# Clear-Brain: A partial randomised clinical trial investigating stimulation of the glymphatic system by either deepening sleep with lower-sodium oxybate or inhibiting cortical spreading depressions with non-invasive vagus nerve stimulation, or both, in patients with Cerebral Amyloid Angiopathy (CAA).

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Objectives:The main objective will be to assess whether treatment with nVNS, LXB or both interventions will increase the clearance of Aβ from the brain, compared to pre-treatment, in patients with CAA. Second objective is to study whether…

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| **Ethical review** | Approved WMO |
| **Status** | Pending |
| **Health condition type** | Central nervous system vascular disorders |
| **Study type** | Interventional |

## Summary

### ID

NL-OMON56712

**Source**
ToetsingOnline

**Brief title**
Clear-Brain

### Condition

- Central nervous system vascular disorders

**Synonym**
CAA, Cerebral Amyloid Angiopathy

**Research involving**
Human

## Sponsors and support

**Primary sponsor:** Leids Universitair Medisch Centrum
**Source(s) of monetary or material Support:** Bedrijf electroCore ondersteunt het onderzoek met het medisch hulpmiddel (gammaCore Sapphire). Het bedrijf financiert het onderzoek niet en heeft verder geen invloed op het protocol of verdere zaken. ,Bedrijf JazzPharma ondersteunt het onderzoek middels de onderzoeksmedicatie (XYWAV). Het bedrijf financiert het onderzoek niet en heeft verder geen invloed op het protocol of verdere zaken. ,Het onderzoek wordt gefinancierd door de Hersenstichting.

## Intervention

**Keyword:** Cerebral amyloid angiopathy, non-invasive vagus nerve stimulation, oxybate, RCT

## Outcome measures

### Primary outcome

The primary endpoint will be the morning Aβ 40 and 42 levels in CSF before and after treatment. CSF will be obtained through a lumbar puncture before the intervention at 3 months and after the intervention at 6 months.

### Secondary outcome

The activity of the glymphatic system will be measured with MRI 7T using quantitative metrics at three points in time. We will probe CSF motion at different locations in the brain: CSF-mobility (in mm2/s), fractional anisotropy and principal orientation of CSF-mobility will be calculated using the CSF-STREAM data in perivascular spaces, as well as larger subarachnoid spaces (e.g. around the middle cerebral artery). The coupling (amplitude and phase) between CSF fluctuations and cerebral blood volume changes will be computed from the phase contrast scan interleaved with a BOLD scan.

Disease progression measured by haemorrhagic and non-haemorrhagic imaging markers on 7T MRI and the CAA-burden score, comparing three months with and without intervention. Comparing disease progression in three months might be a short period to detect an effect on microvascular damage. However, we can see microvascular changes in great detail with ultra-high-field 7T MRI. We know from previous studies from literature and our own experience in our follow-up studies that microbleed development and other microvascular changes can be found in six months* time on 7T (unpublished data). Changes in microvascular MRI-markers in one year have been observed in other small vessel disease studies (Ter Telgte, 2018) and is seen in most of the participants in our follow-up cohorts (unpublished data). In a study by ter Telgte et al (2020), participants with cerebral small vessel disease were scanned monthly on a 3T MR scanner. In one third of the participants, microinfarcts were found which sometimes also disappeared again. Since CAA is a more severe disease and the fact that we also include D-CAA patients (whom in general have an even more aggressive disease course), we use a 3 month interval and we use the ultrasensitive 7T MRI - we expect to find a difference in disease progression measured by (non-)haemorrhagic markers.

Tolerability of nVNS and LXB; reached if less than 10% of the patients with nVNS has to abort the intervention due to side effects. Tolerability of nVNS and LXB will be investigated by telephone and via online questionnaire. Screening for sleep apnea with the Stop-Bang Berlin Sleep Apnea questionnaire. A short questionnaire on side effects and compliance will be sent and stored in

the digital CASTOR EDC database. CASTOR is compliant with 21 CFR Part 11, ICH E6 GCP, GDPR, and HIPAA, ISO27001 and ISO9001 certified.

