The SPYRAL AFFIRM Global Clinical Study of Renal Denervation with the Symplicity Spyral Renal Denervation System in Subjects with Uncontrolled Hypertension (SPYRAL AFFIRM)

Published: 28-11-2022
Last updated: 30-01-2025

The SPYRAL AFFIRM study will evaluate the long-term safety, efficacy, and durability of the Symplicity Spyral system in a population of approximately 1300 renal denervation treated subjects with up to 36 months of follow-up,&...

Ethical review	Approved WMO
Status	Recruiting
Health condition type	Vascular hypertensive disorders
Study type	Interventional

Summary

ID

NL-OMON51861

Source
ToetsingOnline

Brief title
SPYRAL AFFIRM

Condition

- Vascular hypertensive disorders

Synonym
uncontrolled hypertension

Research involving
Human

Sponsors and support

Primary sponsor: Medtronic B.V.
Source(s) of monetary or material Support: Medtronic

Intervention

Keyword: Renal Artery, Renal Denervation, Uncontrolled Hypertension

Outcome measures

Primary outcome

The Primary endpoint of office Systolic Blood Pressure (SBP) change at 6 months will be assessed for all patients in the Main Study Cohort. In addition, comparison to a pre-specified performance goal for subjects treated in the US will be performed.

Key objectives related to RDN efficacy, safety, and durability in the full population and in multiple subgroups will be presented

Secondary outcome

Efficacy objectives will be evaluated for all Main Cohort subjects and for US subjects in the Main Cohort at each follow up visit based on subject cohort assignment. Baseline data for subjects in the Continuation Cohort will be pulled from SPYRAL PIVOTAL-SPYRAL HTN-OFF MED, and SPYRAL HTN-ON MED database and subjects will be evaluated out to 48 and 60-months post-index procedure as a secondary cohort only.

• Change in OBP from baseline at 3, 6, 12, 24, 36, 48 and 60-months post-procedure

• The primary endpoint will be compared to the pre-specified performance goal subgroups at 6 months for subjects treated in the US.:

• Change in home blood pressure (HBP) from baseline at 3, 6, 12, 24, 36 months post-procedure (Main Cohort only)

• Change in 24-hour blood pressure from baseline, including day and night independently, (ABPM Subset & Continuation Cohort) at 3, 6, 12, 24, 36, 48 and 60-months post-procedure

• Change in OBP, HBP and 24-hour blood pressure from baseline will be assessed in each of the following subgroups as applicable:

• Severe hypertension (baseline office systolic BP >=150 mmHg, despite the prescription of >=3 antihypertensive medications)

• Age >=65 years

• Chronic kidney disease (eGFR <60 mL/min/1.73m2)

• Atrial fibrillation

• Baseline atherosclerotic cardiovascular disease (ASCVD) risk score ( )

• Coronary artery disease

• Stroke

• Heart rate

• Diabetes mellitus type 2

• Heart failure with preserved ejection fraction

• Subject is unable or unwilling to take antihypertensive medications

• Number of anti-hypertensive medications and classes

• Patients on Beta-blocker therapy at baseline

• Sleep apnea

• Smoking

• Nocturnal hypertension stage I (Nighttime BP of >120/70 mmHg measured by ABPM

or nighttime home BP)

• Morning hypertension stage II (Home BP >145/90 mmHg, between 6:00 AM and 10:00 AM)

• Obese subjects (defined by BMI and/or abdominal obesity)

• Race / Ethnicity, where possible

• Sex at birth

• Percent of subjects achieving blood pressure target reductions and control of <=140 mmHg as measured by OBP, HBP and ABPM

• Time subject*s blood pressure is controlled through 36-month follow-up or study exit

• Characterization of anti-hypertensive medication burden over time

• Change from baseline in quality of life as measured by the EQ-5D instrument, and change in patients* HTN health status measures

• Evaluation of laboratory and clinical characteristics for predictors of response to renal denervation

• Characterization of procedural characteristics:

• Treatment duration

• Number of ablations per subject

• Number of ablations per kidney

* Branch vs main artery ablations

• Evaluate index procedure costs for subjects participating in the health economics portion of the study.

