A First in Humans Study of Safety and Feasibility of baroloop: The baroloop Study

Published: 18-02-2021
Last updated: 14-03-2025

The primary objectives are to assess the safety and feasibility ofthe baroloop device for the treatment of subjects with hypertension (HTN). The secondary objective is to document the effect of the baroloop device on the blood pressure and quality...

Ethical review	Approved WMO
Status	Completed
Health condition type	Vascular hypertensive disorders
Study type	Observational invasive

Summary

ID

NL-OMON54976

Source
ToetsingOnline

Brief title
The baroloop Study

Condition

- Vascular hypertensive disorders

Synonym
hypertension

Research involving
Human

Sponsors and support

Primary sponsor: neuroloop GmbH
Source(s) of monetary or material Support: neuroloop GmbH

Intervention

Keyword: hypertension, nervus vagus, neuro stimulation

Outcome measures

Primary outcome

4.2. Primary Study Endpoints

4.2.1. Safety

Composite Major Adverse Event (MAE) Rate at six (6) months post-treatment

including:

• All-causes of death

• Hospitalization for hypertensive crisis post-titration

• Any device or procedure-related serious adverse event

All MAEs will be adjudicated by an independent Data Safety Management Board

(DSMB)

4.2.2. Feasibility

The ability of the baroloop System to be placed around a vagal nerve and to

stimulate at Day14/21 post-implantation. .

Secondary outcome

4.3. Secondary Study Endpoints

4.3.1. Efficacy:

• The change in blood pressure recorded during intraoperative stimulation at

the time of implantation.

• Mean reduction in 24-hour ambulatory systolic and diastolic blood pressure

(ambulatory blood pressure monitoring - ABPM) at one (1), three (3), six (6),

twelve (12) and eighteen (18) and twenty-four (24) months post-treatment versus baseline.

• The composite MAE rate at 1, 3, 6, 12, 18 and 24 months post-procedure defined as:

o All-causes of death

o Hospitalization for hypertensive crisis post-titration

o Any device or procedure-related serious adverse event

• The mean reduction in office diastolic and systolic blood pressure, and diastolic and systolic blood pressure at 1, 3, 6, 12, 18, and 24 months.

• Changes in antihypertensive medicines/doses through 1, 3, 6, 12, 18 and 24 months post-implantation as analyzed by Daily Defined Dosages (WHO Definition) and total medications.

• Quality of Life as measured by the Medical Outcomes Study 36-Item Short-Form Health Survey (SF-36).

Study description

Background summary

2.5. Baroreceptor Modulation for Hypertension (for more inforation see pages 19-23 in the Protocol)
The pivotal role of the autonomic nervous system in the pathogenesis of hypertension is well established. However, pharmacological therapies that block sympathetic activity have not achieved the desired outcomes. In the past few years, there have been efforts to develop medical devices and techniques that influence sympathetic nervous system activity. These include endovascular renal sympathetic denervation and continuous electrical baroreceptor nerve pacing. Neuroloop has developed a device-based treatment of hypertension by activating the baroreflex through vagal nerve stimulation (VNS).
2.5.1. Baroreflex activation therapy - background information
Due to the lack of available medication for hypertension (Lohmeier and Iliescu,

2011), in the 1950s and 1960s *electrical stimulation of the carotid sinus and subsequent activation of the baroreflex was conceived to be a therapeutic option for elevated BP* (Bilgutay and Lillehei, 1966; Braunwald et al., 1967; Epstein et al., 1969; Plachta et al., 2014; Warner, 1958). The baroreflex, also known as the arterial baroreflex, controls the arterial blood pressure continuously and is among the most important blood pressure control mechanisms (Benarroch, 2008; Plachta et al., 2014). Strain-sensitive fibers of the baroreceptors are located in the area of the aortic arch and both carotid sinuses near the carotid bifurcation (Ai et al., 2009; Berthoud and Neuhuber, 2000; Plachta et al., 2014; Wallbach and Koziolek, 2018). The afferent nerve terminals in the carotid sinus are innervated by the glossopharyngeal nerve and in the aortic arch by the vagal nerve (Benarroch, 2008). The fibers innervating the carotid and aortic baroreceptors project to the nucleus of the solitary tract in the dorsal medulla, and from there, the information ramifies throughout the central nervous system (Johnson and Wilson, 2018). The baroreflex consists of a negative feedback loop in which increased baroreceptors stretch (from which an increase in blood pressure may be inferred) efferent sympathetic tone is decreased and efferent parasympathetic tone is increased, which leads to vasodilatation, slowing of the heart rate and lowering of blood pressure (Kougias et al., 2010).

