RECOVERY
Randomised Evaluation of COVID-19 Therapy

Position statement on potential co-administration of baricitinib and tocilizumab

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.[1]

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%.

Conclusion: 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.

[1] https://www.medrxiv.org/content/10.1101/2021.02.11.21249258v1

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