RECOVERY Clinical Trial Pharmacy Briefing Document

(Based on Protocol V14.0 15-Feb-2021)

1 Introduction

The following medicines are listed as IMPs for this study. The supply arrangements for each arm is different (see table 1 below).

This clinical trial is being run to make it as easy as possible, while ensuring that the outcome data from the patients is collected to inform future care of patients with Covid-19.

Table 1: Medicines for RECOVERY Clinical Trial for Adults

Medicine	Formulation	Source	Accountability logs	Prescribed	IMP Annex 13 labelling
Randomisation Part A					
No additional treatment					
Colchicine	Oral	NHS Stock. Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No
Dimethyl Fumarate	Oral Capsules	NHS Stock. Biogen product – Standard Pharmaceutical Wholesalers	No	Yes	No
Randomisation Part B					
No additional treatment					
REGN10933&REGN10987 (synthetic neutralising antibodies)	Intravenous	Regeneron	Yes	Yes	Yes
Randomisation Part C					
No additional treatment					
Aspirin	Oral tablet/dispersible tablet/suppositories	NHS stock. Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No
Randomisation Part D					
No additional treatment					

Baricitinib	Oral tablet	NHS stock. Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No

The MHRA is aware and have approved the study to allow any doctor working within the hospital to prescribe for this study (this can include FY1 doctors under supervision as per local practice), without having GCP training or being on a delegation log. Similarly GCP trained research staff to take consent of the patient for this trial is not required. However, it is expected that all staff will complete online Recovery study training.

Further information regarding paediatric dosing and administration can be found on a separate document (RECOVERY Paediatric Guidance Document)

2 Colchicine

2.1 Initial supply and re-ordering

Colchicine will be sourced by local pharmacy procurement team via their normal routes. For the purpose of this study colchicine tablets can be used.

2.2 Storage

As per SmPC

No temperature excursion reporting required. Follow Trust SOPs to manage temperature excursions.

2.3 Dispensing quantities

Colchicine dosage is 1mg after randomisation followed by 500micrograms 12 hours later, and then 500micrograms twice daily for 10 days in total

2.4 Returns and Destructions

During the study any patient returns or if a Trust chooses to ring fence stock for the study and there is still stock at end of study, this can be returned to stock in the usual way or destroyed on site. No approval from Sponsor is required.

2.5 FAQs

Q. My patient is already on colchicine can they still be entered into the study?

A. Yes, they can still be enrolled, but colchicine should be marked as unsuitable if they are taking it regularly. They can still be included in other arms of the trial.

Q. Can the dose be reduced at all for this study?

A. Yes it can. If the patient is taking a moderate CYP3A4 or has an eGFR <30mL/min/1.73m^2 or an estimated body weight <70kg then the dose frequency should be halved (i.e. 500micrograms once

daily) (see protocol - Appendix 2) If more than one of these factors is present, the clinician should consider whether the participant is suitable for this randomisation.

Q. Can the colchicine tablets be crushed for NG administration?

A. Yes the tablets can be crushed. The tablets will also disperse within 2 minutes when placed in 10mL of sterile water. The Handbook of Drug Administration via Enteral Feeding Tubes states for health and safety that standard precautions apply.

Q. How should side effects be managed?

A. If the patient develops any side effects, these should be managed as per the Trust's normal practice. However, the clinician if they felt it was appropriate, they could reduce the colchicine to 500micrograms once daily to help manage the side effects.

3 Dimethyl Fumarate

3.1 Initial Supply and Re-Ordering

Dimethyl Fumarate will be sourced by local pharmacy procurement team via their normal routes. For the purpose of this study only dimethyl fumarate 120mg capsules (Tecfidera® from Biogen) should be used.

A Blueteq form will need to be completed for each patient to ensure that costs can be reimbursed to hospital trusts. The Blueteq form can be completed in retrospect.

Please note that currently hospitals will only be reimbursed for treatment given. Therefore it is not advised to overstock as any unused stock will not be reimbursed.