The current state of the art regarding baroreflex activation therapy uses the *glossopharyngeal part* of baroreflex activation: a carotid sinus stimulator to *trick* the baroreceptor into reporting a stretch that is higher than the actual stretch and blood pressure (Bisognano et al., 2011). The Rheos Pivotal trial demonstrated sustained efficacy of the first generation baroreflex activation therapy (BAT) device (sustained reduction in blood pressure) after 12 months, and baroreflex activation therapy was safe. A meta-analysis of BAT clinical trials (including nine studies, only 2 RCTs, including trials of the *old* system and *Neo*) found a significant reduction of blood pressure after BAT of close to 3.6 mm Hg (analyzing the longest follow-up visits, which was a median of 13.5 months), as well as a blood pressure reduction after short-term follow up (Wallbach and Koziolek, 2018). The lack of more data from randomized trials means that these results have to be interpreted with caution. Nevertheless, these studies established the feasibility of activating the baroreflex to reduce blood pressures and control hypertension.

2.5.2. Vagal Nerve Stimulation (VNS) - state of the art

Over 100.000 patients have been treated with vagal nerve stimulation (VNS) therapy for epilepsy. The surgical procedure to implant the vagal nerve stimulator is well established and appears to be a relatively safe intervention (Garcia-Navarrete et al., 2013; Kahlow and Olivecrona, 2013; Revesz et al., 2016). VNS surgery is associated with an overall surgical complication rate of 8.5% (Selner et al., 2019). *Surgical complications included infection, vocal cord palsy, post-operative hematoma, intra-operative bradycardia during test stimulation, and others, with infection (3.9%)* (Selner et al., 2019). A 6.5% rate of hardware complications were reported, including lead fracture and stimulator malfunction. Lead fracture was the most common complication (5.6%) (Selner et al., 2019). Overall, the implantation is a safe procedure and well

established for more than 25 years (Spuck et al., 2010), and VNS is as a relatively safe treatment (Giordano et al., 2017; Panebianco et al., 2016; Selner et al., 2019).
Specifically with respect to vagal nerve stimulation to control blood pressure, selective stimulation of vagal afferent baroreceptor fibers is preferable to stimulating efferent fibers that may lead to side effects such as bradycardia or heart block (Plachta et al., 2014; Timarova and Steno, 2017). Most of the stimulation associated side effects are derived from stimulation of the inherent functions of the vagal nerve (Timarova and Steno, 2017). The feasibility of selective VNS to elicit baroreflex responses has been shown in rats without occurrence of severe adverse events (bradycardia or heart block) (Plachta et al., 2014). Even when angiotensin converting-enzyme inhibitors (a commonly used antihypertensive medicine) were co-administered with VNS, selective VNS reduced blood pressure (Gierthmuehlen et al., 2016). Moreover, cardiac-cycle-synchronized stimulation triggered to the R-wave of the electrocardiogram in rats successfully reduced blood pressure using constant stimulation parameters with hardly any side-effects (Plachta et al., 2016).
The unique cuff electrode design of the baroloop system permits anatomically selective, vagal nerve stimulation to activate the baroreflex and reduce blood pressure. An implantation procedure similar to that used for VNS to treat epilepsy will be used. However, the lead design of the baroloop system is different, and lead placement has been adapted to the unique aspects of the baroloop design. Nevertheless, similar overall surgically related complications may be expected. Any adverse events associated with VNS using the baroloop device will be evaluated during the proposed First in Human (FIH) study. The anatomically selective stimulation used in the neuroloop system may reduce the occurrence of side-effects associated with VNS, since a relatively higher proportion of baroreceptor active fibers may be stimulated, although, the baroloop electrode may include cardiac branches of the vagal nerve. Selective stimulation delivered by the unique neuroloop electrode design may avoid or reduce some of the cardiac side effects related to stimulation of efferent cardiac branches of the vagus, since the targets of baroreflex activation are the afferent baroreceptor fibers.
2.5.3. Neuromodulation: selection of stimulation parameters
Electrical neuromodulation has a long history in humans and a broad scope of targets, including the brain, spine, peripheral nerve, retina, cochlea, etc. (e.g.: ECoG, Retinal Implants, ActiGait, VNS, DBS, SCS). The form and shape of the electrodes (contacts) have to be designed appropriately to fit the target area. The baroloop cuff electrode contains multiple individual electrode contact areas: cathodes with areas of 264.000 µm2 and anodes with areas of 2.34*106 µm2. The combination of electrode geometry and stimulation parameters (frequency, duty cycle and pulse duration) must be adapted to achieve optimal output and activation of the target and minimal damage to the electrode (corrosion) and the surrounding tissue. An electrode can deliver a certain amount of charge/area without corrosion within the so-called water window within which the charge does not corrode the electrode material nor is water subjected to electrolysis (Cogan, 2008). Pulse width and charge balancing are

