PHARMACY MANUAL

Final v1.0 20250321

Trial Title:	Cerebrovascular disease-Cognition (CVD-Cog) phase-2 trial in non-lacunar ischaemic stroke with cerebral small vessel disease	**EudraCT No:**	N/A
Investigational Medicinal Product (IMP):	1. Isosorbide mononitrate (ISMN) 2. Cilostazol		
Sponsor:	University of Nottingham		
Co-ordinating Centre:	Stroke Trials Unit, University of Nottingham		
Chief Investigator:	Professor Philip M Bath		
Principal Investigator contact details:	<to be added by site>		

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1. Pharmacy Responsibilities

The pharmacy responsibilities for the CVD-Cog trial are as follows:

Pharmacy File

A Pharmacy File must be constructed and maintained for the Trial. Trial sites may construct their own Pharmacy File in accordance with their local format however this **must** include the following documents:

- Trial Protocol
- This Pharmacy Manual
- SmPCs for ISMN and cilostazol
- MHRA Approval letters (including approval for any amendments)
- REC/HRA Approval letters (including approval for any amendments)
- IMP Inventory Log*
- IMP Accountability Log*
- Example prescription
- IMP Destruction Log*
- Correspondence with Coordinating Centre and site
- Temperature records whilst IMP is stored in Pharmacy
- Training material/training logs

Delegation Log

Site Details

2.1 Location of participants

*

2.2 Location of IMP(s)

*

3. Storage, handling & management of IMP

3.1 Description of IMP

The IMP is defined by the active substance only; therefore all authorised brands may be used. Oral ISMN slow release (or standard release) or cilostazol will be prescribed as per the brand available in the participating hospital pharmacy.

Isosorbide mononitrate (ISMN)

- Isosorbide mononitrate slow release, generic, as 25mg XL, 30mg XL,50mg XL or 60mg XL tablets to the target dose of 40-60mg daily; or

- Isosorbide mononitrate, standard release, as 20mg or 40mg tablets to the target dose of 40-60mg daily. This preparation should be used in patients receiving feeding via an enteral tube.

Most ISMN preparations are slow release in the UK. However, where slow-release preparations of ISMN are not available, non-slow release preparations may be used with the dose split with half in the morning (e.g. 08.00 am) and half in the evening (e.g. 18.00hrs). Non-slow release preparations may only be available in 20mg tablets in which case the 20mg should be substituted for the 25mg dose. The target dose of ISMN is 40-60mg daily. Detailed prescribing and administration instructions will be provided in the study treatment sheet.

Cilostazol

This does not apply to participants taking oral anticoagulation
Cilostazol, generic, as 50mg or 100mg tablets.

Cilostazol and ISMN are both licensed products for treatment of vascular diseases in Europe and the example summaries of the product characteristics are appended to this trial protocol. Example Representative Summary of Product Characteristics (SmPC) (for ISMN slow release, ISMN generic and cilostazol) are provided in a separate document with a cover sheet and signature page (signed and verified by the CI and Sponsor) and should be filed in the TMF.

Control

There is no placebo and participants randomised to control will not receive any trial medication.

3.2 Storage conditions of IMPs

Drug supplies will be kept in a secure, limited access storage area under the storage conditions specified by the local hospital's Pharmacy.

3.3 Source of IMP

No specific drug manufacturer is required for the trial. Both ISMN and cilostazol drugs are available from several providers in the UK. Pharmacies may provide the brand of each drug that is available to them.

Multiple doses and brands of ISMN are marketed in the UK. Two examples are:

- Isodur 50XL mg capsules (CAS 16051-787-7). Marketing authorisation holder: Galen Limited, Seagoe Industrial Estate, Craigavon, BT63 5UA, UK. Marketing authorisation number: PL 27827/0022. SmPC updated 9 April 2024 - see https://www.medicines.org.uk/emc/product/11062/smpc.
- Isosorbide mononitrate 20 mg tablets (CAS 16051-787-7). Marketing authorisation holder: Dexcel Pharma Ltd, 7 Sopwith Way, Drayton Fields, Daventry, Northamptonshire, NN11 8PB, UK. Marketing authorisation number: PL 14017/0011. SmPC updated 1 January 2018 - see https://www.medicines.org.uk/emc/product/2698/smpc.

