STRESS-L TRIAL
Study into the Reversal of Septic Shock with Landiolol (Beta Blockade)

IMP Management Manual

FINAL Version:	5.1	**Date:**	01 October 2020
Investigational Medicinal Product (IMP):	Landiolol hydrochloride 300 mg lyophilised powder		
EudraCT number:	2017-001785-14		
Sponsor:	University Hospitals Birmingham NHS Foundation Trust		
Co-ordinating Centre:	Warwick Clinical Trials Unit		
Authors:	Amisha Desai and Emma Skilton		

Contents

1. Introduction

The purpose of this manual is to describe the requirements for IMP management by the local pharmacy and Intensive Care Unit (ICU) / critical care research team for the STRESS-L trial.

2. Site details

2.1 Principal Investigator name and contact details

PI name:

Address:

Email:

Telephone:

2.2 Sponsor

University Hospitals of Birmingham NHS Foundation Trust

2.3 Coordinating Centre and contact details

Trial Manager:	Emma Skilton
Address:	Warwick Clinical Trials Unit (WCTU) University of Warwick Gibbet Hill Campus University of Warwick Coventry CV4 7AL
Email:	stress-l@warwick.ac.uk
Telephone:	+44 (0)2476 572905
Fax:	+44 (0)2476 151136

Chief Investigator:	Dr Tony Whitehouse
Email:	Tony.Whitehouse@uhb.nhs.uk
Telephone:	07932 687308

2.4 Local of participants

Intensive Care Unit (level 3) or High Dependency Unit (level 2)

2.5 Location of IMP

Pharmacy and ICU

3. Responsibilities

The local **pharmacy** responsibilities for the STRESS-L trial are as follows:

- Receive IMP from the UK distributor (Mawdsleys)
- Confirm receipt of IMP
- Store IMP in a secure location with restricted access to trial team
- Undertake regular temperature readings for IMP storage area / ensure procedures are implemented for monitoring equipment temperature and calibration
- Release IMP to ICU
- Complete/maintain Pharmacy IMP Inventory Log
- Receive back unused or expired IMP
- Complete/maintain IMP Destruction Log

The local **critical care research team** responsibilities in relation to the IMP are as follows:

- Receive IMP from local pharmacy
- Store IMP
- Undertake regular temperature readings for IMP storage area / ensure procedures are implemented for monitoring equipment temperature and calibration
- Complete/maintain ICU IMP Inventory Log
- Reconstitute IMP/prepare infusion for participants randomised to receive landiolol and/or provide training and oversight for ICU critical care nurses at the bedside to undertake this task
- Administer and/or oversee administration of IMP to participant
- Inform local pharmacy team when stocks are running low on ICU
- Return any unusable or expired IMP to pharmacy
- Complete/maintain ICU IMP Destruction Log for disposing unused syringes

This IMP Management Manual should be read in conjunction with the current approved trial protocol.

3.1 Pharmacy File

A Pharmacy Site File (PSF) will be provided by the coordinating centre and must be maintained by site.

If trial sites wish to construct their own PSF in accordance with their local format or use their own logs they must contact the coordinating centre (WCTU) for permission to do so. If any of the documents provided in the PSF are stored in a separate location to the PSF, a file note specifying the location of the document(s) must be added to the PSF.

Please contact the Trial Manager at WCTU if you require additional copies of any of the documents/logs provided in the Pharmacy Site File.

The Pharmacy Site File will be issued with a receipt, this must be completed and returned to the coordinating centre at WCTU.

3.2 Delegation log

The trials pharmacist and/or pharmacy technician for STRESS-L will be added to the trial delegation log.

Any staff involved in the following activities should be trained on the trial by the named pharmacy staff member on the delegation log and complete the pharmacy training log:

- Acknowledging receipt of IMP
- Completion of IMP Inventory Log
- Completion of IMP Destruction Log

For practicality, non-delegated trials pharmacists and/or pharmacy technicians can complete the IMP Inventory Log and IMP Destruction Log in the absence of delegated staff provided they are appropriately trained and that this training is reflected in a signed local SOP.

4. Storage, handling and management of IMP

4.1 Description of IMP

Name of product: **Landiolol hydrochloride 300 mg** lyophilised powder
Formulation: 300 mg powder for solution for injection and infusion
Dosage: 1 – 40µg/kg/min

Description, dosage and excipients
Supplied as lyophilisate in vials with a nominal filling volume of 50 ml containing 300mg landiolol hydrochloride (which is equivalent to 280 mg landiolol) and inactive ingredients Mannitol E421 and Sodium hydroxide (for pH adjustment). After reconstitution (see section 4.9), each ml contains 6 mg landiolol hydrochloride. The maximum daily dosage of landiolol for this trial is 57.6mg/kg (based on 40 mcg/kg/min in a 24 hour infusion).

