SYNOPSIS

Title	CerebroVascular Disease-Cognition phase-2 trial in non-lacunar ischaemic stroke with cerebral small vessel disease
Acronym	CVD-Cog
Short title	CerebroVascular Disease-Cognition
Chief Investigator	Professor Philip M Bath
Objectives	*To assess:* a) Feasibility: Recruitment of 400 patients from 25 UK sites at average recruitment rate of 0.9/site/month. b) Retention: >90% participants at end-of-trial/6-months. c) Adherence: ≥75% of participants are taking ≥50% trial dose at end-of-trial. d) Completeness of primary clinical outcome: >85% of participants have a DSM-5-7L ordinal cognition scale at end-of-trial. e) Safety: All cause death; serious adverse events; targeted drug-related adverse events. f) Proof-of-concept: Estimate of effect size and variance on DSM-5-7L ordinal cognition scale.
Trial Configuration	Partial factorial randomised controlled feasibility trial.
Setting	Secondary/tertiary care.
Sample size estimate	As a feasibility trial, there is no formal sample size calculation. However, recruitment of 400 participants will be sufficient to assess the feasibility, retention, adherence, safety and proof of concept aims.
Number of participants	400 participants
Eligibility criteria	***Inclusion****:* 1. Adult, age≥50 years, with no upper limit. 2. Clinical syndrome of cortical or large subcortical stroke or TIA (TACS, PACS or cerebellar POCS). 3. At least 7 days after the index event. 4. Stable medically according to the PI. 5. Has completed any phase of dual anti-platelet therapy. 6. Independent functionally or requires only limited help (mRS 0-3). 7. Able to swallow or has established enteral feeding route. 8. Brain imaging (CT or MRI scan) at the time of the index stroke/TIA shows moderate-severe white matter hyperintensities, Fazekas Score periventricular and deep ⩾2. a. The relevant radiology report will be uploaded as part of eligibility and assessed for these criteria.

	9. Consent: a. Patient has capacity to give consent in the opinion of the PI or any delegated member of the research team; OR b. Patient lacks capacity and a legal representative is available to give proxy consent. 10. Likely to be available for follow-up at 6 months. 11. Women of childbearing potential and men with partners of child baring potential must be willing to use contraception providing they have capacity. ***Exclusion**:* 1. Lacunar infarct (LACS; so is eligible for LACI-3 trial). 2. Brain stem-only posterior circulation stroke syndrome (POCS). Note: cerebellar POCS are eligible. 3. Known monogenic cerebral small vessel disease. 4. Index event was an intracranial haemorrhage. Note: a past history of ICH before the index event is eligible. 5. Other active brain disease e.g. brain tumour, multiple sclerosis, Parkinson's disease, recurrent seizures, neurodevelopmental disorder. 6. Clinical diagnosis of dementia, e.g. letter from a memory clinic and/or taking acetylcholinesterase inhibitor or memantine. 7. Contraindication to both trial drugs. 8. Indication for both trial drugs. 9. Planned surgery during the trial period including carotid endarterectomy. Note: Patient becomes eligible after planned surgery. 10. Diagnosis of hypotension, defined as sitting systolic blood pressure less than 100mmHg. 11. History of drug overdose or attempted suicide. 12. Person is a visitor to the hospital's region so cannot be followed, e.g. on holiday/from overseas. 13. Unlikely to comply with study procedures and follow-up procedures for whatever reason (e.g. history of poor medication compliance) in the opinion of the randomising physician. 14. Pregnancy, breast-feeding, or of child-bearing potential (a negative pregnancy test is needed prior to enrolment) and not using highly effective contraception. 15. Known renal impairment (most recent creatinine clearance <25 ml/min). 16. Known hepatic impairment (most recent transaminase >3 times upper limit normal). 17. Previously enrolled in CVD-Cog. 18. Enrolled in a study that does not have an agreement with CVD-Cog allowing co-enrolment (see up to date list of trials allowing co-enrolment on CVD-Cog website). 19. Women of childbearing potential and men with partners of child baring potential who lack capacity Cilostazol exclusion criteria - still allows randomisation to ISMN:

