Justification of substantial amendment for RECOVERY protocol V13.0

This document is a detailed justification for the changes to the RECOVERY protocol in version 13.0. The change number refers to the Amendment Tool change number included with this amendment.

Change 1: Addition of baricitinib for adults, and children ≥2 years old with COVID-19 pneumonia

Baricitinib is a selective and reversible inhibitor of Janus kinase (JAK)1 and JAK2. In isolated enzyme assays, baricitinib inhibited the activities of JAK1, JAK2, Tyrosine Kinase 2 and JAK3 with IC50 values of 5.9, 5.7, 53 and > 400 nM, respectively (data from Baricitinib SmPC). There are a number of JAK/STAT inhibitors which are used in rheumatoid arthritis. A comparison of the inhibition of JAK1/3-, JAK2/2- and JAK1/2/TYK2-dependent cytokine pathways indicates that baricitinib exhibits slightly lower JAK1/3 inhibition (cytokines important in T cell and NK cell activation) than the comparators but all inhibit GM-CSF, G-CSF, IL6, IFNα. There is some IFNα inhibition, but baricitinib has lesser activity than tofacitinib for this anti-viral cytokine.[1] Baricitinib also decreases receptor-mediated endocytosis by inhibiting APR2- associated protein kinase 1 and also via G-associated kinase, and so is predicted to have anti-viral effects.[2]

JAK 1/2 inhibition prevents downstream phosphorylation (and hence activation) of STAT (signal transducers and activators of transcriptors). The JAK-STAT pathway mediates the effect of several interleukins (including IL-6), so JAK inhibitors reduce the cascade of inflammatory mediators that derive from IL-6 activation of its receptor. Baricitinib also binds tyrosine kinase 2, preventing its activation.[3] Recent genetic data support a causal link between high tyrosine kinase expression (hence activity) and severe COVID-19.[4]

Baricitinib is licensed for the treatment of rheumatoid arthritis and atopic dermatitis. The 4 mg once daily dose of baricitinib selected for this study in a patient population with COVID-19 is based on clinical data showing an effect of baricitinib on inhibition of cytokine signaling. In patients with rheumatoid arthritis, the 4 mg dose of baricitinib (but not lower doses) was shown to significantly reduce IL-6 levels, assessed after 12 weeks of treatment. In a compassionate use program in paediatric patients with chronic atypical neutrophilic dermatosis with lipodystrophy and elevated temperature (CANDLE) syndrome, patients on a mean dose of baricitinib 6 mg once daily showed a striking reduction in cytokine signaling. In healthy volunteers, exposures observed at the baricitinib 4 mg (or higher) doses are associated with reduction of IL-6 induced ex vivo pSTAT3 activation.[5]

In a vaccine response study, individuals treated with 4 mg baricitinib can mount an appropriate immune response to a pneumococcal vaccine, suggesting that transient exposure to baricitinib will not result in clinically meaningful changes to adaptive immunity.[6] In addition, the choice of the 4 mg dose is supported by PK, safety, and efficacy data for baricitinib in Phase 2 and Phase 3 rheumatoid arthritis (RA) studies. The 4 mg dose of baricitinib is approved in multiple countries for the treatment of RA.

Baricitinib was tested in the Adaptive Covid-19 Treatment Trial-2 and shown to improve time to recovery (rate ratio for recovery 1.16, 95% CI 1.01-1.32). The difference in median time to recovery was 1 day (7 days [95% CI 6-8] among those allocated baricitinib versus 8 days [95% CI 7-9] among those allocated placebo). 28-day mortality was 5.1% among participants allocated baricitinib compared to 7.8% allocated placebo (HR 0.65, 95% CI 0.39-1.09).[7] Serious adverse events were less frequent among participants allocated baricitinib (16.0% vs. 21.0%; p=0.03).

Baricitinib is therefore an attractive therapeutic strategy for patients hospitalised with COVID-19, but substantial uncertainty remains about its efficacy in this population. Baricitinib has been recommended by the COVID-19 Therapeutics Advisory Panel and the Chief Medical Officer for inclusion in RECOVERY.

