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

Protocol Number: BL_CIP-FIH
Revision: 2.4
Date: 03 March 2021

Sponsor:

neuroloop GmbH
Breisacher Straße 86
79110 Freiburg im Breisgau
Germany

Phone: +49 761 1543390
Website: www.neuroloop.de/

Medical/Clinical Monitor:

MAXIS Medical GmbH
Stichlingstrasse 1
60327 Frankfurt am Main
Germany
Tel: +49.69.2400.3626
Fax: +49.69.2400.3627
Email: maxis-operations@maxismedical.com

CONFIDENTIALITY STATEMENT

Table of Contents

Table of Tables

Table of Figures

1. Protocol Synopsis

Sponsor	neuroloop GmbH Breisacher Straße 86 79110 Freiburg im Breisgau Germany Phone: +49 761 1543390 Email: study@neuroloop.de Website: www.neuroloop.de
Principal Investigators	Netherlands: Dr. med. Wilko Spiering Division Internal Medicine and Dermatology Dept. of Vascular Medicine UMC Utrecht Heidelberglaan 100 3584 CX Utrecht Germany: Univ. Prof. Dr. med. Florian P. Limbourg Experimentelle Gefäßmedizin und Transplantationsforschung Klinik für Nieren- und Hochdruckerkrankungen Medizinische Hochschule Hannover Carl-Neubergstr. 1 30625 Hannover
Sponsor Representative	MAXIS Medical GmbH Karpfenweg 12 60327 Frankfurt am Main Germany Tel: +49.69.2400.3626 Fax: +49.69.2400.3627 Email: maxisoperations@maxismedical.com
Medical Monitor	James C. Leiter, M.D. Chief Medical Officer MAXIS Medical GmbH
Protocol Title	A First in Human Study of Safety and Feasibility of baroloop
Short Title	**The baroloop Study**
Protocol number	Protocol Number: BL_CIP-FIH Revision: 2.4 Date: 03 March 2021
Device	baroloop System
Indication for Use	The baroloop System is intended to be used to treat hypertension.

Objectives	The primary objectives are to assess the safety and feasibility of the 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	Non-randomized, prospective, single-arm, multi-center feasibility trial for subjects with hypertension
Number of Subjects	Up to ten (10) subjects
Number of Sites	Up to three (3) centers in Europe
Primary Safety Endpoint	Composite Major Adverse Event (MAE) Rate at six (6) month post-treatment including: • All causes of death • Hospitalization for hypertensive crisis post-titration • Any device or procedure-related serious adverse event All MAEs to be adjudicated by an independent Data Safety Management Board (DSMB).
Primary Feasibility Endpoint	The ability of the baroloop System to be placed around a vagal nerve and to stimulate at Day 14/21 post-implantation.

Secondary Endpoints	• 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), 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:
	  ○ All-causes of death
	  ○ Hospitalization for hypertensive crisis post-titration
	  ○ 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-Iterm Short-Form Health Survey (SF-36).

Follow-up Schedule	All subjects will be evaluated at 14 days (+2/-3 days), 1 month (± 7 days), 3 months (± 14 days), 6 months (± 14 days), 12 months (±14 days), 18 months (±14 days), and 24 (±14 days) months post-procedure.
Study Duration	Three (3) years to complete enrollment in this study.
Inclusion Criteria	Each subject must meet all the following criteria: 1. Aged 18 years or older and less than 80 years of age. 2. Persistent office systolic blood pressure (SBP) ≥ 140 mm Hg and diastolic blood pressure (DBP) > 90 mm Hg on antihypertensive medicines on two visits separated by a minimum of four weeks. 3. 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. 4. 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), a 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. 5. 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. 6. Willingness and ability to comply with follow-up requirements. 7. Signed informed consent.
Exclusion Criteria	Each subject may meet none of the following criteria: 1. 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). 2. Any patient with a history of injury to the vagus nerve or its branches (e.g., the recurrent laryngeal nerve). 3. Secondary causes of hypertension. 4. Calculated eGFR < 30 mL/min/1.73m2. 5. Type 1 diabetes mellitus or poorly controlled type 2 diabetes mellitus (HbA1c > 10%). 6. One or more episodes of orthostatic hypotension in the past year 7. Requirement for chronic oxygen therapy or mechanical ventilation. 8. Untreated (no CPAP therapy) sleep apnea (AHI > 15)

	9. Morbid obesity, defined as Body Mass Index >40 kg/m2 or arm circumference 46 cm. 10. Pacemaker and/or implantable defibrillators. 11. History of transient ischemic accident or cerebrovascular accident during six (6) months prior to screening. 12. Symptomatic carotid artery disease or > 70% occlusion of either carotid artery; any carotid malformation or lesion, a carotid bruit or other abnormal carotid sound. 13. 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). 14. Limited mobility of the neck secondary to vertebral disease or prior vertebral surgery, including patients who wear a cervical support. 15. 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. 16. Cardiac arrythmias (atrial fibrillation, atrial flutter, etc.) that require anticoagulation or interfere with a consistent measurement of blood pressure. 17. Syncope in the last 6 months. 18. History of bleeding disorders, thrombocytopenia, hemophilia or significant anemia (hemoglobin (Hgb) < 10 gm/dl). 19. Current anticoagulation therapy (excluding antiplatelet therapy with aspirin as a sole therapy). 20. Works night shifts. 21. History of unresolved drug or alcohol use. 22. Active treatment of a psychiatric ailment. 23. Life expectancy of less than 12 months due to other disease. 24. Subject has a condition that, in the opinion of the investigator, precludes participation, including willingness to comply, with all follow-up procedures. 25. Participation in another clinical study for which follow-up is currently on-going. 26. Women who are of child-bearing age or who have the potential to become pregnant 27. Resting heart rate of <40 beats/min for patients on beta blockers or <60 beats/min for all other patients, confirmed at both baseline visits. 28. Baroreflex failure or autonomic neuropathy 29. Symptomatic, uncontrolled bradyarrhythmias 30. Atrioventricular block of any grade

	31. Patients who are treated with Pacemaker and/or implantable defibrillators 32. Presence of a vagus stimulator 33. Patients who expect to require magnetic resonance imaging (MRI) of the cervical area 34. Occupational exposure to high levels of non-ionizing radiation that may interfere with therapy 35. Patients with a limited ability to read, understand and execute adjustment procedures (for example, persons suffering from dementia). 36. Likely exposure to diathermy.
Statistical Model	• This is a single arm study in which each subject acts as his or her own control. Demographic variables will be tabulated in summary form. Adverse events will be tabulated and summarized. Outcome variables will be compared qualitatively to historical performance of other device-based therapies for hypertension.

2. Introduction and Background

2.1. Rationale for Proposed Research

Hypertension is a disease that affects more than 77.9 million adults in the United States and approximately one billion individuals worldwide (Chobanian et al., 2003; Go et al., 2013). According to a 2014 report from the American Heart Association (AHA), based on NHANES/NCHS data through 2010, one in three adults has high blood pressure (BP), and 74.9% of these subjects are undergoing treatment for hypertension. The overall prevalence has declined in past few decades, according to the trend for high-income countries (Collaboration, 2017). However, "the overall number of adults with raised blood pressure increased from 594 million to 1.13 billion in 2015, also part of a net effect of increase due to population growth and ageing" (Collaboration, 2017). In Germany, in 2015, 31% of males and 25% of females had raised blood pressure (Collaboration, 2017). The high prevalence of hypertension is a major public health issue in developed and developing countries (Vega and Bisognano, 2014). Inevitably, the disease burden causes huge health costs: Gaziano estimated that "high blood pressure will cost nearly US $1 trillion in health spending if current blood pressure levels persist over a 10-year period, and if hypertension goes untreated, indirect costs could be as high as US$ 3.6 trillion annually" (Gaziano et al., 2009).

The 2018 ESC/ESH (European Society of Cardiology/ European Society of Hypertension) Guidelines for the management of arterial hypertension (Williams et al., 2018) defines hypertension as systolic BP ≥ 140 mm Hg and a diastolic BP ≥ 90 mm Hg measured in the office, a mean 24 hour ambulatory BP measurement (ABP) ≥ 130 mm Hg systolic or 80 mm Hg diastolic or a daytime ABMP ≥ 135 mm Hg systolic or 85 mm Hg diastolic. The ESC/ESH Guidelines (Williams et al., 2018) classifies blood pressure as follows:

Table 1: Guidelines for Blood Pressure Categorization.

Category	Systolic (mmHg)		Diastolic (mmHg)
Optimal	<120	and	<80
Normal	120-129	And/or	80-84
High normal	130-139	And/or	85-89
Grade 1 hypertension	140-159	And/or	90-99
Grade 2 hypertension	160-179	And/or	100-109
Grade 3 hypertension	≥180	And/or	≥110
Isolated systolic hypertension	≥140	And	<90

2.2. Treatment targets.

The EACTS (European Association for Cardio-Thoracic Surgery) recommended treatment for patients with hypertension is to lower blood pressure <140/90 mm Hg in all patients using treatment that is well tolerated. Treated systolic blood pressure values should be reduced to 120–129 mm Hg in most patients. In patients page 65 - 80 years, SBP should be targeted to a

BP range of 130–139 mmHg. In patients > 80 years of age, SBP should be targeted to a BP range of 130–139 mmHg, if tolerated. DBP is targeted to <80 mmHg in all patient groups (Williams et al., 2018).The American Guidelines (ACC/AHA) defines the treatment target for all patient as a blood pressure < 130/80 mm Hg.

2.2.1. Treatment according to European Guidelines

According to the ESH guidelines, standard management for elevated pressures should include a thorough patient work-up, medical history, physical examination, evaluation of lifestyle and underlying conditions such as sleep apnea, and evaluation of medications, including compliance to antihypertensive regimens (Williams et al., 2018). Arterial hypertension treatment includes lifestyle changes and drug treatment. Drug treatment has a variety of different medication combination with angiotensin-converting enzymes, angiotensin receptor blocker, calcium channel blocker and diuretics depending on grade of hypertension and therapeutic response to the different drug classes (Williams et al., 2018). However, the AHA further reported that hypertension is under control in only 53% of these patients (Go et al., 2014).

Patient non-adherence and non-persistence using medicines is recognized as a cause of treatment failure, but solutions are limited. The first line of treatment is to simplify complicated medical regimens. However, many hypertensive patients receiving three or more medications continue to have blood pressures above clinical targets due to ineffective therapy and high rates of noncompliance. Moreover, there is significant morbidity associated with taking multiple antihypertensive medications. Diuretics can cause weakness, leg cramps, pain in lower extremities, erectile dysfunction; beta blockers can cause asthma symptoms, depression, erectile dysfunction, insomnia; angiotensin-converting-enzyme inhibitors (ACEi) can cause rashes; Angiotensin II Receptor Blockers (ARBs) can cause dizziness; calcium channel blockers can cause constipation, dizziness, headaches, swollen ankles; α-antagonists can cause dizziness, tachycardia; and centrally acting drugs can cause constipation, dizziness and drowsiness. Thus, it is not surprising that hypertension is associated with high rates of non-adherence (Irvin et al., 2012) and non-persistence (Van Wijk et al., 2005) to medication. In an observational cross-sectional study (Yiannakopoulou et al., 2005), compliance to antihypertensive medication was observed in only 15% of patients. Beyond pharmacologic non-compliance, genuine failure of neuro-humeral interventions to attain adequate control of BP may be due to inherent physiological unresponsiveness – some patients have genuinely difficult to control BP despite adherence to multidrug treatment regimens.

2.3. Resistant hypertension

Hypertension remains uncontrolled in the majority of treated patients, especially those with multiple cardiovascular risk factors. Thus, resistant hypertension is a widely prevalent condition, which is estimated to affect approximately 30% of the population in the United States. The ESC/ESH guidelines define resistance to treatment “when the recommended treatment strategy fails to lower office SBP and DBP values to < 140 mm Hg and /or < 90 mm Hg when the inadequate control of BP is confirmed by ABMP (ambulatory blood pressure measurement) or HBMP (homecare blood pressure measurement) in patients whose adherence to therapy has been confirmed” (Williams et al., 2018). The prevalence of resistant hypertension varies from 5-30% in hypertensive patients depending on the particular definition of resistant hypertension. The AHA defines resistant hypertension as “blood pressure that remains above goal in spite of the current use of 3 antihypertensive agents of different classes (ideally one drug is from the class of diuretics) and all agents should be prescribed at optimal

dose amounts." (Judd and Calhoun, 2014) Patients who require 4 or more medications to control blood pressure should also be considered resistant to treatment (Calhoun et al., 2008). Patients with pseudo-resistant hypertension have elevated blood pressure due to white-coat hypertension, improper blood pressure measurement or medication nonadherence (Judd and Calhoun, 2014) or secondary reasons for hypertension (Williams et al., 2018). For a better differentiation, some studies use the term apparent resistant hypertension, when BP > 140/90 mm Hg while taking ≥ 3 antihypertensive medications. If "pseudo-resistance can be excluded the differentiation of true resistance can be made from apparent resistance" (Calhoun et al., 2008). Therefore, the prevalence of true resistant hypertension is probably <10% (Calhoun et al., 2008; Williams et al., 2018). Nonadherence is one of the main causes of uncontrolled blood pressure (Brinker et al., 2014): Abegaz et al. found nonadherence in 45% of hypertensive patients, and in patients with poorly controlled BP, nonadherence was nearly 84% (Abegaz et al., 2017). Other studies reported a 47% prevalence of noncompliance (Strauch et al., 2013) and inadequate adherence or failing to take 75% of prescribed medications (Egan, 2015). Failure to comply with medical therapy for hypertension and the development of resistant hypertension clearly contribute to the continued high rates of cardiovascular disease attributable to hypertension (Daugherty et al., 2012; Pimenta and Calhoun, 2012).

2.4. Device-based therapies for hypertension

Whether patients simply are not compliant with the prescribed medical regimens for treatment of hypertension or the drugs are genuinely ineffective in particular patients, too many patients fail to reach recommended targets for control of hypertension. Even when patients are compliant with lifelong polypharmacy, there remain significant side effects and morbidities caused by the medicines. For these reasons, new therapies for treatment resistant hypertension are being developed. Devices used for hypertension do not require patient's adherence or compliance and may, therefore, fill an unmet clinical need. Therefore, many efforts have been made to develop device-based therapies for hypertension that are effective and durable and less dependent on patient compliance with pharmacological therapies that are too often associated with unwanted or even harmful side-effects. Device-based therapies for treatment of hypertensions are not currently recommended for routine treatment according to ESC/ESH guidelines (Williams et al., 2018). Currently, device-based therapies mentioned in European Guidelines include carotid-baroreceptor stimulation with a pacemaker or a stent, renal denervation or creation of an arteriovenous fistula (Williams et al., 2018).