A possible effect of the intervention on cognition will be measured with the Montreal Cognitive Assessment (MOCA), depression with the Hospital Anxiety and Depression Scale (HADS), the quality of life with the Short Form health survey (SF-36), the quality of sleep with the Pittsburgh Sleep Quality Index (PSQI) and the severity of insomnia with the Insomnia Severity Index (ISI).

CSF and blood samples will be stored in the LUMC Biobank Neurological Diseases. After analysis of this research these samples can be used for the identification of novel biomarkers in the future. Material in the biobank will be stored indefinitely. The head of the department Neurology will be responsible for the samples in case the principal investigator leaves the LUMC. The regulations of the LUMC Beheerreglement Biobank will be applicable to the LUMC Biobank Neurological Diseases.

The following baseline characteristics will be collected; date of birth, gender, history and current medical conditions, disease history of CAA, family and neurologic history (including previous ischemic and haemorrhagic stroke and migraine), daily intake alcohol/drugs/caffeine, smoking, current use of medication, physical activity and (possible) cardiovascular or CAA related risk factors. Length and weight (to calculate BMI) and blood pressure will be

recorded.

# Study description

**Background summary**

Spontaneous intracerebral haemorrhage (ICH) is a type of stroke caused by rupture of a cerebral vessel within the brain parenchyma. Although ICH accounts for only a minority of strokes (±20%), it is associated with a disproportionately high rate of mortality and morbidity. Cerebral Amyloid Angiopathy (CAA) is one of the major caauses of ICH and vascular dementia in elderly. Approximately 60% of all lobar (cortical) ICHs are CAA related. In CAA, vessel rupture is caused by an accumulation of Aβ, in the leptomeningeal arteries, cortical arterioles and capillaries of the brain, which disrupts the vessel wall integrity. Eventually this damage also leads to cognitive decline and vascular dementia.

Confirmation of diagnosis of sporadic CAA (sCAA) is achieved through brain autopsy, whilst a diagnosis of probable sCAA can be made by a combination of clinical characteristics, brain imaging and, when available, pathology. Dutch-type hereditary CAA (D-CAA; also referred to as Hereditary Cerebral Haemorrhage With Amyloidosis-Dutch type or HCHWA-D) is a hereditary form of CAA in which amyloid deposits are formed due to a mutation at codon 693 of the amyloid precursor protein (APP) gene on chromosome 21. Patients with D-CAA have a severely increased risk of ICH from a relatively young age. Since the underlying pathologies are similar, D-CAA can be seen as a pure form of CAA with an accelerated clinical course.

Currently, there is no treatment to cure or decelerate D-CAA or sCAA. One trial examines the effectiveness of minocycline as a therapy, but is still in the clinical phase. Other studies are exploring the clinical course and evaluation of the disease, which hopefully will lead to target points for eventual treatments. With Aβ-accumulation the vessel wall being the hallmark of CAA and lack of proof of increased production of Aβ, it is hypothesized that CAA is in essence a brain clearance disease.

The brain does not have a classic lymphatic system for the clearance of interstitial fluid and neuronal waste products. Relatively recently the glymphatic system was discovered as a macroscopic waste clearance system that rids the brain of waste products. This system also clears Aβ via cerebrospinal fluid (CSF) via perivascular spaces (PVS) into the subarachnoid space, where dural lymphatic vessels and venous uptake via arachnoid granulations support further egress out of the cranium. Details on CSF and ISF flow are still debated with the original models of IPAD and glymphatics being updated

continuously; in this protocol we will be using the term *Glymphatics* to describe the brain clearance system via perivascular spaces, but not in the strict definition of the original paper, i.e. we explicitly include more recent findings and adaptations under this term. The Radiology department of the LUMC has recently developed a new way to depict CSF-mobility, in large CSF spaces such as the ventricles but also in smaller ones like PVS. This can be done by using the CSF-Selective T2-weighted Readout with Acceleration and Mobility encoding (CSF-STREAM) technique at high-field (7T) MRI. The developed technique is non-invasive and repeatable and therefore useable for disease monitoring and for studying brain clearance in longitudinal fashion.

