

Justification of substantial amendment for RECOVERY protocol V14.0

This document is a detailed justification for the changes to the RECOVERY protocol in version 14.0. The change number refers to the Amendment Tool change number included with this amendment.

Change 1: Addition of dimethyl fumarate

Dimethyl fumarate (DMF) is thought to prevent NLRP3 inflammasome activation and the process of pyroptosis (inflammatory cell death) through its action on the protein gasdermin D.¹ SARS-CoV-2 induces inflammasome activation and the degree of activation is thought to correlate with disease severity.² DMF has demonstrated anti-viral and anti-inflammatory effects against SARS-CoV-2 *in vitro*.³ Other inflammasome-modulating drugs, such as colchicine, have demonstrated provisionally promising results in small randomised trials.^{4,5}

DMF is licensed to treat relapsing remitting multiple sclerosis and plaque psoriasis as a long-term immunomodulatory agent and generally well-tolerated with no major safety concerns.^{6,7} The UK COVID-19 Therapeutics Advisory Panel has recommended that RECOVERY investigate the safety and efficacy of DMF in an early phase assessment among patients hospitalised with COVID-19.

We therefore wish to conduct an early phase assessment of DMF at a subset of RECOVERY sites which have the necessary resources to conduct the additional assessments described below. We estimate that about 20 sites will be required in order to recruit the required number of participants in a reasonable time frame.

Based on unpublished data from 8500 patients with COVID-19, assuming a mean (standard deviation) S/F₉₄ ratio of 3.3 (1.7) at day 5, and a correlation between an individual's baseline and day 5 S/F₉₄ ratio of 0.5, randomisation of 400 participants will provide 90% power (at 2p=0.05) to detect a difference in S/F₉₄ ratio of 0.5 (the chosen minimum clinically meaningful difference [which is similar to the difference in 1 point on the WHO ordinal scale]), even if 10% of participants discontinue study treatment before day 5.

Dose selection

The selected dose is 240 mg twice daily (the standard dose used for its licensed indications). When DMF is used for its licensed indications the dose is built up gradually, but because COVID-19 is an acute life-threatening disease there is not sufficient time to build up slowly. Therefore treatment will start at 120 mg twice daily (as in multiple sclerosis), but then increase to 240 mg twice daily after four doses, to ensure that the full effect of the drug on COVID-19 can be utilised.

Participant population

It is possible that DMF may have benefits across the disease spectrum. For patients with early disease its antiviral properties may be of particular benefit, whereas those with later stages of disease may benefit from its immunomodulatory effects. Therefore adult hospitalised patients will be eligible as long as their responsible clinician does not consider treatment with DMF to be absolutely indicated or absolutely contraindicated. We do not intend to recruit children to this early phase assessment.

There are limited data from the use of DMF in pregnant women and animal studies suggest possible reproductive toxicity. Therefore women of child-bearing potential will only be eligible if they have a negative pregnancy test. All such women are advised not to get pregnant for 3 months after receiving study treatment. It is uncertain whether DMF or its metabolites are

excreted in human milk. For the purposes of this early phase assessment breast-feeding mothers will be excluded.

Based on the mode of action there are no theoretical grounds to modify the dose in elderly patients, or those with renal or hepatic impairment. Kidney function and markers of liver damage (ALT or AST) will be collected because toxicity to these systems has been reported. If abnormalities occur they would be managed by the local clinicians which may include reducing the dose or discontinuing dimethyl fumarate if thought to be implicated.

Although the SmPC recommends caution over prolonged lymphopaenia (and associated risk of progressive multifocal leukoencephalopathy [PML]), these risks are related to long-term use in people with multiple sclerosis and not relevant to a 10 day course in people with COVID-19. We are not excluding people with known PML for similar reasons, and because it is very rare in the UK population.

Outcomes

The primary outcome for this early phase assessment will be the S/F_{94} ratio. The $SaO_2:FiO_2$ (S/F) ratio is the ratio of peripheral blood oxygen saturation to inspired oxygen concentration. This is a measure of how well the lungs are oxygenating the blood, and is a non-invasive equivalent to the $PaO_2:FiO_2$ ratio which requires arterial blood gas sampling to measure (and is often used in early phase trials). The $SaO_2:FiO_2$ ratio is limited by a ceiling effect because when blood oxygen saturation exceeds 94% it is relatively insensitive to inspired oxygen concentration. Therefore to improve the accuracy we propose to measure S/F_{94} which is the $SaO_2:FiO_2$ ratio at which SaO_2 is $\leq 94\%$.

In order to measure S/F_{94} , the participant should be resting in bed with the head of the bed at 30° for at least 10 minutes. If they are receiving oxygen via simple nasal prongs or face mask, this will be switched to a Venturi mask (which controls FiO_2 more precisely). The FiO_2 will then be reduced gradually until $SaO_2 \leq 94\%$ (or the participant is receiving room air, ie $FiO_2 = 0.21$).

Short periods of hypoxia (e.g. SaO_2 of 80% or more) are not considered harmful. The participant should be monitored throughout and if they become breathless or distressed after a reduction in FiO_2 it will be immediately increased. Once $SaO_2 \leq 94\%$ (or the participant is breathing room air) the details of oxygen delivery mode, SaO_2 , FiO_2 and respiratory rate will be recorded. The participant's oxygen will then be returned to baseline.

S/F_{94} will be recorded at baseline and on days 3, 5 and 10. Further details will be provided in a Standard Operating Procedure.