Please note the Summary of Product Characteristics (SPC) for Malta is available in English, and will be used for the purposes of this study.

Indication
Landiolol is a beta blocker used for supraventricular tachycardia and for the rapid control of ventricular rate in patients with atrial fibrillation or atrial flutter in perioperative, postoperative, or other circumstances where short-term control of the ventricular rate with a short acting agent is desirable. Landiolol is also indicated in non-compensatory sinus tachycardia where, in the physician's judgment the rapid heart rate requires specific intervention. Landiolol is not intended for use in chronic conditions.

Treatment
Landiolol can be prescribed up to a maximum of 14 days for the STRESS-L trial. Following randomisation allocation to standard treatment plus landiolol, participants will be started on a dose of 1.0 mcg/kg/min landiolol intravenous infusion, progressively increasing every 15 minutes at increments of 1.0 mcg/kg/min, to reach the target heart rate of 80-94 bpm usually

occurring over a period of 6 hours. Landiolol has an elimination half-life of 2.3 to 4 minutes and so a loading dose is unnecessary. The intervention treatment will be reduced if the patient's heart rate falls below 80 bpm. The landiolol infusion will continue until the patient's heart rate is persistently below 95 bpm, and will be reduced when all vasopressor agents have stopped for 12 hours. Once the landiolol infusion has been stopped for more than 12 hours, it should not be recommenced.

Packaging and labelling
Final trial labelling and packaging of trial drug will be carried out by CSM Germany. Final QP release of trial drug will be carried out by AOP Orphan Pharmaceuticals (Austria) IMP will be distributed to sites by a UK based distribution company, Mawdsleys.

4.2 Storage conditions of IMP

IMP supplied to participating sites requires refrigeration storage between 2°C and 8°C.

IMP must be kept in a secure location on ICU which can only be accessed by the research team or bedside nurses involved in reconstituting the drug where appropriate handover of IMP reconstitution and/or infusion management has been documented in the patients' medical notes. Ideally, IMP should be stored in a dedicated IMP fridge on ICU. Where this is not possible, IMP can be stored in a general ICU fridge provided access is restricted, IMP is clearly labelled with trial details and stored on a dedicated shelf within the fridge to assure the drug is not used for a non-trial patient.

It is expected that temperature monitoring records will be maintained for refrigerators in pharmacy and ICU. As a minimum, daily minimum and maximum temperature recordings are required excluding weekends and bank holidays (unless routinely undertaken at site). Access to temperature records must be granted upon request to WCTU and AOP Orphan QM.

On-site Temperature Excursions:
Any temperature excursion outside of 2-8.4°C for a refrigerated batch must be reported via email containing temperature log data to AOP Orphan QM (batchrelease@aoporphan.com, Marion.Pacher@aoporphan.com, stress-l@aoporphan.com and STRESS-L@warwick.ac.uk) for evaluation and release.