3.2 Storage

As per SmPC
Keep the blisters in the outer carton in order to protect from light.
No temperature excursion reporting required. Follow Trust SOPs to manage temperature excursions.

3.3 Dispensing quantities

Dimethyl Fumarate dosage is 120mg every 12 hours for 4 doses followed by 240mg every 12 hours for 8 days (total 10 days or discontinued on discharge from hospital if sooner). If 240mg every 12 hours cannot be tolerated, the dose may be reduced (see below).

The dose should be taken with food. For those patients who may experience flushing or gastrointestinal adverse reactions, taking with food may improve tolerability

We are awaiting confirmation from Biogen about whether the blister strips can be cut without affecting stability.

3.4 Returns and Destructions

During the study any patient returns or if a Trust chooses to ring fence any dimethyl fumarate for the study and there is still stock at end of study, this can be returned to stock in the usual way or destroyed on site. Remaining stock that has been returned for non-trial use should only be dispensed to patients whom have prior approval to be treated with dimethyl fumarate. No approval from Sponsor is required.

3.5 FAQs

Q. Can the dose be reduced for this study?
A. Yes at the discretion of the treating doctor. The dose can be reduced from 240mg twice daily to 120mg twice daily or 120mg once daily.

Q. Can the capsules be opened for patients who have swallowing issues or require nasogastric administration?

No; these patients should not be randomised to this receive this drug. As per the SmPC the contents of the capsule should **not** be crushed, divided, dissolved, sucked or chewed as the enteric coating of the micro-tablets prevents irritant effects on the gut.

Q. Should participants have their liver function tests monitored?

The protocol for participants in this comparison (including those allocated to the usual care arm) requires ALT to be checked on day 3, 5 and 10 (but not required if they have been discharged sooner).

4 REGN10933 & REGN10987 (Synthetic neutralising antibodies)

4.1 General

See Pharmacy manual for REGN10933 and REGN10987 on the RECOVERY website for further information regarding supply, storage, drug preparation and administration.

As REGN10933 and REGN10987 are novel drugs, these need to be treated in pharmacy as per any type C clinical trial. Therefore, full accountability, temperature monitoring and Annex 13 compliant labelling will be required.

Not all sites will be opened to this arm. Sites that will be taking part initially will be contacted by the RECOVERY team.

4.2 FAQs

Q. Is there any expectation from the sponsor for any additional temperature monitoring whilst transporting either the REGN10933 & REGN10987 vials from one site to another, or when transporting the final infusion bag from the aseptic unit to the ward?

A. Sponsor's permission is not required for the transport of REGN10933 and REGN10987 vials from one site to another, but temperature monitoring is required for such transfers. Temperature monitoring is not required when transporting the final infusion bag from the aseptic unit to the ward

(unless the ward is on a separate site in which case temperature monitoring is recommended, except where a validated shipper is used). The transport and temperature monitoring of stock or final prepared product should be carried out as per site's local SOPs.

Q. Can the REGN10933 & REGN10987 infusion be made on the ward by nurses?

A. This would have to be an individual site decision based on the outcome of a documented risk assessment; retained within trial file. Please see Oxford University Hospitals NHS Foundation Trust (OUH) local risk assessment in the Pharmacy Manual. The NPSA risk score is 6 (red) and the health and safety risk is moderate; .therefore, OUH have assessed that locally the infusion will be prepared within the aseptic unit. Please read Pharmacy Manual for further information.

Sites will also need to consider that wherever the drug is being prepared or infused, that staff have access to a monoclonal antibody spillage kit or similar eg cytotoxic one.

Q. Do patients need to be treated with any pre-medications prior to receiving the REGN10933 & REGN10987 infusion?

A. No, we are not recommending any pre-medication prior to infusion.

Q. What are the major drug-drug interactions for REGN10933 and REGN10987?

A. There are currently no known drug-drug interactions with REGN10933 and REGN10987. All reactions must be reported to the Central Coordinating Centre as detailed in the protocol.