Several studies show that the glymphatic system is mostly active during sleep and especially deep sleep. LXB is a naturally occurring neurotransmitter and a psychoactive substance that deepens sleep (increased slow wave). It is safely and effectively used in treatment for the primary sleep disorder narcolepsy in adults and children and and Idiopathic Hypersomnia (IH) in adults. Sodium oxybate (SXB) has the same active moiety as LXB. Several studies assessed the efficacy and safety of SXB in various other disorders such as alcohol withdrawal syndrome, fibromyalgia and Parkinson*s Disease. Thus, LXB can be used safely for deepening sleep and we would also expect for stimulating the glymphatic system.

Cortical Spreading Depolarisations (CSDs) are a mechanism that appears to disrupt the glymphatic system. CSD*s are pathological waves of neuronal and glial depolarisations throughout the cortex, the underlying cause of migraine aura, transient focal neurologic episodes (TFNEs) and play a detrimental role in secondary damage after stroke and microinfarcts. A recent study has shown that CSD*s produce a reduction of outflow of interstitial fluid into the PVS as a consequence of a rapid closure of the PVS*s. Therefore CSD*s may play a vital role in brain dysfunction. The vagus nerve encompasses an intriguing network of neuro-endocrine-immune modulating fibers with connections to multiple brain regions. Research in animal models has shown that (invasive as well as non-invasive) stimulation of the vagus nerve is very effective in inhibiting spreading depolarisations (SD*s). Furthermore, vagus nerve stimulation (VNS) has been tested safely for several purposes in humans. Although the effect of nVNS on the glymphatic system in humans is unknown we expect an effect in CAA patients specifically due to the high incidence of migraine with aura, TFNEs and cerebral cortical microinfarcts in these patients.

Our hypothesis is that treatment of D-CAA and sCAA patients with LXB, nVNS or both will improve clearance of Aβ by stimulating the glymphatic.

**Study objective**

Objectives:
The main objective will be to assess whether treatment with nVNS, LXB or both interventions will increase the clearance of Aβ from the brain, compared to

pre-treatment, in patients with CAA. Second objective is to study whether CAA disease progression is modified by increasing Aβ clearance with disease modification measured by assessing haemorrhagic and non-haemorrhagic imaging markers on 7T MRI.

Exploratory objectives:
An exploratory objective is to measure the activity of the glymphatic system before and after the interventions, compared to the same time period without intervention, by using CSF mobility scans on ultra-high field 7 Tesla MRI.

Overall long-term goal:
To prevent CAA related ICH and cognitive decline with new disease modifying treatment. Data from Clear-Brain! will be used to power a larger clinical trial. Data and (left over) material will be stored in the LUMC Biobank Neurological Diseases for use in future research.

**Study design**

Our study design is a randomised controlled proof-of-concept trial with randomisation in three groups of 20 persons with CAA. Patients will receive LXB, nVNS or a combination of both interventions. The study period will take six months and the intervention will start at 3 months until 6 months.

Study period
- T0 = 0 months (baseline; MRI 7T, medical questions and several questionnaires; in subjects who will receive LXB also screening for sleep apnea by polygraphy)
- T1 = 3 months (start intervention; MRI 7T, lumbar puncture, collection of blood samples and several questionnaires)
- T2 = 6 months (end intervention; MRI 7T, lumbar puncture, blood withdrawal and several questionnaires)

Before inclusion participants will be screened for MRI safety by means of an MRI checklist. To minimize the number of study visits, the screening - in subjects who will receive LXB - for sleep apnea with a questionnaire and polygraphy will be done at baseline. During the intervention with LXB participants will be screened for developing sleep apnea with a validated questionnaire.

To avoid unnecessary burden for patients, we will use LUMC Biobank Neurological Diseases data from the placebo group from the current BATMAN trial as a control group. Informed consent for further research was already obtained during the start of the BATMAN trial (P19.110). This is a randomised controlled trial in the LUMC with minocycline versus placebo as intervention for 3 months.