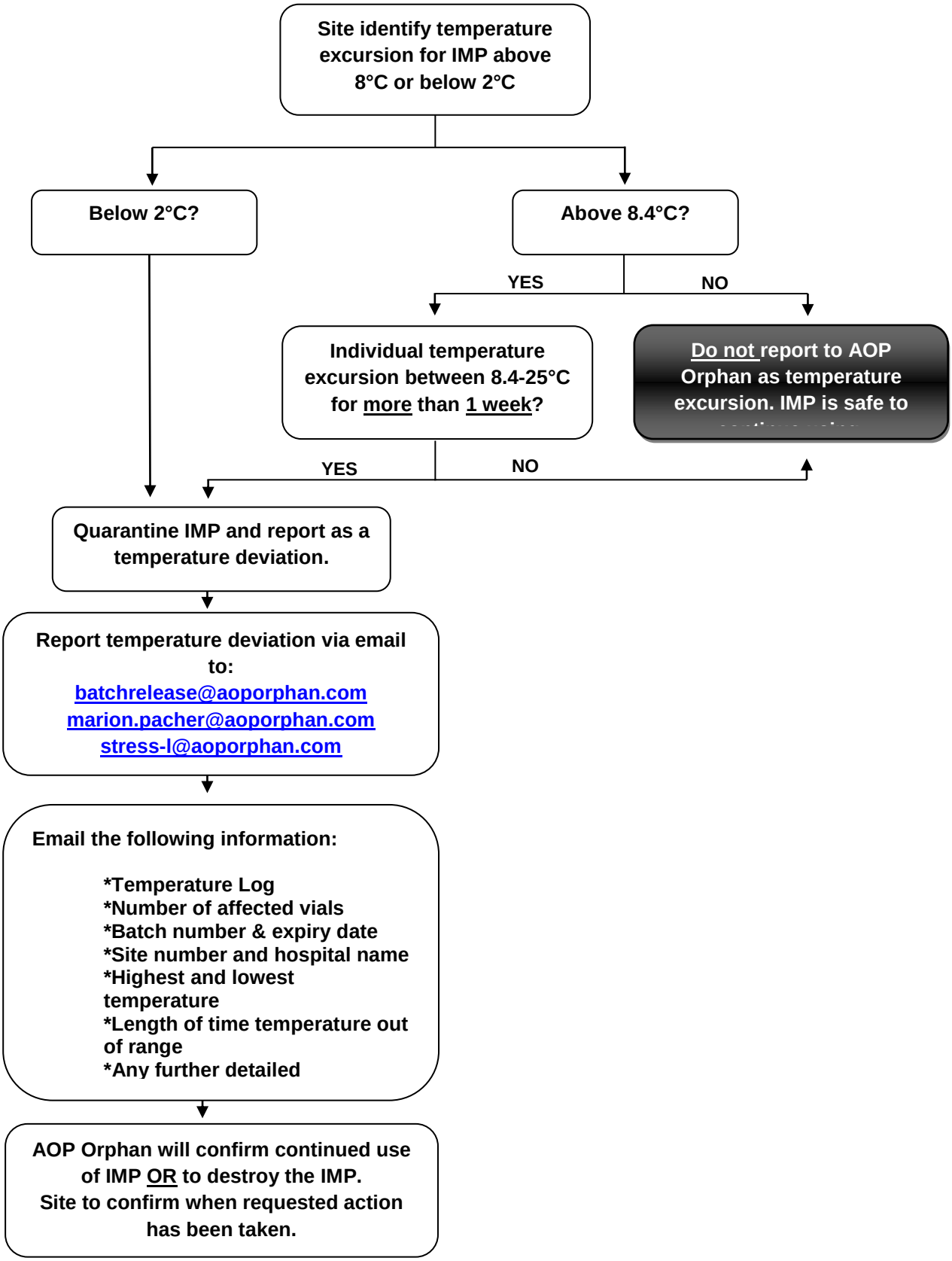
Temperature excursions, which do not exceed 25.4°C for a **maximum** duration of **1 week,** are **NOT** reportable to AOP (see Appendix 1). The 1 week clock **starts** when the temperature exceeds 8.4°C and **stops** when the temperature returns to 2-8.4°C. Therefore, if multiple temperature excursions occur within a 1 week period **but individually** each temperature excursion does not exceed 1 week these are **NOT** reportable to AOP and you can continue using the IMP stock.

Stability data has confirmed temperature excursions up to 25.4°C for less than 1 week do not pose any negative impact on the project quality or safety; therefore, the IMP can continue to be used.

PLEASE NOTE: Although Appendix 1 states up to 25°C, rounding rules apply; therefore, temperature excursions between 25.1 – 25.4 are rounded down to 25°C.

Temperature excursions between 8.1 to 8.4°C should **always** be rounded down to 8°C and are **not** reportable to AOP (see Appendix 2).

Figure 1: STRESS-L Temperature Excursion Reporting Flow Chart



AOP aim to respond in 1-3 working days. However in cases of urgency state this in your email and request a response within 24 hours.

In the event of recall of IMP, quarantine as per local procedure and follow instructions as provided by the coordinating centre.

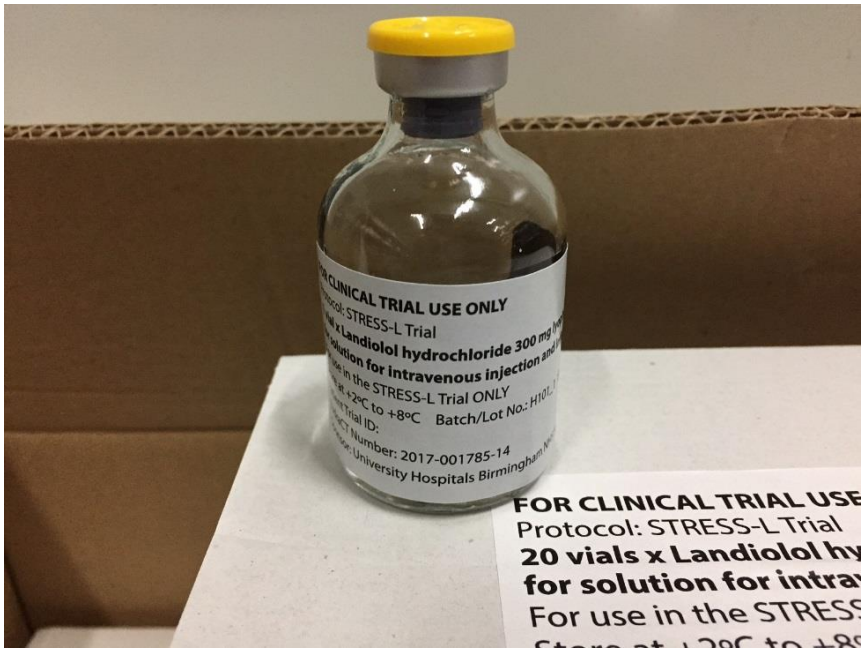
4.3 Storage space requirements

The storage space requirement is under 0.5m (=0.3m x 1.5m). The secondary packaging holds 20 vials and has the following dimensions:

