021.11.26 NI CLEAN  
UK REMAP CAP COVID19 Retro PIS ICF v1.11 2021.11.26 TC  
UK REMAP CAP COVID19 Retro PIS ICF v1.11 2021.11.26 CLEAN

Many Thanks  
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