**Intervention**

Medicinal product: Xywav* (LXB)
Investigational product: gammaCore Sapphire*

60 Patients will be randomised and receive either LXB, nVNS or both.
If patients are randomised to nVNS, two stimulations of two minutes each will be applied in the neck twice per day, using the hand-held gammaCore Sapphire*. One stimulation needs to be done before bedtime, within one hour before sleeping. The second stimulation needs to be done within an hour after wake-up. Except for the last day (T6), than the nVNS needs to be done within one hour before the start of the MRI 7T. Depending on the preference of the participant the amplitude of the gammaCore Sapphire* will be between 15 and 25. The stimulation protocol was developed in close collaboration with electroCore*, the manufacturer of the gammaCore Sapphire*. They have an extensive experience with this device. Stimulation will be explained to the patient by a pool of trained researchers.

LXB is used in treatment of narcolepsy with a safe and effective starting dose of 4.5 g per night divided in two intakes. In treatment of narcolepsy the first intake is administered immediately before bedtime and the second intake 2.5-4 hours later. The starting dosage can be changed with 1.5 g per night (divided in two intakes) until the maximum of 9 g per night (divided in two intakes) is reached. Between every change of dosage a period of at least 1-2 weeks is necessary. Recently a study showed a safe and efficient treatment of idiopathic hypersomnia with SXB not only twice-nightly with a maximum of 9 g per night but also once-nightly with a maximum of 6 g per night. In this study LXB will be administered orally in fluid form with a starting dose of 2 g before bedtime. Because of a short half-life of 30-60 minutes the subjects need to take the LXB immediately before going to bed. Initially patients will only take one dose per night. The dose will be titrated with a weekly increase of 0.5 g until a dose of 5 g is reached after 6 weeks. Therefore, each patient will have a stable dose period of at least 6 weeks. If patients suffer from side effects a lower dose than 5 g will be accepted and if patients suffer from LXB initiated hypersomnia a second dose 2.5-4 hours after can be added. When a second dosage is necessary a maximum of 9 g is allowed, preferably equally divided in two doses but if needed unequally division is allowed. Furthermore, certain anti-epileptica (valproic acid, phenytoin, ethosuximide and topiramate) can interact with LXB and therefore a dosage reduction of 20% should be considered when these anti-epileptica will be continued during the intervention period.

**Study burden and risks**

The burden mainly consists of three study visits, blood withdrawal, 7 Tesla MRI and two lumbar punctures. Travel costs will be reimbursed for the study visits. The measurements are routine procedures at the Department of Neurology. Lumbar puncture will be performed by experienced physicians. We will use atraumatic spinal needles to reduce the risk of post-lumbar puncture headache. Participants will be informed extensively about the potential risks of these

procedures, after which written informed consent will be obtained. To avoid unnecessary burden for patients, we will use the placebo group from the current BATMAN trial as a control group in the analysis of amyloid-beta. The risks of MRI are minimal and comparable to the risk of everyday life. Contra-indications will be carefully examined per subject. Burden will be kept to a minimum by using short protocols. The burden of respiratory polygraphic measurement will be minimal because we will use sleep wearables, which can be used at home. Invasive VNS (iVNS) has already been approved for treatment of depression and refractory epilepsy and was safe in a small pilot study in ischemic stroke patients. Non-invasive VNS (nVNS) has not yet been studied in CAA patients so the safety profile for this condition is not fully known. However, based on results in earlier trials, we don*t expect major risks to be associated with nVNS. Since LXB is already an established treatment for cataplexy or excessive daytime sleepiness (EDS) in patients 7 years of age and older with narcolepsy and Idiopathic Hypersomnia (IH) in adults, we feel that the risks are small. Benefit for the participants may be improved sleep when using LXB. If LXB and nVNS proves to be effective for improving Aβ clearance, participants may benefit from participating. Furthermore, participation in this study will result in further insight in treatment options for CAA.

## Contacts

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## Trial sites

### Listed location countries

Netherlands

# Eligibility criteria

**Age**
Adults (18-64 years)
Elderly (65 years and older)

## Inclusion criteria

1. Patients with D-CAA with a proven APP mutation or a history of >=1 lobar ICH and a positive family history for D-CAA in >=1 first degree relative - Age >=30 years old - <= 2 symptomatic ICH (occurrence of ICH at least > 1 year ago) or presence of >= 1 haemorrhagic marker (cortical superficial siderosis, cortical microbleeds) or non-haemorrhagic marker (white matter hyperintensities, microinfarcts, enlarged perivascular spaces, lobar lacunes). - When presymptomatic, patients are aware that they have D-CAA 2. Probable sCAA according to the Modified Boston criteria 2.0 - Age >=50 years old - <= 2 symptomatic ICH (occurrence of ICH at least > 1 year ago) 3. Provisional CAA when the criteria for probable sCAA are not met due to presence of deep haemorrhagic lesions but there are mostly lobar MB and cSS present or a ratio of 10 times more lobar MB than deep MB without cSS. - Age >=50 years old - <= 2 symptomatic ICH 4. Written informed consent