18cm X 24.5cm X 9cm

Pharmacy will release 1 or 2 boxes at a time for storage in ICU. The minimum back-up supply held at site will be 2 boxes at any given time; either 2 boxes held in pharmacy or 1 box held in pharmacy and a further 1 box held on ICU.

Images of the IMP



4.4 Source of IMP

Landiolol is currently unlicensed in the UK, however regulatory approval was issued in Europe on 29 June 2016 via the decentralised procedure.

The sponsor has contracted AOP Orphan Pharmaceuticals (Austria) to supply the study drug for STRESS-L free of charge for the duration of the trial. AOP have contracted CSM Germany to label the primary (vials) and secondary (outer carton) packaging according to the requirements of the STRESS-L trial and Annex 13 of EU Guidelines to Good Manufacturing Practice. The final product will be QP released for use in the STRESS-L trial by the designated person at AOP Orphan Pharmaceuticals.

CSM Germany will ship bulk trial supplies to a 3rd party distributor in the UK for storage and distribution (Mawdsleys).

4.5 Receipt of goods

Initial delivery of IMP will follow the site initiation visit and only when all necessary documentation required by the sponsor are in place.

Supplies are delivered free of charge to the study sites by Mawdsleys (Doncaster). The WCTU trial team will submit a drug despatch request to Mawdsleys with site shipping address, consignee details and the initial number of vials required. An email confirming the order and estimated delivery date will be sent to the named site pharmacy personnel. Mawdsleys will send automated emails to site for expected timeframes for delivery.

IMP will be delivered temperature controlled and a member of the pharmacy team will be required to take receipt of the IMP shipment, unpack and **refrigerate immediately**. A temperature logger will be provided with every shipment and instructions for downloading the data will be included with each delivery. This must be downloaded and a copy printed for filing with the shipment paperwork.

The shipment paperwork must be filed in the Pharmacy Site File.

Please confirm receipt of IMP on the same day by completing the ACKNOWLEDGMENT OF RECEIPT section and email the paperwork and the temperature logger data clinical@mawdsleys.co.uk and at STRESS-L@warwick.ac.uk.

First delivery of IMP:
If the received shipment is the initial delivery of IMP, IMP should be quarantined in pharmacy until receipt of QP release from Mawdsleys **and** green light to recruitment has been issued by WCTU.

Re-supply of IMP:
If the received shipment is a subsequent resupply, IMP should be quarantined in pharmacy until QP release from Mawdsleys has been received.

QP release for the whole batch of IMP must be filed in the Investigator and Pharmacy site files.

If sites are unable to unpack IMP shipments immediately, it should be discussed with the WCTU during site set up.

4.6 Accountability

Pharmacy IMP Inventory Log and ICU IMP Inventory Log are supplied.

4.7 Obtain further supplies

Resupply from Mawdsleys is at the request of the Trial Manager at the coordinating centre ONLY.

A minimum back-up supply of 3 boxes will be held at site at any given time; either 3 or 2 boxes held in pharmacy and a further 1 or 2 box held on ICU. The Trial Manager must be notified by email on STRESS-L@warwick.ac.uk, should stock levels fall below this threshold. **It is essential local research teams communicate with their colleagues in pharmacy to highlight when drug is running low on the ICU.** The research nurses will check stock levels regularly and contact pharmacy for release of another box (containing 20 vials) when supplies are running low. **This is particularly important on a Friday to ensure there is enough drug on ICU to cover the weekend.**

Stock levels will be monitored by the Trial Manager remotely at the coordinating centre using an electronic inventory system. Research nurses will complete the landiolol infusion eCRF on a daily basis to record the number of vials used to prepare infusions for each day. The landiolol infusion eCRF will be completed retrospectively on a Monday to document how many vials were used over the weekend. Additional orders may be placed via the site pharmacy team who will contact the Trial Manager.

