STATISTICAL ANALYSIS PLAN

Effect of renal denervation on blood pressure in patients with chronic kidney disease and uncontrolled hypertension

Study code: RDN2019CKD

Short title: Renal Denervation in Chronic Kidney Disease **RDN-CKD Study**

Sponsor: Universitätsklinikum Erlangen

vertreten durch den Dekan der Medizinischen Fakultät

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This final statistical analysis plan for RDN-CKD study in the present version V 1.0 dated 9th of September 2023 is deemed binding by the signatures:

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Confidentiality statement .

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Table of contents

List of abbreviations

ABP	Ambulatory Blood Pressure
AE	Adverse Event
ADE	Adverse Device Effect
AIx	Augmentation Index
AESI	Adverse Event of Special Interest
BP	Blood Pressure
Bpm	beats per minute
BMI	Body Mass Index
BCM	Body Composition Monitoring
CKD	Chronic Kidney Disease
CT	Computer Tomography
CRF	Case Report Form
DSMB	Data Safety Monitoring Board
ESRD	End Stage Renal Disease
EPI	Epidemiology
ESC	European Society of Cardiology
eGFR	estimated Glomerular Filtration Fraction
ESH	European Society of Hypertension
FU	Follow Up
FAU	Friedrich Alexander University
HDL	High Density Lipoprotein
HMV	Heart Minute Volume
ITT	Intention To Treat
LKP	Leading Investigator
LDL	Low Density Lipoprotein
MRA	Magnetic Resonance Angiography
MRI	Magentic Resonance Imaging
MDRD	Modification of Diet in Renal Disease
MAE	Major Adverse Event
mITT	modified Intention To Treat
mPPP	modified Per Protocol Population
NA	Not Applicable
ND	Not Done
NSTEMI	Non-ST Elevation Myocardial Infarction
OH	Overhydration
PWV	Pulse Wave Velocity

PPP	Per Protocol Population
RDN	Renal Denervation
SAF	Safety population
SGPT	Serum Glutamic Pyruvic Transaminase
SGOT	Serum Glutamic Oxalacetate
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
SAE	Serious Adverse Event
SADE	Serious Adverse Device Effect
STEMI	ST Elevation Myocardial Infarction
UNK	Unknown
UACR	Urinary Albumin to Creatinine Ratio
UV	Unscheduled Visit
USADE	Unanticipated Serious Adverse Device Effect
IDE	Investigational Device Exemption
zSys	zentral Systolic
zDia	zentral Diastolic

1. Protocol summary

1.1.   Study Objectives

The purpose of the RDN-CKD Study is to demonstrate the ability of the ReCor catheter system to effectively reduce systolic and diastolic ambulatory BP in hypertensive subjects with uncontrolled hypertension and CKD stage 3. The objective of the RDN-CKD Study is to demonstrate the efficacy and verify the safety of RDN in hypertensive subjects with CKD stage 3. Patients included in this study are hypertensive despite of receiving 1-5 antihypertensive drug classes.

1.1.1.   Primary objective

The primary efficacy parameter is:

-   Change in systolic 24-h ambulatory BP at 6 months post-RDN-procedure from pre-procedure (including 1. Pre-treatment value **(P)** = average of the pre-procedure visit (week -1) value and screening visit (week -4) value, 2. Baseline value **(B)** = pre-procedure visit (week -1) value only) compared *between the 2 groups* (RDN-Treatment group vs. Sham group).

1.1.2.   Secondary objectives

The secondary efficacy parameters of the study are (*between the 2 groups* - RDN-Treatment group vs. Sham group*)*:

-   Change in systolic 24-h ambulatory BP at 3 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups (RDN-Treatment group vs. Sham group).
-   Change in diastolic 24-h ambulatory BP at 3, 6 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups (RDN-Treatment group vs. Sham group).
-   Change in office systolic and diastolic BP at 3, 6 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups (RDN-Treatment group vs. Sham group).
-   Change in home systolic and diastolic BP at 3, 6 and 12 months post-procedure from pre-procedure (including B only) compared between the 2 groups (RDN-Treatment group vs. Sham group).
-   Responder rate in BP (systolic office BP ≥10 mmHg,or 24-h systolic ambulatory BP ≥5