Table 2: Overview device-based therapy for hypertension (from Lobo et al (2017)

Technology	Mode of action	Stage of development	limitations
Renal (sympathetic) denervation Ablation catheters and generators available from several	Sympatho-modulatory—results in destruction of renal afferent and efferent sympathetic nerves and BP reduction through mechanisms that remain	CE Mark approval for hypertension for most catheters A variety of catheters/platforms now available includes: Radiofrequency ablation, ultrasound ablation, chemical ablation, and cryoablation using	Lack of markers of procedural success Inability to screen for increased renal nerve signaling prevents identification of best responders Damage to renal artery from endovascular approach using thermal energy

manufacturers including Medtronic, St Jude Medical, Boston Scientific, Terumo, and Verve Medical	unclear in human hypertension	balloon/non-balloon and irrigated catheters	
Baroreflex activation therapy Barostim neo™ (CVRx Inc, Minneapolis, MN, USA)	Sympatho-modulatory: unilateral electrical field stimulation of the carotid sinus stimulates the baroreflex and down-regulates sympathetic outflow while increasing parasympathetic tone	CE Mark approval for hypertension Pivotal study published with the first-generation device (Bisognano et al., 2011). Small proof of concept study with the second-generation device (Hoppe et al., 2012)	Open loop system lacks feedback mechanism Exceedingly high cost Implantable generator must be replaced at end of battery life (currently 3 years)
Baroreceptor amplification therapy Mobius HD™ (Vascular Dynamics, Mountain View, CA, USA)	Sympatho-modulatory: dramatic increase in carotid bulb strain causes durable amplification of baroreceptor feedback and BP reduction	European and US studies now enrolling Case report and early report from first-in-man study published (Devireddy and Bates, 2014; van Kleef et al., 2018)	Concerns over instrumentation of the carotid artery, risks of distal embolization. Open loop system with no feedback mechanism
Carotid body ablation Cibiem Carotid Body Modulation System™ (Cibiem,	Sympatho-modulatory: unilateral carotid body ablation reduces sympathetic vasomotor tone without affecting	Proof of concept study using unilateral surgical excision in resistant hypertension (Narkiewicz et al., 2016) Endovascular ablation planned using novel	Only appears effective in those with high carotid body tone. Screening for this will be essential Endovascular approach is complicated by the difficulty of accessing the target and risks to important adjacent structures

Los Altos, CA, USA)	respiratory drive	catheter-based system	
Deep brain stimulation Activa Neurostimulator, (Medtronic Inc., Minneapolis, MN, USA) Vercise™ DBS System (Boston Scientific, Marlborough, MA, USA)	Sympatho-modulatory: electrical field stimulation of the dorsal and ventrolateral periaqueductal grey region within the midbrain reduces BP through mechanisms that are not clearly defined in human hypertension	The technology was primarily developed for management of movement disorders and chronic pain syndromes. (O'Callaghan et al., 2014) Isolated reports of BP-lowering independent of pain control (Green et al., 2007; Patel et al., 2011)	Limited efficacy/safety data High costs of therapy Open loop system Frequent generator recharging required
Vagal nerve stimulation CardioFIT™ Systems (BioControl Medical, Yehud, Israel) Precision™ System, (GUIDANT Europe/Boston on Scientific)	Sympatho-modulatory—unilateral vagal nerve stimulation restores vagal tone and improves sympatho-vagal balance	Under investigation for use in heart failure and hypertension. Lack of efficacy regarding reduction of death/heart failure events in chronic HF patients (Gold et al., 2016) Animal data only for hypertension indication (Plachta et al., 2014; Sevcencu et al., 2018)	Inability to selectively target nerve fibers to avoid bradycardia and bradypnea
Median nerve stimulation Subcutaneous Neuromodulation System (Valencia Technologies,	Sympatho-modulatory—subcutaneous unilateral implantation of a coin-sized device (in a 20-min office	According to clinicaltrial.gov the study NCT02926495 was withdrawn https://clinicaltrials.gov/ct2/show/NCT02926495?intr=ecoin+system&rank=1 Proof of concept study has shown profound reductions in systolic BP (Bang et al., 2018)	No published randomized controlled data

Valencia, CA, USA)	procedure) causing electrical stimulation of the median nerve and subsequent down-regulation of sympathetic outflow		

2.5. Baroreceptor Modulation for Hypertension

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 μm^2 and anodes with areas of $2.34*10^6$ μm^2. 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 changing pH values. The amount of charge to be applied via the electrode contacts is limited not only by material parameters as described above. Thresholds also arise from physiological constraints. The “Shannon Criteria” provide a conservative estimate of the limits of charge that may be safely applied in terms of the amount of charge/area/cycle to avoid neural damage (Shannon, 1992). In most cases, the Shannon Criteria are below the water window of the working electrode.

To evaluate the safety of the stimulation presets used by the baroloop system it is necessary to consider the **total energy delivered** and the **potential for tissue damage** of the electrodes used for neural stimulation, rather than the individual values within each preset. The amount of energy absorbed by the tissue is dependent on many variables, including the stimulus intensity (typically measured in microamperes), the duty cycle, the frequency of stimulation, and the duration of stimulation. Different combinations of these parameters can result in the delivery of the same equivalent energy to the tissue. To provide a common scale to assess ranges of stimulation characteristics, scientists focus on the **number of electrons delivered**. This value is the total electrical charge which is measured in coulombs. One coulomb is equivalent to one ampere x one second (1 C = 1 A × 1 s).

In addition to the number of electrons delivered to tissue, the potential for tissue damage also varies as a function of the **area over which the electrons are delivered** (smaller electrode area for any given charge increases the risk of tissue damage), and so the size of the electrode is a consideration. To account for this, the charge delivered is divided by the geometric surface area of the electrode and expressed as the charge density.

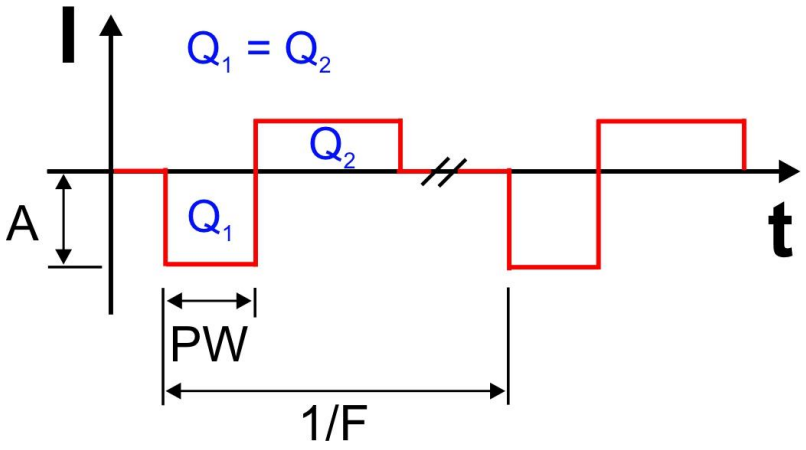
The **charge delivered per phase** also affects the risk of tissue damage. These terms are captured by the Shannon equation and the Shannon limit.

The presets defined for use in the baroloop Study are all well below the Shannon limit and within the range tested in animals. In this way, the electrical charge delivered to tissue in all of the FIH preset stimulation sequences is covered by the animal studies. The variety of charges delivered to tissue in the Sponsor’s animal studies were all shown to be safe. For more details, please see also Section 2.20 of the Investigator’s Brochure.

Based on these considerations, the baroloop device has performance characteristics similar to the LivaNova VNS systems in terms of charge, pulse width and frequency used. The charge is biphasic and balanced asymmetrically so that the intensity of depolarizing stimulation is greater, but of shorter duration than the repolarizing phase which is of lower intensity and longer duration. In addition, the baroloop device is a multichannel stimulation device, and optimal electrode pairs may be selected to active the vagus with the lowest possible energy input. The baroloop cuff electrode has multiple, small active electrode areas, rendering the charge injection in any electrode pair closer to the Shannon Criteria, without reaching it. The pulse width can be as long as 500 µs, and this enables the baroloop implant to reach and stimulate small axonal fibers. The physician may choose among a variety of presets, which are pre-defined sets of stimulation parameters (e.g., duty cycle, stimulus amplitude, and pulse

width) that may be selected through the Programmer to activate the baroreflex. The wave form of an individual stimulus for the baroloop system is shown below (Figure 1.).

Figure 1: Schematic of the elementary parameterization of a stimulation pulse



In Figure 1 above, the stimulation channel (not shown here) was set to apply a given number of pulses with a defined strength (current I), a given pulse width (PW) and repetition interval (1/F). Not shown either is the duty cycle based on intervals between bursts of pulses. To avoid polarization of the cathode, the pulses are biphasic and charge balanced (Q_1=Q_2).

In summary, the strength and magnitude of baroloop stimulation is comparable to existing VNS stimulation parameters. The conditioning of the stimulation is slightly better as the baroloop device applies charge balanced, biphasic pulses. The spatial pattern of selective stimulation made possible by the multielectrode baroloop cuff permits application of strong, local stimuli to activate specific, small circumferential sectors of the vagal nerve, where the relative number of baroreceptor active fibers may be increased The temporal pattern of stimulation (in intermittent bursts) is unique as well, since the baroloop stimulation pattern may mimic the grouping of afferent sensory activity triggered by the blood pressure wave of the expelled blood that passes the aortic arch and carotid bifurcation.

2.5.4. The baroloop System: vagal nerve stimulation to control blood pressure

neuroloop has developed a novel cuff electrode for use with a safe and effective mechanism of vagal nerve stimulation to activate the baroreflex and lower blood pressure in the context of hypertension. The neuroloop device fits well within the current trends of treatment of hypertension in that resistant hypertension is remarkably common, and inadequate treatment of hypertension to achieve treated blood pressure levels less than 140/90 mm Hg (and better still according to current recommendations less than 130/80 mm Hg) is associated with increased risks of adverse cardiovascular outcomes from hypertension. Pharmacological therapy of hypertension is inadequate in many patients either because patients do not take the medicines, suffer side-effects from the medicines, or the medicines are ineffective controlling blood pressure. Given the novel design and treatment features of the neuroloop device, the Sponsor will conduct a First in Human Study to evaluate the safety and feasibility of treating hypertension using VNS.

2.5.5. VNS to Treat Hypertension

The vagal nerve consists of afferent and efferent fibers for visceral organs carrying information regarding autonomic functions. The vagus transmits afferent information about the internal state of the body to the central nervous system, and transmits efferent information from the central nervous system, especially autonomic control information from the brainstem to effector organs of the autonomic nervous system (largely the parasympathetic part of the autonomic nervous system) (Johnson and Wilson, 2018). Among many autonomic functions, which are under control of the vagal nerve, it is known that baroreceptive fibers merge with the vagal nerve (Benarroch, 2008). It is, however, not clear where they are located within the vagal nerve. In some mammals, the fibers are bundled in the aortic depressor nerve (ADN) (Kobayashi et al., 1999). Stimulation of ADN-fibers activates the baroreflex and therefore leads to a drop of blood pressure (De Paula et al., 1999; Fan and Andresen, 1998; Gao et al., 2006; Tosato et al., 2006). The cardiovascular efferents differs between the right and left vagal nerves; the right innervates the sinoatrial node ,and the left innervates the atrioventricular node (Johnson and Wilson, 2018; Panebianco et al., 2016). Saxena et al. described the effect of acute vagal stimulation in humans, which resulted in blood pressure lowering that was dependent on the current- and frequency of stimulation (Ng et al., 2016). At higher currents, atrio-ventricular (AV) block and ventricular asystole were observed as side-effects during stimulation, which may result from direct activation of efferent cardiac fibers (Mirkovic et al., 2012). However, this was not a systematic evaluation of VNS and baroreflex activation as a therapy for hypertension, and the efficacy of chronic vagal nerve stimulation in humans to activate the baroreflex has not been proven. Therefore, neuroloop has developed a clinical feasibility study: A First-in-Human study will be performed to assess the efficacy/ feasibility and safety of blood pressure lowering in humans via stimulation of the left vagal nerve to activate the baroreflex.

2.6. Preclinical Experience with the baroloop System

The baroloop System has been subjected to a comprehensive pre-clinical testing program to verify design, safety, and performance against pre-specified engineering, mechanical and system requirements. Pre-clinical testing included bench, biocompatibility, animal, and sterilization testing. In addition to evaluation against internal specifications and international standards, the baroloop System was also tested in accordance with appropriate international standards as described in the Investigators Brochure for this First in Human Study.

Complete biocompatibility evaluation was performed on the baroloop device according to ISO10993, Biological Evaluation of Medical Devices Part 1: Evaluation and testing within a risk management process .After gathering physical and chemical data on the device, based on risk assessment, further studies were performed on baroloop device included physical and/or chemical information, cytotoxicity, sensitization, irritation, material related pyrogenicity, implantation studies (also included acute, subacute, sub-chronic and chronic studies), and genotoxicity. Based on overall biological evaluation performed on the device, baroloop device can be considered biocompatible without the need to perform pre-clinical additional tests and could be considered suitable for its clinical application study.

In conclusion, the baroloop System has been fully evaluated through pre-clinical testing per the identified risks and demonstrates compliance with its predetermined performance specifications.

Animal studies have been performed to further support the safety and performance of the baroloop System. The device elicited no adverse blood or tissue response, and no gross injuries were associated with the placement of the device, thereby demonstrating the safety

and feasibility of the device in an animal model (BL_ER_Efficacy_Report; BL_Safety_GLP_19-55_Interim_Report, BL_PCS2_Safety_GLP_19-55_Study_Report). Pre-clinical animal studies have been conducted and support the safety and performance of the baroloop System through simulated use under in vivo conditions in a porcine model (performance in minipig) and in an ovine model (safety in sheep).

3. Test System (Investigational Device)

3.1. Product name

baroloop®

3.2. General description

neuroloop has developed a platform based on thin-film technology for selective stimulation of the vagus nerve. The core part of the platform is a multi-channel electrode based on a thin-film cuff.

The goal of baroloop therapy is to achieve clinically effective blood pressure control while minimizing adverse reactions and provide superior usability of the implant for the surgeon, treating physician and the patients.

The system includes auxiliary devices and services to allow the patient to recharge the device and treating physicians to adjust the therapy.

The neuroloop product baroloop® is a stimulator platform for treating hypertension. The implantable parts of the stimulator platform will be used by the surgeon only. The non-implantable parts, as described in the following sections, interact with and direct the activity of the implanted system and will be used only by professionals in this study.

The implanted parts of the stimulator platform are intended to remain in the patient, whereas the programmer and recharging platform remain outside each patient's body. The recharging interval is every 1 to 4 weeks (depending on the stimulation parameters). However, patients enrolled in the study will have the device charged by professionals during protocol-required follow-up visits to the study site.

The nomenclature in the technical documentation for the implanted parts is as follows:

- The Lead consists of four elements: the "Cuff", "Pill", the "Cable" and the "Connector".
    - The Cuff is a thin film electrode, which surrounds the nerve. The Cuff is wrapped around the left vagus nerve to establish an electrical connection to the nerve.
        - Please see the Instructions for Use, Section 2.11 of the Investigators Brochure and p. 8 of the Implantation Manual for information regarding available cuff sizes and selection criteria.
    - The Pill is the interface between Cuff and Cable, which is required to establish the electrical connection between thin-film and wires that communicate with the Implantable Pulse Generator (IPG).
    - The Cable consists of medical-grade, insulated wires encapsulated in a biocompatible mantle.
    - The Connector is the electrical interface between the Lead and the IPG.

- This stimulator device, the “Implantable Pulse Generator” (IPG) completes the stimulator platform. The IPG generates the stimulus as well as recording electrical signals derived from the Cuff electrodes and other components of the device. The IPG is controlled by an external programmer (see below).

The non-implanted parts are the following:

- A free-standing, wearable, transcutaneous charging device, the “Charger,” will be used to recharge the batteries within the IPG. The Charger is designed for professional use only . Besides the transfer of power, the Charger also transfers data from and to the IPG.
- A programming device, the “Programmer,” directs the IPG to provide vagal nerve stimulation tailored to the needs of each patient and accepts data from the IPG that was recorded to monitor the performance of the internal components of the baroloop. The Programmer is for professional use only.
- For the First-in-Human study, the Charger will be recharged using a laptop computer or USB power supply and a USB cable. The Charger will be used only in the professional environment (hospital or doctor’s office).

3.3. Code identification of the device

IPG: A-1-I-#

Lead A-1-L-#

Charger: A-1-C-#

Programmer: A-1-P-#

Strap: A-1-S-#

3.4. Intended purpose

3.4.1. Indication

The baroloop device is indicated for the treatment of hypertension.

3.4.2. Intended patient group

The intended patient group is adults greater than or equal to 18 years of age.

3.4.3. Target/intended body parts

The implantable pulse generator (IPG) is implanted subcutaneously in the left upper chest outside the rib cage, and the Lead is tunneled subcutaneously from IPG on the chest wall to the left side of the neck. The Cuff is wrapped around the left vagus nerve in the neck.

3.4.4. Target user profile

Medical professional surgical implantation of the device - surgeon: The implantable parts of the stimulator will be used by surgeons who are trained and experienced in the field of neurosurgery or in carotid sheath-related surgical procedures (e.g. vascular surgeons or otorhinolaryngologists).

Medical professional adjustment of vagal nerve stimulation to control blood pressure - physician: the physician should be board-certified and have experience and expertise treating hypertension.

3.4.5. User environment

The Charger is used in a professional environment (hospital or doctor's office).

Programmer is used in a professional environment (hospitals, clinics, doctors' offices)

3.5. Mode of action of the device and principles of operation of the device

baroloop uses adjustable electrical pulses to neuromodulate the left vagus nerve. The pulses generated by the implantable pulse generator (IPG) are delivered selectively over the neuroelectronic interface of the Cuff. The cathodes of the Cuff surround the vagus nerve.

The Programmer is used to select cathodes to stimulate segments of the nerve. Stimulation of an appropriate segment of the vagus nerve triggers the baroreflex and lowers blood pressure.

3.6. Contraindications

Vagotomy (no usage of device after bilateral or left cervical vagotomy possible)

Diathermy – The use of shortwave diathermy, microwave diathermy, or therapeutic ultrasound diathermy on patients with an implanted VNS device is contraindicated

Baroreflex failure or autonomic neuropathy

Symptomatic, uncontrolled bradyarrhythmia's

Atrioventricular block of any grade

Patients who are treated with Pacemaker and/or implantable defibrillators

Presence of a vagus stimulator

Patients who require magnetic resonance imaging (MRI)

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)

3.7. Warnings

The warnings are also included in the manuals.

General warnings, warnings and precautions must be followed to avoid system failures.

The baroloop system is indicated only for the treatment of hypertension. Implantation for other treatments or indications has not been tested and is NOT permitted.

The baroloop system must be implanted by surgeons experienced and trained in the field of neurosurgery or in carotid sheath-related surgical procedures.