Issues concerning stock levels at site should be reported to the Trial Manager as soon as possible. **If an urgent resupply is required, an expedited order can be requested.**

With regards to turnarounds on the orders:

ORDER PLACED		TIMEFRAME FOR DELIVERY									
		WEEK 1					WEEK 2				
		Monday	Tuesday	Wednesday	Thursday	Friday	Monday	Tuesday	Wednesday	Thursday	NO. OF DAYS TO ARRIVE AT SITE*
Monday	**Before 12pm**	Paperwork processed	Despatched	Delivered							3
	After 12pm		Paperwork processed	Despatched	Delivered						3
Tuesday	**Before 12pm**		Paperwork processed	Despatched	Delivered						3
	After 12pm			Paperwork processed	Despatched	Delivered					3
Wednesday	**Before 12pm**			Paperwork processed	Despatched	Delivered					3
	After 12pm				Paperwork processed	No orders despatched on a Friday	Despatched	Delivered			5
Thursday	**Before 12pm**				Paperwork processed	No orders despatched on a Friday	Despatched	Delivered			6
	After 12pm					Paperwork processed	Despatched	Delivered			6
Friday	**Before 12pm**					Paperwork processed	Despatched	Delivered			6
	After 12pm						Paperwork processed	Delivered	Delivered		6

**including Saturday & Sunday*

- No orders will be despatched on a Friday.
- Consideration should be made for bank holidays.

4.8 Prescribing

Landiolol can be prescribed up to a maximum of 14 days. Landiolol supplied for use in the STRESS-L Trial must only be prescribed for participants randomised into this trial. The trial drug should be prescribed on the participant's inpatient chart and clearly identified as for the STRESS-L Trial. Sites may use local prescribing systems, including paper and electronic systems. The prescription must be signed by an authorised prescriber named on the trial delegation log. Known allergies should be completed with details of any allergies or 'none'. Prescriptions should be made available for review as source data, if required.

4.9 Dispensing

Pharmacy should ensure the PI and site details are added to the secondary packaging before releasing a box to the ICU. Please find example label below:

FOR CLINICAL TRIAL USE ONLY
Protocol: STRESS-L Trial
20 vials x Landiolol hydrochloride 300 mg lyophilised powder for solution for intravenous injection and infusion
For use in the STRESS-L Trial ONLY
Store at +2°C to +8°C
Batch/Lot No.: xxxxxxxx Expiry: xxxxxxxx
EudraCT Number: 2017-001785-14
PI: _____ Site Name/No.:_____
Sponsor: University Hospitals Birmingham NHS Foundation Trust,
Edgbaston, Birmingham. B15 2GW Tel: +44 (0) 121 371 4185
Chief Investigator: Dr Tony Whitehouse

The ICU research team will add the Patient Trial ID to the label on the vial (primary packaging) when issued and prior to reconstitution of IMP. Please find example label below:

FOR CLINICAL TRIAL USE ONLY
Protocol: STRESS-L Trial
1 vial x Landiolol hydrochloride 300 mg lyophilised powder for solution for intravenous injection and infusion
For use in the STRESS-L Trial ONLY
Store at +2°C to +8°C
Batch/Lot No.: xxxxxxxx Expiry: xxxxxxxx
Patient Trial ID: _____
EudraCT Number: 2017-001785-14
Sponsor: University Hospitals Birmingham NHS Foundation Trust

IMP preparation / reconstitution

A vial contains 300 mg landiolol hydrochloride which is equivalent to 280 mg landiolol.

After reconstitution each ml contains 6 mg landiolol hydrochloride. The IMP is a white to almost white powder for solution for infusion.

Method of administration
Landiolol must reconstituted prior to administration. Further dilution is not permitted.

Landiolol must not be mixed with other medicinal products except those listed in the instructions for use section below.

Landiolol should be administered intravenously via a central line or a peripheral line and should **NOT** be administered through the same intravenous line as other medicinal products.

Please refer to the SPC for further instructions.

Instructions for use
Reconstitute 1 vial with 50 ml of one of the following solutions:

- NaCl 9 mg/ml (0.9%) solution
- Glucose 50 mg/ml (5%) solution
- Ringer's solution
- Ringer-lactate solution

Information on the pH and osmolality of the landiolol solutions ready for administration:

Landiolol hydrochloride 300 mg reconstituted with	**pH**	**Osmolality [Osm/kg]**
	Reconstituted solution (free from visible particles)	
NaCl 9 mg/ml (0.9%) solution	6.5/6.5	0.341/0.401
Glucose 50 mg/ml (5%) solution	6.6/6.1	0.358/0.412
Ringer's solution	6.4/6.0	0.342/0.391
Ringer-lactate solution	6.5/6.2	0.313/0.360

The white to almost white powder dissolves completely after reconstitution. Mix gently until a clear solution is obtained. Reconstituted solutions should be visually examined for visible particles and discoloration. Only clear and colourless solutions should be used. Any unused medicinal product or waste material should be disposed of in accordance with local requirements.