Safety

Baricitinib is well-tolerated when used for its standard indications. The ACTT-2 trial demonstrated that participants allocated baricitinib had fewer serious adverse events than participants allocated placebo. We propose to use the same dose as used in routine care and in ACTT-2 (i.e. 4 mg once daily). Of note, many of the risks associated with baricitinib related to long-term use whereas in RECOVERY the maximum duration of treatment is 10 days.

Baricitinib is primary excreted via the kidney so the RECOVERY protocol recommends dose reduction among participants with renal impairment (see protocol appendix 2):

- eGFR ≥30 <60 mL/min/1.73m^2: 2 mg once daily
- eGFR ≥15 <30 mL/min/1.73m^2: 2 mg alternate days
- eGFR <15 mL/min/1.73m^2: baricitinib is contraindicated

This is in accordance with the US FDA's Emergency Use Authorisation factsheet for healthcare providers (enclosed), except for the dosing when eGFR ≥15 <30 mL/min/1.73m^2: 1 mg tablets are not available in the UK so we propose 2 mg on alternate days. Given the excretion is largely renal, increasing the dosing interval should avoid toxicity while maintaining reasonable efficacy.[5]

Similarly, the RECOVERY trial protocol also excludes baricitinib for participants with known active tuberculosis or an absolute neutrophil count <0.5 x10^9 cells/L. We have not adopted the exclusion if absolute lymphocyte count <0.2 x10^9 cells/L because lymphopaenia is a risk marker for severe COVID-19 so this would potentially exclude the participants who had the most to gain from baricitinib therapy.

Baricitinib has very few drug-drug interactions and the only relevant interaction is with strong OAT3 inhibitors, such as probenecid. The RECOVERY protocol therefore recommends halving the dose of baricitinib if probenecid is co-prescribed. Tocilizumab and baricitinib act on the same pathway and there is concern among experts about giving together, so prior use of tocilizumab during the admission will exclude baricitinib from the randomisation for that participant.

There are some reports of an increased risk of venous thromboembolic (VTE) disease with baricitinib (although not with other JAK1/2 inhibitors). However, a meta-analysis of 42 trials found no increased risk (incidence rate ratio 0.68; 95% CI 0.36-1.29).[8] All RECOVERY participants will receive standard VTE prophylaxis according to their hospital policy (which is often intensified among patients with COVID-19) and may also receive aspirin as part of the RECOVERY protocol (main randomisation part C). All thrombotic events will recorded as part of the trial follow-up.

Participants will also have routine monitoring for other infections and abnormal liver function tests as part of their routine care. The protocol does not mandate any additional monitoring.

Women of child-bearing potential, pregnancy and breast-feeding

The JAK/STAT pathway is involved in early embryonic development and there are very few data on the use of baricitinib in pregnant women (or in women taking it who become pregnant). Baricitinib may be teratogenic in animals. Therefore women of child-bearing potential will not

be allocated baricitinib by the RECOVERY randomisation unless they have had a negative pregnancy test since admission. It will also be excluded from the randomisation of women who are breast-feeding.

Children

There are several ongoing paediatric studies assessing the efficacy and safety of baricitinib in the treatment of chronic autoimmune disorders requiring long-term treatment:

- I4V-MC-JAIP (atopic dermatitis)
- I4V-MC-JAHV (polyarticular juvenile idiopathic arthritis),
- I4V-MC-JAHW (juvenile idiopathic arthritis associated uveitis)
- I4V-MC-JAHU (systemic juvenile idiopathic arthritis)
- I4V-MC-JAHX (Long term extension study for JAHV and JAHU).

In addition, studies for other conditions such as systemic lupus erythematosus and severe COVID-19 infection are planned and study JAGA was an expanded access, compassionate use program in children with Type 1 interferonopathies.

Study JAHV is a global, Phase 3 study in patients who have had inadequate response or intolerance to treatment with at least 1 conventional or biological disease modifying therapy. The study has been running since 2020 and aims to enroll up to 197 patients aged between 2 and <18 years of age. In this study, patients have safety assessments performed regularly. Such assessments include review of adverse events (including serious adverse events) by their physician; collection and review of laboratory measures such as WBC, ANC, lymphocyte count, platelet count, haemoglobin, estimated glomerular filtration rate, liver function tests, lipid tests; safety monitoring measures assessing immune, growth, and bone effects (including height and weight; bone imaging; gonadal hormones). Safety monitoring for patients in this study includes regular, periodic blinded data review by the internal Lilly study team. In addition, an independent external data monitoring committee (DMC) oversees the conduct of this and the other ongoing paediatric Phase 3 clinical trials. This DMC includes specialists with expertise in paediatrics, rheumatology, statistics, and other appropriate specialties. The DMC has met to review and evaluate planned interim safety and futility analyses every 6 months, and has recommended that the studies continue without modification.