The physician who is treating the patient with baroloop system should be board-certified and have experience and expertise treating hypertension.

Patients with an implanted baroloop system should not be subjected to MRI. The baroloop system has not been tested for MRI use. Exposure to the magnetic field in an MRI might result in dislocation, heating of metallic components of the device, induced electrical currents in the Lead and/or tissue damage.

Shortwave diathermy, microwave diathermy, or therapeutic ultrasound (all of which may result in diathermy) should not be used on patients in whom the baroloop system has been implanted. Energy generated by diathermy may be transferred through implanted baroloop system and could lead to tissue or nerve damage or result in severe injury or death. Furthermore, the IPG may be damaged by the energy generated by diathermy.

Ultrasound energy may damage the Lead of the baroloop system. Therefore, physicians must avoid using ultrasound focused on regions containing implanted components of the baroloop device.

Extracorporeal lithotripsy may damage the IPG. Therefore, physicians must avoid using extracorporeal lithotripsy in the region containing the implanted IPG.

Radiation therapy may damage the baroloop system. Physicians must avoid using radiation therapy in the region of the implanted components of the baroloop system

X-ray and CT Scans may affect the IPG, if the IPG is active and turned on. Physicians must be aware that the baroloop device must be turned off prior obtaining X-rays or CT scans in the region of the implanted components of the baroloop device.

Images obtained using X-ray and CT Scanning may be influenced by the presence of implanted components of the baroloop system when the components of the baroloop system overlay or distort the X-ray or CT scan images.

Magnetic fields may influence the function of the IPG and temporarily interrupt therapy by the baroloop system.

Potential effects of the baroloop system on the function of other implanted devices, e.g. cardiac pacemakers, defibrillators and other electronic devices and neurostimulators, are unknown. Therefore, use of the baroloop system in individuals with any of the aforementioned devices is not recommended. Moreover, the aforementioned implanted devices could affect the functionality of the baroloop system.

Physicians must advise each patient or the patient's caregivers to avoid manipulation of the baroloop system through the skin. Manipulation of any implanted components of the baroloop system could damage the device, cause lead migration and/or skin damage, or damage the vagus nerve.

Physicians should advise the patient that external mechanical forces may damage the implanted components of the baroloop system. For this reason, physicians should discuss with each patient his or her activities so that physical activities that might damage the baroloop system may be avoided.

Physicians must advise each patient that strong electromagnetic fields may influence the performance of the implantable components of the baroloop device. Sources of strong electromagnetic fields can lead to system failures or disrupted communication between Charger and IPG.

Physicians must advise each patient that excessive movement during the ingrowth phase may displace implanted components of the baroloop system and must be avoided.

Physicians must advise each patient or the patient's caregivers that the Charger should not be covered with any material (e.g., a blanket, sheet, or clothing) that could prevent heat loss from the Charger during the charging process. If the patient feels any discomfort during charging of the IPG through the skin, the charging should be stopped.

3.8. Risk class of the device

The baroloop device is an active implant intended for use in humans for the treatment of hypertension.

The baroloop device is a programable vagal nerve stimulator for the monitoring, treatment and alleviation of hypertension. Its mode of action is electrical and mechanical, and it does NOT rely on any biological, immunological or metabolic means to alter the function of the human body. It contains no products derived from animal or human tissue.

The Lead + IPG and the Charger are Class III devices and the Programmer Software is also a Class III device.

3.9. Novel features

Selective stimulation of segments of the left vagus nerve for blood pressure reduction.

3.10. Accessories of the device

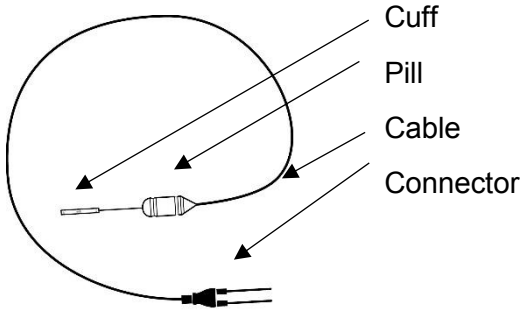
The Programmer is intended to be used together with the stimulator platform to directly assist medical functionality of the IPG (via the Charger) in terms of its intended purpose.

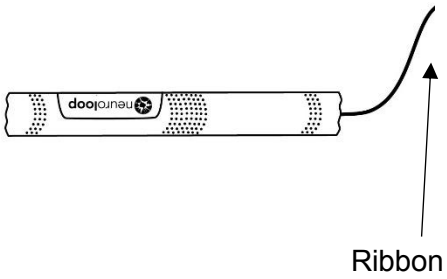
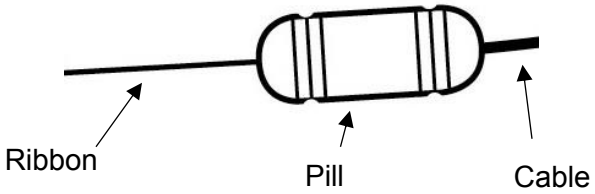
The Strap is an adjustable, external holder that keeps the Charger in close proximity to the IPG during battery charging and data transfer.

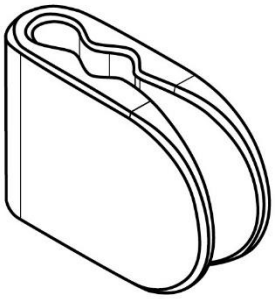
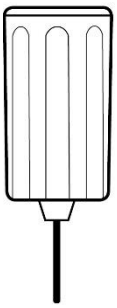
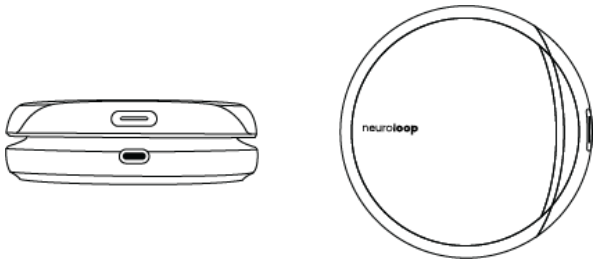
3.11. Available configurations of the device

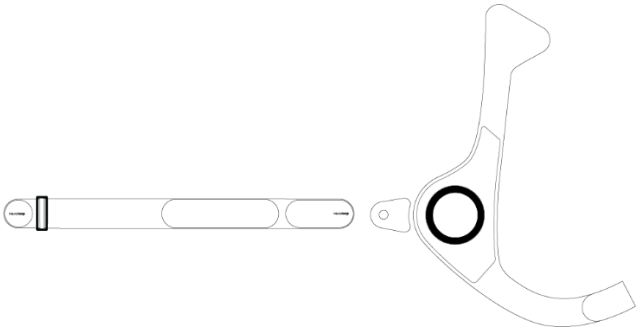
The baroloop system consists of the IPG, the Lead and the Charger. The Programmer is provided to the professional medical user and can be used in combination with more than one baroloop system.

3.12. General description of key functional elements

<u>Lead</u> The Lead is an assembly that consists of the Cuff, the Pill, the Cable, and the Connector. It is used to transfer electrical energy from the IPG to the vagus nerve.	

<u>Cuff</u> The Cuff is the interface between the epineurium of the vagus nerve with the stimulator. It contains 12 fractal-shaped, cathodic electrode contacts and two anodal rings. The substrate of the Cuff is made of flexible polyimide, and a flexible extension of the Cuff, the Ribbon, connects the electrode contacts to the Pill. The Cuff is pre-shaped and wraps (curls) around the nerve in conformity with preset shape of the Cuff. The implantation of the Cuff is suture-less.	
<u>Pill</u> The Pill consists of a ceramic interface with a silicone overmoulding. The ceramic element is the electrical interface between the Cuff and the Cable. The silicone overmoulding has two notches in its external surface that may be used to facilitate surgical fixation of the Pill near the neurovascular bundle that contains the vagus nerve.	
<u>Cable</u> The Cable passes subcutaneously from the Cuff to the IPG and is used for transmission of the electrical signals to and from the Cuff electrode to the IPG.	See above.
<u>Connector</u> The Connector is the electrical interface between the Lead and the IPG.	
<u>Suture Sleeve</u> The Suture Sleeves provide anchoring brackets to fix the cable to the surrounding tissue.	

	
IPG The IPG is the active part of the baroloop stimulator system. It generates the stimulation pulses, which are transmitted via the Lead to the vagus nerve. The IPG also records information related to the impedance and continuity of each electrode element in the Cuff and the heart rate. The IPG contains a rechargeable battery as an energy source and a wireless power transmission module for charging.	
Torque key The torque key is a tool for fastening or loosening the fixation screws to fix the Connector in the header of the IPG.	
Charger The Charger is an external device, which is used to program the IPG, to transfer recorded data from, and electrical energy (recharge) to the IPG. It acts as the interface between the implanted IPG and the Programmer. The power for the Charger is derived from a rechargeable battery. The Charger communicates wirelessly with the IPG and allows configuration of the IPG through the Programmer.	 Charger

The Charger fits into an adjustable, external Strap to hold the Charger close to the IPG during charging, programming, and data transfer.	 Strap
Programmer (software) The Programmer is used to adjust the stimulation parameters of the IPG. For this purpose, it communicates with the Charger, which is the interface to the IPG. The Programmer itself does not establish a direct connection to the IPG. The programming device used will be obtained from third-party manufacturer and consists of a computer or tablet. The software is developed by neuroloop.	

3.13. Device Accountability

Access to baroloop System inventory will be controlled and will be housed in a secure location. Records will be maintained to document the physical location of inventory from shipment / removal from the Sponsor's facility through use and / or return or disposal.

The site will be responsible for keeping a Device Accountability Log provided by the Sponsor or its designated representative in which will be recorded, at a minimum, date of receipt, baroloop System identification number, expiration date, date of use, subject unique identity code and date of disposal of the device.

If there is a product malfunction or other need to return the system or system components to the Sponsor, the Sponsor should be contacted for safe product disposal and / or return details.

NOTE: Please complete a Device Malfunction Form and immediately email to maxisoperations@maxismedical.com or fax to +49 69 2400 3627 if a device malfunction / failure has occurred.

The Investigator is responsible for ensuring that the investigational devices are used only under the Investigator's supervision and are only used according to this protocol and any approved amendments. The Investigator will not supply an investigational device to any person not authorized to participate in the study. The Investigator shall document in the Case Report Forms the lot numbers of the devices used during each case.

3.14. Return of Devices

All unused investigational devices will be returned to the study Sponsor upon completion of the clinical study. Any investigational device that fails to perform correctly will be returned to the study Sponsor or its designated representative for analysis. The study Sponsor or its designated representative will conduct device reconciliation during monitoring, the completion of subject enrollment, and at the conclusion of the study.

4. Study Overview

The Sponsor plans to conduct a clinical trial of the baroloop System. The study plan was developed according to the guidance given by EN ISO 14155 and the Declaration of Helsinki. The rationale for the trial design, endpoints and variables selected for study are described below. The justification for the study design and the content of the study are fully described below.

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.

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 Systems to be placed around a vagal nerve and the ability to stimulate at Day 14/21 post-implantation.

4.3. Secondary Study Endpoints

- 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), 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:
    - All-causes of death
    - Hospitalization for hypertensive crisis post-titration
    - 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).

4.4. Number of Subjects and Sites

Up to 10 subjects may be enrolled at up to 3 clinical study centers.

4.5. Study Population

The study population comprises subjects with resistant hypertension as defined in the 2018 ESC/ESH Guidelines for the management of arterial hypertension.

4.6. Enrollment Criteria

A potential subject must meet all of the criteria as outlined below in order to be considered eligible to participate in this study.

4.6.1. Inclusion Criteria

Subjects eligible to participate must meet all of the following criteria at screening and / or baseline visits:

1. Aged 18 years or older and less than 80 years of age.
2. Persistent office systolic blood pressure (SBP) ≥ 140 mm Hg and diastolic blood pressure (DBP) > 90 mm Hg on antihypertensive medicines on two visits separated by a minimum of four weeks.
3. 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.
4. Stable drug regimen of 3 antihypertensive medicines consisting of a renin-angiotensin blocker(ACE) or Angiotensin II Receptor Blocker (ARBs), a calcium channel blocker (CCB), a 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.

5. 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.
6. Willingness and ability to comply with follow-up requirements.
7. Signed informed consent.

4.6.2. Exclusion Criteria

Potential subjects with one or more of the following criteria shall be excluded from the study even if they meet the inclusion criteria:

1. 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).
2. Any patient with a history of injury to the vagus nerve or its branches (e.g., the recurrent laryngeal nerve).
3. Secondary causes of hypertension.
4. Calculated eGFR < 30 mL/min/1.73m2.
5. Type 1 diabetes mellitus or poorly controlled type 2 diabetes mellitus (HbA1c > 10%).
6. One or more episodes of orthostatic hypotension in the past year
7. Requirement for chronic oxygen therapy or mechanical ventilation.
8. Untreated (no CPAP therapy) sleep apnea (AHI > 15)
9. Morbid obesity, defined as Body Mass Index >40 kg/m2 or arm circumference 46 cm.
10. Pacemaker and/or implantable defibrillators.
11. History of transient ischemic accident or cerebrovascular accident during six (6) months prior to screening.
12. Symptomatic carotid artery disease or > 70% occlusion of either carotid artery; any carotid malformation or lesion, a carotid bruit or other abnormal carotid sound.
13. 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).
14. Limited mobility of the neck secondary to vertebral disease or prior vertebral surgery, including patients who wear a cervical support.
15. 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.
16. Cardiac arrythmias (atrial fibrillation, atrial flutter, etc.) that require anticoagulation or interfere with a consistent measurement of blood pressure.
17. Syncope in the last 6 months.
18. History of bleeding disorders, thrombocytopenia, hemophilia or significant anemia (hemoglobin (Hgb) < 10 gm/dl).

19. Current anticoagulation therapy (excluding antiplatelet therapy with aspirin as a sole therapy).
20. Works night shifts.
21. History of unresolved drug or alcohol use.
22. Active treatment of a psychiatric ailment.
23. Life expectancy of less than 12 months due to other disease.
24. Subject has a condition that, in the opinion of the investigator, precludes participation, including willingness to comply, with all follow-up procedures.
25. Participation in another clinical study for which follow-up is currently on-going.
26. Women who are of child-bearing age or who have the potential to become pregnant
27. Resting heart rate of <40 beats/min for patients on beta blockers or <60 beats/min for all other patients, confirmed at both baseline visits.
28. Baroreflex failure or autonomic neuropathy
29. Symptomatic, uncontrolled bradyarrhythmias
30. Atrioventricular block of any grade
31. Patients who are treated with Pacemaker and/or implantable defibrillators
32. Presence of a vagus stimulator
33. Patients who are likely to require magnetic resonance imaging (MRI) of the cervical area
34. Occupational exposure to high levels of non-ionizing radiation that may interfere with therapy
35. Patients with a limited ability to read, understand and execute adjustment procedures (for example, persons suffering from dementia).
36. Likely exposure to diathermy.

4.7. Informed consent

Subjects who meet the entry criteria will be asked to sign a Patient Informed Consent form as approved by the relevant regulatory authorities before any study-specific tests or procedures are performed. The Investigator or a designated member of his / her staff should approach the subject to obtain written informed consent. As far as possible, non-technical language should be used that is understandable to the subject. The background of the proposed study and the benefits and risks of the procedures and study should be explained. The subject should be provided with ample time to read the consent form and discuss it with his / her family and/or physician. The subject shall be informed that his / her participation in the clinical investigation is completely voluntary, may be withdrawn at any time without consequences, and is confidential. The Informed Consent Form must be read and understood by the subject and the subject's questions answered and must include information and a separate explicit consent regarding the patient's rights under the GDPR and/or national data protection laws or regulations. The form must be signed and dated by both the subject and Investigator. Each subject is to receive a copy of his / her signed and dated Informed Consent Form. A copy of the approved informed consent form along with a copy of each patient's signed consent form will be maintained by each Investigator in a designated clinical study administrative file.

Investigator Study personnel should explain that even if a subject agrees to participate in the study and signs the Patient Informed Consent form, the subject may not be eligible to participate if he / she fails to meet the inclusion or exclusion criteria.

Once written consent has been obtained, the subject's information will be entered on a Consent and Screening Log, which will be maintained at each site. All subjects who provide written informed consent will be entered on the log regardless of whether or not they are enrolled in the study.

As appropriate, important and new information will be provided to new and existing subjects throughout the duration of the study.

4.8. Unique Study Identification Code

Each subject will be assigned a unique study identification code in an effort to protect subject confidential information. The unique study identity code will be pseudonymized and will not include date of birth or subject's first and last initials and will be used to link study data and other study information to the subject in lieu of the subject name. The Subject Name Log will be used to link the unique study identity code to the subject and will be maintained at each site. This log will remain confidential and will not be provided to the Sponsor, but only used for reference when monitoring at the study site.