Following reconstitution the syringes will have a label added to identify the drug and patient details as per standard local medicines policies. For the purposes of the trial the following information should also be included on the label prior to administration. These labels can be provided by the coordinating centre upon request to the Trial Manager.

For Clinical Trial Use Only
Trial Name: STRESS-L
Participant ID:
PI Name:
Sponsor: University Hospitals Birmingham NHS Foundation Trust

The manufacturer has confirmed there are no restrictions regarding in-use stability for the IMP. Syringes containing reconstituted IMP may be kept in the fridge or by the bedside at ambient conditions but must not be frozen. If syringes are kept at the bedside the dedicated nurse must not leave drug unattended (as would be the case with any other medications).

Conversion table for continuous intravenous infusion: micrograms/kg/min to ml/h (Landiolol hydrocholoride 300 mg/50 ml = **6 mg/ml strength**):

Body weight (kg)	1 mcg/kg/min	2 mcg/kg/min	3 mcg/kg/min	4 mcg/kg/min	5 mcg/kg/min	6 mcg/kg/min	7 mcg/kg/min	8 mcg/kg/min	9 mcg/kg/min	10 mcg/kg/min	
40	0.4	0.8	1.2	1.6	2.0	2.4	2.8	3.2	3.6	4.0	ml/h
45	0.5	0.9	1.4	1.8	2.3	2.7	3.2	3.6	4.1	4.5	ml/h
50	0.5	1.0	1.5	2.0	2.5	3.0	3.5	4.0	4.5	5.0	ml/h
55	0.6	1.1	1.7	2.2	2.8	3.3	3.9	4.4	5.0	5.5	ml/h
60	0.6	1.2	1.8	2.4	3.0	3.6	4.2	4.8	5.4	6.0	ml/h
65	0.7	1.3	2.0	2.6	3.3	3.9	4.6	5.2	5.9	6.5	ml/h
70	0.7	1.4	2.1	2.8	3.5	4.2	4.9	5.6	6.3	7.0	ml/h
75	0.8	1.5	2.3	3.0	3.8	4.5	5.3	6.0	6.8	7.5	ml/h
80	0.8	1.6	2.4	3.2	4.0	4.8	5.6	6.4	7.2	8.0	ml/h
85	0.9	1.7	2.6	3.4	4.3	5.1	6.0	6.8	7.7	8.5	ml/h
90	0.9	1.8	2.7	3.6	4.5	5.4	6.3	7.2	8.1	9.0	ml/h
95	1.0	1.9	2.9	3.8	4.8	5.7	6.7	7.6	8.6	9.5	ml/h
100	1.0	2.0	3.0	4.0	5.0	6.0	7.0	8.0	9.0	10.0	ml/h

Body weight (kg)	11 mcg/kg/min	12 mcg/kg/min	13 mcg/kg/min	14 mcg/kg/min	15 mcg/kg/min	16 mcg/kg/min	17 mcg/kg/min	18 mcg/kg/min	19 mcg/kg/min	20 mcg/kg/min	
40	4.4	4.8	5.2	5.6	6.0	6.4	6.8	7.2	7.6	8.0	ml/h
45	5.0	5.4	5.9	6.3	6.8	7.2	7.7	8.1	8.6	9.0	ml/h
50	5.5	6.0	6.5	7.0	7.5	8.0	8.5	9.0	9.5	10.0	ml/h
55	6.1	6.6	7.2	7.7	8.3	8.8	9.4	9.9	10.5	11.0	ml/h
60	6.6	7.2	7.8	8.4	9.0	9.6	10.2	10.8	11.4	12.0	ml/h
65	7.2	7.8	8.5	9.1	9.8	10.4	11.1	11.7	12.4	13.0	ml/h
70	7.7	8.4	9.1	9.8	10.5	11.2	11.9	12.6	13.3	14.0	ml/h
75	8.3	9.0	9.8	10.5	11.3	12.0	12.8	13.5	14.3	15.0	ml/h
80	8.8	9.6	10.4	11.2	12.0	12.8	13.6	14.4	15.2	16.0	ml/h
85	9.4	10.2	11.1	11.9	12.8	13.6	14.5	15.3	16.2	17.0	ml/h
90	9.9	10.8	11.7	12.6	13.5	14.4	15.3	16.2	17.1	18.0	ml/h
95	10.5	11.4	12.4	13.3	14.3	15.2	16.2	17.1	18.1	19.0	ml/h
100	11.0	12.0	13.0	14.0	15.0	16.0	17.0	18.0	19.0	20.0	ml/h