Study I4V-MC JAGA is assessing baricitinib among paediatric patients with type 1 interferonopathies. These rare interferonopathies are serious or life-threatening autoinflammatory syndromes and patients enrolled had no available or remaining treatment options. The observed adverse events were consistent with the known safety profile of baricitinib and are expected for patients with these serious interferonopathies, based on the comorbidities observed from historical data in these patient populations, especially in the context of their immunocompromised state and concomitant steroid use. These paediatric patients typically receive doses higher than the 4-mg once daily dose (mean dose of 6 mg/day) and typically receive baricitinib and are monitored over an extended period of time (up to 7 years in the JAGA program).

The US FDA EUA guidance allows its use for children aged ≥2 years. Children should have equity of access to novel treatment within clinical trials, to enable them the opportunity to benefit from such treatments. The dose would be modified for children as follows:

eGFR (mL/min/1.73 m²)	2 to < 9 yr	≥ 9 yr
≥60	2mg	4mg

≥30 to <60	2mg alt die	2mg
≥15 to <30	Excluded	2mg alt die
<15	Excluded	Excluded

This dosing is based on that used in the trials cited above which has been informed by pharmacokinetic modelling done by the manufacturer.

Elderly patients

Although the Summary of Product Characteristics recommends treating elderly patients with baricitinib 2mg once daily, these patients are at very high risk of death from COVID-19 so under-treatment is to be avoided. Furthermore, the treatment course in RECOVERY is a maximum of 10 days, whereas the SmPC is focussed on long-term treatment.

Change 2: Addition of anakinra to second randomisation for children

Anakinra is an antagonist of the interleukin-1 receptor licensed for the treatment of rheumatoid arthritis, periodic fever syndromes and Still's disease. Anakinra is widely used in several paediatric conditions with hyperinflammation including macrophage activation syndrome, systemic JIA and autoinflammatory disorders.[9] The hyperinflammatory syndrome associated with COVID-19 in children (PIMS-TS) is characterised by high inflammatory markers and wide range of elevated cytokines. Immunomodulatory therapy with IL-1 inhibition using anakinra has been used in the management of the children with PIMS-TS,[10] but controlled trials are lacking. The NHS England Delphi consensus process identified equipoise for anakinra as one of the biologicals that could be used and tested for use in PIMS-TS.[11] Anakinra has been shown to be safe in sepsis and has a short half-life which may be advantageous for use in very ill children with PIMS-TS.[12-15]

Safety

Anakinra is well-tolerated when used for its usual indications. It is eliminated by the kidney; although the SmPC recommends dose-reduction in renal impairment the dose proposed for RECOVERY is relatively low (2 mg/kg per day, compared to maximum licensed dose of 8 mg/kg per day) so no dose reduction is recommended.

Anakinra is contraindicated according to the protocol with neutrophils <1.5 x10^9/L. Children will be monitored closely during treatment for infections and the very short half-life means once the treatment is stopped this risk rapidly returns to baseline (as would responses to vaccinations).

There are no direct drug-drug interactions with anakinra. Therapeutic drug monitoring of drugs with narrow therapeutic indices (whose metabolism may be altered in PIMS-TS) would be done as part of routine care of these children.

Women of child-bearing potential, pregnancy and breast-feeding

Data on the use of anakinra in pregnancy data are currently limited. Although renal agenesis and oligohydramnios have been described in exposed infants, controlled studies are lacking. Anakinra will only be included in the randomisation of women of child-bearing potential if they have had a negative pregnancy test since admission.