4.9. Subject Recruitment

Subjects who present with resistant hypertension consistent with the 2018 ESC/ESH Guidelines for the management of arterial hypertension will be considered potential study candidates. The Sponsor does not intend to advertise or otherwise actively recruit subjects.

4.10. Subject Reimbursement

Subjects will not be reimbursed or compensated for participating in the trial. Reasonable travel costs associated with follow-up visits may be reimbursed upon request.

4.11. Enrollment

Patient eligibility will be confirmed prior to insertion of the investigational device, and subjects will be considered enrolled in the study at the time that the skin is broken to implant the baroloop System.

Subjects who sign consent but are excluded before enrollment will not be included in the primary analysis of the study endpoints. The reason for exclusion will be documented in the Consent and Screening Log and the consent document maintained in the site's study records.

4.12. Duration of Subject Participation

Subjects enrolled in the trial will participate for approximately 2 years and 2 months.

4.13. Study Duration

This study is expected to enroll up to 10 subjects within approximately 36 months. The closeout phase of the study is expected to be completed within 6 months following the last subject follow-up visit. The total duration of the study is estimated to be 5.5 years.

4.14. Withdrawal of Subjects

Each subject may voluntarily withdraw his / her participation from the study at any time. Investigators may discontinue a subject's participation in the study as deemed appropriate for safety considerations and / or if the subject's medical condition contraindicates further study participation. All enrolled subjects will undergo the complete study follow-up for safety evaluation.

4.15. Loss to Follow-up Considerations

A subject will be considered lost to follow-up and terminated from the study when all of the following criteria have been met:

- Documentation of three unsuccessful attempts on three different days over a period of three (3) months by the Investigator or his / her designee to contact the subject or next of kin, one of which should be by certified mail with signature confirmation.
- Prior agreement of the Sponsor to remove the subject from the clinical investigation.

If permitted by the subject in the informed consent, contact with the family doctor may be made only after three unsuccessful attempts have been made to contact the study subject.

4.16. Subject Confidentiality

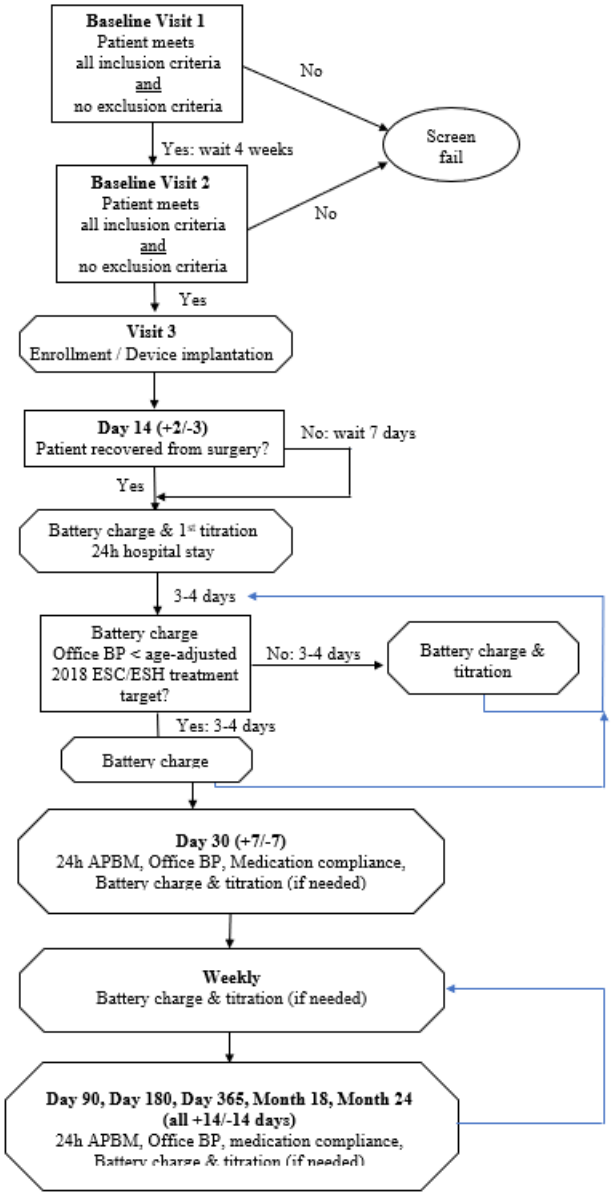
All information concerning subjects or their participation in this trial will be considered confidential. Only authorized representatives, designated personnel of the CRO, designated consultants, or regulatory agencies will have access to these confidential files. Subject names or other non-pseudonymous data that could directly identify a patient will not be captured on the case report forms. In addition, all patient identifiers except the unique study identification code will be redacted from any X-ray, CT and MRI images submitted from the participating site to the Sponsor or the Sponsor's designated reviewers for analysis.

4.17. Study Procedures

4.17.1. Screening and Enrollment

The overall screening and enrollment scheme for the study is shown in schematic form in Figure 2 and identifies the various phases for screening, consenting, continued eligibility assessment and assignment into the subject cohorts for the study.

Figure 2: baroloop Trial Screening and Enrollment Scheme



4.17.2. Consent Phase

Prior to obtaining written informed consent, the subject's existing medical records may be reviewed by the site to determine whether or not the subject might be an acceptable candidate for this study.

If initial review of the medical records indicate that the subject may be eligible (i.e., the patient has uncontrolled or resistant hypertension as defined in the 2018 ESC/ESH Guidelines for the management of arterial hypertension), the informed consent process may commence.

4.17.3. Screening Phase

Each patient's medical records will be reviewed to assess compliance with the eligibility of the baroloop Study. Patients who are eligible based on the study enrollment criteria will proceed to the next phase of the study.

4.17.4. Eligibility Assessments

Baseline evaluation will be performed after the subject has provided written informed consent in order to ensure that the subject is an appropriate candidate for this study and to obtain baseline values for study endpoint evaluation.

If the subject continues to meet the study's enrollment criteria and continues to be willing and able to participate in the study protocol, the subject will be enrolled.

All subjects will undergo a series of baseline evaluations (if not already available as part of the existing medical records). Baseline visit and data collection can occur anytime within 6 months before the implantation procedure of the baroloop System (see Figure 2).

4.18. Procedural Treatment and Timing

4.18.1. Medication Regimen

All participants in the study will be on a minimum of three (3) anti-hypertensive drugs such as, but not limited to, a diuretic (usually a thiazide or loop diuretic), a calcium channel blocker and an angiotensin converting enzyme inhibitor. Patients may be on additional antihypertensive drugs such as alpha- or beta-blockers, direct acting vasodilators angiotensin receptor blockers or combinations of these drugs. Where possible, simpler (fewer drug) regimens are preferred. Regardless of the of the particular three or greater combination of drugs, every effort should be made to maintain each patient on a stable regimen of antihypertensive medicines during the course of the study.

4.19. Baseline Assessment: Visit 1

The following information will be assessed, and the documentation will be maintained as source records at the study site:

- Medical history;
- Office cuff blood pressure;
- Check for orthostatic blood pressure and orthostatic pulse assessments;
- Current medication history including all hypertensive medication;
- Physical examination;
- Laboratory testing;
- Quality of Life SF-36 questionnaire.

4.20. Baseline Assessment: Visit 2 (four weeks after visit 1)

- Office cuff blood pressure;

- Current medication history including all hypertensive medication including changes of medication regimen;
- Review and assessment of adverse events;
- 24 hour ambulatory blood pressure measurement (24hr ABPM) after observed therapy for hypertension.
- Medication compliance testing
- Quality of Life SF-36 questionnaire.

4.21. Day of Implantation procedure

- Physical examination;
- Changes of medication regimen;
- Review and assessment of adverse events;
- Office cuff blood pressure; and
- Assessment of all Inclusion/Exclusion criteria.

4.22. baroloop System Implantation Procedure

The implantation operation should be performed as described in the baroloop Implantation Manual (BL_IM_Implantation_Manual_FIH). In brief, the procedure should be performed using a neurosurgical microscope after the initial incision in the left side of the neck is made over the location of the vagus nerve (from point 3 on). A subcutaneous pocket (size 6 x 7 cm) should be created under the skin and over the pectoralis muscle below the left clavicle to house the IPG. To access the left vagal nerve, a horizontal cervical skin incision 4-5 cm in length on the left neck should be made between the clavicle and mandible. The tissue should be carefully dissected to expose the neurovascular sheath containing the vagus. The sheath should be opened to expose the left vagus nerve over a length of approximately 3 cm. A neuroloop Cuff size should be select that matches the approximate size of the vagal nerve diameter. Before placing the Cuff, the Pill should be fixed to the underlying tissue according to the instructions in the baroloop Implantation Manual. After fixing the Pill, the Cuff should be wrapped around the vagus nerve, and proper rim alignment of the Cuff edges should be reviewed to make sure that both ends of the cuff are square and perpendicular to the long axis of the cuff. Strain relief loops in the Cable leading to the IPG should be created using the suture sleeves. The Lead should be passed subcutaneously from the cervical incision site to the pectoral pocket where the IPG is placed. The Connector should be cautiously passed through tunnelling device to the subcutaneous pectoral pocket. After removing the Tunnelling device by pulling in pectoral direction, which was inserted from the pectoral pocket to the neck, the Connector to the IPG should be cleaned, if necessary, prior to connecting it to the IPG. The Connector should be fixed in the appropriate receiving slot in the IPG using the torque key. Perform initial device testing, described below, before closing the surgical incisions.

After the Cuff, Pill, Lead and IPG are connected, the device must be tested. Please see the Implantation Manual and Programmer Manual for complete details of testing. Briefly, an impedance test should be performed before the IPG is placed. If impedance test is ‘Passed’,

place the IPG in the prepared pectoral pocket. If impedance is 'Failed', follow the steps in flow chart in the Implantation Manual to obtain a 'Passed' impedance test. After the Impedance test is passed, place the IPG in the pectoral pocket with the neuroloop logo pointing to the skin surface. Perform a 2nd impedance test. If impedance 'Passed', follow the tests. If impedance 'Failed', follow steps in Implantation Manual flow chart to obtain a 'Passed' impedance test.

Once the impedance tests have been passed, both surgical sites should be irrigated with saline before closure of each surgical incision. Incision closure should be completed with sutures in layers, and a stapler must NOT be used to close the wounds!

After wound closure, a brief 'intraoperative' stimulation test must be performed to confirm proper functioning of the neuroloop device. Please consult the Programmer Manual and Implantation Manual for detailed instructions (BL_PM_Programmer_Manual_FIH and the BL_IM_Implantation_Manual_FIH). To begin, place the Charger within its sterile cover on the implanted IPG. Use the programmer to select 'Surgery Mode' and login into the Programmer. The Charger and the IPG will connect automatically, which will be reflected on the Programmer screen. Once the 'Surgery Mode' screen appears, press the 'START STIMULATION TEST' button on the Programmer screen. The electrode that is currently being tested will be highlighted. The stimulation or pause time is displayed. The stimulation time for each electrode is 30 seconds, and the pause time between two stimulations is 30 seconds. The overall test time, if all electrodes are functional, will be 12 minutes. Once the test is finished, completion of the test is displayed in the Programmer screen. The data from the intraoperative testing may be downloaded for analysis by neuroloop.

Please note that intra-operative testing is done to confirm that the device is properly connected, that the batteries effectively drive and control the device, and that the device contacts the proper therapeutic anatomical target. The stimulation parameters used to test the device and its relationship to each patient's anatomy in the operating room are not suitable as a guide for subsequent therapy. The nature of the anatomical relationship between the electrode(s) and the device is modified by the processes of wound granulation and healing so that the impedance characteristics and the exact anatomical relationship of the electrode to the target neurological tissue change during the post-operative period. As with other neuro-modulatory devices, the baroloop device is tested in the operating room, but the therapeutic stimulation delivered by the device is titrated only after ca. 2-3 weeks of healing has occurred. The intra-operative stimulation characteristics are not used to guide the titration to therapeutic effect - the device is tested in the operating room to make sure that it is operational, and the actual titration of stimulation to modify blood pressure will begin only after a period of post-surgical healing.

WARNING: Be aware of severe side effects, such as profound bradycardia.

If a severe side effect occurs (including severe bradycardia), stimulation must be stopped immediately, and appropriate corrective actions taken.

Any stimulation-related effects (blood pressure decrease, heart rate decrease, or any other possible response due to stimulation) should be recorded in the study Case Report Forms.

After intraoperative impedance, self-test and stimulation testing, set the IPG in shelf-mode by selecting 'Activate Shelf Mode' in the status dropdown menu on the Programmer screen.

WARNING: The IPG must be in INACTIVE MODE after implantation during the recovery from surgery.

4.23. 14-Day Follow-up Visit (+2 / -3 days)

- Clinical assessment of the subject;
- Physical examination;
- Changes of medication regimen;
- Review and assessment of adverse events;
- Office cuff blood pressure; and
- Initial testing and titration of stimulation to achieve up to a 20% reduction in systolic blood pressure or age-adjusted 2018 ESC/ESH treatment target office blood pressure (OBP), whichever blood pressure achieved during stimulation is lower.

N.B.:

1. If the patient is not judged to be ready for a first titration on day 14, the patient may return on or before day 21 for the first titration.

2.The first titration of blood pressure using baroloop stimulation (not earlier than 14 days after surgery when wound healing is complete) will be followed by a brief, one day hospitalization to observe the initial response to baroloop therapy.

4.24. Stimulation Settings/Titration First-in-Human

Blood pressure titration using VNS will take several 'titration sessions' to obtain optimal control of blood pressure. The titration sessions will take place weekly after the first titration is completed 14 days after surgery until the blood pressure has reached a target value less than the age-adjusted 2018 ESC/ESH treatment target office blood pressure (OBP). In between each titration session for the first four (4) weeks, the patient will return to the hospital or office where the titration takes place to have the IPG recharged, data downloaded from the IPG, and a check of OBP. Thus, there will be two alternating types of visits each week for the first 4 weeks of titration, one for titration, data downloading from the IPG and IPG charging and one for an OBP check, data downloading from the IPG and IPG charging.

After 4 weeks, titration may be done weekly, and the IPG charging may be done weekly when the titration is conducted. The titration process will continue until the target OBP is reached or the patient's responses to VNS are sufficiently reliable to allow less frequent follow-up after each new titration of OBP. Once a stable, target OBP is reached, blood pressure follow-up may occur at an interval appropriate for blood pressure control as determined by the treating physician.

During the first titration of baroloop stimulation, the Investigator should explore as fully as possible the range of responses to different electrode positions and stimulation settings so that an optimal set of stimulation settings may be selected with full knowledge of the range of responses in each subject at each visit.

During the titration of blood pressure responses to baroloop stimulation, each subject's blood pressure should be monitored continuously using a Finapres device. The patient should be supine and blood pressure and heart rate should be recorded continuously. After stable BP and HR are observed in the patient, the titration of the VNS may begin. Blood pressure responses to specific stimulation tests should be recorded by the Finapres device, and it is also important to record the baseline blood pressure and recovery periods after stimulation to characterize each patient's response to baroloop stimulation. The blood pressure should also

be measured using an arm cuff 60 seconds after the onset of the stimulation sequence. Each titration stimulation should last at least 2 minutes, and the arm cuff blood pressure should be measured 1 minute after the stimulation starts while the stimulation is still present, and once again 1 minute after the titration stimulation has stopped. These values establish the correlation between arm cuff blood pressure and Finapres readings, which will be useful for subsequent titration visits in each patient.

The Cuff completely surrounds the vagus, and some combinations of stimulation parameters can optimally increase the effective depth of penetration of the stimulating electric field into the vagus nerve. The IPG provides a biphasic charge-balanced stimulation to achieve cathodal activation of the vagus nerve, and the IPG has been programmed to provide specific combinations of the following stimulation parameters, so called presets, which may be selected using the Programmer:

- Amplitude in µA
- Pulse width in µs
- Repetition rate in Hz
- Duty cycles in ratios of ON-OFF-Sequences

Preset name	Amplitude (µA)	Pulse width (µs)	Frequency (Hz)	Duty cycle	Comment
Impedance	96	400	4 single pulses with distance of 320µs	-	Used for impedance measurement
P1A	96	240	40	0.3	-
P1B	96	400	40	0.3	-
P1C	96	240	40	0.5	-
P1D	96	400	40	0.5	-
P2A	144	240	40	0.3	-
P2B	144	400	40	0.3	-
P2C	144	240	40	0.5	-
P2D	144	400	40	0.5	-
P3A	300	240	40	0.3	-
P3B	300	400	40	0.3	-
P3C	300	240	40	0.5	-
P3D	300	400	40	0.5	-
P4A	444	240	40	0.3	-
P4B	444	400	40	0.3	-
P4C	444	240	40	0.5	-
P4D	444	400	40	0.5	-
P5A	600	240	40	0.3	-
P5B	600	400	40	0.3	-
P5C	600	240	40	0.5	-
P5D	600	400	40	0.5	-
P6A	744	240	40	0.3	-
P6B	744	400	40	0.3	-
P6C	744	240	40	0.5	-
P6D	744	400	40	0.5	Used during Surgery Mode

The purpose of titration is to determine which electrode(s) and which preset stimulation parameters (which deliver different levels of energy and strength of stimulation) provide an optimal blood pressure reduction at the lowest and most effect stimulation intensity. The preset collections of stimulation parameters were derived from animal studies and represent a limited range of the values tested in animals so that the minimally effective stimulation parameters determined during animal studies may be used in humans. The general strategy during the titration should be to select all individual active electrodes (inactive electrodes do not need to be tested) and deliver a low and a high intensity stimulation from among the preset stimulation sequences provided by the Sponsor to define the range of blood pressure responses possible in each patient. Thus, the presets may be used during the process of selecting an optimal dose

of baroloop stimulation, and the preset stimulation that provides an effect blood pressure reduction may be selected for therapeutic stimulation.