Several doses and brands of cilostazol is marketed in the UK. An example is:

- Cilostazol 100 mg tablets (CAS 73963-72-1). Marketing authorisation holder: Generics (UK) Ltd t/q Mylan [now part of part of Viatris], Station Close, Potters Bar, Hertfordshire, EN6 1TL, UK. Marketing authorisation number: PL 04569/1427. SmPC updated 9 March 2020 – see https://www.medicines.org.uk/emc/product/2609/smpc.

There is no placebo and there are no modifications to the IMP.

Refer to the representative SmPC examples of the drug manufacturers provided for CVD-Cog investigators and as above.

3.4 Accountability

Randomised treatment(s) will be prescribed by the principal investigator or their designate in the hospital ward or stroke/TIA clinic. The prescription will be for 6 months of treatment(s) and account for the weaning-up period in the first month. Prescriptions will be taken to the hospital site for dispensing. Following the day 183 telephone call by the hospital site, participants will be asked to take any unused medications to a local community pharmacy for destruction.

Prescription, date of changing from half to full dose(s), dose at end of treatment and the request for destruction will be recorded in the eCRF.

The investigator and the local site pharmacist shall maintain records of the study drug's delivery to the pharmacy, an inventory at the site, the distribution to each participant, and the return to the pharmacy or alternative disposition of unused study drugs. These records will include dates, quantities received, batch / serial numbers, expiration dates, and the unique code numbers (patient trial number) assigned to the trial participant. Investigators and /or the local site pharmacists will maintain records that document adequately that the participants were provided with the correct study medication. These records will be also form part of each participant's Case Report Form (CRF). All study medication packs and bottles received by the pharmacy shall be accounted for.

3.5 Obtaining further supplies

The participant should contact the CVD-Cog Investigators at their hospital site and request an additional supply(s) of the randomised drug(s) at the appropriate dose (subject to tolerability). The Principal Investigator or their designate should then prescribe this taking account of remaining time so that the participant has trial medication(s) for a total of 6 months.

Participants randomised to control, i.e. no trial drug, will not need re-supply.

3.6 Prescribing

Drug prescribing should be relevant to the brand and formulation held by the hospital site's pharmacy.

3.7 Labelling and Dispensing

Standard pharmacy supplies will be used. The IMP will be clearly labelled for clinical trial use only with the trial specific label by the issuing pharmacist. The participant's trial ID number will be displayed on the study treatment pack. Each pack will be labelled in accordance with

Annex 13 of Volume 4 of The Rules Governing Medicinal Products in the EU: Good Manufacturing Practices, with the primary and secondary packaging remaining together throughout the trial. They will include storage conditions for the drug, but no information about the patient.

Detailed prescribing and administration instructions will be provided with the study treatment pack. Dose initiation in first 2-4 weeks will be guided by a regular phone calls and instructions.

Do we need an example label?
Medication labels will be in English and comply with the legal requirements of Annex 13 of the European Union's Good Manufacturing Practice (GMP). They will include storage conditions for the drug, but no information about the patient.

3.8 Post trial arrangements for the IMP

There are no arrangements in place for access to ISMN or cilostazol after participants have completed the trial.

3.9 Returned IMP

Unused drug will be destroyed as per the usual practice for the pharmacies. There are no special requirements for CVD-Cog.

3.10 Disposal of IMP

Unused drug will be returned by participants to community pharmacies or to participating hospital pharmacies if more convenient for destruction as per usual practices at pharmacies. There are no special requirements for CVD-Cog.