RECOVERY Clinical Trial Pharmacy Briefing Document

(Based on Protocol V21.0 17-Dec-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 E					
No additional treatment					
Dexamethasone	Oral tablet, oral suspension, intravenous ampoules	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
Randomisation Part J					

No additional treatment					
Sotrovimab	Solution for Intravenous Infusion	GSK trial specific stock	No	Yes	No
Randomisation Part K					
No additional treatment					
Molnupiravir	Oral capsule	TBC	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 Dexamethasone

2.1 Initial supply and re-ordering

Dexamethasone will be sourced by local pharmacy procurement team via their normal routes.

2.2 Storage

As per SmPC

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

2.3 Dispensing quantities

Different randomisation parts have different doses and duration – please check carefully.

Randomisation Part **E**: Dexamethasone **20mg** (base) once daily by mouth, nasogastric tube or intravenous infusion for **5** days followed by dexamethasone **10mg** (base) once daily for **5** days. Treatment should be discontinued at 10 days or on discharge from hospital if sooner.

Randomisation Part **I**: Dexamethasone **6mg** once daily by mouth or intravenously for **10** days or discontinued on discharge from hospital if sooner.

2.4 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.

Randomisation Part **E**: Pregnant or breastfeeding women should be prescribed:
Prednisolone 130mg once daily orally or hydrocortisone (sodium succinate) 180mg three times a day or 135mg four times a day intravenously or methylprednisolone (sodium succinate) 100mg once daily intravenously for 5 days.

Followed by either prednisolone 65mg once daily orally or hydrocortisone (sodium succinate) 90mg three times a day or 70mg four times a day intravenously or methylprednisolone (sodium succinate) 50mg once daily intravenously for 5 days.
Sites are free to choose between three times a day or four times a day dosing for the hydrocortisone (sodium succinate) treatment course.
Administration: Hydrocortisone 70-180mg IV – give slowly over 5-10 minutes.
Methylprednisolone 50mg or 100mg IV – give slowly over 5 minutes.

Randomisation Part **I**: Pregnant or breastfeeding women should be prescribed oral prednisolone 40mg once a day or intravenous hydrocortisone (sodium succinate) 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 6mg and 20mg dose of dexamethasone base of the 3.3mg/mL comes to 1.82mL or 6.06mL which cannot be measured accurately in a 2mL or 10mL syringe. What do we do?

A. Volume to be rounded to 6mg/1.8mL and 20mg/6mL, which is measurable.

Q. The IV 67.5mg dose of hydrocortisone (sodium succinate) comes to 1.65mL (50mg/mL) or 3.375mL (20mg/mL) which cannot be measured accurately in a 2mL or 5mL syringe. What do we do?

A. Volume to be rounded to 70mg/1.4mL or 70mg/3.5mL, 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.

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 2mg/mL suspension is bioequivalent to baloxavir tablet, and the suspension is a simple 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 Sotrovimab

6.1 Initial supply and re-ordering

Sotrovimab is available as 500mg in 8mL vials, 1 vial per carton. The initial supply of sotrovimab will be sent by Fisher to each site for this arm (under instruction from the sponsor). The Principal Investigator will need to have completed the necessary training for this arm and the site activated before IMP is shipped.

Sites are to re-order supplies of sotrovimab when stock levels are running low by emailing the RECOVERY trial team: recoverytrial@ndph.ox.ac.uk

6.2 Receipt and Storage

As per SmPC.
Pharmacy department should receive all shipments.

All shipments will come with a temperature monitoring device. Follow the temperature monitoring device instructions included in the shipment. Please email the shipment temperature data to the RECOVERY trial team (see below) to confirm receipt. Discard the temperature monitoring device after the temperature readout report has been downloaded and emailed.

If there has been a temperature excursion during shipping or during storage at site, then affected stock must be physically quarantined until further guidance is given. Sites will need to complete the 'Clinical Investigational Medicinal Product (IMP) Temperature Excursion or Damage Form'. Send the completed form to the RECOVERY trial team only: recoverytrial@ndph.ox.ac.uk

All sites will need to ensure clear storage separation between stock for this study and general stock, 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.