The immediate goal of each titration is to reduce the blood pressure slowly and modestly over a sequence of weeks. Therefore, the reduction in blood pressure should not exceed 20% of the blood pressure preceding the titration effort. Moreover, if the blood pressure at the time the patient returns for a titration visit is at or below the age-adjusted OBP target values described in the 2018 ESC/EHS Guidelines, then no additional titration need be done. If this is obtained during any one of the titration tests described above, the stimulation characteristics that achieved a blood pressure less than the age-adjusted OBP may be used as the therapeutic level of stimulation until the next follow-up visit so long as the titrated blood pressure is not lower than 80% of the baseline value just prior to the titration, and the patient has no symptoms of dizziness, orthostatic hypotension or other adverse effects.

If a 20% reduction in baseline blood pressure is greater than the age-adjusted OBP target, then the target blood pressure should be approached in a series of incremental steps in which an intermediate target blood pressure not below 80% of the baseline blood pressure is targeted. This intermediate target blood pressure should then be maintained for a week (at least) until the next visit for further titration, when a further 20% reduction in blood pressure may be targeted so long as the patient has no symptoms of dizziness, orthostatic hypotension or other adverse effects

Once an effective set of stimulation parameters has been selected, this setting should be used for treatment until the next study visit, when the blood pressure response can be re-evaluated, and stimulation parameters may be adjusted as appropriate to reach the goal of a blood pressure less than the age-adjusted OBP target.

Once the first treatment stimulation level has been selected, the patient should be observed in the hospital for 24 hours (as noted above). The titration of blood pressure will be retested after 24 hours prior to discharge following the titration strategy described above over a more limited range of electrode combinations and preset stimulation values. If the treatment is well tolerated and no adverse effects of VNS are identified during the hospital stay, the patient may be discharged on the prescribed pattern of VNS. Patients need not be hospitalized following subsequent blood pressure/stimulation titrations so long as the patient has no symptoms of dizziness, orthostatic hypotension or other adverse effects.

It is the Sponsor's expectation that most patients will achieve an OBP less than the age-adjusted target of hypertension treatment within a small number of weekly titration sessions. If the titration process persists beyond 12 sessions (~ 3 months), it is permissible to extend the interval between titrations up to six weeks. The patient and physician may work together to achieve a titration schedule that achieves the age-adjusted target OBP as quickly as is safe.

N.B.: The IPG should be charged at every visit to the physician's office for follow-up. In the first four weeks of titration, the IPG will be recharged twice a week. After four weeks of titration, the IPG may be charged weekly when the well-being of the patient will also be assessed. There is no home charging possible in this First in Human Study.

4.25. Follow-up titration every 7 days (± 2-3 days)

- Clinical assessment of the subject;
- Physical examination;
- Changes of medication regimen;

- Review and assessment of adverse events;
- Office cuff blood pressure; and
- Titration of vagal nerve stimulation should be repeated weekly to achieve up to a 20% reduction in systolic blood pressure or office BP < the age-adjusted 2018 ESC/ESH treatment target office blood pressure (OBP), whichever blood pressure achieved during stimulation is lower. The titration protocol described above should be followed each time the patient returns for adjustment of baroloop stimulation. The data from the IPG will also be downloaded at each visit for subsequent analysis.

4.26. 30-Day Follow-up Visit (+7 / -7 days)

- Clinical assessment of the subject;
- Physical examination;
- Changes of medication regimen;
- Review and assessment of adverse events;
- Office cuff blood pressure;
- Medication compliance testing;
- 24hr ABPM after observed therapy for hypertension;
- Quality of Life SF-36 questionnaire; and
- Further testing and titration of stimulation to achieve an OBP less than the age-adjusted target of hypertension treatment, as described in the titration directions.

4.27. 90-Day Follow-up Visit (+14 / -14 days)

- Clinical assessment of the subject;
- Physical examination;
- Changes of medication regimen;
- Review and assessment of adverse events;
- Office cuff blood pressure;
- Medication compliance testing;
- 24hr ABPM after observed therapy for hypertension;
- Quality of Life SF-36 questionnaire; and
- Further testing and titration of stimulation to achieve an OBP less than the age-adjusted target of hypertension treatment, as described in the titration directions

4.28. 180-Day Follow-up Visit (+14 / -14 days)

- Clinical assessment of the subject;
- Physical examination;
- Changes of medication regimen;

- Review and assessment of adverse events;
- Office cuff blood pressure;
- Medication compliance testing;
- 24hr ABPM after observed therapy for hypertension;
- Quality of Life SF-36 questionnaire; and
- Further testing and titration of stimulation to achieve an OBP less than the age-adjusted target of hypertension treatment, as described in the titration directions

4.29. 365-Day Follow-up Visit (+14 / -14 days)

- Clinical assessment of the subject;
- Physical examination;
- Changes of medication regimen;
- Review and assessment of adverse events;
- Office cuff blood pressure;
- Medication compliance testing;
- 24hr ABPM after observed therapy for hypertension;
- Quality of Life SF-36 questionnaire; and
- Further testing and titration of stimulation to achieve an OBP less than the age-adjusted target of hypertension treatment, as described in the titration directions

4.30. Long Term Follow-up Visits – 18 and 24-Month Follow-up Visit (+14 / -14 days)

- Clinical assessment of the subject;
- Physical examination;
- Changes of medication regimen;
- Review and assessment of adverse events;
- Office cuff blood pressure;
- Medication compliance testing;
- 24hr ABPM after observed therapy for hypertension;
- Quality of Life SF-36 questionnaire; and
- Further testing and titration of stimulation to achieve n OBP less than the age-adjusted target of hypertension treatment, as described in the titration directions

4.31. Unscheduled Follow-up Visit

If an unscheduled follow-up visit is required, the study subject should be assessed for new or unresolved adverse events. Any testing required, including imaging studies, should be provided to the study Sponsor for DSMB adjudication. Office cuff blood pressure will be taken

and will be reviewed. Change of medications, diagnostic test results, or interventions should be documented.

4.32. 4.32 Schedule of Study Visits and Assessments

Table 3: Schedule of Study Visits and Assessments

	Follow-up										Long Term Follow-up
Visit	**Visit 1**	**Visit 2**	**Visit 3/ Procedure**	**Discharge**	**14 Days (+2/-3 days)**	**Weekly Office visits (1x/2x)***	**30 Days (+/- 7 days)**	**90 Days (+/- 14 days)**	**180 Days (+/- 14 days)**	**365 Days (+/- 14 days)**	**18, and 24, Months (+/- 14 days)**
Eligibility	✓	✓	✓								
Informed Consent	✓										
Medical History	✓										
Physical Examination	✓		✓		✓		✓	✓	✓	✓	✓
Concomitant medications	✓	✓	✓		✓		✓	✓	✓	✓	✓
Baseline 12 lead ECG	✓										
Blood Testing	✓			✓							
24 hour ABPM		✓					✓	✓	✓	✓	✓
Medication compliance testing		✓					✓	✓	✓	✓	✓
Quality of Life SF-36	✓	✓					✓	✓	✓	✓	✓
neuroloop implantation			✓								
neuroloop titration*,**					✓	(✓)	✓	✓	✓	✓	✓
IPG recharging and data downloading*					✓	✓					
Office cuff BP Measurement	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓
Discharge				✓							
Adverse Events	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓	✓

*Titration after Day 14 takes place 1x per week. The second weekly visit through Day 30 is for Office BP and IPG battery charging only. After Day 30, only one visit per week for charging and (if necessary) titration is required.

**The heart rate and blood pressure will be recorded using a Finapres device during each titration.

4.33 Study Completion

After the subject has completed the 2-Year follow-up visit, the Subject Termination must be recorded and completed within the EDS. During the course of the study, it is possible that subjects will be withdrawn from the study early. Factors leading to subject withdrawal may include, but are not limited to, the following:

- **Subject Withdrawal** - A subject may voluntarily withdraw from the study at any time without affecting his or her future medical treatment or benefits. In addition, the Investigator may withdraw a subject from the study if the subject refuses further testing or follow-up evaluations, or for any other reason as determined by the Investigator.

- **Subject Lost to Follow-Up** – If the Investigator has attempted to contact a subject at least three (3) times and receives no response, the subject may be lost to follow-up. The research staff should document at minimum three (3) attempts to contact the subject prior to terminating the subject from the trial, one of which should be a registered letter to the subject's address.

- **Subject Death** - When a subject expires, the Serious Adverse Event and Report of Patient Death must be completed in the data collection system. must be completed promptly. Source documents such as death summary, autopsy report (if done), and a copy of the death certificate should be redacted of personal identifiers and provided to the designated clinical monitor and DSMB to describe the cause of the subject's death. The Investigator will notify Sponsor or designated CRO within 24 hours of learning of the event.

The Study Exit Case Report Form should be completed for each study subject, to record date and reason for early termination (if subject does not complete the study) or at the final visit (if subject completes all study time points).

The Sponsor or the designated CRO will notify the competent authority of Serious Adverse Events in accordance with national regulations and requirements. .

4.34 Concomitant medications

To be eligible for enrollment, study participants be taking a minimum of three (3) anti-hypertensive medications at the time of entry into the study. Additionally, all subjects will remain on at least three (3) anti-hypertensive medications for the duration of the study, ideally the same medications at the same dosages.

Appropriate management of subject's individual risk factors such as statins, smoking cessation, nutrition, diabetes will remain as standard of care and any changes to this regimen will be documented by the study team.

Subjects should be advised of the importance of continuing their medical therapy regimen. Subjects should not reduce or stop their anti-hypertensive medication dosage until the 6-month time point, at which time the Principal Investigator may decide to reduce medication per the site's standard of care protocol.

All medications will be recorded on the Concomitant Medication log.

4.35 Study Exit or Premature Withdrawal

Subjects will be exited from the study by completion of a Study Exit form in the data collection system at the time of study completion provided the subject has not experienced an adverse event that is ongoing and unexplained.

Subjects may be terminated or withdrawn from the study early for, including but not limited to, the following reasons:

- Subject death.
- Voluntary withdrawal – meaning that the subject voluntarily chooses not to further participate in the study.
- Lost to follow-up – meaning that the subject is more than 14 days late to a study visit and 3 documented attempts to contact the subject are unsuccessful. A subject who misses a study visit but attends a subsequent visit will no longer be considered lost to follow-up. A missed visit will be considered a protocol deviation and the deviation will be documented and reported.
- In the physician's opinion, it is not in the best interest of the subject to continue study participation.

All subjects enrolled (including those withdrawn or lost to follow-up) shall be accounted for and documented.

5. Risk Benefit Assessment

Sponsor has conducted an analysis of the benefits and risks of the baroloop System and procedures necessary for implantation and use of the baroloop System. A detailed Risk Assessment has been completed, and the conclusion of this review is that this investigational study is justified because the overall potential benefit to the population outweighs its attendant 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.

6. Statistical Analysis Plan

6.1. Overview

The primary objective of this study is to characterize the safety and feasibility of the baroloop System in subjects with uncontrolled or resistant hypertension. All subjects will be followed on an intent-to-treat basis (ITT). The device performance will also be assessed based on a per-protocol analysis of the primary safety and feasibility endpoints and secondary efficacy endpoints. An intent-to-treat analysis, along with other secondary analyses, will also be completed and reported.

This is not a hypothesis driven study, and no formal power analysis or hypothesis-driven statistical analysis has or will be performed. Standard summary statistics will be calculated for all study variables. For continuous variables, statistics will include means, standard deviations, medians and ranges. Categorical variables will be summarized using frequency distributions.

The primary endpoints will be analyzed on an intent-to-treat (ITT) basis, for which data from all subjects enrolled will be included. In order to evaluate a true treatment effect, the primary analysis will include those subjects achieving technical success, the definition of which includes successful completion of the study procedure.

If there are no more than 4 failures to implant, combined with a safety level that is determined by the independent DSMB to be acceptable, together with any reduction in blood pressure as a result of the baroloop therapy, this will be considered a successful outcome to this First-in-Human study.

6.2. Primary Safety Endpoint

The primary safety endpoint is:

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

- All-causes of death

- Hospitalization for hypertensive crisis
- Any device or procedure-related serious adverse event

All MAEs to be adjudicated by an independent Data Management Safety Board (DSMB).:

6.3. Primary Feasibility Endpoint

The primary feasibility endpoint is technical success, defined as the ability of the baroloop System to be placed around a vagal nerve and the ability to stimulate at 14 days post-implantation.

6.4. Secondary Endpoints

- 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:
    - All-causes of death
    - Hospitalization for hypertensive crisis post-titration
    - 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-Iterm Short-Form Health Survey (SF-36).

6.5. Demographic, Safety, Feasibility and Efficacy Data

Demographic and baseline clinical and disease characteristics will be summarized in tables. For continuous variables, the summary will include number, mean, and standard deviation and 95% confidence intervals. Summaries for categorical variables will include the number and percent of subjects in each category.

6.6. Imputation of Missing Data

Imputations for missing data in (e.g. withdrawn subjects, loss to follow-up, missing data) will not be performed. Analyses will be performed with all available data only.

7. Adverse Event and Incident Reporting

The occurrence of Adverse Events will be monitored during this study. All Adverse Events will be recorded on the Adverse Event Form and followed until resolved. The study will be conducted in accordance with EN ISO 14155: 2018-08: Clinical investigation of medical devices for human subjects - Good Clinical Practice. All Serious Adverse Event will be adjudicated by an independent DSMB and adjudicated results will be included in the data analysis.

7.1. Adverse Event (AE)

An **Adverse Event (AE)** is any untoward medical occurrence, unintended disease or injury or any untoward clinical signs (including an abnormal laboratory finding) in subjects, users or other persons whether or not related to the medical device. This includes events related to the device or events related to the procedures involved.

An **Adverse Device Effect** is an adverse event related to the use of a medical device, including adverse events resulting from insufficient or inadequate Instructions for Use, deployment, implantation, installation or operation, or any malfunction of the medical device or any event resulting from user error or intentional misuse of the medical device.

The Investigator is responsible for assessing the severity of the AE, the causal relationship between any events and the clinical study procedure, activities or device. Additionally, the Investigator is responsible for providing appropriate treatment for the event and for adequately following the event until resolution. The following categories of adverse event severity are to be used:

- **Mild:** Awareness of a sign or symptom that does not interfere with the subject's usual activity or is transient, resolved without treatment and with no clinical sequelae.
- **Moderate:** Interferes with the subject's usual activity.
- **Serious:** Any fatal or immediately life-threatening clinical experience that requires a subject to be hospitalized, or hospitalization is unduly prolonged because of potential disability or danger to life or because an intervention has been necessitated. This includes any permanently disabling event.

7.2. Serious Adverse Events (SAE)

A **Serious Adverse Event (SAE)** is any problem or unwanted event encountered in a clinical trial or a performance evaluation that has led, or could have led, directly or indirectly to death or to a serious deterioration in the health of a subject or user or any other person, without regard to whether the event was caused by a medical product. The following events (including laboratory results and outcome events) will be considered to be SAEs and must immediately (within 24 hours) be reported to the study Sponsor and / or designated representative by telephone, fax and / or email. These events must be reported whether or not the Investigator believes they are related to study procedures, activities or device:

- Death
- Serious deterioration in the health of the subject, that either resulted in
    - a life-threatening illness or injury, or
    - a permanent impairment of a body structure or a body function, or
    - in-patient or prolonged hospitalization, or
    - medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function.
    - chronic disease
- Fetal distress, fetal death or a congenital physical or mental impairment or birth defect

7.3. Serious Adverse Device Effect (SADE)

A **Serious Adverse Device Effect** is an adverse device effect that has resulted in any of the consequences of a Serious Adverse Event.

NOTE: Planned hospitalization for a pre-existing condition, a condition unrelated to the treatment or a procedure required by this study, that is without serious deterioration in health, is not considered a serious adverse event.