Safety reporting for baricitinib and anakinra

In keeping with the streamlined nature of RECOVERY, but to also facilitate a robust test of the safety of baricitinib and anakinra we will collect specific safety information at various time points in the trial.

a) <u>4 weeks after randomisation:</u> Information about **mortality** (the primary outcome), **respiratory status** (including need for any ventilator support), **renal status** (need for haemodialysis or haemofiltration), **cardiac arrhythmias**, **thrombotic events** and **bleeding events** will be recorded. These data are also regularly reviewed by the DMC. In addition, more detailed information about **paediatric participants** is collected which includes additional safety information.

b) <u>6 months after randomisation:</u> Information on **mortality**, **other key study outcomes** and **any subsequent hospitalisations** will be captured by linkage to routinely collected NHS data and the protocol specifies analyses be conducted at 6 months. This would capture any later benefits or harms of these IMPs.

c) <u>At any time after randomisation:</u> Investigators are required to report any **suspected serious adverse reactions** at any time. These will be reported to MHRA and the REC if they are confirmed to be serious, related to study treatment with reasonable probability and unexpected (according to the latest reference safety information in the investigators' brochure).

Change 3: Removal of tocilizumab from second randomisation for adults

Following completion of recruitment of 4000 participants (as planned) on 24th January 2021, the Steering Committee wish to remove tocilizumab from the trial protocol.

Change 4: Addition of pregnancy test for women of child-bearing potential

The previous version of the protocol only included one IMP which was contraindicated in pregnancy (namely colchicine). The addition of baricitinib and anakinra to the protocol has required this decision to be re-considered because there are now three IMPs contraindicated in pregnancy, and we do not wish to unnecessarily exclude all women of child-bearing potential from these comparisons as this is not equitable. We therefore now require such women to have a pregnancy test (which is very often done as part of routine care for both adults and adolescents) before these IMPs can be included in their randomisation. If they do not wish to have a pregnancy test then these IMPs would be excluded from their randomisation.

Change 5: Change to colchicine eligibility criteria

As the protocol now includes a pregnancy test, we wish to allow adult women of child-bearing potential to enter colchicine comparison as long as they are not pregnant (confirmed by a pregnancy test). If they decline a pregnancy test, colchicine (and baricitinib) would be excluded from their randomisation.

Change 6: Update concerning REGN10933+REGN10987 and pregnant women

The current version (V12.1) of the RECOVERY protocol states (appendix 2, page 30):

> *Pregnant women that are administered REGN10933 and REGN10987 must be advised that live vaccines should be avoided in children with in utero exposure to biologics for at least the first 6 months of life.*

We propose that this sentence is deleted. It was originally inserted as a cautious note, but we have subsequently reviewed the biological rationale.

The synthetic monoclonal antibodies (REGN10933+REGN10987) bind to the SARS-CoV-2 spike protein on the surface of cells, blocking the interaction between the spike protein and its canonical receptor angiotensin-converting enzyme 2. There are no human protein targets of the Regeneron monoclonal antibodies. This is in contrast to infliximab, the biologic drug implicated in a single case report published of a 4 month old infant in London who died of probable disseminated TB following maternal infliximab use in pregnancy and infant BCG vaccination at 3 months of age.[16] Infliximab targets human TNF-alpha, such that if used in later pregnancy, the immune system of the neonate may be compromised, leading to potential systemic disease following administration of live vaccines. Regeneron monoclonal antibodies are more similar in type to other immunoglobulins that we already give in pregnancy such as anti-D, varicella zoster immunoglobulin etc., for which we do not have such an advisory warning against live vaccine administration in the infant.

Change 7: removal of convalescent plasma arm

The Data Monitoring Committee advised the Chief Investigators on 15th January to discontinue recruitment into the convalescent plasma comparison. This has therefore been removed from the protocol and associated documents. Follow-up is ongoing and results will be disseminated once available.

Change 8: vaccination after therapeutic antibody administration

We have added information to the protocol and PIS about this question. There is no evidence of any safety concerns from vaccinating individuals with a past history of COVID-19 infection, or with detectable COVID-19 antibody whether that is naturally acquired or through treatment with plasma or monoclonal antibody products.[17] Vaccination should be deferred for 90 days for participants allocated convalescent plasma or REGN-COV2.[18] Investigators will be requested to include such information in discharge summaries being given to participants and sent to general practitioners.

Change 9: substitution of methylprednisolone with dexamethasone for children

Due to unexpected demand, NHS supplies of methylprednisolone are limited and it may not be available for children presenting with PIMS-TS. Our paediatric working group has considered this and recommends substituting dexamethasone should this occur.

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