• Evaluation of blood pressure as measured by OBP, HBP and ABPM, adjusting for

anti-hypertensive medication burden through 36-months

Study description

Background summary

Pls see section 3.1

Pls see Sub-study of SPYRAL AFFIRM:
Streamlined denervation With spYral For an optimized Treatment (SPYRAL SWYFT) CIP addendum V2.0, 18 April 2025

Study objective

The SPYRAL AFFIRM study will evaluate the long-term safety, efficacy, and durability of the Symplicity Spyral system in a population of approximately 1300 renal denervation treated subjects with up to 36 months of follow-up, including several sub-populations. A minimum of 700 subjects will be from the US. Subsequently, these data will be used to complement data from the SPYRAL PIVOTAL-SPYRAL HTN-OFF MED trial, SPYRAL HTN-ON MED trial, as well as the Global SYMPLICITY Registry.

Additionally, in order to gather long-term follow-up data, up to 100 eligible subjects, initially randomized to the treatment arm in the SPYRAL PIVOTAL-SPYRAL HTN-OFF MED and SPYRAL HTN-ON MED studies and successfully treated via the renal denervation procedure, are eligible to be consented for continued follow up in the SPYRAL AFFIRM study at time of exit from the prior study. These subjects will attend follow up visits at 48 month and 60 month post renal denervation procedure they received during the aforementioned studies.

The SPYRAL AFFIRM SPYRAL SWYFT sub-study will further complement the data obtained in SPYRAL AFFIRM by providing additional data on the procedural approach used and its effect on procedure time and blood pressure reduction. A procedure focused on the main renal arteries and first order branches suggests similar blood pressure reductions but with the potential for shorter procedure times, less radiation exposure and less contrast usage. The risk-benefit profile for
SPYRAL AFFIRM and SPYRAL SWYFT is similar, with the exception that the risk in the SPYRAL AFFIRM - SPYRAL SWYFT sub-study is estimated to be lower due to the potential for less radiation and contrast usage. Together, the data generated from SPYRAL AFFIRM - SPYRAL SWYFT sub-study will add to the comprehensive dataset supporting the clinical use and safety of renal denervation. Additional data on the SPYRAL SWYFT procedure approach can support future physician procedural training, with the objective to shorten procedure time and decrease radiation and contrast use, while continuing to ensure blood pressure

reductions.

Study design

The SPYRAL AFFIRM study will consist of two cohorts (visit schedules see Tables 1-1 and 1-2 of the Protocol
version 5.0) :
a) Main Cohort: The SPYRAL AFFIRM Main Cohort will consist of all subjects consented to the AFFIRM study who undergo the renal denervation procedure once enrolled.
• ABPM Subset: The SPYRAL AFFIRM study will also collect ABPM data for the first 250 Main Cohort subjects who have a valid ABPM at baseline. (Invalid ABPMs at baseline are not required to be repeated, those subjects will not be included in the subset).

b) Continuation Cohort: SPYRAL AFFIRM sites that also participate in the SPYRAL PIVOTAL-SPYRAL HTN-OFF MED and/or SPYRAL HTN-ON MED studies can enroll subjects initially randomized to the treatment arm, successfully treated via the renal denervation procedure for continued follow up through 60 months after the renal denervation procedure they received in the aforementioned studies. All subjects that meet the criteria above are eligible to be consented for continued follow up in the SPYRAL AFFIRM study within one week (+ or -) of exit from the prior study.

In addition to the 2 SPYRAL AFFIRM cohorts, there will also be a SWYFT sub-study in which 130 patients of the 1300 treated as part of AFFIRM will be treated with the SWYFT sub-study procedural approach.

Intervention

Procedure and Follow Up
Upon completion of the required baseline procedures, subjects in the Main Cohort and Swift substudy will undergo renal denervation and be followed for 36-months post
procedure. Once all follow-up visits are completed, the subjects will be exited from the study.
Subjects consented to the SPYRAL AFFIRM Continuation Cohort will be followed at 48 and 60-month post index procedure from their previous SPYRAL study, for up to an additional 24 months of study participation from the time of enrollment

to study exit in SPYRAL AFFIRM.

For subjects enrolled in the SPYRAL SWYFT sub-study. Specifically, a consent visit is added, drug testing is added at baseline and 6-months follow-up, Quality of Life EQ5D is removed at baseline and follow-up visits, 12-month imaging is removed, ABPM measurement is required for all subjects, witnessed pill intake prior to ABPM measurements is added and CKD-EPI 2021 calculation will be used to calculate eGFR (rather than MDRD formula).