7.4. Unanticipated Serious Adverse Device Effect (USADE)

Unanticipated Serious Adverse Device Effect (USADE): Serious adverse device effect which, by its nature, incidence, severity or outcome has not been identified in the risk analysis.

7.5. Anticipated Serious Adverse Device Effect (ASADE)

Anticipated Serious Adverse Device Effect (ASADE): An effect, which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

7.6. Unanticipated Adverse Device Effect (UADE)

Unanticipated Adverse Device Effect (UADE): An adverse device effect which by its nature, incidence, severity or outcome has not been identified in the risk analysis report.

7.7. Anticipated Adverse Device Effect (AADE)

Anticipated Adverse Device Effect (AADE): An effect, which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

7.8. Reporting of Adverse Events (AEs) and Serious Adverse Events (SAEs)

Documentation of all AEs / SAEs: All incidents will be captured as a part of this clinical study. At each contact with the subject, the Investigator will seek information on adverse events by specific questioning and, as appropriate, by examination. Information on all adverse events will be recorded immediately on the Adverse Event Form in the data collection system. All clearly related signs, symptoms, and abnormal diagnostic procedures results should be recorded. .

Reporting of SAEs: All SAEs, UADEs and possible device and / or procedure- related adverse events must be recorded in the Adverse Event Form in the data collection system by the Investigator (or his / her designee) and reported to the Sponsor and its designated representative (MAXIS Medical GmbH) within 24 hours via fax or email. The report should include: Description of incident, severity, duration, action taken, treatment outcome and relationship of the adverse event to the study device, procedure, concomitant medications, pre-existing condition, etc. (i.e., unrelated, relation or relationship unknown).

In the case of serious adverse events (SAE), procedure and / or device failures and malfunctions, medical record documentation (e.g., procedure notes, operative notes, discharge summary, relevant progress notes, imaging or lab studies) must be provided to the Sponsor and its designated representative, if requested .This information shall be faxed or sent by email as requested as soon as possible but latest within 24 hours to the MAXIS Medical / Sponsor. If appropriate, Sponsor shall inform the Competent Authority and the relevant Ethics Committee about the event within the appropriate timelines and in accordance with all national regulations. Reporting of Device Failures and Malfunctions

All reported device malfunctions or failures of the baroloop System are required to be documented and must be immediately reported to the study Sponsor or its designated representative (MAXIS Medical GmbH) by telephone, fax and / or email within 24 hours. Device failures and malfunctions should also be documented in the subject's medical record. Instructions for returning the investigational device will be provided.

NOTE: Device failures or malfunctions are NOT to be reported as adverse events. However, if there is an adverse event that results from a device failure or malfunction, that specific event would be recorded in the usual way as per the previous chapter.

7.9. Documentation, Evaluation and Notification of Serious Adverse Events

The Investigator shall report all serious adverse events (anticipated or unanticipated) to Sponsor and Sponsor's designated representative within 24 hours upon becoming aware of events.

Authorized Representative / CRO Contact Information:

MAXIS Medical GmbH
Stichlingstrasse 1
60327 Frankfurt am Main
Germany
Tel: +49 69 2400 3626
Fax: +49 69 2400 3627
Email: maxisoperations@maxismedical.com

Sponsor:

neuroloop GmbH
Breisacher Straße 86
79110 Freiburg im Breisgau
Tel: + 49 151 7305 5089
Email: study@neuroloop.de

The Sponsor and / or its designated representative will ensure compliance with all country-specific reporting requirements to the appropriate Ethics Committees and Competent Authorities.

8. Monitoring

The Sponsor or its designated representative, qualified by training and experience, will be responsible for monitoring and overseeing the conduct of the trial. The accuracy of all collected data will be verified for:

- Eligibility criteria
- Baseline characteristics
- Primary safety and feasibility endpoints
- Adverse events
- Secondary endpoints.

Source documents including, but not limited to, medical records, office / clinic notes, procedure reports, laboratory results, physician and nursing progress notes will be verified. Verification

and quality of data, monitoring of clinical study progress and Investigator compliance with the approved protocol will be conducted by the Sponsor or its designated representative (MAXIS Medical GmbH).

The Sponsor or its designated representative (MAXIS Medical GmbH) must be allowed to visit the clinical site and have direct access to all study records throughout the duration of the study. The monitor will review all source data and compare them to the data documented in the case report forms, in addition to performing a review of the Regulatory Binder and conducting device accountability. The Investigator and / or institution will provide direct access to source data / documents for trial-related monitoring, audits, and regulatory review and inspection.

It is important that the Investigator and relevant study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

Additionally, telephone, email contact, and onsite visits will be conducted on a regular basis with the Investigator and the site staff to ensure that the protocol is being followed and to address any issues that may occur during the trial.

If a deficiency is noted during the course of the trial the clinical monitor is required to discuss the situation with the site and the Sponsor (if required) to secure compliance.

9. Study Management

The Sponsor has overall responsibility for the conduct of the study according to EN ISO 14155 as well as any conditions imposed by local and national regulatory authorities.

For this study, Sponsor will have direct responsibilities and will delegate other responsibilities to appropriate and qualified consultants, contractors and / or Contract Research Organizations (CROs). Together, the Sponsor, consultants and CROs will ensure that the study is conducted according to the Clinical Investigational Plan and all applicable and governing regulations. All personnel to participate in the conduct of this clinical trial will be qualified by education and / or experience to perform their tasks.

9.1. Key Contributors

9.1.1. Study Sponsor

neuroloop GmbH
Breisacher Straße 86
79110 Freiburg im Breisgau
Germany
Tel: +49 761 1543390
Fax: +49 151 7305 5089
Email: study@neuroloop.de

9.1.2. Authorized CRO / Representative

MAXIS Medical GmbH
Stichlingstrasse 1
D-60327 Frankfurt am Main
Tel.: +49 69 2400 3626
Fax: +49 69 2400 3627
Email: maxisoperations@maxismedical.com

9.1.3. Clinical Sites

A complete listing of all clinical sites will be maintained by the Sponsor and will be available upon request.

9.2. Ethical Considerations

The rights, safety and well-being of clinical investigation subjects shall be protected consistent with the ethical principles as defined in the Declaration of Helsinki 2013. These principles shall prevail over interests of science and society and shall be understood, observed and applied at every step in this clinical investigation.

It is expected that all parties will share in the responsibility for ethical conduct in accordance with their respective roles in the investigation. The Sponsor and the Investigator(s) shall avoid improper influence or inducement of the subject, monitor, the clinical investigator(s) or other parties participating in or contributing to the clinical investigation.

9.3. Insurance

The Sponsor will maintain the appropriate and necessary insurance coverage for the duration of the study.

9.4. Study Conduct

This study will be performed in accordance with EN ISO 14155:2018-08 Clinical investigation of medical devices for human subjects, -, the Declaration of Helsinki 2013, Council Directive 93/42/EEC, and any applicable regional and / or national regulations. The clinical investigation shall not begin until the required approval has been obtained from the relevant national regulatory authority and the local Ethics Committee. Any additional requirements imposed by the regulatory authority or EC shall be followed.

9.5. Audits and Inspections

The Principal Investigator will also allow and support representatives of the governing EC, the Competent Authority, and other applicable regulatory agencies to inspect all study records, the content of the data collection system, and corresponding portions of the subject's office and / or hospital medical records at regular intervals throughout the trial. The Principal Investigator will provide direct access to source data / documents. These inspections are for the purpose of verifying adherence to the protocol, completeness and exactness of the data and compliance with European Union or other regulatory agency regulations.

The Principal Investigator will inform the Sponsor or the Sponsor's designee should they be inspected by any regulatory agencies. The Sponsor or the Sponsor's designee will also inform the site if they are made aware of a pending inspection by a regulatory agency.

Audits may also be conducted by the Sponsor or the Sponsor's designee to evaluate compliance with the protocol, written procedures, EN ISO 14155:2018-08, and other applicable regulatory requirements. These audits are independent of and separate from routine monitoring visits. The audit results will be documented and communicated to relevant parties, if applicable.

9.6. Sponsor Responsibilities

Sponsor has the overall responsibility of the study and will:

- Select qualified Principal Investigators, clinical investigators and study sites
- Select qualified monitors
- Provide the Investigational Plan and any subsequent amendments
- Provide appropriate information and baroloop System training to Investigators and study site staff
- Ensure that all deviations from the Investigational Plan are reviewed with the appropriate Investigator(s) and reported in the data collection system and the final report and that any necessary preventative or corrective action is taken
- Ensure that all adverse events and all adverse device effects (ADEs) are reported and reviewed with the Investigator(s), and where appropriate, that all serious adverse events (SAEs) and all serious adverse device effects (SADEs) are appropriately reported
- During the course of the investigation, inform in writing all Investigators about adverse events and adverse device effects that have been reported to Sponsor (this information shall be sent to each Investigator based on perceived risk)
- Promptly inform the Investigators and where applicable, any regulatory authorities, if the study is prematurely terminated or suspended and the reason for the termination or suspension
- Ensure proper device usage, uniform data collection and protocol compliance
- Provide protocol initiation training to include review of the baroloop system instructions for use, the Investigational Plan, entry of complete data into the data collection system, and guidelines for obtaining informed consent
- Provide the baroloop System to participating study sites, in quantities to support study activities
- Coordinate ongoing communication with CRO(s), consultants and study sites to resolve any problems concerning the protocol or data collection
- Every effort will be made to ensure compliance with the protocol
- Retain ownership of all clinical data generated in this study, and control the use of the data for purposes of regulatory submissions to CAs
- Protect subject confidentiality

A description of this clinical study will be made available on http://clinicaltrials.gov.

9.7. Monitor Responsibilities

The Sponsor has contracted MAXIS Medical as the Clinical Monitor to support the Sponsor in implementing and monitoring the clinical investigation until its termination. Clinical monitors, qualified by training and experience, will be responsible for monitoring and overseeing the conduct of the trial.

Clinical monitors will conduct site initiation visits at each investigational site to ensure that the Principal Investigator and other investigational site personnel involved in the conduct of this investigation have received and understood the requirements and contents of the clinical investigational protocol, the Investigators Brochure, the patient informed consent form, the data collection system, the Instructions for Use and the institution and / or Investigator agreement.

Clinical monitors will ensure that the site facilities are adequate for the conduct of this investigation and that resources, laboratories, equipment and personnel remain adequate throughout the investigation.

The clinical monitors will conduct routine on-site monitoring visits and phone calls to evaluate compliance with the protocol, any specific recommendations made by the site's Ethics Committee (EC) and the signed Institution and/or Investigator Agreement and to ensure that the protocol is being followed and that any protocol deviations are properly documented on respective form. Clinical monitoring will include a verification that Informed Consent Form was properly obtained for all enrolled trial participants, a review of clinical records for accuracy and completeness, resolution of missing or inconsistent results and a review of source documents.

Clinical monitoring will include a review of all adverse events and device malfunctions to ensure that all information has been reported to the sponsor, EC and regulatory authorities as required by this investigational plan and applicable standards and laws.

The clinical monitor will verify that the information in the data collection system is complete and in agreement with the source documentation and other records. The clinical monitor will ensure that data has been entered into the data collection system and is signed and dated by the investigator.

The Investigator will make available to the clinical monitor for review all Informed Consent documents, all completed information in the data collection system, source documentation and other relevant records for all enrolled subjects at the site. It is important that the Investigator and other relevant site personnel are available for consultation with the clinical monitors during the monitoring visits and that sufficient time is devoted at the site for the monitoring process.

If a deficiency is noted during an on-site visit or at any other time during the course of the trial, the clinical monitor is required to discuss the situation with the Investigator and the Sponsor, and to subsequently monitor the implementation of corrective actions that are required to address the situation.

All monitoring activities will be documented by the clinical monitor and will include, at a minimum, the date, investigational site visited, names of all personnel involved in the visit, a listing of all documents reviewed and a summary of all findings, facts, deviations conclusions and recommended actions to be taken. Key findings will be reviewed with the clinical investigator.

Upon completion of the study, a study close out visit will be conducted to ensure that all data collection and study requirements are complete.

9.8. Investigator Responsibilities

At a minimum, the following documents will be provided by the investigational site to the Sponsor prior to study start (consent of the first subject):

- Signed Clinical Trial Agreements
- Signed Financial Disclosure Form
- Signed Clinical Investigational Plan Signature Page
- Relevant regulatory approvals
- Investigator and Co-Investigator's current Curriculum Vitae
- Any other additional documents as required by the Sponsor

The Investigator is responsible for ensuring that the investigation is conducted according to all signed agreements, the study protocol, governing regulations, data protection regulations, the Declaration of Helsinki and any other conditions imposed by the relevant regulatory authorities. The Investigator is responsible for maintaining medical and study records for every subject participating in the clinical study (including information maintained electronically such as digital imaging). The Investigator will also maintain original source documents from which study-related data are derived.

The Investigator(s) shall be responsible for the day to day conduct of the investigation as well as for the safety and well-being of the human subjects involved in the clinical investigation.

The Investigator(s) shall:

- Have the resources to conduct the investigation properly
- Ensure that conducting the investigation will not give rise to a conflict of interest
- Obtain from the Sponsor the information which the Investigator(s) judges essential about the device and be familiar with this information
- Be well acquainted with the Clinical Investigation Protocol (CIP) before signing the signature page
- Support the monitor, auditor, if applicable, in their activities to verify compliance with the CIP, to perform source data verification and to correct the information in the data collection system where inconsistencies or missing values are identified
- Discuss with the Sponsor management any question of modification of the CIP
- Make sure that the CIP is followed by all responsible for the conduct of the study at his / her institution. Any deviation shall be documented and reported to the study Sponsor
- Make the necessary arrangements to ensure the proper conduct and completion of the investigation
- Make the necessary arrangements for emergency treatment, as needed, to protect the health and welfare of the subject
- Ensure that appropriate regulatory approval is obtained prior to the start of the investigation
- Provide regulatory approvals to the Sponsor
- Inform Sponsor about adverse events in a timely manner
- Endeavor to ensure an adequate recruitment of subjects
- Ensure that the subject has adequate information to give informed consent
- Ensure that informed consent is obtained and documented
- Ensure that clinical records are clearly marked to indicate that the subject is enrolled in this study
- Provide subjects with well-defined procedures for any emergency situation and safeguard the subject's interest. Under these circumstances, deviations from the CIP shall not require the prior approval of the Sponsor or the national and local regulatory authorities. Such deviations shall not be considered as a breach of agreement but shall be documented and reported to Sponsor
- Ensure that information which becomes available as a result of the clinical investigation which may be of importance to the health of a subject and the continuation of the

investigation shall be made known to the Sponsor and, if pertinent to the safety or well-being of the subject, and the private clinician

- Inform the subject and / or the subject's physician about any premature termination or suspension of the investigation with a rationale for study termination
- Have primary responsibility for the accuracy, legibility and security of all investigation data, documents and subject records both during and after the investigation
- Sign each subject's data in the data collection system, as applicable
- Be responsible for the supervision and assignment of duties at his / her clinical center
- Ensure that all investigational devices are kept in a secure location and that all Systems are accounted for (number of devices used, discarded and returned to Sponsor)

9.9. Study Funding

This clinical investigation is fully funded by the Sponsor. The Sponsor will enter into clinical research / clinical trial agreements with all clinical sites participating in the study. Comparable research agreements will be executed with core laboratories or other contributors in this clinical investigation, if applicable.

9.10. Investigator Training

The baroloop System is intended for use by experienced physicians. A limited number of Investigators at each site will be authorized to use the study device. These Investigators will be trained by Sponsor personnel (or designated representative) in a didactic session using a 'briefing checklist' to make sure that all user-related, risk mitigations for the baroloop System are fully understood by each investigator.

9.11. Medical Monitor

A Medical Monitor will be responsible for overseeing the overall progress of the protocol. The Medical monitor will review patient recruitment, any Serious Adverse Events, any Unanticipated Adverse Events, and non-compliance with the protocol at individual centers. All Serious Adverse Events will be reviewed and adjudicated by the Medical Monitor.

9.12. Data Management

Investigators are responsible for the accurate completion and timely submission of the data collected during the trial. All data from the trial will be entered into a data collection system. Incoming data will be frequently reviewed to identify inconsistent or missing data and any adverse events. Any data issues are to be promptly addressed with the Investigator by the CRO (MAXIS Medical). By quality assurance procedures it is ensured that complete, accurate and timely data are submitted; that protocol requirements are followed; and that complications, adverse events and adverse device effects are correctly reported and investigated, as appropriate.

9.13. Study Suspension or Early Termination

The study will be terminated early if the DSMB determines at any time during the study that the composite MAE rate is unacceptably high. Furthermore, the study will be terminated early if the number of failures to implant the devices exceeds 4 (four) failures.