typical countermeasures to avoid both corrosive processes and cha

Study objective

The primary objectives are to assess the safety and feasibility ofthe baroloop device for the treatment of subjects with hypertension (HTN).
The secondary objective is to document the effect of the baroloop device on the blood pressure and quality of life in subjects with hypertension (HTN).

Study design

4.1. Study Design
The baroloop Study is a First in Human (FIH) study of the safety and feasibility of using the baroloop System in subjects with uncontrolled hypertension. As described above, an adequate body of historical data pertaining to device-based treatment of uncontrolled hypertension exists against which neuroloop can test the safety and performance of the baroloop System in a FIH study.
As described in the Background for the current study, the appropriate safety endpoint is defined by the occurrence of device- and treatment-related (both procedural and postprocedural) adverse events. Previous studies have used a similar definition of safety and, therefore, results of these previous studies provide useful historical comparison data to evaluate the safety of the baroloop System. Similarly, feasibility is defined as the ability to implant the baroloop Cuff electrode and IPG, and the ability to reduce blood pressure by VNS. The secondary objective is to document the effect of the baroloop device on the blood pressure and quality of life in subjects with hypertension.

Study burden and risks

5.1. Potential Adverse Events
There are Adverse Events associated with any endovascular / cardiovascular intervention and complications may develop. The following anticipated events have been identified as possible complications of transcatheter procedures in general and these and others may be associated with the baroloop System:
5.2. Potential risks
Adverse events which might occur with the usage of baroloop are listed as below in alphabetical order and are based on potential risks which are reported during the usage of other vagus nerve stimulators and/or baroreflex activation therapy:
5.3. Potential Adverse Events
Surgery-related
• hematoma
• infection
• pain
• voice alteration (hoarseness)

Stimulation-related
• bradycardia
• dyspepsia (indigestion)
• dysphagia (difficulty swallowing)
• dyspnea (difficulty breathing, shortness of breath)
• hypotension
• increased coughing
• laryngismus (throat, larynx spasms)
• pain
• paresthesias (prickling of the skin)
• pharyngitis (inflammation of the pharynx, throat)
• satiety (reduced appetite)
• sensation of stimulation
• syncope
• voice alteration (hoarseness)
It is anticipated that subjects will be exposed to operative and post-operative risks similar to related surgical procedures involving the neck and/or a pacemaker implant. These risks and potential risks of chronic device based baroreflex activation may include, but are not limited to:
• Surgical or anesthetic complications
• Infection - the need for antibiotics or possible removal of the system
• Wound Complication -including hematoma (i.e. bruising and/or swelling)
• Arterial damage -including carotid artery rupture or hemorrhage (sudden and significant blood loss at a site of blood vessel rupture that may require reoperation or transfusion)
• Pain - an unpleasant sensory experience
• Nerve Damage/Stimulation -including injury to or stimulation of Cranial, Marginal Mandibular, Glossopharyngeal, Recurrent Laryngeal, Vagus and Hypoglossal Nerves (numbness in head and neck, facial palsy/paralysis, altered speech, altered sense of taste, respiratory constriction, stertorous breathing, excessive salivation, dry cough, vomiting and/or regurgitation, altered sensory and motor function of tongue, altered sensory function of pharynx and oropharynx, altered sensation in external auditory canal), stimulation of extravascular tissue (muscle twitching (fasciculation), pain, tingling, oral sensations)
• Hypotension - a decrease in systolic and diastolic blood pressure below normal levels that may result in dizziness, fainting, and/or falls
• Hypertensive crisis - uncontrolled rise in blood pressure
• Respiratory - including low oxygen saturation, respiratory distress, shortness of breath
• Exacerbation of heart failure
• Cardiac arrhythmias
• Tissue erosion/IPG migration - movement of device resulting in need for reoperation
• Fibrosis - replacement of normal tissue by the ingrowth of fibroblasts and the deposition of connective tissue
• Allergic Reaction