7

mmHg) at 3, 6, and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Change in serum creatinine, cystatin C at all time points from pre-procedure (pre-procedure visit (week -1) value and screening visit (week -4)) compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Change in eGFR (calculated based on CKD-epi formula) derived from serum creatinine at all time points from pre-procedure (pre-procedure visit (week -1) value and screening visit (week -4)) compared between the 2 groups (RDN-Treatment group vs. Sham group). [1]

- Change in eGFR derived from cystatin C at all time points from pre-procedure (pre-procedure visit (week -1) value and screening visit (week -4)) compared between the 2 groups (RDN-Treatment group vs. Sham group). [2, 3]

- Change in eGFR derived from creatinine/Cystatin-C formula at all time points from pre-procedure (pre-procedure visit (week -1) value and screening visit (week -4)) compared between the 2 groups (RDN-Treatment group vs. Sham group) [3]

- Change of the slope of eGFR (derived from creatinine; CKD-epi formula)after half year and one year post-procedure from pre-procedure (pre-procedure visit (week -1) value and screening visit (week -4) eGFR values) compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Change of the slope of eGFR (derived from creatinine; CKD-epi formula) after half year and at 1 year post-procedure from pre-procedure (pre-procedure visit (week -1) value and screening visit (week -4) eGFR values) compared to the historical slope the year before

- Change in proteinuria (per g urinary creatinine), albuminuria (per g urinary creatinine), urine sodium (per g urinary creatinine), urine potassium (per urinary creatinine), urine creatinine concentration at 3, 6 and 12 months post-procedure from pre-procedure (pre-procedure visit (week -1) value and screening visit (week -4)) compared between the 2 groups (RDN-Treatment group vs. Sham group).Win ratio analysis will be conducted, with the criteria 24h ambulatory systolic BP change > 5 mmHg, and office systolic BP change > 10 mmHg at 3, 6 and 12 months from pre-procedure (including P and B) in both groups (RDN-Treatment group vs. Sham group). [4]

- Win ratio analysis will be conducted, with the criteria 24h ambulatory systolic BP change > 5 mmHg, office systolic BP change > 10 mmHg, and decrease of medication number at 3, 6 and 12 months from pre-procedure (including P and B) in both groups (RDN-Treatment group vs. Sham group). [4]

- Win ratio analysis will be conducted, with the criteria 24h ambulatory systolic BP change > 5 mmHg, office systolic BP change > 10 mmHg, and any decrease of drug burden index in both groups at 3, 6 and 12 months from pre-procedure (including P and B) in both groups

(RDN-Treatment group vs. Sham group). [4]

- Win ratio analysis will be conducted, with the criteria 24h ambulatory systolic BP change > 5 mmHg, office systolic BP change > 10 mmHg, and any decrease of antihypertensive load index at 3, 6 and 12 months from pre-procedure (including P and B) in both groups (RDN-Treatment group vs. Sham group). [4]

1.1.3. Observational Efficacy Assessment *between the 2 groups*

- Change in average daytime/night-time ambulatory systolic BP at 3, 6 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Change in average daytime/night-time ambulatory diastolic BP at 3, 6 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Change in average daytime/night-time ambulatory heart rate at 3, 6 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Change in average 24 hour ambulatory heart rate at 3, 6 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Change in office heart rate at 3, 6 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups.

- Incidence of ambulatory systolic BP (daytime/24-h/night-time) reductions of ≥5 mmHg, ≥10mmHg, and ≥15 mm Hg at 3, 6 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Percentage of subjects who are controlled in the absence of changes in hypertensive medication at 3, 6 and 12 months post-procedure compared between the 2 groups. (Four different criteria of "controlled" will be used: daytime ambulatory BP <135/85 mmHg; night-time ambulatory BP < 120/75; 24-h ambulatory BP< 130/80 mmHg; office BP <140/90 mmHg)

- Percentage of subjects who are controlled irrespective of any changes in hypertensive medication at 3, 6 and 12 months post-procedure compared between the 2 groups (Four different criteria of "controlled" will be used: daytime ambulatory BP <135/85 mmHg; night-time ambulatory BP< 120/70; 24-h ambulatory BP< 130/80 mmHg; office BP <140/90 mmHg).