Please note that the expiry date on the carton is not accurate. A batch specific variation has been approved by MHRA which extends this expiry date by 6 months.

6.3 Dispensing quantities

Sotrovimab dispense 2 x 500mg vials for a single **1000mg dose** to be administered as an intravenous infusion over **60 minutes** using a 0.2micron low protein binding in-line filter.

Note: *The dose and duration are different to SmPC license.*

6.4 Preparation Guidance

Doses of Sotrovimab may be made on the ward as per individual Trust guidance and risk assessment for monoclonal antibodies. Trust must have an IV monograph available on the wards where doses will be prepared.

Preparation steps

1. Remove **TWO** vials of sotrovimab from the refrigerator to allow the vials to equilibrate to room temperature, protected from light, for approximately 15 minutes
2. Obtain one **100mL** sodium chloride 0.9% or glucose 5% infusion bag
3. Visually inspect each vial to ensure it is a clear, colourless or yellow to brown solution, free from visible particles and that there is no visible damage to the vial
4. Gently swirl each vial several times before use without creating air bubbles. Do not shake or vigorously agitate the vials
5. Withdraw **16mL** of sotrovimab from the two vials
6. Add **16mL** of sotrovimab to a 100mL sodium chloride 0.9% or glucose 5% infusion bag
7. Gently rock the infusion bag back and forth 3 to 5 times. Do NOT invert the infusion bag. Avoid forming air bubbles

The stability concentration range is 1 – 10mg/mL. Sites must ensure that the brand of IV bag being used can hold this additional volume safely and that there is no additional risk of spillage/inadvertent loss when the ward nurse spikes the bag. The diluted solution should be administered immediately. If not possible then it may be stored at room temperature (up to 25°C) for up to 6 hours or refrigerated (2 – 8°C) for up to 24 hours from the time of dilution.

Please ensure the time of infusion is recorded in the medical records (if not done routinely).

6.5 Returns and Destructions

During the study if there is any damaged or expired stock, or if there is still stock at end of study, this can be destroyed on site. No approval from Sponsor is required.

FAQs

Q. My patient has renal impairment and/or hepatic impairment, can they be treated with sotrovimab?

A. Yes, no dose adjustment is required.

Q. My patient weighs less than 40kg, can they be treated with Sotrovimab?

A. Yes, unless they are ≥12 <18 years old in which case they must weight >40 kg.

Q. Can adolescents under 12 years receive sotrovimab?

No, and see protocol for other arms.

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

A. Yes; pregnant or breastfeeding women can be randomised to receive sotrovimab, but the consent process must explain the risks and benefits.

7 Molnupiravir

7.1 Initial supply and re-ordering

Molnupiravir is available as 200mg capsules, 40 capsules per bottle.

Ordering: To Be Determined

7.2 Storage

As per SmPC

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

7.3 Dispensing quantities

Molnupiravir 800mg twice daily for 5 days orally ie 40 capsules = one bottle.

Note: Women of child-bearing potential **must** have a negative pregnancy test before being randomised to molnupiravir.

If the participant is discharged before the course is complete, the participant should be provided with medication to complete the course at home. Please ensure the provision of such medication does not delay the discharge.

7.4 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 and/or hepatic impairment, can they receive molnupiravir?

A. Yes, and no dose adjustment is required.

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

A. No; pregnant or breastfeeding women must not be randomised to receive molnupiravir.

Q. Can adolescents under 18 years receive molnupiravir?

No, and see protocol for other arms.

Q. My patient has swallowing difficulties or has a nasogastric tube, can they receive molnupiravir?

A. No; the capsules should not be opened, crushed or chewed. Molnupiravir can be taken with or without food and swallowed whole with a glass of water.

8 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 empagliflozin from NHS England by completing a Blueteq form for each patient. Baloxavir and oseltamivir will be free of charge from Alliance (or Movianto in NI). Dexamethasone, hydrocortisone, methylprednisolone and prednisolone 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.

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