RECOVERY Clinical Trial Pharmacy Briefing Document

(Based on Protocol V19.1 16-Nov-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 D					
No additional treatment					
Baricitinib	Oral tablet	NHS stock. Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No
Randomisation Part F					
No additional treatment					
Empagliflozin	Oral tablet	NHS stock. Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No
Randomisation Part G					
No additional treatment					
Baloxavir marboxil	Oral tablet	NHS stock. Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No
Randomisation Part H					
No additional treatment					
Oseltamivir	Oral capsule, Oral suspension	NHS stock. Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No
Randomisation Part I					
No additional treatment					
Dexamethasone	Oral tablet, oral suspension, intravenous ampoules	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). 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 Baricitinib

2.1 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.

2.2 Storage

As per SmPC

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

2.3 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.

2.4 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.

2.5 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.

3 Empagliflozin

3.1 Initial supply and re-ordering

Empagliflozin will be sourced by local pharmacy procurement team via their normal routes. Empagliflozin is available as 10mg tablets in packs of 28 tablets.

In England, 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. [Reimbursement arrangements are yet to be confirmed for the devolved nations.]

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

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

3.3 Dispensing quantities

Empagliflozin 10 mg once daily by mouth for 28 days in total or discontinued on discharge from hospital if sooner.

3.4 Returns and Destructions

During the study any patient returns or if the Trust chooses to ring fence any empagliflozin 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 empagliflozin. No approval from Sponsor is required.

3.5 FAQs

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

A. Dose reductions are not expected including for patients with renal impairment or who develop renal impairment.

Q. My patient has severe hepatic impairment, can they be randomised to receive empagliflozin?

A. Yes, they can, this would be at the treating doctor's discretion.

Q. My patient has diabetic ketoacidosis, can they be randomised to receive empagliflozin?

A. No; these patients should not be randomised to receive this medicine.

Q. Do I need to follow MHRA/CHM advise on risk of diabetic ketoacidosis with empagliflozin?

A. Yes. You must continue to monitor patients for the signs and symptoms of DKA, (including rapid weight loss, nausea or vomiting, abdominal pain, fast and deep breathing, sleepiness, a sweet smell to the breath, a sweet or metallic taste in the mouth, or a different odour to urine or sweat) and if

suspected stop treatment and test for raised blood ketones even if plasma glucose levels are near-normal.

Q. My patient is volume depleted, can they still have empagliflozin?

A. Correct the fluid depletion and then randomise to treatment and continue to monitor fluid balance and renal function closely.

Q. Can empagliflozin tablets be cut or crushed for patients who have swallowing difficulties or who have a feeding tube?

A. No; these patients should not be randomised to receive this drug. The tablets must be swallowed whole with or without food. Please also note that these tablets contain lactose as an excipient, so patients who are lactose intolerant should not be randomised to receive this medicine.

Q. My patient is 85 years old or older, can they be randomised to receive empagliflozin in this trial?

A. Yes, they can, this would be at the treating doctor's discretion.

4 Baloxavir marboxil

4.1 Initial supply and re-ordering

For sites within England, Scotland and Wales: Baloxavir marboxil will be sourced by local pharmacy procurement team free of charge from Alliance Health Hospital system. Baloxavir is available as 40mg tablets in packs of 2 tablets.

For your initial order, order 10 packs of baloxavir 40mg using the PIP code provided in your site's activation e-mail (please ask your PI if you did not receive this) and NOT the usual PIP code for ordering normal hospital supplies.

Orders placed before 15:00 will be delivered to site the following working day.

For resupplies when sites are down to 2 packs of baloxavir, then place a re-order for a further supply of 10 packs. For your initial order and re-orders, then only order as 10 packs using the above PIP code to help Roche distinguish between commercial and stock for this trial.

For sites in Northern Ireland: Baloxavir tablets will be sourced by local pharmacy procurement team free of charge. For your initial order, order 10 packs of baloxavir tablets (2 x 40mg), complete the Recovery Drug Order Form and email the completed form to Movianto (form and e-mail address will be attached to your site's activation e-mail; please ask your PI if you did not receive this).

Orders placed before 15:00 will be delivered to site the following working day.

For resupplies, when sites are down to 2 packs of baloxavir, then place a re-order for a further supply of 10 packs. For your initial order and re-orders, then only order as 10 packs to help Movianto distinguish between commercial and stock for this trial.

All sites will need to ensure clear storage separation between stock for this study and general hospital stock for flu patients, as well as having some way of identifying the difference between stock when dispensing and checking. This could be done via a number of ways such as adding an additional label on receipting of stock stating 'to be used in the RECOVERY trial only' and storing in different areas of pharmacy.