- Change in office and 24 hour ambulatory pulse pressure at 3, 6 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups.

- Changes in percentages of dipper/non-dipper patterns at 3, 6 and 12 months post-procedure compared between the 2 groups (Criteria for non-dipping is less thn 10% decrease of nigh time systolic ambulatory BP from daytime BP).

- Change in number of antihypertensive drugs at 3, 6 and 12 months post-procedure from pre-procedure (pre-procedure visit (week -1)) compared between the 2 groups.

- Change in drug burden index at 3, 6 and 12 months post-procedure compared from pre-procedure (pre-procedure visit (week -1)) between the 2 groups (RDN-Treatment group vs. Sham group).

- Change in antihypertensive load index at 3, 6 and 12 months post-procedure from pre-procedure (pre-procedure visit (week -1)) compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Percentage of subjects requiring initiation of additional antihypertensive drug therapy between 3 and 6 months post-procedure compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Change in following body fluid composition parameters measured by the Body Composition Monitor (BCM), Fresenius Medical Care at 3, 6 and 12 months post-procedure from pre-procedure (pre-procedure visit (week -1)) compared between the 2 groups (RDN-Treatment group vs. Sham group)
  - Weight, height, BMI, Overhydration (OH), OH % of extra cellular water

- Change in following parameters at all ambulatory BP measurements (24 hours ambulatory values, ambulatory values- day time and ambulatory values- night time) derived from Mobilograph® examination at 3, 6 and 12 months post-procedure from (pre-procedure visit (week -1) compared between the 2 groups (RDN-Treatment group vs. Sham group).
  - Pulse pressure, zentral systolic pressure (zSys), zentral diastolic pressure (zDia), augmentation index at 75 beats per minute (AIx at 75 bpm), heart minute volume (HMV), peripheral resistance, reflexion coefficient, pulse wave velocity (PWV)

All the analyses with respect to the 24 hour ambulatory parameters or office blood pressure parameters described under 1.1.1, 1.1.2 and 1.1.3 will be performed by comparing the treatment values at 3, 6, and 12 months from the pre-procedure value (1. Pre-treatment value **(P)** = average of the pre-procedure visit (week -1) value and screening visit (week -4) value, 2. Baseline value **(B)** = pre-procedure visit (week -1) value only) in the RDN group and the sham group, separately (paired analyses) and compared *between the 2 groups*.

1.1.4. Procedure details in both groups (RDN group vs. sham group)

Procedure details in both groups (RDN group vs. sham group) will be presented as a table:

- Volume of contrast agent (cc)

- Minutes of exposure to fluoroscopy (mm:ss)

- Anesthesia Medications (Name, Dosage)

- No. of patients with accessory renal artery

- No pf patients with proximal artery branching

- Main Right Renal artery distal diameter (mean)

- Main Right Renal artery proximal diameter (mean)

- Main Right Renal artery length (mean)

- Main Left Renal artery distal diameter (mean)

- Main Left Renal artery proximal diameter (mean)

- Main Left Renal artery length (mean)

Renal denervation treatment details (RDN group only)

- Number of Left Main Renal Emissions

- Number of Right Main Renal Emissions

- Number of Left Renal BRANCH Emissions

- Number of Right Renal BRANCH Emissions

- Number of Left Renal Accessory Emissions

- Number of Right Renal Accessory Emissions

- Total Emissions (System Calculated)

1.1.5. Safety analysis

- Safety endpoints and adverse effects during 3, 6 and 12 months post-procedure compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Listing of AE and ADE in original term provided for each patient (Solo-Population)
Listing of SAE, AESI, SADE in original term provided for each patient
Comparison of number / percentages of SAE, AE, AESI, escape rate between the 2 groups (RDN-Treatment group vs. Sham group)