Body weight (kg)	21	22	23	24	25	26	27	28	29	30	
	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	
40	8.4	8.8	9.2	9.6	10.0	10.4	10.8	11.2	11.6	12.0	ml/h
45	9.5	9.9	10.4	10.8	11.3	11.7	12.2	12.6	13.1	13.5	ml/h
50	10.5	11.0	11.5	12.0	12.5	13.0	13.5	14.0	14.5	15.0	ml/h
55	11.6	12.1	12.7	13.2	13.8	14.3	14.9	15.4	16.0	16.5	ml/h
60	12.6	13.2	13.8	14.4	15.0	15.6	16.2	16.8	17.4	18.0	ml/h
65	13.7	14.3	15.0	15.6	16.3	16.9	17.6	18.2	18.9	19.5	ml/h
70	14.7	15.4	16.1	16.8	17.5	18.2	18.9	19.6	20.3	21.0	ml/h
75	15.8	16.5	17.3	18.0	18.8	19.5	20.3	21.0	21.8	22.5	ml/h
80	16.8	17.6	18.4	19.2	20.0	20.8	21.6	22.4	23.2	24.0	ml/h
85	17.9	18.7	19.6	20.4	21.3	22.1	23.0	23.8	24.7	25.5	ml/h
90	18.9	19.8	20.7	21.6	22.5	23.4	24.3	25.2	26.1	27.0	ml/h
95	20.0	20.9	21.9	22.8	23.8	24.7	25.7	26.6	27.6	28.5	ml/h
100	21.0	22.0	23.0	24.0	25.0	26.0	27.0	28.0	29.0	30.0	ml/h

Body weight (kg)	31	32	33	34	35	36	37	38	39	40	
	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	mcg/kg/min	
40	12.4	12.8	13.2	13.6	14.0	14.4	14.8	15.2	15.6	16.0	ml/h
45	14.0	14.4	14.9	15.3	15.8	16.2	16.7	17.1	17.6	18.0	ml/h
50	15.5	16.0	16.5	17.0	17.5	18.0	18.5	19.0	19.5	20.0	ml/h
55	17.1	17.6	18.2	18.7	19.3	19.8	20.4	20.9	21.5	22.0	ml/h
60	18.6	19.2	19.8	20.4	21.0	21.6	22.2	22.8	23.4	24.0	ml/h
65	20.2	20.8	21.5	22.1	22.8	23.4	24.1	24.7	25.4	26.0	ml/h
70	21.7	22.4	23.1	23.8	24.5	25.2	25.9	26.6	27.3	28.0	ml/h
75	23.3	24.0	24.8	25.5	26.3	27.0	27.8	28.5	29.3	30.0	ml/h
80	24.8	25.6	26.4	27.2	28.0	28.8	29.6	30.4	31.2	32.0	ml/h
85	26.4	27.2	28.1	28.9	29.8	30.6	31.5	32.3	33.2	34.0	ml/h
90	27.9	28.8	29.7	30.6	31.5	32.4	33.3	34.2	35.1	36.0	ml/h
95	29.5	30.4	31.4	32.3	33.3	34.2	35.2	36.1	37.1	38.0	ml/h
100	31.0	32.0	33.0	34.0	35.0	36.0	37.0	38.0	39.0	40.0	ml/h

Laminated copies of the Landiolol conversion table are provided in Investigator Site Files.

For participants under 40kg or over 100 kg **ideal body weight** will be used. The above dosing chart should be used as a guide and the method used will be as per local practice.

The landiolol infusion would ideally not be prepared in advance, however if the critical care research team are preparing infusion in advance for availability overnight, this is permitted.

The following caveats apply if there is a requirement to prepare infusions in advance:

- The syringe would only be prepared once confirmation that the patient was likely to continue through the night.
- Any syringe prepared would have a maximum expiry of 24 hours and would be labelled clearly with the patient details, the contents of the syringe and the expiry date and time. This is double-checked by a 2nd nurse as per standard local practices.

- The number of syringes to be prepared in advance would be based on average requirements over the previous 24 hour.

Details of how landiolol is to be administered, reduced and stopped for the purposes of the STRESS-L trial are provided in the study protocol.

4.10 Post trial arrangements for the IMP

The drug manufacturer have agreed to supply IMP for a maximum of 14 days per participant for the STRESS-L trial. There are no arrangements for extension of study duration, compassionate use, or post trial supply usage.

4.12 Returned IMP

Empty vials or IMP containers will not be retained. However the ICU research team will be required to keep an accurate record of number of vials used and issued to participants on the inventory log.

4.13 Disposal of IMP

The local research nurse team can dispose of unused reconstituted drug inside of syringes. This must be recorded on the ICU IMP Destruction Log.

Pharmacy must wait for written confirmation from the sponsor prior to disposal. Unused or expired IMP will be disposed of at site according to local Trust procedures. Pharmacy IMP Destruction Log is supplied.