• General injury to user or patient -may be due to surgical procedure, device use, or interaction with other devices
• Need for reoperation - operation to explant/replace IPG or Cuff electrode or Lead due to tissue damage, infection, and/or device failure
• Secondary operative procedure -An increase in the complexity and risk of secondary operative procedures of the neck due to scar tissue and the presence of prosthetic material implanted for this device.
• Death

5.4. Potential Risks to Subject Confidentiality and Privacy

In all clinical studies, confidentiality of protected health information may be breached due to study-related activities beyond those of routine clinical care. This also includes risks of privacy and release of protected health information (PHI). This risk will be minimized through the use of a unique and anonymous study identification code. No identifying information will be reported in the data collection system or other study related documentation that is provided to the Sponsor.

5.5. Minimization of Anticipated Risks

Efforts to minimize risk include the following:

1. Clearly defining the subject inclusion / exclusion criteria.
2. Selecting a sufficient number of intended users and only qualified, experienced Investigators who have participated in a training program to assure thorough knowledge of the Investigational Plan and proper technique for implantation of the baroloop System.
3. Monitoring electrocardiographic and hemodynamic parameters during placement of the device to evaluate for any compromise of the subject*s condition.
4. Ensuring that treatment and follow-up of subjects is consistent with standard and current medical practice.
5. Providing clinical support for device-related guidance during the implantation, titration and follow-up procedures.
6. Safety oversight by Medical Monitor and the DSMB, for individual subjects as well as across the entire study population.
7. If the Investigator and / or the Medical Monitor or DSMB determine that an AE is sufficiently severe to remove the subject from the study, a termination assessment will be performed. The subject will then be given appropriate treatment under medical supervision.
8. If the Medical Monitor or DSMB determines a negatively high rate for a particular safety issue across the subject population, a termination assessment will be performed, and the Medical Monitor or DSMB may recommend enrollment in the study to be stopped.

PHI protection measures, such as use of a unique study identification code and a commitment from all participants to protect subject confidentiality at every step during the investigation, must be maintained.

5.6. Potential Benefits

Based upon literature review and pre-clinical evaluations performed to date, it is expected that the baroloop system may provide benefit to the subject by reducing blood pressure to or toward recommended target blood pressure values

as outlined in the 2018 ESC/ESH Guidelines for the management of arterial hypertension. Without the baroloop system, blood pressure may remain poorly controlled in this population. The potential benefits include a reduction in blood pressure toward more normal values, which has been associated with a reduction in cardiovascular risks associated with hypertension (the 2018 ESC/ESH Guidelines for the management of arterial hypertension).
However, the actual benefits are not known and are the subject of this investigational study. There may be no direct benefits of study participation. Nevertheless, subject participants will undergo an enhanced level of clinical scrutiny of health compared to routine clinical care, which may provide some indirect health benefits.

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

• Aged 18 years or older and less than 80 years of age.
• Persistent office systolic blood pressure (SBP) >= 140 mm Hg or diastolic blood pressure (DBP) > 90 mm Hg on antihypertensive medicines on two visits separated by a minimum of four weeks.
• Mean 24-hour systolic ABPM >= 130 mm Hg and mean 24-hour diastolic ABPM >= 80 mm Hg conducted after direct observed therapy to confirm that antihypertensive medicines were taken as prescribed during the ABPM measurement.
•. Stable drug regimen of 4 antihypertensive medicines consisting of a renin-angiotensin blocker(ACE) or Angiotensin II Receptor Blocker (ARBs), a calcium channel blocker (CCB), and a diuretic for 4 weeks at treatmenta diuretic and spironolactone for 4 weeks at treatment. If spironolactone is not tolerated, the regimen must include instead the addition of further diuretic therapy with either eplerenone, amiloride, higher-dose thiazide/thiazide-like diuretic or a loop diuretic, or the addition of bisoprolol or doxazosin. If none of these medicines are tolerated, then patients on a 3-drug regimen may be included.
. The Investigator has confirmed that the patient has already tried and/or is not suitable for treatment with currently CE-marked device-based therapies for resistant hypertension as an alternative to baroloop therapy.
• Negative pregnancy test for women of child-bearing age
• Willingness and ability to comply with follow-up requirements.
• Signed informed consent.