- Increase of serum creatinine / eGFR (calculated based on CKD-epi) between visit 3a (week 0) and visit 3b, and visit 3a and visit 4 (week +3) between the 2 groups (RDN-Treatment group vs. Sham group) and in each group separately

Following events will be presented at all-time points post-procedure comparing 2 groups

All-cause mortality
New onset ESRD (eGFR<15 mL/min/m² or need for renal replacement therapy)
Significant embolic event resulting in end-organ damage
Renal artery perforation or dissection requiring an invasive intervention
Major vascular complications requiring surgical repair, interventional procedure, thrombin injection, or blood transfusion
Hospitalization for hypertensive or hypotensive crisis
Hospitalization for major cardiovascular or hemodynamic related events
New onset stroke
New onset myocardial infarction
Suspicion of new onset renal artery stenosis by renal duplex ultrasound

Following AESIs will be presented as a table at all time points post-procedure comparing 2 groups

- All-cause mortality

- Hypertensive emergency resulting in hospitalization

- Hypotensive emergency resulting in hospitalization

- Hospitalization for heart failure

- Stroke, transient ischemic attack, cerebrovascular accident

- Acute myocardial infarction (STEMI/non-STEMI)

- Any coronary revascularization

- End stage renal disease, the need for permanent renal replacement therapy (i.e. the need for dialysis); doubling of plasma creatinine, eGFR <15ml/min/1.73m²

- Any renal artery complication requiring intervention (e.g. dissection; perforation)

- Major access site complications requiring intervention

- Significant embolic events resulting in end organ damage

- Procedure-related pain lasting for > 2 days

- Acute renal injury, defined as:

- Increase in serum/plasma creatinine to ≥1.5 times pre-procedure visit (week -1) or decrease of eGFR (derived from creatinine, CKD-epi) by 25% known to have occurred during 7 days post procedure or

- Urine volume <0.5 ml/kg/h for 6 hours

- Significant (>50%) and severe (>70%) new onset renal stenosis as diagnosed by renal angiogram or CTA/MRA

- Need for renal artery angioplasty or stenting

In addition, these AESIs will also be reported as 1-month post-procedure event rates:

- Any renal artery complication requiring intervention (e.g. dissection; perforation)

- Major access site complications requiring intervention

- Significant embolic events resulting in end organ damage

- Procedure-related pain lasting for > 2 days

- Acute renal injury, defined as:

- increase in serum/plasma creatinine to ≥1.5 times pre-procedure visit (week -1) or decrease of eGFR (derived from creatinine, CKD-epi) by 25% known to have occurred during 7 days post procedure or,

- Urine volume <0.5 ml/kg/h for 6 hours

Following major combined safety endpoint (incidence of any major adverse events (MAE) through the FU) at all time points post-procedure comparing 2 groups

- All-cause mortality

- eGFR <15 ml/min/1.73m² or permanent need for renal replacement therapy

- Hospitalization for hypertensive crisis defined by office (attended) BP ≥ 180/110 mmHg with clinical symptoms

- Clinical manifestation of hypertension associated target organ damage requiring hospitalization

- New renal artery stenosis >75% as assessed by computer tomography (CT)/magnetic resonance angiography (MRA) or diagnosed/confirmed by renal angiogram

- Individual components of the combined endpoint above

1.2.   Design of the Trial

RDN-CKD Study is a prospective, randomized (1:1, central randomization), double-blind (unblinded interventionalist and blinded study team at each center), sham controlled, multicenter feasibility study. All centers have participated at least in one of the sham-controlled trials in primary hypertension thereby having established an unblinded and a blinded team.

The RDN-CKD Study has been conducted at 5 clinical investigational sites, which are the University Hospitals in Erlangen, Homburg/Saar, Düsseldorf, Berlin and Nürnberg.

We aimed to include 80 patients with CKD stages 3a or 3b (according to the currently used estimation formulas [MDRD, CKD-EPI] and uncontrolled hypertension in the RDN-CKD study. This number of patients could not be achieved due to diverse reasons (pandemic, low recruitement). Therefore the recruitment got stopped by 31.12.2022.