Study burden and risks

Current treatments for uncontrolled hypertension are limited to lifestyle modifications and pharmacological treatment. Many patients are non-responsive, non-adherent, or unable to tolerate pharmacological treatment and are left with few options. The inexorable progression from asymptomatic hypertension to evidence of end organ disease is well known. Both embolic and thrombotic stroke as well as both systolic and diastolic heart failure, and progressive renal dysfunction are known to be companions of chronic hypertension. Beyond contributing to renal failure, hypertension plagues the treatment of patients with end stage renal disease treated with dialysis and transplant. In aggregate, reduction of blood pressure is linearly related to reduction of mortality and cardiovascular events in population studies , with large individual patient variability depending on the presence of additional cardiovascular risk factors, such as lipid abnormalities, diabetes, cigarette smoking, and antecedent heart disease. Despite the availability of numerous pharmaceuticals from many different pharmaceutical classes, patients often fail to attain adequate blood pressure control.
Additionally, pharmaceutical interventions that rely on numerous medications are plagued with drug interactions and side effects, which contribute to physician decisions to discontinue medications and patient decisions to not remain persistent or compliant with the prescribed drug strategies. Non-adherence to medications is also a well-recognized and common challenge to blood pressure control. The development of an effective alternative treatment of hypertension, which offers an adjunct to pharmaceutical care or an alternative to undesirable pharmaceutical complications, may prove to be of obvious value to patients, physicians and the health system.
The detrimental effects of uncontrolled hypertension are well established, an alternative treatment is worth investigation. Renal denervation using the Symplicity Spyral Renal Denervation system is one such alternative. Although there are several theoretical risks that could be associated with the device and procedure, they don*t differ from the commercial setting, in countries where the device has CE mark.
Also, the likelihood of those risks is believed to be low and will be carefully monitored in the study.
The potential benefits, including blood pressure reduction and the associated effects of lowered blood pressure, justify the investigation of renal

denervation in this study.

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

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

Inclusion criteria

1) Individual is >=18 years of age at time of enrollment (consent)
2) Individual is diagnosed with hypertension and has an average baseline office systolic blood pressure >=140 mmHg (measured per Appendix B)
3) >=7 days of valid pre-procedure HBP measurements within 30 days prior to the procedure; consecutive days are preferred but not required (measured per Section 9.5) Not applicable for the Continuation Cohort
4) Individual agrees to have all study procedures performed and is competent

and willing to provide documented informed consent to participate in this clinical study. Continuation Cohort must again meet this criterion at time of SPYRAL AFFIRM Consent
5) Individual was initially randomized to the treatment arm and successfully underwent the RDN procedure, in either the SPYRAL-PIVOTAL- SPYRAL -HTN-OFF MED or SPYRAL HTN-ON MED study. Continuation Cohort only
6) Individual has completed their 36- month visit and been exited from the SPYRAL-PIVOTAL- SPYRAL-HTN OFF MED or SPYRAL HTN-ON MED study. Continuation Cohort only
7) Individual has a baseline office diastolic blood pressure >=90 mmHg (measured per Appendix B)
8) Individual has an average systolic baseline home blood pressure >=135 mmHg (calculated using home blood pressure readings from the first 7 valid days post-baseline).

Subjects enrolled in the SPYRAL SWYFT sub-study will also have to meet the following inclusion criterion; Specifically, it requires that subjects have a valid ABPM at baseline:

- Individual has a valid 24-hour ABPM measured at Baseline visit according to guidelines in section 12 of the Spyral SWYFT CIP addendum after witnessed antihypertensive drug ingestion prior to applying the ABPM device. (ABPM is considered valid if the number of successful daytime readings captured is ≥21 and the number of successful nighttime readings captured is ≥ 12)