The study can be discontinued at the discretion of the Investigator or study Sponsor for reasons including, but not limited to, the following:

- Occurrence of adverse events unknown to date in respect to their nature, severity, or duration, or the unexpected incidence of known adverse events
- Obtaining new scientific knowledge that shows that the study is no longer valid or necessary
- Insufficient recruitment of subjects
- Unanticipated adverse device effect (UADE) presenting an unreasonable risk to subjects (Sponsor may terminate the study immediately)
- Persistent non-compliance with the protocol
- Persistent non-compliance with regulatory requirements

If the study is discontinued or suspended prematurely, the Sponsor shall promptly inform all clinical investigator(s) / investigational center(s) of the termination or suspension and the reason(s) for this. The national and local regulatory authorities shall also be informed promptly and provided with the reason(s) for the termination or suspension by the Sponsor or by the clinical Investigator / investigation center(s).

9.14. Criteria for Suspending / Terminating a Study Center

Sponsor reserves the right to stop the screening of subjects at a study center at any time after the study initiation visit if no subjects have been enrolled or if the center has multiple or severe protocol violations without justification or fails to follow remedial actions.

Possible reasons for suspending / terminating a study center include, but are not limited to:

- Repeated failure to complete case report forms prior to scheduled monitoring visits;
- Failure to obtain written Informed Consent;
- Failure to report SAEs / UADEs to Sponsor within 24 hours of knowledge;
- Loss of (or unaccounted for) investigational product inventory.

9.15. Final Report

A Final Report will be prepared even if the study is prematurely terminated. The Final Report will be submitted to each participating Investigator, and regulatory agencies, as required.

9.16. Protocol Deviations

A protocol deviation is defined as an event where the Investigator or site personnel did not conduct the study according to the protocol.

Investigators shall be required to obtain prior approval from Sponsor or its designated representative before knowingly deviating from the protocol, except where necessary to protect the life or physical well-being of a subject in an emergency. Such approval shall be documented in writing and maintained in clinical study management and Investigator files. Prior approval is generally not expected in situations where unforeseen circumstances are beyond the Investigator's control, (e.g., subject was not available for scheduled follow-up office visit, blood sample lost by laboratory, etc.); however, the event is still considered a deviation and will be reported in the data collection system.

Deviations must be reported to Sponsor or designated representative regardless of whether medically justifiable, pre- approved by Sponsor or designated representative, or taken to protect the subject in an emergency. Subject specific deviations will be reported on the Protocol

Deviation case report form. Non-subject specific deviations, (e.g., unauthorized use of an investigational device outside the study, unauthorized use of an investigational device by a physician who has not signed an Investigator agreement or not been trained in the use of the device, etc.), will be reported to Sponsor or designated representative. Investigators will also adhere to procedures for reporting study deviations to their Ethics Committee or Competent Authority, where required, in accordance with their specific reporting policies and procedures.

Regulations require that Investigators maintain accurate, complete and current records, including documents showing the dates of and reasons for each deviation from the protocol.

10. Regulatory Considerations

10.1. Maintaining Records

The Sponsor will maintain copies of critical correspondence, clinical data, shipment of devices, serious adverse device effects and other records related to the clinical trial.

10.2. Site Record Retention Policy

The Sponsor and clinical sites will maintain all records pertaining to this study in accordance with local and national regulations. Prior to the destruction of study records the Investigator or his representative should contact the Sponsor to ensure that they no longer need to be retained. In addition, Sponsor should be contacted if the Investigator plans to leave the investigational site so that arrangements can be made for the handling or transfer of study records.

10.3. Ethics Committee (EC) and Competent Authority (CA) Approval

Regulatory approvals must be obtained prior to enrolment of the first patient. The Sponsor or its designated representative is responsible for obtaining regulatory and local approvals for the study. The Sponsor or its designated representative will require a copy of any Ethics Committee and Competent Authority correspondence, as well as the final approval letter from the Ethics Committee and Competent Authority, where applicable. The Sponsor confirms and is aware that the Competent Authority may contact the Ethics Committee that is assessing or has assessed the application.

An Investigator may not make protocol changes without prior approval by Sponsor. All significant protocol changes that may affect the following must be submitted and approved by the Ethics Committee and Competent Authority before initiating the change:

- Validity of the data or information resulting from the completion of the approved protocol;
- Relationship of the likely subject risk to benefit relied upon to approve the protocol;
- Scientific soundness of the investigational plan;
- Rights, safety, or welfare of the human subjects involved in the investigation.

The Sponsor may make certain administrative changes to the protocol without prior approval of the relevant Ethics Committee and Competent Authority. The Sponsor will notify all investigative sites of such changes to ensure the study continues to be conducted consistently across all sites.

11. Publication Policy

The Sponsor will be responsible for publishing the results of this study in a timely manner. In all publications related to this study, credit shall be given to Sponsor for its sponsorship of the study, and appropriate recognition of the contribution made by the institutions and principal Investigators will be given, as applicable. Sponsor may use, refer to, and disseminate reprints of scientific, medical, and other published articles relating to the study, including such reprints that disclose the name of Investigators and / or the relevant institution.

A description of this clinical study will be made available on http://clinicaltrials.gov.

12. Definitions

Acute Cardiovascular Surgery

An immediate transfer from the catheterization lab to the operative room during the initial treatment phase due to the need for emergency coronary artery bypass graft surgery, cardiac valve surgery, or other vascular surgical intervention.

Allergic Reaction

An overreaction of the body's immune system to a component of an investigational device (e.g., nitinol metal, polyester, plastics), contrast agents and / or anesthesia medication given to the subject for completion of a study related procedure (e.g., MSCT, angiogram, investigational device), which requires medical intervention to treat the allergic reaction.

Acute Kidney Injury (AKI)

- Stage 1: Increase in serum creatinine to 150–199% (1.5– 1.99 × increase compared with baseline) OR increase of ≥0.3 mg / dL (≥26.4 µmol / L) OR Urine output <0.5 ml / kg per hour for >6 but <12 hours
- Stage 2: Increase in serum creatinine to 200–299% (2.0– 2.99 × increase compared with baseline) OR Urine output <0.5 ml / kg per hour for >12 but <24 hours
- Stage 3: Increase in serum creatinine to ≥300% (>3 × increase compared with baseline) OR serum creatinine of ≥4.0 mg / dL (≥354 mmol / L) with an acute increase of at least 0.5 mg / dL (44 mmol / L) OR Urine output <0.3 ml / kg per hour for ≥24 hours OR Anuria for ≥12 hours [Subjects receiving renal replacement therapy are considered to meet Stage 3 criteria irrespective of other criteria]

AV Block

Atrioventricular block is a type of heart block in which the conduction between the atria and ventricles of the heart is impaired.

Blood Loss

- Major Blood Loss – Defined as transfusion of >2 units packed red blood cells (PRBC)).
- Estimated Procedural Blood Loss – Defined as the total estimated blood loss (mL) during the index procedure. Includes blood loss resulting from adjunctive procedures performed during the index-procedure.

Bleeding

- Life-threatening or disabling bleeding:
  - Fatal bleeding (BARC type 5) OR
  - Bleeding in a critical organ, such as intracranial, intraspinal, intraocular, or pericardial necessitating pericardiocentesis, or intramuscular with compartment syndrome (BARC type 3b and 3c) OR
  - Bleeding causing hypovolemic shock or severe hypotension requiring vasopressors or surgery (BARC type 3b) OR
  - Overt source of bleeding with drop in hemoglobin of ≥5 g / dL or whole blood or packed red blood cells (RBCs) transfusion ≥4 units* (BARC type 3b)
  - Given one unit of packed RBC typically will raise blood hemoglobin concentration by 1 g / dL, an estimated decrease in hemoglobin will be calculated; BARC: Bleeding Academic Research Consortium.

- Major bleeding:
  - Overt bleeding either associated with a drop in the hemoglobin level of at least 3.0 g / dL or requiring transfusion of 2 or 3 units of whole blood / RBC, of causing hospitalization or permanent injury, or requiring surgery AND
  - Does not meet criteria of life-threatening or disabling bleeding.
- Minor bleeding:
  - Any bleeding worthy of clinical mention (e.g. access site hematoma) that does not qualify as life-threatening, disabling or major.

Cerebral Infarction

Evidence of brain cell death from imaging studies or pathological examination. If there are clinical symptoms, then it is a stroke; otherwise, it is an asymptomatic cerebral infarction.

Death

Death is divided into two categories and will be reported anytime in a subject's study participation:

- Device or procedure related death - Death related to the Study Device or to any procedure (index or subsequent) intended to treat the target.
- Non-device or procedure related death – Death NOT related to any procedure (index or subsequent) intended to treat the target or death not related to the Study Device.

Device Deficiency

Inadequacy of the Study Device with respect to its identity, quality, durability, reliability, safety or performance. Device deficiencies include malfunctions, use errors, and inadequate labeling.

Explant

Removal of the study device implant for any reason.

Major Adverse Cardiovascular and Cerebrovascular Event (MACCE)

MACCE is defined as:

- All-cause mortality
- All strokes (major, minor and TIA)
- Acute kidney injury – Stage 3 (including renal replacement therapy)

Myocardial Infarction (MI)

Peri-procedural MI (≤72 h after the index procedure):

- New ischemic symptoms (e.g. chest pain or shortness of breath), or new ischemic signs (e.g. ventricular arrhythmias, new or worsening heart failure, new ST-segment changes, hemodynamic instability, new pathological Q waves in at least two contiguous leads, imaging evidence of new loss of viable myocardium or new wall motion abnormality),
- Elevated cardiac biomarkers (preferably CK-MB) within 72 h after the index procedure, consisting of at least one sample post-procedure with a peak value exceeding 15x upper reference limit (troponin) or 5x for CK-MB. If cardiac biomarkers are increased at baseline (> 99th percentile), a further increase of at least 50% post-procedure is required AND the peak value must exceed the previously stated limit.

Spontaneous MI (>72 h after the index procedure):

Any one of the following criteria:

- Detection of rise and / or fall of cardiac biomarkers (preferably troponin) with at least one value above the 99th percentile URL, together with evidence of myocardial ischemia with at least one of the following:
  - Symptoms of ischemia
  - ECG changes indicative of new ischemia [new ST-T changes or new left bundle branch block [LBBB]
  - New pathological Q waves in at least two contiguous leads
  - Imaging evidence of new loss of viable myocardium or new wall motion abnormality
- Sudden, unexpected cardiac death, involving cardiac arrest, often with symptoms suggestive of myocardial ischemia, and accompanied by presumably new ST elevation, or new LBBB, and / or evidence of fresh thrombus by coronary angiography and / or at autopsy, but death occurring before blood samples could be obtained, or at a time before the appearance of cardiac biomarkers in the blood.
- Pathological findings of an acute myocardial infarction.

Post-Procedure Intensive Care Unit Time

Number of hours a patient is in an intensive care unit prior to discharge or moving to a step down or standard care unit.

Post-Procedure Length of Hospital Stay

Number of days from the end of the procedure until the patient is discharged from the hospital. This does not include time spent in a skilled care facility.

Procedural Success

Successful delivery of the investigational baroloop System placed around a vagal nerve providing effective stimulation at 14 days post-implantation.

Procedure Time

Number of minutes needed to perform the index procedure from time of initial skin incision to time of final skin closure and final intra-operative device testing.

Renal Failure

Need for dialysis or a laboratory finding of serum creatinine > 3.5 mg / dL.

Respiratory Failure

The need for mechanical ventilation beyond the first 24 hours post-index procedure (and / or reintervention) or the need for re-intubation or ventilator support after the first 24 hours (unless the subject was ventilator dependent pre-procedure).

Stroke Diagnostic Criteria:

- Acute episode of a focal or global neurological deficit with at least one of the following: Change in level of consciousness, hemiplegia, hemiparesis, numbness or sensory loss affecting one side of the body, dysphasia or aphasia, hemianopia, amaurosis fugax, or other neurological signs or symptoms consistent with stroke

- Stroke - Duration of a focal or global neurological deficit ≥24 h; OR, <24 h, if available neuroimaging documents a new hemorrhage or infarct; OR the neurological deficit results in death
- TIA – Duration of a focal or global neurological deficit < 24 h, any variable neuroimaging does not demonstrate a new hemorrhage or infarct
- No other readily identifiable non-stroke cause for the clinical presentation (e.g. brain tumor, trauma, infection, hypoglycemia, peripheral lesion, pharmacological influences), to be determined by or in conjunction with designated neurologist
- Confirmation of the diagnosis by at least one of the following:
    - Neurologist or neurosurgical specialist
    - Neuroimaging procedure (CT scan or brain MRI), but stroke may be diagnosed on clinical grounds alone
    -
- Ischemic Stroke:
    - An acute symptomatic episode of focal cerebral, spinal, or retinal dysfunction caused by an infarction of central nervous system tissue.
- Hemorrhagic Stroke:
    - An acute symptomatic episode of focal or global cerebral or spinal dysfunction caused by an intraparenchymal, intraventricular, or subarachnoid hemorrhage.

(A stroke may be classified as undetermined if there is insufficient information to allow categorization as ischemic or hemorrhagic)

Transient Ischemic Attack (TIA)

A transient (<24 hours) episode of neurological dysfunction caused by focal brain, spinal cord, or retinal ischemia, without acute infarction. No evidence of infarction if imaging performed.

Surgical Access Site and Access-related Complications

- Major Surgical Complications:
    - Access site or access-related injury (bleeding, hematoma, irreversible nerve injury, or vascular injury) leading to either death, need for significant blood transfusions (≥4 U), unplanned percutaneous or surgical intervention, or irreversible end-organ damage
- Minor Surgical Complications:
    - Access site injury (bleeding or hematomas requiring transfusion of ≥2 but not more than 4 U) not requiring unplanned percutaneous or surgical intervention and not resulting in irreversible end-organ damage

13. Acronyms

AADE	Anticipated adverse device effect
ABPM	Ambulatory blood pressure monitoring
ACC	American College of Cardiology
ACE	Angiotensin converting enzyme
ADN	Aortic depressor nerve
AE	Adverse Event
AHA	American Heart Association
AHI	Apnea hypopnea index
AKI	Acute kidney injury
AMI	Acute myocardial infarction
ASADE	Anticipated serious adverse device effect
ARB	Angiotensin receptor blocker
ASA	Acetylsalicylic acid
AV	Atrioventricular
BARC	Bleeding academic research consortium
BAT	Baroreflex activation therapy
BMI	Body mass index
CA	Competent Authority
CCB	Calcium channel blocker
CE	Conformité Européene
CEA	Carotid endarterectomy
CEC	Clinical Events Committee
CIP	Clinical Investigation Protocol
CK	Creatine kinase
CK-MB	Creatine kinase-MB fraction

CPAP	Continuous positive airway pressure
CRO	Contract Research Organization
CT	Computed tomography
CVA	Cerebrovascular accident
DBP	Diastolic blood pressure
DBS	Deep brain stimulation
DSMB	Data Safety Management Board
EACTS	European Association for Cardio-Thoracic Surgery
EC	Ethics Committee
ECG	Electrocardiogram
ECoG	Electrocorticogram
EDC	Electronic Data Capture
EDS	Electronic Data System
eGFR	Estimated Glomerular Filtration Rate
ESC	European Society of Cardiology
ESH	European Society of Hypertension
EU	European Union
F	Frequency
GDPR	General Data Protection Regulation
FIH	First in Human
GCP	Good Clinical Practices
HGB	Hemoglobin
HTN	Hypertension
IFU	Instructions for Use
IPG	Impulse generator
ITT	Intention to treat

IV	Intravenous
MACCE	Major Adverse Cardiac and Cerebrovascular Events
MAE	Major adverse event
MDD	Medical Device Directive
MDR	Medical Device Regulation
MI	Myocardial Infarction
MRI	Magnetic resonance imaging
MSCT	Multi-Slice Computed Tomography
NIHSS	National Institutes of Health Stroke Scale
NYHA	New York Heart Association
OBP	Office blood pressure
PCI	Percutaneous coronary intervention
PHI	Protected health information
PRBC	Packed red blood cells
PW	Pulse width
RBC	Red blood cells
RCT	Randomized controlled trial
SADE	Serious adverse device effect
SAE	Serious Adverse Event
SBP	Systolic blood pressure
TIA	Transient ischemic attack
UADE	Unanticipated adverse device effect
USADE	Unanticipated serious adverse device effect
USB	Universal serial bus
VARC	Valve Academic Research Consortium
VNS	Vagal nerve stimulation

WHO	World Health Organization

14. Bibliography

Abegaz, T.M., Shehab, A., Gebreyohannes, E.A., Bhagavathula, A.S., Elnour, A.A., 2017. Nonadherence to antihypertensive drugs: A systematic review and meta-analysis. Medicine (Baltimore) 96, e5641.

Ai, J., Wurster, R.D., Harden, S.W., Cheng, Z.J., 2009. Vagal afferent innervation and remodeling in the aortic arch of young-adult fischer 344 rats following chronic intermittent hypoxia. Neuroscience 164, 658-666.