If the patient fulfils inclusion criteria and in the absence of exclusion criteria at visit 1, the patient has been enrolled into the trial, and the study visits were scheduled. All subjects have their office BP measured, a limited medical history review, physical exam and current medication review and a safety laboratory evaluation. Furthermore, an ABP measurement was conducted. Visit 2 serves a FU in the run-in phase. All subjects were checked for medication adherence. A 24-h ambulatory BP measurement was conducted. Additionally, all subjects had their office BP measured, physical exam and current medication review and a safety laboratory evaluation. Once a subject has met all the screening criteria for the study the visit was scheduled for the renal angiogram and RDN/Sham procedure. Subjects of child bearing potential must have a documented negative pregnancy test dated within a maximum of 7 days prior to the procedure.

Randomization occurred following the diagnostic renal angiogram. Only randomized patients counted towards the enrollment ceiling. FU Visits took place 3 weeks, 6 weeks, 12 weeks, 19 weeks, 26 weeks, 39 weeks, 52 weeks post procedure. All baseline measurements were repeated 12 weeks, 26 weeks and 52 weeks post-procedure. Due to early recruitment stop of the study certain number of patients had only FU visits till 26 weeks post procedure.

Escape Criteria

Enrolled subjects will be excluded if office BP exceeds ≥170/105 mmHg confirmed by 7-day average of home blood pressure measurements ≥ BP >160/100 mmHg (excluding white coat effect) and confirmed by office BP ≥170/105 mmHg at another study visit.

Unscheduled visit (UV)

In case subjects will be seen at additional times other than regular scheduled study visits, if deemed necessary by the Investigator, the following safety assessments will be performed: safety laboratory, urinalysis, vital signs, physical examination, AE assessment, checking concomitant medication.

1.3. Trial Flow Sheet

Enrollment of subjects occurred at the clinical sites only after the appropriate local study approvals, "Approval to Enroll" documentation from the Sponsor and written informed consent from subjects have been obtained.

Visit #	V1	V2	V3	V4	V5	V6	V7	V8[7]	V9	V10
Week	-4	-1	0	3	6	12	19	26	39	52
Informed consent	X									
Inclusion/exclusion criteria	X									
Medical history	X									
RDN/Sham Procedure			X							
Physical exam	X	X	X	X	X	X	X	X	X	X
24-h ABP measurement[1]	X	X				X		X		X
Office (attended) BP[2]	X	X	X	X	X	X	X	X	X	X
Safety and efficacy lab	X	X	X	X	X	X	X	X	X	X
AEs/ADEs	X	X	X	X	X	X	X	X	X	X
UACR[3], eGFR, Cystatin C	X	X				X		X		X
Urinary toxicological analyses[4]		X				X		X		X
Body fluid composition		X						X		X
MRA of Renal Arteries[5]		X								
Duplex ultrasound[6]		X								X
Medication review	X	X	X	X	X	X	X	X	X	X

Visit schedule (# all visits can be scheduled +/-5days)

1. 24-h ambulatory BP measurements will be conducted by mobilograph (IEM, Aachen) allowing also the assessment of central systolic BP in addition to brachial BP readings.

2. Office (attended) BP according to ESH guidelines with automated oscillometric device while nurse/physician is in the room (attended visits).

3. UACR – albumin/creatinine ratio.

4. To assess adherence to prescribed medication

5. MRA has only to be performed if no images (previous MRI, previous CT, previous angiogram) of anatomy of renal artery supply is available

6. If the last duplex sonography examination displays signs of renal artery stenosis or is not fully evaluable according to the investigator`s discretion, an angiogram needs to be performed to rule out or

diagnose any renal artery abnormality which can be compared with the angiogram performed at baseline.

7. Patients who will not have 12 months follow up visit until June 2023 but thereafter will have a shorter follow up period of 6 months only and unblinding will take place after all data of the 6 months FU visit have been entered and secured in the database (the rationale is that the primary objective is change in blood pressure after 6 months!

