Justification of substantial amendment for RECOVERY protocol V21.0

This document is a detailed justification for the changes to the RECOVERY protocol in version 21.0. The change number refers to the Amendment Tool change number included with this amendment.

Change 1a: Addition of sotrovimab for adults and children aged ≥12 years old

Sotrovimab (VIR-7831) is a neutralising monoclonal antibody targeting the SARS-CoV-2 spike glycoprotein receptor binding domain. It was identified by screening antibodies from a patient who had been infected during the 2003 SARS-CoV-1 outbreak, and its ability to also neutralise SARS-CoV-2 implies that its binding site is highly conserved, maybe meaning mutational escape will be difficult.[1] The Fc portion of the parent antibody has been modified to extend sotrovimab's half-life to around 49 days. It is given as a single intravenous dose and has been well tolerated in clinical studies: mild to moderate hypersensitivity reactions were reported in 6/430 sotrovimab-allocated participants versus 5/438 placebo-allocated participants in COMET-ICE (see below), but none led to dose interruption or delay.

It is licenced in the UK for the treatment of COVID-19 in patients (aged ≥12 years old) who do not require oxygen and are at high risk of developing severe disease. The COMET-ICE trial, conducted in 583 such patients, showed that when given within five days of symptom onset it reduced the risk of hospitalisation by 85%, from 7% in the control group to 1% in the sotrovimab group.[2] Evidence in hospitalised patients is limited, and the sotrovimab arm of ACTIV-3 was stopped due to futility after recruiting 344 participants, although no safety concerns were raised.[3] However, the sotrovimab futility decision was based on an analysis of all subjects, regardless of baseline serostatus. By recruiting around 10,000 patients, RECOVERY subsequently showed that another neutralising monoclonal antibody treatment (Ronapreve, also previously stopped for futility in a previous small study of hospitalised patients) reduced mortality by 20% in hospitalised patients who were anti-spike antibody negative at baseline.

The Omicron SARS-CoV-2 variant that emerged in late 2021 has multiple spike protein mutations, which have led to its rapid expansion in immune populations. These also appear to cause near complete loss of neutralising activity by the monoclonal antibodies in casirivimab+imdevimab,[4] and reducing the neutralising activity of sotrovimab about 10-fold.[5,6]

Dose selection

The COMET-ICE trial used a 500mg dose, but peak and day 29 concentrations of sotrovimab were lower than those observed following 2.4g casirivimab+imdevimab.[7] This – combined with the reduced neutralising activating of sotrovimab against the Omicron variant – has led to the COVID-19 Therapeutics Advisory Panel to recommend that it be evaluated in RECOVERY using a dose of 1g. Given the safety profile observed with the 500mg dose, and the safety of this class of medication (anti-spike human monoclonal antibodies) in general (including the data from RECOVERY using 8g casirivimab+imdevimab), this increase is unlikely to cause major safety problems. The incidence and severity of any infusion reactions will be recorded on the trial case report form.

The Data Monitoring Committee will review the emerging safety data (both overall and in particular subgroups of interest eg, pregnant women, patients on high-flow oxygen or invasive mechanical ventilation) regularly, including a review after the first few hundred participants have been recruited.

Population selection

RECOVERY identified a mortality benefit only in (predominantly unimmunised) hospitalised patients who were anti-spike antibody negative at baseline. However, the clinical relevance of anti-spike antibody positivity is now more uncertain since immunisation is widespread and the omicron variant has demonstrated capability to evade both natural and vaccine induced immunity. As such, selecting patients who are most likely to benefit based on serostatus is extremely challenging. The presence of SARS-CoV-2 antigen in biological samples may be a more directly relevant biomarker of potential benefit than antibody status. Antigen is a direct reflection of viral replication, does not suffer from the current interpretation challenges of serology, and is correlated with serostatus (personal communication Jens Lundgren). However, we do yet have data to be sure that antigen is a valid marker of clinical risk or response to therapeutic antibodies, and standardised real-time antigen testing is not yet feasible. As such we propose that eligibility to enter the sotrovimab randomisation is not restricted by serostatus or antigen status, but a baseline blood sample is collected to allow us to undertake analyses stratified by serostatus or antigen status and assess if these biomarkers are associated with therapeutic response.