Q. Does the mixing of 2 separate mAbs together in the same infusion bag count as manufacturing?

A. No, a senior pharmaceutical advisor at the MHRA has confirmed that the reconstitution of REGN-COV2 does not count as manufacturing. Therefore, this reconstitution process can be done within an unlicensed aseptic unit. Please read Pharmacy Manual for further information.

5 Aspirin

5.1 Initial supply and re-ordering

Aspirin will be sourced by local pharmacy procurement team via their normal routes. For the purpose of this study aspirin tablets, enteric coated/gastro-resistant tablets, dispersible tablets or suppositories can be used.

5.2 Storage

As per SmPC

No temperature excursion reporting required. Follow Trust SOPs to manage temperature excursions.

5.3 Dispensing quantities

Aspirin dosage is 150mg once daily for the duration of the hospital admission.

5.4 Returns and Destructions

During the study any patient returns or if the Trust chooses to ring fence any aspirin for the study and there is still stock at end of study, this can be returned to stock in the usual way or destroyed on site. No approval from Sponsor is required.

5.5 FAQs

Q. My patient is already on aspirin. Can they participate in this part?

A. No. Current use of aspirin (or other antiplatelets like clopidogrel, prasugrel, ticagrelor) will be recorded on the randomisation form and exclude the participant from this comparison.

Q. My patient is on warfarin or a DOAC. Can they participate in this part?

A. Yes. However, there is an increased risk of bleeding which should be taken into consideration.

Q. Should we modify their VTE prophylaxis if they are allocated aspirin?

A. No. Hospital VTE prophylaxis should continue as normal (see Protocol section 2.4.3).

Q. What about gastro-protection?

A. This can be used according to the discretion of the managing doctor.

6 Baricitinib

6.1 Initial supply and re-ordering

Baricitinib will be sourced by local pharmacy procurement team via their normal routes. Baricitinib is available as 2mg and 4mg film coated tablets.

A Blueteq form will need to be completed for each patient to ensure that costs can be reimbursed to hospital trusts. The Blueteq form can be completed in retrospect.

Please note that currently hospitals will only be reimbursed for treatment given. Therefore it is not advised to overstock as any unused stock at present will not be reimbursed.

6.2 Storage

As per SmPC

No temperature excursion reporting required. Follow Trust SOPs to manage temperature excursions.

6.3 Dispensing quantities

Baricitinib 4 mg once daily by mouth or nasogastric tube for 10 days in total or discontinued on discharge from hospital if sooner.

Eli Lilly have confirmed that from a stability standpoint the tablet expiration date will not be affected by cutting the blister strip as long as long as the tablet remains sealed in the strip. Therefore, sites can pack down to minimise waste.

6.4 Returns and Destructions

During the study any patient returns or if the Trust chooses to ring fence any baricitinib for the study and there is still stock at end of study, this can be returned to stock in the usual way or destroyed on site. Remaining stock that has been returned for non-trial use should only be dispensed to patients whom have prior approval to be treated with baricitinib. No approval from Sponsor is required.

6.5 FAQs

Q. Can the dose be reduced at all for this study?

A. Yes. Dose should be reduced in presence of renal impairment:

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

Dose should be halved in patients also taking an organic anion transporter 3 (OAT3) inhibitor such as probenecid.

At a local level, if the treating doctor feels that a dose reduction due to side effects is required then this is allowed.

Q. Can the Baricitinib tablets be cut in half?

A. Eli Lilly do not advise cutting the baricitinib tablets in half as these tablets are not scored.

Q. Can the Baricitinib tablets be dispersed in water for NG administration?

A. Yes. For patients unable to swallow whole baricitinib tablets – tablet(s) can be dispersed in a container with 10mL (5mL minimum) of room temperature water and dispersed with gently swirling. Take the contents orally immediately. The container should be rinsed with an additional 10mL (5mL minimum) of room temperature water and the entire contents swallowed by the patient.