2. Outcome Measures and Target Parameters

2.1. Efficacy

Primary efficacy endpoint:

- Change in systolic 24-h ambulatory BP at 6 months post-RDN-procedure from pre-procedure (including 1. Pre-treatment value **(P)** = average of the pre-procedure visit (week -1) value and screening visit (week -4) value, 2. Baseline value **(B)** = pre-procedure visit

(week -1) value only) compared *between the 2 groups* (RDN-Treatment group vs. Sham group).

<u>Secondary efficacy endpoints:</u>

The secondary efficacy parameters of the study are:

- Change in systolic 24-h ambulatory BP at 3 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Change in diastolic 24-h ambulatory BP at 3, 6 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Change in office systolic and diastolic BP at 3, 6 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Change in home systolic and diastolic BP at 3, 6 and 12 months post-procedure from pre-procedure (including B only) compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Responder rate in BP (systolic office BP ≥10 mmHg,or 24-h systolic ambulatory BP ≥5 mmHg) at 3, 6, and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Change in serum creatinine, cystatin C at all time points from pre-procedure (pre-procedure visit (week -1) value and screening visit (week -4)) compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Change in eGFR (calculated based on CKD-epi formula) derived from serum creatinine at all time points from pre-procedure (pre-procedure visit (week -1) value and screening visit (week -4)) compared between the 2 groups (RDN-Treatment group vs. Sham group). [1]

- Change in eGFR derived from cystatin C at all time points from pre-procedure (pre-procedure visit (week -1) value and screening visit (week -4)) compared between the 2 groups (RDN-Treatment group vs. Sham group). [2, 3]

- Change in eGFR derived from creatinine/Cystatin-C formula at all time points from pre-procedure (pre-procedure visit (week -1) value and screening visit (week -4)) compared between the 2 groups (RDN-Treatment group vs. Sham group) [3]

- Change of the slope of eGFR (derived from creatinine; CKD-epi formula)after half year and one year post-procedure from pre-procedure (pre-procedure visit (week -1) value and

screening visit (week -4) eGFR values) compared between the 2 groups (RDN-Treatment group vs. Sham group).

-        Change of the slope of eGFR (derived from creatinine; CKD-epi formula) after half year and at 1 year post-procedure from pre-procedure (pre-procedure visit (week -1) value and screening visit (week -4) eGFR values) compared to the historical slope the year before

-        Change in proteinuria (per g urinary creatinine), albuminuria (per g urinary creatinine), urine sodium (per g urinary creatinine), urine potassium (per urinary creatinine), urine creatinine concentration at 3, 6 and 12 months post-procedure from pre-procedure (pre-procedure visit (week -1) value and screening visit (week -4)) compared between the 2 groups (RDN-Treatment group vs. Sham group).Win ratio analysis will be conducted, with the criteria 24h ambulatory systolic BP change > 5 mmHg, and office systolic BP change > 10 mmHg at 3, 6 and 12 months from pre-procedure (including P and B) in both groups (RDN-Treatment group vs. Sham group). [4]

-        Win ratio analysis will be conducted, with the criteria 24h ambulatory systolic BP change > 5 mmHg, office systolic BP change > 10 mmHg, and decrease of medication number at 3, 6 and 12 months from pre-procedure (including P and B) in both groups (RDN-Treatment group vs. Sham group). [4]

-        Win ratio analysis will be conducted, with the criteria 24h ambulatory systolic BP change > 5 mmHg, office systolic BP change > 10 mmHg, and any decrease of drug burden index in both groups at 3, 6 and 12 months from pre-procedure (including P and B) in both groups (RDN-Treatment group vs. Sham group). [4]

-        Win ratio analysis will be conducted, with the criteria 24h ambulatory systolic BP change > 5 mmHg, office systolic BP change > 10 mmHg, and any decrease of antihypertensive load index at 3, 6 and 12 months from pre-procedure (including P and B) in both groups (RDN-Treatment group vs. Sham group). [4]

Other Observational Efficacy Assessments:
-   Change in average daytime/night-time ambulatory systolic BP at 3, 6 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups (RDN-Treatment group vs. Sham group).
-   Change in average daytime/night-time ambulatory diastolic BP at 3, 6 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups (RDN-Treatment group vs. Sham group).
-   Change in average daytime/night-time ambulatory heart rate at 3, 6 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Change in average 24 hour ambulatory heart rate at 3, 6 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Change in office heart rate at 3, 6 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups.