## Exclusion criteria

A patient who meets any of the following criteria will be excluded from participation in this study: - Modified Rankin Score >= 4 - A life expectancy of less than six months - Pregnancy/breast feeding - Contraindications for lumbar puncture - Contraindications for nVNS and LXB - Unwillingness to refrain from consuming <= 1 alcohol unit per day and not later than 8 pm. Specific contraindications for certain measurements or intervention: 1. Contraindications for using LXB: - Sleep apnea; patients will be screened with respiratory polygraphy before inclusion and screening by questionnaire during intervention with LXB. - Restless legs (RLS) needing active treatment with RLS medication. - Currently suffering from severe depression and using medication or receiving cognitive therapy. - Porphyria - Succinic semialdehyde dehydrogenase (SSADH-)deficiency - Use of opiates, barbiturates, sedatives (dexmedetomidine, temazepam, oxazepam, midazolam) - Use certain medication before inclusion: * When benzodiazepine is used: a two nights washout before the intervention (T3) will be started, is needed. * When LXB is used before inclusion: one week washout before inclusion and no use of LXB during inclusion except for the intervention dose. 2. Contraindications for lumbar puncture: - Compression of the spinal cord - Signs and symptoms of increased intracranial pressure - Local infections of the skin at the puncture site - Coagulopathy or

thrombocytopenia (<100) - (Use of acetylsalicylic acid, NSAIDs, COX2 inhibitors or low-molecular-weight heparin are no contraindications for lumbar puncture.) 3. Contraindications for nVNS: - An active implantable medical device such as a pacemaker, deep brain stimulator, or any implanted electronic device. - A recent (< 1 month) brain infarction or transient ischemic attack due to a symptomatic stenosis or dissection of the carotid artery (in these patients the other side will be stimulated unless a significant stenosis or dissection on the other side is present as well). - If someone knows to have a structural abnormality e.g. lymphadenopathy, previous surgery or abnormal anatomy (in these patients the other side will be stimulated) - Metal cervical spine hardware or metallic implant near the stimulation site - Cervical vagotomy (in these patients the other side will be stimulated) 4. Contraindications for 7T MRI as determined by the 7Tesla safety committee. Examples of possible contra-indications are: - Claustrophobia - Pacemakers and defibrillators - Nerve stimulators - Intracranial clips - Intraorbital or intraocular metallic fragments - Cochlear implants - Ferromagnetic implants - Hydrocephalus pump - Intra-uterine device - Permanent make-up - Tattoos above the shoulders 5. Specific contraindications for checkerboard fMRI: - Seizure within prior year - Photosensitive epilepsy - Non-correctable visual impairment

# Study design

## Design

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|---|---|
| Study phase: | 2 |
| Study type: | Interventional |
| Masking: | Open (masking not used) |
| Control: | Uncontrolled |
| Primary purpose: | Treatment |

## Recruitment

NL

| | |
|---|---|
| Recruitment status: | Pending |
| Start date (anticipated): | 01-12-2023 |
| Enrollment: | 60 |
| Type: | Anticipated |

## Medical products/devices used

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|---|---|
| Generic name: | gammaCore Sapphire |
| Registration: | Yes - CE outside intended use |

## Ethics review

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|---|---|
| Approved WMO Date: | 08-04-2024 |
| Application type: | First submission |
| Review commission: | METC Leiden-Den Haag-Delft (Leiden)<br><br>metc-ldd@lumc.nl |

## Study registrations

### Followed up by the following (possibly more current) registration

No registrations found.

### Other (possibly less up-to-date) registrations in this register

No registrations found.

### In other registers

| Register | ID |
|---|---|
| CCMO | NL85811.058.23 |