RECOVERY Clinical Trial Pharmacy Briefing Document

(Based on Protocol V27.0 13-Sep-2023)

Contents

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 influenza and community-acquired pneumonia (CAP) caused by other pathogens.

Table 1: Medicines for RECOVERY Clinical Trial

Medicine	Formulation	Source	Accountability logs	Prescribed	IMP Annex 13 labelling
Randomisation Part G (influenza)					
No additional treatment					
Baloxavir marboxil	Oral tablet	Roche trial specific stock	No	Yes	No
Randomisation Part H (influenza)					
No additional treatment					
Oseltamivir	Oral capsule, Oral suspension	Roche trial specific stock	No	Yes	No
Randomisation Part I (dexamethasone for influenza)					
No additional treatment					
Dexamethasone	Oral tablet, oral suspension, intravenous ampoules	NHS stock. Licensed products – Standard Pharmaceutical Wholesalers	No	Yes	No
Randomisation Part M (dexamethasone for community-acquired pneumonia)					
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.

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

Randomisation Part I (dexamethasone for influenza) and **Randomisation Part M** (dexamethasone for CAP): Dexamethasone **6mg** (base) once daily by mouth, nasogastric tube or intravenously for **10**

days, discontinued on discharge from hospital if this happens sooner. See below for details of alternative corticosteroids for use in pregnant women.

Children aged under 18 years (Randomisation Part I only)

Greater than 36 weeks corrected gestational age: Dexamethasone 150 micrograms/kg (as base) once daily (max: 6 mg once daily) for 10 days (or until discharge if sooner). Enteral or intravenous route.

Less than 36 weeks corrected gestational age: Hydrocortisone (IV) 0.5 mg/kg every 12 hours for 7 days and then 0.5mg/kg once daily for 3 days. Enteral or intravenous route.

2.4 Returns and Destructions

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.

2.5 FAQs

Also see the intervention sheets here https://www.recoverytrial.net/for-site-staff/site-teams

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 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 base

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

A. Yes, the dose will be as the 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. 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 Baloxavir marboxil

3.1 Initial supply and re-ordering

Baloxavir marboxil will be sourced by local Pharmacy Procurement team free of charge from Roche Products Ltd. Baloxavir is available as packs of 1 x 40mg tablets.

Initial Order:
Please order 10 packs of baloxavir tablets (1 x 40mg) by emailing the electronic drug delivery request form to welwyn.cpg_general@roche.com. A copy of the form can be downloaded from www.recoverytrial.net/for-site-staff/pharmacy. Please complete this form electronically & save as a Word document, rather than doing it by hand. For the first order at your site, copy in recoverytrial@ndph.ox.ac.uk, so the trial team can confirm that your site can be supplied.

Reordering:
When stock falls to 4 packs of baloxavir tablets (1 x 40mg), please re-order by sending a new electronic drug delivery request form to welwyn.cpg_general@roche.com. The maximum stock holding should not exceed the initial supply (if this creates logistical problems because of high recruitment please discuss with the trial team).

Orders placed before 12:00 will aim to be delivered to site the following working day, however, some sites in the Highlands and islands will be in line with the delivery schedule followed for all other orders placed with Roche. If you have any questions/concerns about the medicine delivery, please contact welwyn.cpg_general@roche.com.

All sites will need to ensure clear storage separation between stock for this study and general hospital stock for flu patients (or stock used for other clinical trials), 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.

3.2 Storage

As per SmPC

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

3.3 Dispensing quantities

Adults and adolescents (≥ 12 years of age)

<40kg	Not eligible for baloxavir comparison
40kg to <80kg	Baloxavir 40mg once daily by mouth on day 1 and day 4 ie 2 x 1 x 40mg pack
≥80kg	Baloxavir 80mg once daily by mouth on day 1 and day 4 ie 4 x 1 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.

3.4 Returns and Destructions

Any remaining stock at the end of the trial should be disposed of according to local pharmacy procedures.

3.5 FAQs

Also see the baloxavir intervention sheet https://www.recoverytrial.net/for-site-staff/site-teams

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, but see the advice in the intervention sheet.

4 Oseltamivir

4.1 Initial supply and re-ordering

Oseltamivir will be sourced by local Pharmacy Procurement team free of charge from Roche Products Ltd. 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.

Initial Order:
Please order the following by emailing the electronic drug delivery request form to welwyn.cpg_general@roche.com:

- 5 packs of oseltamivir capsules (10 x 75mg).
- 5 bottles of powder for reconstitution containing 390 mg of oseltamivir.