Special populations

The Summary of Product Characteristics states that no dose modification is required for renal or hepatic impairment, or in the elderly. It is licensed in adolescents aged ≥12 years. Although some small trials have raised concerns about monoclonal antibody therapy among patients on high-flow oxygen or mechanical ventilation, the largest such assessment (RECOVERY) found no evidence of harm from casirivimab+imdevimab among over 3,000 such patients (see figure 1).

There are no data from the use of sotrovimab in pregnant women. Since sotrovimab is a human immunoglobulin G animal studies have not been evaluated with respect to reproductive toxicity. No off-target binding was detected in a cross-reactive binding assay using a protein array enriched for human embryofetal proteins. Since sotrovimab is a human immunoglobulin G, it has the potential for placental transfer from the mother to the developing foetus. The potential treatment benefit or risk of placental transfer of sotrovimab to the developing foetus is not known.

There are no data on the excretion of sotrovimab in human milk. The potential treatment benefit or risk to the newborn or infants via breastfeeding is not known. Decisions on whether to breastfeed during treatment or to abstain from sotrovimab therapy should take into account the benefit of breast-feeding for the child and the potential benefit of therapy for the woman.

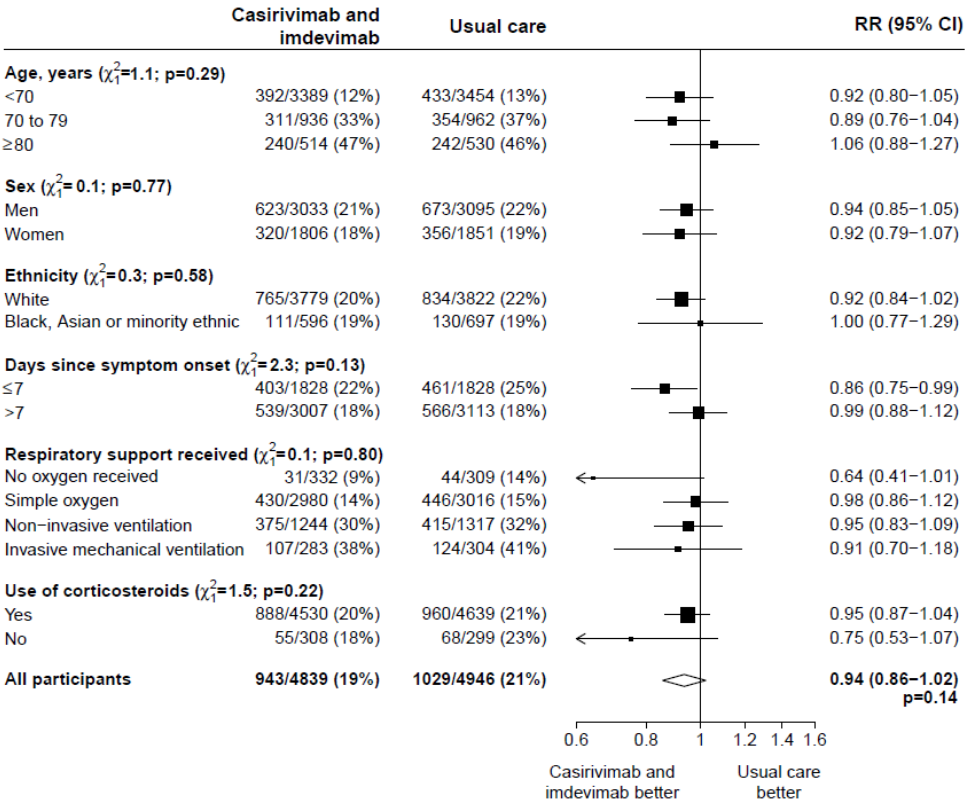

Figure 1: Effect of allocation to casirivimab+imdevimab on 28-day mortality in <u>all</u> participants

The supply of sotrovimab will provided by GlaxoSmithKline/Vir and is separate to the NHS supplies, thus ensuring that supplies for RECOVERY will not interfere with its availability for routine care or other trials also assessing sotrovimab. The details of this supply are described in the enclosed document “Sotrovimab supply details”.

Change 1b: Addition of molnupiravir for adults

Molnupiravir is a prodrug of the ribonucloside analogue N-hydroxycytidine (NHC), being rapidly converted into this form in plasma after absorption. NHC is then converted into the active triphosphate form in host cells by endogenous kinases. The SARS-CoV-2 viral RNA polymerase incorporates this into nascent viral RNA, resulting in copying errors that accumulate every replication cycle, ultimately preventing replication by a mechanism known as error catastrophe. This molecular target is conserved between Coronaviruses, and appears to have a high genetic barrier to resistance.[8] Molnupiravir is given orally and has been well tolerated in clinical studies so far, with infrequent reports of gastrointestinal and allergic reactions.