Exclusion criteria

1) Individual has renal artery anatomy that is ineligible for treatment including:
a) At least one main renal artery with a diameter of less than 3 mm or greater than 8 mm
2) Individual has >50% stenosis in any treatable vessels.
3) Individual has a treatment area within 5mm of a segment in the renal artery which contains any of the following:
a) Atheroma
b) Calcification, or
c) Renal artery stent
4) Individual has a renal artery stent placed <3 months prior to procedure
5) Individual has undergone prior renal denervation
6) Presence of fibromuscular dysplasia (FMD) (defined as visible beading of the artery on angiography)
7) Individual has untreated secondary cause of hypertension (either known or suspected). Secondary cause does not include obstructive sleep apnea
8) Individual has a documented condition that would prohibit or interfere with ability to obtain an accurate blood pressure measurement using the

protocol-specified blood pressure monitors (e.g., upper arm circumference outside cuff size ranges or arrhythmia that interferes with monitor*s pulse sensing or prohibits an accurate measurement) Continuation Cohort must not meet this criterion again at time of SPYRAL AFFIRM Consent.
9) Individual has a documented confounding medical condition, which in the opinion of the investigator, may adversely affect the safety of the participant (e.g., individuals with clinically significant peripheral vascular disease, or aortic aneurysm)
10) Individual requires chronic oxygen support or mechanical ventilation other than nocturnal respiratory support for sleep apnea (e.g. CPAP, BiPAP)
11) Individual has an estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73m2, using the 4 variable MDRD calculation (in mL/min per 1.73m2 = 175 x SerumCr -1.154 x Age -0.203 x 1.212 (if subject is of African descent) x 0.742 (if subject is female).
12) Individual has had >= 1 episode(s) of orthostatic hypotension not related to medication changes within the past year or has a reduction of SBP of >= 20 mmHg or DBP of >=10 mmHg within 3 minutes of standing coupled with symptoms during the screening process
13) Individual is pregnant, nursing or planning to become pregnant during the study. (Note: Pre-menopausal participants must have a negative serum or urine human chorionic gonadotropin (hCG) pregnancy test prior to angiography) Continuation Cohort must not meet this criterion again at time of SPYRAL AFFIRM Consent
14) Individual has polycystic kidney disease, unilateral kidney, atrophic kidney, or history of renal transplant
15) Individual has a history of narcotic drug abuse or is currently on Methadone, and would be unlikely or unable, in the opinion of the investigator, to comply with study follow-up requirements
16) Individual has a history of bleeding diathesis (bleeding disorders such as thrombocytopenia, hemophilia, significant anemia, or evidence of autonomic dysfunction where imbalance of sympathetic and parasympathetic tone may alter disease process in an unpredictable manner) or coagulopathy or will refuse blood transfusions
17) Individual has documented primary pulmonary hypertension (pulmonary artery (mPA) >=25 mm Hg at rest, as assessed by right heart catheterization) ( )
18) Individual has severe cardiac valve stenosis for which, in the opinion of the investigator, a significant reduction of blood pressure is contradicted.
19). Individual has documented type 1 diabetes mellitus or poorly-controlled type 2 diabetes mellitus with glycosylated hemoglobin greater than 8.0%. (If the glycosylated hemoglobin in the subjects *s records is >3 months old (from the date of baseline visit), or history of uncontrolled blood sugars raises concern it is required to analyze glycosylated hemoglobin as part of baseline labs).

The following text amends exclusion criteria 11 of the SPYRAL AFFIRM CIP for subjects enrolled in the SPYRAL SWYFT sub-study. Specifically, it amends the use of the CKD-EPI calculation 2021 rather than the MDRD formula, to calculate eGFR:

11) Individual has an estimated glomerular filtration rate (eGFR) of <45 mL/min/1.73m2, using the CKD-EPI Creatinine 2021 calculation (eGFR=142 x min(standardized SCr/K, 1)α x max(standardized SCr/K, 1)-1.200 x 0.9938Age x 1.012 [if female]) [K = 0.7 (females) or 0.9 (males), α = -0.241 (female) or -0.302 (males)].

Study design

Design

Study type: Interventional

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

Recruitment

NL

Recruitment status:	Recruiting
Start date (anticipated):	18-07-2023
Enrollment:	20
Type:	Actual

Medical products/devices used

Generic name:	Symplicity Spyral multi-electrode renal denervation catheter (Symplicity Spyral catheter) and a re
Registration:	Yes - CE intended use

Ethics review

Approved WMO Date:	28-11-2022
Application type:	First submission
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	06-10-2023
Application type:	Amendment

Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	30-10-2023
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	22-04-2024
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)
Approved WMO Date:	07-10-2024
Application type:	Amendment
Review commission:	METC Z: Zuyderland-Zuyd (Heerlen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

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

No registrations found.

In other registers

Register	ID
ClinicalTrials.gov	NCT05198674
CCMO	NL81433.096.22