Other outcomes will include:

- WHO Ordinal Score each day after randomisation until day 10 (or discharge if sooner), recorded at 0800h each day from the medical records.

Score	Descriptor
1	Discharged (alive)
2	Hospital admission, not requiring supplemental oxygen, no longer requiring medical care (hospitalisation extended for infection control or other nonmedical reasons e.g. social care. Sometimes documented as "medically fit for discharge" or "medically stable for discharge")
3	Hospital admission, not requiring supplemental oxygen, but requiring ongoing medical care
4	Hospital admission, requiring supplemental oxygen (by face mask or nasal prongs)
5	Hospital admission, requiring high flow nasal oxygen, non-invasive ventilation or both

6	Hospital admission, requiring invasive mechanical ventilation or extracorporeal membrane oxygenation (ECMO)
7	Death

- Blood C-reactive protein, creatinine and alanine (or aspartate) transaminase on days 3, 5 and 10. These will use the results from tests done as part of routine care if available.
- Incidence and severity of flushing, gastrointestinal symptoms and any non-COVID-19 infections.
- Reasons for stopping dimethyl fumarate.

In addition, the standard trial follow-up (which collects information on survival, need for ventilation or renal replacement therapy and safety outcomes including cardiac arrhythmias, bleeding and thrombotic events) will also be completed. Given that dimethyl fumarate is in regular use, other adverse events will not be collected unless they are considered to be serious and related with reasonably probability to study treatment.

Efficacy will be assessed using the S/F94 ratio, WHO ordinal scale and blood CRP. Safety and tolerability will be assessed using creatinine and liver function blood tests, incidence of infections, incidence of severity of flushing and gastrointestinal symptoms and reasons for stopping dimethyl fumarate. The results of these will be reviewed by the steering committee and inform the decision whether to proceed to a larger phase 3 comparison.

Change 2: Clarification of eligibility of children for REGN-COV2

The paediatric working group have further considered the role of REGN-COV2 monoclonal antibodies in the treatment of children with COVID-19. While there is a strong rationale for their use in COVID-19 pneumonia (as in adults), they recommend that they are not used for the treatment of PIMS-TS (which may in part be antibody-driven). No children with PIMS-TS have so far been recruited to this comparison, but we wish to formalise this in the protocol.

Change 3: Informing participant's GPs of their participation

We wish to clarify that participants' GPs will be informed of their participation (typically through routine clinical communications) and of any relevant information that may arise during the trial.

Change 4: Modifying contraindications and cautions for baricitinib comparison

The RECOVERY trial added baricitinib to the trial protocol on 2 February 2021. Patients hospitalised with COVID-19 are eligible for this randomisation, regardless of whether they are receiving oxygen or other forms of respiratory support or whether they have evidence of systemic inflammation. The results of the trial's tocilizumab comparison were not known at that time, so the protocol required that participants who had already received tocilizumab during that admission (or for whom there was a plan to give it in the next 24 hours) should not receive baricitinib in addition.

The RECOVERY trial has just completed the assessment of tocilizumab. This was limited to patients hospitalised with COVID-19 with hypoxia (oxygen saturation <92% or receiving oxygen therapy plus CRP ≥75 mg/L). The results of the tocilizumab comparison (released on 11 February 2021) show that among patients who were hypoxic and had on-going inflammation, tocilizumab reduces the risk of death, shortens the duration of admission and, among people not on invasive mechanical ventilation, reduces the risk of requiring invasive mechanical ventilation or death.⁸

Ongoing medical need: Nonetheless, despite treatment with tocilizumab (combined with a corticosteroid) the risk of death remains substantial: 28-day mortality was 29% among participants allocated tocilizumab. There is a clear clinical need for treatments that can reduce this further. Combining targeted immunomodulatory therapies have the potential to further reduce mortality.

Potential synergy: Tocilizumab provides high IL-6 receptor occupancy and therefore very effective inhibition of IL-6 signalling. The addition of baricitinib would likely provide little or no additional inhibition of IL-6 mediated inflammation. However, baricitinib inhibits the signalling of a much wider range of cytokines and might therefore provide additional benefits.

Safety considerations: Both baricitinib and tocilizumab increase the risk of other (non-COVID) infections. Giving both might increase this risk further. With both treatments the risk of infection tends to increase with prolonged therapy. There are several mitigating factors: In the treatment of COVID-19, tocilizumab is given as just one or two doses; the half-life of baricitinib is short (so it can be stopped and the effects reversed); and the safety concerns must be weighed against the potential benefits in a population with 28-day mortality in excess of 20%.

The RECOVERY Trial Steering Committee has considered this information and believe that combination treatment with tocilizumab and baricitinib within the context of a clinical trial is reasonable given the uncertainties and will provide an answer to an important clinical question.

The protocol has therefore been modified such that:

- Patients who have already received tocilizumab may be included in the baricitinib comparison. Managing clinicians can exclude participants from this comparison if the risk of other infections is considered to be too great (e.g. in patients with uncontrolled non-coronavirus infection at the time of randomisation, and/or who have underlying impaired immunity due to a pre-existing disease)
- Participants who have been allocated baricitinib may receive tocilizumab if they meet the relevant criteria outlined in NHS clinical guidance materials. The baricitinib may be continued unless the managing clinician no longer considers it to be in participants' best interest (such as those relating to risks associated with other infections, described above)
- Additional information on non-coronavirus infections will be collected on the trial Follow-up form, classified by site and presumed type of infection (viral, bacterial, fungal or other), so the risk of infection can be quantified

References

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