Molnupiravir is licensed in the United Kingdom for the treatment of mild-moderate COVID-19 within 5 days of symptom onset. In the MOVe-OUT trial of 1433 such patients it reduced the risk of hospitalisation or death by 30%, from 9.7% in the placebo group to 6.8% in molnupiravir group.[9] Evidence in hospitalised patients is limited, and the MOVe-IN trial randomised patients 1:1:1:1 to placebo vs. molnupiravir at 3 different doses (200mg, 400mg, 800mg). This study was abandoned after recruiting 304 inpatients as the manufacturer decided it was unlikely to demonstrate clinical benefit, although no safety concerns were raised.[10] With approximately 75 subjects randomised to the 800mg dose versus 75 controls, the study was substantially underpowered to identify moderate but important benefits in hospitalised patients, so a larger trial is needed.

It is licensed in the UK and is being rolled out for outpatient treatment of patients at risk of severe disease.

The safety concerns and proposed mitigations are as follows:

1. Embryofoetal toxicity: pregnant women excluded; negative pregnancy test required in women of childbearing potential; women of childbearing potential advised to avoid getting pregnant while taking the drug and for 4 days after last dose of molnupiravir.
2. Bone and cartilage growth: eligibility restricted to adults ≥18 years only.
3. Spike glycoprotein substitutions and potential resistance: monitoring of SARS-CoV-2 genotype and resistance markers.
4. Mutagenic potential with prolonged use: Previous treatment with molnupiravir for the same index illness will be a contraindication to randomisation between molnupiravir and control in RECOVERY.

Special populations

Molnupiravir is not metabolised or excreted by the liver or kidneys, so no dose modification is required for patients with renal or hepatic impairment. The Summary of Product Characteristics does not recommend any dose adjustment for elderly participants. It is not recommended for use in pregnant or breast-feeding women so such patients will be excluded.

The supply of molnupiravir will be discussed with the Department of Health and Social Care, to ensure that supplies for RECOVERY do not interfere with its availability for either routine care or other trials also assessing molnupiravir. Since the primary endpoint for the PANORAMIC trial is hospitalisation (or death), patients who were randomised to the control arm of PANORAMIC would be eligible for this randomisation within RECOVERY.

Change 2: Addition of baseline and follow-up samples

The collection of baseline serum samples to determine serostatus (ie, presence of anti-SARS-CoV-2 antibodies) in RECOVERY participants was included in the RECOVERY protocol to inform the convalescent plasma and casirivimab+imdevimab (REGN-COV2) comparisons, and was removed from the protocol once these comparisons were complete. As described above, it was critical to identifying the potential benefits of casirivimab+imdevimab, so we wish to add it back to the protocol and will also use this sample to assess antigen status at baseline, as a potential biomarker for therapeutic effect.

In addition, we also wish to collect baseline (and follow-up) swab samples on which the SARS-CoV-2 viral load (or influenza virus) will be measured. We also wish to collect such swabs on days 3 and 5 so the effect of study treatment (sotrovimab or molnupiravir) on viral load and resistance-associated mutations can be assessed. Because the RECOVERY casirivimab+imdevimab comparison has demonstrated that monoclonal antibody therapies can improve outcomes in certain groups of patient, it is essential that the information to allow rapid regulatory decision making be collected.

Once the trial steering committee determine (based on blinded information) that sufficient information on virological outcomes has been collected, this part of the protocol would be stopped and the results made public.

Change 3: allow patients previously recruited into RECOVERY to be recruited again

Until now, patients have only been able to be randomised once into RECOVERY. Entry of the same patient details a second time leads to the randomisation system warning the user and re-randomisation has not been accepted. However, in view of the duration of the pandemic

and the immune escape demonstrated by Omicron, patients with second infections will become more common and important to study. Recruitment to comparisons not in the protocol at the time of the original randomisation would be allowed if >6 months have elapsed since their previous illness. This ensures that any previous treatments given have been cleared and that any treatments given will not interfere with the assessment of outcomes at 28 days or 6 months after their first randomisation. Patients will not be recruited into the same randomised comparison (e.g. sotrovimab vs. usual care) on more than one occasion, regardless of how far apart they occur.

References

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