- Incidence of ambulatory systolic BP (daytime/24-h/night-time) reductions of ≥5 mmHg, ≥10mmHg, and ≥15 mm Hg at 3, 6 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Percentage of subjects who are controlled in the absence of changes in hypertensive medication at 3, 6 and 12 months post-procedure compared between the 2 groups. (Four different criteria of "controlled" will be used: daytime ambulatory BP <135/85 mmHg; night-time ambulatory BP < 120/75; 24-h ambulatory BP< 130/80 mmHg; office BP <140/90 mmHg)

- Percentage of subjects who are controlled irrespective of any changes in hypertensive medication at 3, 6 and 12 months post-procedure compared between the 2 groups (Four different criteria of "controlled" will be used: daytime ambulatory BP <135/85 mmHg; night-time ambulatory BP< 120/70; 24-h ambulatory BP< 130/80 mmHg; office BP <140/90 mmHg).

- Change in office and 24 hour ambulatory pulse pressure at 3, 6 and 12 months post-procedure from pre-procedure (including P and B) compared between the 2 groups.

- Changes in percentages of dipper/non-dipper patterns at 3, 6 and 12 months post-procedure compared between the 2 groups (Criteria for non-dipping is less thn 10% decrease of nigh time systolic ambulatory BP from daytime BP).

- Change in number of antihypertensive drugs at 3, 6 and 12 months post-procedure from pre-procedure (pre-procedure visit (week -1)) compared between the 2 groups.

- Change in drug burden index at 3, 6 and 12 months post-procedure compared from pre-procedure (pre-procedure visit (week -1)) between the 2 groups (RDN-Treatment group vs. Sham group).

- Change in antihypertensive load index at 3, 6 and 12 months post-procedure from pre-procedure (pre-procedure visit (week -1)) compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Percentage of subjects requiring initiation of additional antihypertensive drug therapy between 3 and 6 months post-procedure compared between the 2 groups (RDN-Treatment group vs. Sham group).

- Change in following body fluid composition parameters measured by the Body Composition Monitor (BCM), Fresenius Medical Care at 3, 6 and 12 months post-procedure from pre-procedure (pre-procedure visit (week -1)) compared between the 2 groups (RDN-Treatment group vs. Sham group)
  - Weight, height, BMI, Overhydration (OH), OH % of extra cellular water
- Change in following parameters at all ambulatory BP measurements (24 hours ambulatory values, ambulatory values- day time and ambulatory values- night time) derived from Mobilograph® examination at 3, 6 and 12 months post-procedure from (pre-procedure visit (week -1) compared between the 2 groups (RDN-Treatment group vs. Sham group).
  - Pulse pressure, zentral systolic pressure (zSys), zentral diastolic pressure (zDia), augmentation index at 75 beats per minute (AIx at 75 bpm), heart minute volume (HMV), peripheral resistance, reflexion coefficient, pulse wave velocity (PWV)

2.2.   Safety

All adverse events were collected, coded and reported, for the duration of the study according to the definitions of "Clinical investigation of medical devices for human subjects -Good clinical practice" ISO: 14155: 2011.

The occurrence rate for all the clinical events defined below [referred to as adverse events of special interests (AESIS)] will be calculated for each cohort, characterized by the Data Safety Monitoring Board (DSMB) and compared between and within arms (where applicable) for the duration of the study. In addition, specific events within this list will also be reported as event rates within specific time frames post procedure.

The assessment of safety was based primarily on the frequency of serious adverse device effects (SADEs) serious adverse events (SAEs), adverse device effects (ADEs), adverse events(AEs) and laboratory abnormalities classified by Investigators as related to the RDN and confirmed by the DSMB. Occurrence and frequency of SADES and ADEs and AE(s) and SAE(s) was summarized by treatment group at baseline, last visit and by changes from baseline to last visit for laboratory values. Other safety data were summarized as appropriate.