Appendix 1: AOP signed QP statement regarding stability data for temperature excursions above 8°C for 1 week

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AOP ORPHAN
FOCUS ON RARE DISEASES

To whom it may concern

Vienna, 13 August 2020

Declaration

The study medication for the STRESS-L study (EudraCT 2017-001785-14) is to be stored between 2-8 °C according to the study protocol.

Regarding temperature excursions AOP Orphan can give the following confirmation:

According to existing stability data we can confirm that temperature excursions up to 25 °C for a maximum duration of 1 week do not pose any negative impact on the product quality or safety.

As a consequence, temperature excursions falling in the above definition (1 week up to max. 25 °C) do not have to be reported and can be handled with this statement.

For the sake of clarity, deviations below 2 °C must be reported.

AOP Orphan Pharmaceuticals AG
Dr. Klaus Hofstaedter
Qualified Person

Appendix 2: AOP signed QP statement regarding temperature excursion rounding

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AOP ORPHAN
FOCUS ON RARE DISEASES

To whom it may concern

Vienna, 06-Jun-2017

Temperature control

We confirm that any measured temperature has to be rounded commercially (also see Ph. Eur. 1. *General Notices*) to the significant digits shown by the respective limit. The rounded value is the one to be compared against the specified limit.
This is applicable for temperature monitoring of shipping and storage of any material with specified temperature range (e.g. IMP, commercial products, reference standards, etc.)

Example:
The measured value of 8.3 °C is rounded to 8 °C, which is within the specified limit 2-8 °C.

Prepared by:
DI (FH) Iris Koller
QM Manager
AOP Orphan Pharmaceuticals AG

06 JUN 2017 / Date
/ Signature

Approved by:
DI (FH) Katharina Schornsteiner
Qualified Person
AOP Orphan Pharmaceuticals AG

06 JUN 2017 / Date
/ Signature

PHARMACY IMP Inventory Log
Landiolol hydrochloride 300 mg/vial

Trial Title:	STRESS-L: Study into the Reversal of Septic Shock with Landiolol (Beta Blockade)	**EudraCT No:**	2017-001785-14
Principal Investigator:		**Site:**	

PLEASE USE A NEW LINE FOR EACH NEW TRANSACTION

Date	Number of vials received	Batch Number	Expiry Date	Received by Initials	Date issued to ICU	Issued to: (ICU Research team – Name & Sign)	Number of vials issued	Issued by Initials	Date returned to pharmacy	Return date recorded by (initials)	Balance in Pharmacy	Comments

ICU IMP Inventory Log
Landiolol hydrochloride 300 mg

Trial Title:	STRESS-L: Study into the Reversal of Septic Shock with Landiolol (Beta Blockade)	**EudraCT No:**	2017-001785-14
Principal Investigator:		**Site:**	

PLEASE USE A NEW LINE FOR EACH NEW TRANSACTION

Date	Number of vials received	Batch Number	Expiry Date	Received by Initials	Issued to Participant Study ID	Participant initials	Date issued to participant	Issued by	Date returned to pharmacy	returned by initials	Quantity returned	Balance in ICU	Comments

Pharmacy Training Log

Trial Title:	STRESS-L: Study into the Reversal of Septic Shock with Landiolol (Beta Blockade)	**EudraCT No:**	2017-001785-14
Principal Investigator:		**Site:**	

If dispensing or checking this study for the first time please read through the study specific procedure carefully before proceeding.
If you have any questions please refer to one of the clinical trials team. Sign and date this form when you are satisfied that you have read and understood the medicines management aspects of the study.

Name	Designation	Signature	Initials	Date

IMP Destruction Log

Trial Title:	STRESS-L: Study into the Reversal of Septic Shock with Landiolol (Beta Blockade)	**EudraCT No:**	2017-001785-14
Principal Investigator:		**Site:**	
At the request of:		**Sponsor:**	University Hospitals Birmingham NHS Foundation Trust

The following IMP have been destroyed in pharmacy according to local Trust procedure for destruction of pharmaceutical waste

Description	Quantity	Batch Number	Expiry Date	Reason for Destruction

DESTROYED BY					
Name (Print):		Title:		Date:	
WITNESSED BY					
Name (Print):		Title:			

1 copy in the pharmacy file

IMP Destruction Log

Trial Title:	STRESS-L: Study into the Reversal of Septic Shock with Landiolol (Beta Blockade)	**EudraCT No:**	2017-001785-14
Principal Investigator:		**Site:**	
At the request of:		**Sponsor:**	University Hospitals Birmingham NHS Foundation Trust

The following IMP have been destroyed in ICU according to local Trust procedure for destruction of pharmaceutical waste

Description	Quantity	Batch Number	Expiry Date	Reason for Destruction

DESTROYED BY					
Name (Print):		Title:		Date:	
WITNESSED BY					
Name (Print):		Title:			

1 copy in the investigator site file.