4.2 Storage

As per SmPC

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

4.3 Dispensing quantities

Adults and adolescents (≥ 12 years of age)
< 80kg Baloxavir 40mg once daily by mouth on day 1 and day 4 ie 1 x 2 x 40mg pack
≥80kg Baloxavir 80mg once daily by mouth on day 1 and day 4 ie 2 x 2 x 40mg packs

If the participant is discharged before the course is complete, the participant should be provided with medication to complete the course at home.

4.4 Returns and Destructions

During the study any patient returns should be destroyed on site. If there is still stock at end of study, please seek guidance from the sponsor.

4.5 FAQs

Q. Can baloxavir tablets be cut or crushed for patients who have swallowing difficulties or who have a feeding tube?

A. The tablet must **not** be crushed or split. It can be dissolved if needed: Place tablet in 100ml medicine bottle, add 50ml of water for irrigation at ambient temperature and shake for 10 minutes. Add 50ml ORA-Blend to mask the taste, shake again to mix well. The mixture has not been tested for enteral administration. ORA-Blend is the only option: do NOT mix with food or juice.

If administering via a feeding tube (where taste is not an issue), the tablets can be dissolved in 100ml water. (While the company's in house data on dispersing tablet has not been tested for enteral administration, baloxavir suspension is licensed in the US for administration via enteral feeding tube, suggesting drug interaction with tubing is unlikely to be an issue. Given the licensed baloxavir suspension is bioequivalence to baloxavir tablet, and the suspension is a simple 2mg/mL suspension formulation (excipients: non-colloidal silicon dioxide, hypromellose, maltitol, mannitol, povidone K25, sodium chloride, strawberry flavour, sucralose and talc), the administration of dispersed tablet suspension is likely to have minimal impact on bioavailability.)

Q. How should the tablets be taken?
A. The tablets must be swallowed whole with or without food.
Baloxavir should not be taken with products that contain polyvalent cations such as laxatives, antacids or oral supplements containing iron, zinc, selenium, calcium or magnesium

Q. Do tablets contain lactose?
The tablets contain lactose as an excipient, so patients who are lactose intolerant should not be randomised to receive this medicine.

Q. My patient is pregnant or breastfeeding can they be treated with baloxavir?

A. Yes; pregnant or breastfeeding women can be randomised to receive baloxavir in this trial.

5 Oseltamivir

5.1 Initial supply and re-ordering

For sites within England, Scotland and Wales: Oseltamivir will be sourced by local pharmacy procurement team free of charge from Alliance Health Hospital system. Oseltamivir is available as 75mg capsules in packs of 10 capsules and as 6mg/mL powder for oral suspension (65mL = 390mg oseltamivir) in packs of 1 bottle per carton.

For your initial order please order 8 packs of oseltamivir 75mg capsules and 2 bottles of 6mg/mL powder for oral suspension using the PIP codes provided in your activation e-mail (please ask your PI if you have not received this directly), and NOT the usual PIP code for ordering normal hospital supplies.

Orders placed before 15:00 will be delivered to site the following day.

For resupplies when sites are down to 2 packs of oseltamivir 75mg capsules and/or 1 bottle of 6mg/mL powder for oral suspension, then place a re-order for a further supply of 8 packs of oseltamivir 75mg capsules and/or 2 bottles of 6mg/mL powder for oral suspension. For your initial order and re-orders, then only order pack quantities stated using the above PIP code to help Roche distinguish between commercial and stock for this trial.

For sites in Northern Ireland: Oseltamivir will be sourced by local pharmacy procurement team free of charge. For your initial order of 8 packs of oseltamivir capsules (10 x 75mg) and 2 bottles of oseltamivir 6mg/mL powder for oral suspension (65mL), complete the Recovery Drug Order Form and email the completed form to Movianto (form and e-mail address will be attached to your site's activation e-mail; please ask your PI if you did not receive this). .

Orders placed before 3pm will be delivered to site the following working day.

For resupplies, when sites are down to 2 packs of oseltamivir 75mg capsules and/or 1 bottle of 6mg/mL powder for oral suspension, then place a re-order for a further supply of 8 packs of oseltamivir 75mg capsules and/or 2 bottles of 6mg/mL powder for oral suspension. For your initial order and re-orders, then only order pack quantities stated to help Movianto distinguish between commercial and stock for this trial.

All sites will need to ensure clear storage separation between stock for this study and general hospital stock for flu patients, as well as having some way of identifying the difference between

stock when dispensing and checking. This could be done via a number of ways such as adding an additional label on receipting of stock stating 'to be used in the RECOVERY trial only' and storing in different areas of pharmacy.

5.2 Storage

As per SmPC

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

5.3 Dispensing quantities

Adult or children over 40 kg:
Oseltamivir 75mg capsules twice daily by mouth for five* days.