Bang, S.K., Ryu, Y., Chang, S., Im, C.K., Bae, J.H., Gwak, Y.S., Yang, C.H., Kim, H.Y., 2018. Attenuation of hypertension by C-fiber stimulation of the human median nerve and the concept-based novel device. Scientific reports 8, 14967.

Benarroch, E.E., 2008. The arterial baroreflex: functional organization and involvement in neurologic disease. Neurology 71, 1733-1738.

Berthoud, H.R., Neuhuber, W.L., 2000. Functional and chemical anatomy of the afferent vagal system. Auton Neurosci 85, 1-17.

Bilgutay, A.M., Lillehei, C.W., 1966. Surgical treatment of hypertension with reference to baropacing. The American journal of cardiology 17, 663-667.

Bisognano, J.D., Bakris, G., Nadim, M.K., Sanchez, L., Kroon, A.A., Schafer, J., de Leeuw, P.W., Sica, D.A., 2011. Baroreflex activation therapy lowers blood pressure in patients with resistant hypertension: results from the double-blind, randomized, placebo-controlled rheos pivotal trial. Journal of the American College of Cardiology 58, 765-773.

Braunwald, E., Epstein, S.E., Glick, G., Wechsler, A.S., Braunwald, N.S., 1967. Relief of angina pectoris by electrical stimulation of the carotid-sinus nerves. The New England journal of medicine 277, 1278-1283.

Brinker, S., Pandey, A., Ayers, C., Price, A., Raheja, P., Arbique, D., Das, S.R., Halm, E.A., Kaplan, N.M., Vongpatanasin, W., 2014. Therapeutic drug monitoring facilitates blood pressure control in resistant hypertension. Journal of the American College of Cardiology 63, 834-835.

Calhoun, D.A., Jones, D., Textor, S., Goff, D.C., Murphy, T.P., Toto, R.D., White, A., Cushman, W.C., White, W., Sica, D., Ferdinand, K., Giles, T.D., Falkner, B., Carey, R.M., 2008. Resistant hypertension: diagnosis, evaluation, and treatment. A scientific statement from the American Heart Association Professional Education Committee of the Council for High Blood Pressure Research. Hypertension 51, 1403-1419.

Chobanian, A.V., Bakris, G.L., Black, H.R., Cushman, W.C., Green, L.A., Izzo, J.L., Jr., Jones, D.W., Materson, B.J., Oparil, S., Wright, J.T., Jr., Roccella, E.J., 2003. The Seventh Report of the Joint National Committee on Prevention, Detection, Evaluation, and Treatment of High Blood Pressure: the JNC 7 report. Jama 289, 2560-2572.

Cogan, S.F., 2008. Neural stimulation and recording electrodes. Annual review of biomedical engineering 10, 275-309.

Collaboration, N.C.D.R.F., 2017. Worldwide trends in blood pressure from 1975 to 2015: a pooled analysis of 1479 population-based measurement studies with 19.1 million participants. Lancet 389, 37-55.

Daugherty, S.L., Powers, J.D., Magid, D.J., Masoudi, F.A., Margolis, K.L., O'Connor, P.J., Schmittdiel, J.A., Ho, P.M., 2012. The association between medication adherence and treatment intensification with blood pressure control in resistant hypertension. Hypertension 60, 303-309.

De Paula, P.M., Castania, J.A., Bonagamba, L.G., Salgado, H.C., Machado, B.H., 1999. Hemodynamic responses to electrical stimulation of the aortic depressor nerve in awake rats. The American journal of physiology 277, R31-38.

Devireddy, C.M., Bates, M.C., 2014. Experience with an innovative new Food and Drug Administration pathway for first-in-human studies: carotid baroreceptor amplification for resistant hypertension. JACC. Cardiovascular interventions 7, 1328-1330.

Egan, B.M., 2015. Treatment Resistant Hypertension. Ethn Dis 25, 495-498.

Epstein, S.E., Beiser, G.D., Goldstein, R.E., Stampfer, M., Wechsler, A.S., Glick, G., Braunwald, E., 1969. Circulatory effects of electrical stimulation of the carotid sinus nerves in man. Circulation 40, 269-276.

Fan, W., Andresen, M.C., 1998. Differential frequency-dependent reflex integration of myelinated and nonmyelinated rat aortic baroreceptors. The American journal of physiology 275, H632-640.

Gao, X.Y., Wang, H.J., Zhang, Y., Lu, Z.H., Wang, W., Zhu, G.Q., 2006. Resetting blood pressure by a closed-loop implanted chip system in normotensive rats. Life sciences 78, 1129-1134.

Garcia-Navarrete, E., Torres, C.V., Gallego, I., Navas, M., Pastor, J., Sola, R.G., 2013. Long-term results of vagal nerve stimulation for adults with medication-resistant epilepsy who have been on unchanged antiepileptic medication. Seizure 22, 9-13.

Gaziano, T.A., Bitton, A., Anand, S., Weinstein, M.C., International Society of, H., 2009. The global cost of nonoptimal blood pressure. Journal of hypertension 27, 1472-1477.

Gierthmuehlen, M., Stieglitz, T., Zentner, J., Plachta, D.T., 2016. Haemodynamic Responses to Selective Vagal Nerve Stimulation under Enalapril Medication in Rats. PloS one 11, e0147045.

Giordano, F., Zicca, A., Barba, C., Guerrini, R., Genitori, L., 2017. Vagus nerve stimulation: Surgical technique of implantation and revision and related morbidity. Epilepsia 58 Suppl 1, 85-90.

Go, A.S., Mozaffarian, D., Roger, V.L., Benjamin, E.J., Berry, J.D., Blaha, M.J., Dai, S., Ford, E.S., Fox, C.S., Franco, S., Fullerton, H.J., Gillespie, C., Hailpern, S.M., Heit, J.A., Howard, V.J., Huffman, M.D., Judd, S.E., Kissela, B.M., Kittner, S.J., Lackland, D.T., Lichtman, J.H., Lisabeth, L.D., Mackey, R.H., Magid, D.J., Marcus, G.M., Marelli, A., Matchar, D.B., McGuire, D.K., Mohler, E.R., 3rd, Moy, C.S., Mussolino, M.E., Neumar, R.W., Nichol, G., Pandey, D.K., Paynter, N.P., Reeves, M.J., Sorlie, P.D., Stein, J., Towfighi, A., Turan, T.N., Virani, S.S., Wong, N.D., Woo, D., Turner, M.B., American Heart Association Statistics, C., Stroke Statistics, S., 2014. Heart disease and stroke statistics--2014 update: a report from the American Heart Association. Circulation 129, e28-e292.

Go, A.S., Mozaffarian, D., Roger, V.L., Benjamin, E.J., Berry, J.D., Borden, W.B., Bravata, D.M., Dai, S., Ford, E.S., Fox, C.S., Franco, S., Fullerton, H.J., Gillespie, C., Hailpern, S.M.,

Heit, J.A., Howard, V.J., Huffman, M.D., Kissela, B.M., Kittner, S.J., Lackland, D.T., Lichtman, J.H., Lisabeth, L.D., Magid, D., Marcus, G.M., Marelli, A., Matchar, D.B., McGuire, D.K., Mohler, E.R., Moy, C.S., Mussolino, M.E., Nichol, G., Paynter, N.P., Schreiner, P.J., Sorlie, P.D., Stein, J., Turan, T.N., Virani, S.S., Wong, N.D., Woo, D., Turner, M.B., 2013. Heart disease and stroke statistics--2013 update: a report from the American Heart Association. Circulation 127, e6-e245.

Gold, M.R., Van Veldhuisen, D.J., Hauptman, P.J., Borggrefe, M., Kubo, S.H., Lieberman, R.A., Milasinovic, G., Berman, B.J., Djordjevic, S., Neelagaru, S., Schwartz, P.J., Starling, R.C., Mann, D.L., 2016. Vagus Nerve Stimulation for the Treatment of Heart Failure: The INOVATE-HF Trial. Journal of the American College of Cardiology 68, 149-158.

Green, A.L., Wang, S., Bittar, R.G., Owen, S.L., Paterson, D.J., Stein, J.F., Bain, P.G., Shlugman, D., Aziz, T.Z., 2007. Deep brain stimulation: a new treatment for hypertension? Journal of clinical neuroscience : official journal of the Neurosurgical Society of Australasia 14, 592-595.

Hoppe, U.C., Brandt, M.C., Wachter, R., Beige, J., Rump, L.C., Kroon, A.A., Cates, A.W., Lovett, E.G., Haller, H., 2012. Minimally invasive system for baroreflex activation therapy chronically lowers blood pressure with pacemaker-like safety profile: results from the Barostim neo trial. Journal of the American Society of Hypertension : JASH 6, 270-276.

Irvin, M.R., Shimbo, D., Mann, D.M., Reynolds, K., Krousel-Wood, M., Limdi, N.A., Lackland, D.T., Calhoun, D.A., Oparil, S., Muntner, P., 2012. Prevalence and correlates of low medication adherence in apparent treatment-resistant hypertension. J Clin Hypertens (Greenwich) 14, 694-700.

Johnson, R.L., Wilson, C.G., 2018. A review of vagus nerve stimulation as a therapeutic intervention. J Inflamm Res 11, 203-213.

Judd, E., Calhoun, D.A., 2014. Apparent and true resistant hypertension: definition, prevalence and outcomes. Journal of human hypertension 28, 463-468.

Kahlow, H., Olivecrona, M., 2013. Complications of vagal nerve stimulation for drug-resistant epilepsy: a single center longitudinal study of 143 patients. Seizure 22, 827-833.

Kobayashi, M., Cheng, Z.B., Tanaka, K., Nosaka, S., 1999. Is the aortic depressor nerve involved in arterial chemoreflexes in rats? Journal of the autonomic nervous system 78, 38-48.
Kougias, P., Weakley, S.M., Yao, Q., Lin, P.H., Chen, C., 2010. Arterial baroreceptors in the management of systemic hypertension. Medical science monitor : international medical journal of experimental and clinical research 16, RA1-8.

Lobo, M.D., Sobotka, P.A., Pathak, A., 2017. Interventional procedures and future drug therapy for hypertension. European heart journal 38, 1101-1111.
Lohmeier, T.E., Iliescu, R., 2011. Chronic lowering of blood pressure by carotid baroreflex activation: mechanisms and potential for hypertension therapy. Hypertension 57, 880-886.

Mirkovic, T., Knezevic, I., Radan, I., Rozman, J., Gersak, B., Podbregar, M., 2012. Frequency dependent effect of selective biphasic left vagus nerve stimulation as a therapeutic intervention. Signa Vitae 7, 63-68.

Narkiewicz, K., Ratcliffe, L.E.K., Hart, E.C., Briant, L.I.B., Chrostowka, M., Wolf, J., Szyndler, A., Hering, D., Abdala, A.P., Manghat, N., Burchell, A.E., Durant, C., Lobo, M.D., Sobotka, P.A., Patel, N.K., Leiter, J.C., Engelman, Z.I., Nightingale, A.K., Paton, J.F.R., 2016. Unilateral

carotid body resection in resistant hypertension: a safety and feasibility trial. Eur. J. Hypertension submitted.

Ng, F.L., Saxena, M., Mahfoud, F., Pathak, A., Lobo, M.D., 2016. Device-based Therapy for Hypertension. Current hypertension reports 18, 61.

O'Callaghan, E.L., McBryde, F.D., Burchell, A.E., Ratcliffe, L.E., Nicolae, L., Gillbe, I., Carr, D., Hart, E.C., Nightingale, A.K., Patel, N.K., Paton, J.F., 2014. Deep brain stimulation for the treatment of resistant hypertension. Current hypertension reports 16, 493.

Panebianco, M., Zavanone, C., Dupont, S., Restivo, D.A., Pavone, A., 2016. Vagus nerve stimulation therapy in partial epilepsy: a review. Acta Neurol Belg 116, 241-248.

Patel, N.K., Javed, S., Khan, S., Papouchado, M., Malizia, A.L., Pickering, A.E., Paton, J.F., 2011. Deep brain stimulation relieves refractory hypertension. Neurology 76, 405-407.

Pimenta, E., Calhoun, D.A., 2012. Resistant hypertension: incidence, prevalence, and prognosis. Circulation 125, 1594-1596.

Plachta, D.T., Gierthmuehlen, M., Cota, O., Espinosa, N., Boeser, F., Herrera, T.C., Stieglitz, T., Zentner, J., 2014. Blood pressure control with selective vagal nerve stimulation and minimal side effects. Journal of neural engineering 11, 036011.

Plachta, D.T., Zentner, J., Aguirre, D., Cota, O., Stieglitz, T., Gierthmuehlen, M., 2016. Effect of Cardiac-Cycle-Synchronized Selective Vagal Stimulation on Heart Rate and Blood Pressure in Rats. Advances in therapy 33, 1246-1261.

Revesz, D., Rydenhag, B., Ben-Menachem, E., 2016. Complications and safety of vagus nerve stimulation: 25 years of experience at a single center. Journal of neurosurgery. Pediatrics 18, 97-104.

Selner, A.N., Rosinski, C.L., Chiu, R.G., Rosenberg, D., Chaker, A.N., Drammeh, H., Esfahani, D.R., Mehta, A.I., 2019. Vagal Nerve Stimulation for Epilepsy in Adults: A Database Risk Analysis and Review of the Literature. World neurosurgery 121, e947-e953.

Sevcencu, C., Nielsen, T.N., Struijk, J.J., 2018. An Intraneural Electrode for Bioelectronic Medicines for Treatment of Hypertension. Neuromodulation : journal of the International Neuromodulation Society 21, 777-786.

Shannon, R.V., 1992. A model of safe levels for electrical stimulation. IEEE transactions on bio-medical engineering 39, 424-426.

Spuck, S., Tronnier, V., Orosz, I., Schonweiler, R., Sepehrnia, A., Nowak, G., Sperner, J., 2010. Operative and technical complications of vagus nerve stimulator implantation. Neurosurgery 67, 489-494.

Strauch, B., Petrak, O., Zelinka, T., Rosa, J., Somloova, Z., Indra, T., Chytil, L., Maresova, V., Kurcova, I., Holaj, R., Wichterle, D., Widimsky, J., Jr., 2013. Precise assessment of noncompliance with the antihypertensive therapy in patients with resistant hypertension using toxicological serum analysis. Journal of hypertension 31, 2455-2461.

Timarova, G., Steno, A., 2017. Late-onset jaw and teeth pain mimicking trigeminal neuralgia associated with chronic vagal nerve stimulation: case series and review of the literature. BMC Neurol 17, 113.

Tosato, M., Yoshida, K., Toft, E., Nekrasas, V., Struijk, J.J., 2006. Closed-loop control of the heart rate by electrical stimulation of the vagus nerve. Med Biol Eng Comput 44, 161-169.

van Kleef, M., Bates, M.C., Spiering, W., 2018. Endovascular Baroreflex Amplification for Resistant Hypertension. Current hypertension reports 20, 46.

Van Wijk, B.L., Klungel, O.H., Heerdink, E.R., de Boer, A., 2005. Rate and determinants of 10-year persistence with antihypertensive drugs. Journal of hypertension 23, 2101-2107.

Vega, J., Bisognano, J.D., 2014. The prevalence, incidence, prognosis, and associated conditions of resistant hypertension. Seminars in nephrology 34, 247-256.

Wallbach, M., Koziolek, M.J., 2018. Baroreceptors in the carotid and hypertension-systematic review and meta-analysis of the effects of baroreflex activation therapy on blood pressure. Nephrology, dialysis, transplantation : official publication of the European Dialysis and Transplant Association - European Renal Association 33, 1485-1493.

Warner, H.R., 1958. The frequency-dependent nature of blood pressure regulation by the carotid sinus studied with an electric analog. Circulation research 6, 35-40.

Williams, B., Mancia, G., Spiering, W., Agabiti Rosei, E., Azizi, M., Burnier, M., Clement, D.L., Coca, A., de Simone, G., Dominiczak, A., Kahan, T., Mahfoud, F., Redon, J., Ruilope, L., Zanchetti, A., Kerins, M., Kjeldsen, S.E., Kreutz, R., Laurent, S., Lip, G.Y.H., McManus, R., Narkiewicz, K., Ruschitzka, F., Schmieder, R.E., Shlyakhto, E., Tsioufis, C., Aboyans, V., Desormais, I., Authors/Task Force, M., 2018. 2018 ESC/ESH Guidelines for the management of arterial hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension: The Task Force for the management of arterial hypertension of the European Society of Cardiology and the European Society of Hypertension. Journal of hypertension 36, 1953-2041.

Yiannakopoulou, E., Papadopulos, J.S., Cokkinos, D.V., Mountokalakis, T.D., 2005. Adherence to antihypertensive treatment: a critical factor for blood pressure control. Eur J Cardiovasc Prev Rehabil 12, 243-249.