	20. Definite indication for cilostazol: i.e. already prescribed. 21. Definite contraindication to cilostazol: see SmPC. 22. Prohibited medications to cilostazol: see SmPC. 23. Active cardiac disease. 24. Bleeding tendency. 25. Uncontrolled high blood pressure: systolic BP >200 mmHg. ISMN exclusion criteria: 26. Definite indication for ISMN: i.e. already prescribed. 27. Definite contraindication to ISMN: see SmPC. 28. Prohibited medications to ISMN: see SmPC - phosphodiesterase type 5 inhibitors, e.g. avanafil, sildenafil, tadalafil and verdenafil.
Description of interventions	IMP is defined by the active substance only, so any brand of isosorbide mononitrate (ISMN) and cilostazol that are available in the hospital pharmacy may be used. Dose, formulation, brand and manufacturer must be recorded. Follow up calls to the participant will be conducted by the hospital site at 1-2 weeks, 3-4 weeks and Day 183. The research staff at the hospital site will check compliance and guide participants through the titration process. The research team will also check for any adverse events. A follow up call will be made by a blinded follow up coordinator at the coordinating centre (University of Nottingham) at Day 183 to complete cognitive, mood and function assessments with the participant. ***All patients***: Participants will be randomised to ISMN 25 mg od po SR/MR for two weeks then 50 mg od po SR/MR for 5½ months, versus no ISMN. If a slow release ISMN is not available, non-slow release tablets may be used. The target dose of ISMN is 40-60mg daily. ***Patients on mono-platelet therapy (not an oral anticoagulant, OAC)***: Participants will also be randomised to cilostazol 50 mg bd po for two weeks then 100 mg bd po for 5½ months versus no cilostazol. Hence, participants on mono-antiplatelet therapy will be randomised to start one of four treatments: • ISMN only; • Cilostazol only; • Both ISMN and cilostazol; • Neither ISMN nor cilostazol. Patients with contraindications to one drug may be randomised to the other drug versus control; patients who develop a contraindication to one of the drugs during the trial may continue taking the other drug. ***Comparator***: None (PROBE design).

	Standard of care: UK guideline-based stroke prophylaxis with antithrombotic, blood pressure lowering, lipid lowering, carotid endarterectomy, lifestyle etc and recorded. Trial drug will be dispensed in original manufacturer's packaging from participating hospital pharmacies. Drug will be supplied in a treatment pack marked with the participant ID and including instructions on how to take the tablets including the dose initiation and escalation phase. Patients will be phoned by the local centre at one to two weeks and three to four weeks after starting medication to check and advise on dose escalation. A maximum of six-months supply will be dispensed.
Duration of study	The trial's funding is for 3 years. Participants will be treated and followed for 6 months in total.
Randomisation and blinding	Computerised randomisation to reduce bias with: ***Stratification***: No oral anticoagulation - ISMN: cilostazol: both: neither 1:1:1:1. On oral anticoagulation - ISMN: no ISMN 1:1. ***Minimisation***: Age, sex, premorbid mRS, stroke impairment (NIHSS), age of leaving education, cognition (DSM-5 7L), time from stroke/TIA onset to randomisation, systolic blood pressure, smoking. Treatment is given open label (PROBE design).
Outcome measures	***Feasibility***: Recruitment of 400 patients from 25 UK sites. ***Retention***: >90% participants at end of trial/6-months. ***Adherence***: ≥75% of participants are taking ≥50% trial dose. ***Completeness of primary clinical outcome***: ≥85% of participants have a DSM-5-7L ordinal cognition scale at end-of-trial. ***Safety***: All cause death; serious adverse events targeted drug-related adverse events (headache, loose stools, palpitations, nausea, dizziness, falls). ***Proof-of-concept***: Diagnostic and Statistical Manual of Mental Disorders, Fifth Edition (DSM-5) 7-level ordinal cognition scale at end-of-trial. ***Health economics***: Not to be assessed. ***Process evaluation***: Not to be assessed.
Statistical methods	Tabulations of feasibility, retention, adherence, completeness of follow-up, safety and proof-of-concept. Data will be shown as number (%), median [interquartile range] or mean (standard deviation). Safety, symptoms and proof of concept will involve statistical comparisons between ISMN vs no ISMN, cilostazol vs no cilostazol and dual therapy vs no therapy. Comparisons will use adjusted binary logistic regression, Cox proportional hazards regression, ordinal logistic regression or multiple linear regression as appropriate. Primary

	analyses will use modified intention-to-treat (no imputation). There will be no adjustment for multiplicity.

Expression of Interest Form

Hospital name	
Trust name	
R&D Contact	Name: Email: Phone:
PI	Name: Email: Phone:
Research nurse / Study lead	Name: Email: Phone:
Please indicate which, *if any*, of these stroke trials your site has participated in in the past or expect to participate in	ENOS / LACI-2 / LACI-3 / MACE-ICH / MAPS-2 / PhEAST / PODCASST / RECAST-2 / RECAST-3 / RIGHT-2 / TARDIS / TICH-2 / TICH-3 *Note: although there it is not mandatory for sites to participate in both the LACI-3 and CDV-Cog trials, their similar protocols, interventions and outcomes support the synergy and efficiency in doing both, i.e., lacunar patients may enter LACI-3, and non-lacunar ischaemic stroke/TIA could enrol in CVD-Cog.*
Is a recruitment target of 0.9 participants per-month a realistic for your site?	
How many stroke admissions does your site have per year?	