Children or under 40kg:

Body Weight	Recommended dose for 5* days
10 kg to 15 kg	30 mg (5ml of 6mg/ml liquid) twice daily, 1 x 65ml bottle
> 15 kg to 23 kg	45 mg (7.5ml of 6mg/ml liquid) twice daily, 2 x 65ml bottle
> 23 kg to 40 kg	60 mg (10ml of 6mg/ml liquid) twice daily, 2 x 65ml bottles
> 40 kg	75 mg (12.5ml of 6mg/ml liquid) twice daily, 2 x 65ml bottles

Neonates (age <36 weeks corrected gestational age): 1 mg/kg twice daily for 5* days.

Infants (age 0-12 months and ≥36 weeks corrected gestational age): 3 mg/kg twice daily for 5* days.

*Course can be extended to 10 days for immunosuppressed patients at the managing clinician's discretion. If the participant is discharged before the course is complete, the participant should be provided with medication to complete the course at home.

5.4 Returns and Destructions

During the study any patient returns or if there is still stock at end of study, please contact the sponsor.

FAQs

Q. My patient has renal impairment, can they receive oseltamivir?

A. Yes; 75mg twice a day dose should be reduced if their renal function is:

- eGFR ≥10 <30mL/min/1.73m^2 to 75mg once daily
- eGFR <10mL/min/1.73m^2 to 75mg as a single dose on day 1.

Q. My patient is pregnant or breastfeeding can they be treated with oseltamivir?

A. Yes; pregnant or breastfeeding women can be randomised to receive oseltamivir.

6 Dexamethasone

6.1 Initial supply and re-ordering

Dexamethasone will be sourced by local pharmacy procurement team from UKHSA (formerly PHE). Dexamethasone is available as 2mg tablets in packs of 50 or 100 tablets, 2mg/5mL oral solution in 75mL or 150mL bottles and 3.3mg/mL intravenous 1mL ampoules in packs of 10.

Please note that the stock sent may be short dated.

Stock can be ordered via ImmForm portal (as was used when dexamethasone was assessed for COVID-19). If you need additional stock (either because the original allocation has been used or has expired), e-mail recoverytrial@ndph.ox.ac.uk who can authorise this, stating the reason for needing the stock.

If Pharmacy does not already have an ImmForm account, complete a change form found at https://portal.immform.phe.gov.uk/Registration.aspx (option 1). If a new delivery location is required this can be requested on the same form (option 3). The completed form should be sent to helpdesk@immform.org.uk.]

6.2 Storage

As per SmPC

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

6.3 Dispensing quantities

Dexamethasone 6mg once daily by mouth or intravenously for ten days or discontinued on discharge from hospital if sooner.

6.4 Returns and Destructions

During the study any patient returns or if 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.

FAQs

Q. My patient is pregnant or breastfeeding can they be treated with dexamethasone?

A. No; pregnant or breastfeeding women should be prescribed oral prednisolone 40mg or intravenous hydrocortisone 80mg twice daily

Q. How is dexamethasone to be prescribed as there are different salts available?

A. To be prescribed as dexamethasone 6mg base

Q. Is the dose the same for oral and IV for dexamethasone despite differences in bioavailability?

A. Yes, the dose will be 6mg base for both IV and oral.

Q. How should the oral dose be taken?
Dexamethasone should be taken with or after food to minimise irritation to the gastrointestinal tract. Drinks containing alcohol or caffeine should be avoided.

Q. The IV dose of dexamethasone base of the 3.3mg/mL comes to 1.82mL which cannot be measured accurately in a 2mL syringe. What do we do?

A. Volume to be rounded to 1.8mL which is measurable.

Q. Our normal hospital practice is to dissolve dexamethasone 2mg tablets instead of using soluble tablets or oral liquid, is this permitted?

A. Yes. If sites cannot source the soluble tablets or liquid, then the 2mg tablets can be dissolved in 10mL of water. There are no issues with this going down a fine bore nasogastric tubes (Reference: Handbook of Drug Administration via Enteral Feeding Tubes).

Q. Is IV dexamethasone to be given as an IV bolus or infusion?

A. Either is acceptable, treating clinician to decide.

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. Trusts will be able to recoup the costs of baricitinib and empagliflozin from NHS England by completing a Blueteq form for each patient. Dexamethasone will be free of charge from UKHSA. Baloxavir and oseltamivir will be free of charge from Alliance (or Movianto in NI).

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 early 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 REGN10933 and REGN10987?

A. All remaining stock of REGN10933 and REGN10987 should be returned to Regeneron. This includes stock which is beyond its given 'expiry' date. Contact the RECOVERY trial team for further instructions.