A copy of the form can be downloaded from www.recoverytrial.net/for-site-staff/pharmacy. Please complete this form electronically & save as a word document, rather than doing it by hand. For the first order at your site, copy in recoverytrial@ndph.ox.ac.uk, so the trial team can confirm that your site can be supplied.

Reordering:

When stock falls to 2 packs of oseltamivir capsules (10 x 75mg) or 2 bottles of powder for suspension containing 390 mg of oseltamivir, please re-order by sending a new electronic drug delivery request form to welwyn.cpg_general@roche.com. The maximum stock holding should not exceed the initial supply (if this creates logistical problems because of high recruitment please discuss with the trial team).

Orders placed before 12:00 will aim to be delivered to site the following working day, however, some sites in the highlands and islands will be in line with the delivery schedule followed for all other orders placed with Roche. If you have any questions/concerns about the drug delivery, please contact welwyn.cpg_general@roche.com.

All sites will need to ensure clear storage separation between stock for this study and general hospital stock for flu patients (or stock used for other clinical trials), 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 or children weighing >40 kg:

Oseltamivir 75mg capsules twice daily by mouth for 5* days.

Adults and children aged ≥ 1 year - dose for those weighing ≤40kg:

Body Weight	Recommended dose for 5* days
<10 kg	3 mg/kg twice daily
≥10 kg to 15 kg	30mg (5ml of 6mg/ml liquid) twice daily, 1 x 65ml bottle
>15 kg to 23 kg	45mg (7.5ml of 6mg/ml liquid) twice daily, 2 x 65ml bottle
>23 kg to 40 kg	60mg (10ml of 6mg/ml liquid) twice daily, 2 x 65ml bottles

Children aged 0-12 months (≥36 weeks corrected gestational age):

Body Weight	Recommended dose for 5* days
<10 kg	3 mg/kg twice daily
≥10kg	30mg (5ml of 6mg/ml liquid) twice daily, 1 x 65ml bottle

Neonates less than 36 weeks corrected gestational age:
1 mg/kg twice daily for 5* days.

Reconstitution of oseltamivir powder (390mg) to provide oral suspension 6mg/ml or 30mg/5ml and 65ml total volume:
1. Tap the closed bottle gently several times to loosen the powder.
2. Measure 55 ml of water by filling the measuring cup to the indicated level (measuring cup included in the box).
3. Add all 55 ml of water into the bottle, recap the bottle and shake the closed bottle well for 15 seconds.
4. Remove the cap and push the bottle adapter into the neck of the bottle.
5. Close the bottle tightly with the cap (on the top of the bottle adapter). This will make sure that the bottle adapter fits in the bottle in the right position.
Suspension will appear as an opaque and white to light yellow suspension after reconstitution.

*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.

4.4 Returns and Destructions

Any remaining stock at the end of the trial should be disposed of according to local pharmacy procedures.

4.5 FAQs

Also see the oseltamivir intervention sheet https://www.recoverytrial.net/for-site-staff/site-teams

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

A. Yes; the twice a day dose should be reduced if renal function is impaired (this dose is 75mg in adults and children weighing >40kg, but a lower dose should be used in children weighing <40kg, as above):

- eGFR ≥10 to <30mL/min/1.73m^2 dose to be given once daily
- eGFR <10mL/min/1.73m^2 single dose to be given 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.

5 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. Baloxavir and oseltamivir will be free of charge from Roche. Corticosteroids are provided by the site and are not directly reimbursed, but are treated as research costs in the SoECAT (with a treatment course of dexamethasone typically costing a few pounds).

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?

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 for use within one trust, with appropriate documentation and checks.
It is not legal to pre-pack for another Trust, unless the trust holds the relevant MHRA licenses.

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

6 Version History

Version number	Date	Brief Description of Changes
23.0	29-Jun-2023	Removal of empagliflozin, Paxlovid & molnupiravir comparisons. Update of section 5.2 & Appendix 1 to reflect sotrovimab expiry extension to 36 months.
24.0	14-Dec-2023	Addition of Part M (community-acquired pneumonia dexamethasone comparison). Minor update to baloxavir & oseltamivir re-ordering.
24.1	19-Feb-2024	Update of section 5.2 & Appendix 1 to reflect sotrovimab expiry extension to 48 months. Addition of version history.
24.2	17-Sep-2024	Update baloxavir packaging and disposal, update oseltamivir disposal, removal of covid comparisons (sotrovimab and high dose steroids)