Exclusion criteria

• Any patient in whom access to the vagal nerve is .limited by the size of the vagus (a size not compatible with the baroloop cuff).
. Any patient with a history of injury to the vagus nerve or its branches (e.g., the recurrent laryngeal nerve).
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• Secondary causes of hypertension.
• Calculated eGFR < 30 mL/min/1.73m2.
• Type 1 diabetes mellitus or poorly controlled type 2 diabetes mellitus (HbA1c > 10%).
• One or more episodes of orthostatic hypotension in the past year
• Requirement for chronic oxygen therapy or mechanical ventilation.
• Untreated (no CPAP therapy) sleep apnea (AHI > 15)
• Morbid obesity, defined as Body Mass Index >40 kg/m2 or arm circumference 46 cm.
• Pacemaker and/or implantable defibrillators.
• History of transient ischemic accident or cerebrovascular accident during six (6) months prior to screening.

• Symptomatic carotid artery disease or > 70% occlusion of either carotid artery ; any carotid malformation or lesion, a carotid bruit or other abnormal carotid sound.
. Prior surgery, radiation therapy or scarring in the neck in the region of the carotid artery (e.g., patients with a tracheostomy, extensive thymectomy or thyroid surgery).
. Limited mobility of the neck secondary to vertebral disease or prior vertebral surgery, including patients who wear a cervical support.
• History of heart failure (NYHA class III-IV or ejection fraction < 30%), myocardial infarction, unstable angina, coronary bypass or coronary angioplasty during six (6) months prior to screening.
• Cardiac arrythmias (atrial fibrillation, atrial flutter, etc.) that require anticoagulation or interfere with a consistent measurement of blood pressure.
women of childbearing age are excluded for participation in this trial
• Syncope in the last 6 months.
• History of bleeding disorders, thrombocytopenia, hemophilia or significant anemia (hemoglobin (Hgb) < 10 gm/dl).
• Current anticoagulation therapy (excluding antiplatelet therapy with aspirin as a sole therapy).
• Works night shifts.
• History of unresolved drug or alcohol use.
• Active treatment of a psychiatric ailment.
• Life expectancy of less than 12 months due to other disease.
• Subject has a condition that, in the opinion of the investigator, precludes participation, including willingness to comply, with all follow-up procedures.
• Participation in another clinical study for which follow-up is currently on-going.
. Baroreflex failure or autonomic neuropathy
. Symptomatic, uncontrolled bradyarrhythmias
. Atrioventricular block of any grade
. Patients who are treated with Pacemaker and/or implantable defibrillators
. Presence of a vagus stimulator
. Patients who expect to require magnetic resonance imaging (MRI) of the cervical area
. Occupational exposure to high levels of non-ionizing radiation that may interfere with therapy
. Patients with a limited ability to read, understand and execute adjustment procedures (for example, persons suffering from dementia).
. Likely exposure to diathermy.

Study design

Design

Study type: Observational invasive

Masking:	Open (masking not used)
Control:	Uncontrolled
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	13-04-2021
Enrollment:	6
Type:	Actual

Medical products/devices used

Generic name:	baroloop
Registration:	No

Ethics review

Approved WMO Date:	18-02-2021
Application type:	First submission
Review commission:	METC NedMec
Approved WMO Date:	22-04-2021
Application type:	Amendment
Review commission:	METC NedMec
Approved WMO Date:	25-05-2021
Application type:	Amendment
Review commission:	METC NedMec

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	NL75109.041.20

Study results

Date completed: 14-02-2024

Actual enrolment: 6

Summary results
Trial ended prematurely