For patients with a gastrostomy feeding tube – tablet(s) should be dispersed in a container with 15mL (10mL minimum) of room temperature water and dispersed with gentle swirling. Ensure the tablet(s) are sufficiently dispersed to allow free passage through the tip of the syringe. Withdraw entire contents from the container into an appropriate syringe and immediately administer. The container should be rinsed with 15mL (10mL minimum) of room temperature water, withdraw the contents into the syringe and administer through the tube

For patients with an enteral feeding tube – tablet(s) should be dispersed in a container with 30mL of room temperature water and dispersed with gentle swirling. Ensure the tablet(s) are sufficiently dispersed to allow free passage through the tip of the syringe. Withdraw the entire contents from the container into an appropriate syringe and immediately administer through the enteral feeding tube. To avoid clogging of small diameter tubes (smaller than 12 Fr) the syringe can be held horizontally and shaken during administration. Rinse container with sufficient amount (minimum of 15mL) of room temperature water, withdraw the contents into the syringe and administer through the tube.

Tablets may be crushed to facilitate dispersion. It is not known if powder from the crushed tablets may constitute a reproductive hazard to the preparer. Use proper control measures (e.g. ventilated enclosure) or personal protective equipment (i.e. N95 respirator)

Dispersed tablets are stable in water for up to 4 hours.

Q. If patients are already on an immunosuppressive drug can they also be randomised to receive baricitinib?

A. Yes they can.

7 General FAQs

Q. What happens if our site does not have one of the medications used in the study in stock?

A. The co-ordinating centre should be informed (e-mail to recoverytrial@ndph.ox.ac.uk). It is possible to indicate on the randomisation form if a treatment is unavailable (and this can be set at a site level), so participants would not be assigned it.

Q. How will the cost of IMPs be covered?

A. The low cost of aspirin and colchicine could be covered by assigning to the government's COVID-19 cost centre as part of their overall treatment costs. Please liaise with your finance department to identify the mechanism set-up on how to claim for these extra COVID-19 costs. REGN10933&REGN10987 (synthetic neutralising antibodies) are supplied by Regeneron free of charge. Trusts will be able to recoup the costs of baricitinib and dimethyl fumarate from NHS England by completing a Blueteq form for each patient.

Q. Can patients treated according to local pathway/protocol guidance still be considered for the RECOVERY trial further down the line?

A. All patients should receive standard care according to their local protocol. Randomisation is in addition to that.

Q. Are you allowing co-enrolment into other clinical trials of COVID-19?

A. Yes, as long as the clinical trial does not directly conflict with RECOVERY. Please see the trial website for further information.

Q. To ensure consistency for all patients, can the sponsor provide some guidance on how urgent (hours) the trial patient needs to receive the first dose of treatment?

A. We have no specific guidance on this, but within 6 hours would be ideal.

Q. Is Sponsor happy for sites to 'pre-pack' tablets into patient courses?

A. Yes

Q. If patients are discharged earlier than 10 days are pharmacy expected to use the left over medication to maximise stock (if sites SOPs allow)?

A. Yes if local site SOPs allow

Q. Are sites able to add their own dispensing/additional labels to manage the study as they feel is most appropriate?

A. Yes

Q. Can non-medical prescribers be utilised to prescribe trial medications?

A. Yes if local SOPs allow

Q. If a patient has suspected COVID-19, but the test results come back negative are they expected to come off the study?

A. If COVID swabs come back negative, but the treating clinician feels that clinically the patient does have COVID-19 then the patient can continue on study. However, the patient should stop if it is thought that the symptoms are due to another cause.

Q. What do we do with the remaining stock of dexamethasone, hydroxychloroquine, lopinavir/ritonavir and azithromycin?

A. The remaining stock of dexamethasone, hydroxychloroquine, azithromycin and tocilizumab can be moved into hospital's own stock, if appropriate. The remaining stock of lopinavir/ritonavir needs to be ring fenced and kept for now as there may be future UPH trials which may require it.