The RDN-CKD Study DSMB is comprised of independent experts in hypertension, interventional radiology or cardiology and biostatistics. The DSMB was responsible for the oversight, review of all relevant SAEs including but not limited to:

- All unanticipated events

- All events pre-specified as part of the overall safety assessment

- All device- or procedure-related events (ADEs and SADEs)

- Deaths

During the course of the study, the DSMB reviewed accumulating safety data blinded to subject randomization in order to monitor the incidence of protocol-defined events and other trends that would warrant modification or termination of the study. Responsibilities, qualifications, membership, and committee procedures were outlined in the DSMB Charter.

All safety aspects mentioned in chapter 1.1.5 will be listed and compared between RDN and sham group.

2.3.   Analysis populations

For the analyses of the study, following populations are pre-specified:

1. The **Safety population (SAF population)** included all patients who provided informed consent

2. The **Intention-to-treat population (ITT population)** consisted of all randomised patients having a post-procedure measurement of at least one (primary) efficacy parameter.

3. The **modified ITT population (mITT)** include only participants from the ITT population without adherence violations.

4. The **Per Protocol population (PPP)** included all patients of the ITT population who did not show any major protocol violation (defined prior to unblinding of the data). These patients received at least two measurements of 24-h ambulatory BP (one pre-procedure (week -4 or week -1) and one 3 or 6 months post-procedure), performed in technically high quality.

5. The **Modified Per Protocol Population (mPPP)** include only patients of the PPP without adherence violations

6. The **Bavarian population** include only patients from 2 centres (Erlangen and Nürnberg)

Use of analysis sets

Demographic data and clinical characteristics of the patients will be displayed on all the pre-specified populations. Prior and concomitant medications as well as prior and concomitant medical conditions will be reported on all pre-specified populations.

The ITT population will be the basis for the primary analysis.

2.4. Analyses

Statistical analyses will be based on the basis of international guidelines (CPMP/ICH/363/96:E9). Due to the early stop of the study, only an exploratory and descriptive analysis takes place. Statistical methods used to compare groups for primary and secondary outcomes:

Efficacy: Change of systolic 24-h ambulatory BP at 6 months post-procedure (primary efficacy endpoint) compared between the RDN and sham group will be analyzed in a linear mixed model including the covariates that were significantly different between the groups at baseline. All secondary (see 1.1.2) and observational endpoints (1.1.3 and 1.1.4) are analyzed also via a modelling approach adjusting for potential imbalances in baseline characteristics. The type I error for the analysis of the primary endpoint is set at 5% (two-sided), all analyses of secondary endpoints have an exploratory character avoiding multiplicity issues in this trial.

In addition, a win ratio analysis will be conducted, with the criteria 24h ambulatory systolic BP change > 5 mmHg, office systolic BP change > 10 mmHg, and decrease of medication as defined by following 3 parameters (number of antihypertensive drugs, drug burden index and antihypertensive load index).

Analysis will be performed for the following populations:

1. Primary analysis is based on *the intention-to-treat* (ITT) population consisting of all randomized study subjects that are all either RDN treated or sham treated.

2. A secondary analysis will be done with a *modified ITT* population (mITT) in which participants with adherence violations will be excluded (sensitivity analyses).

3. A secondary analysis will be done with the *per protocol population* (PPP) in which study subjects with predefined protocol deviations (defined prior to unblinding of the data) are excluded.

4. A secondary analysis will be done with the modified *per protocol population* (mPPP) in which study subjects of the PPP with adherence violation are excluded.

5. A secondary analysis will be done with the safety population (SAF) in which all study subjects signing informed consent are included.

6. A secondary analysis will be done with those patients that are investigated by the Erlanger and Nürnberger center (CRC staff), with a total of N=20 randomized patients (Bavarian cohort)

2.5. Computer system and Software

The statistical analysis will be performed using Statistical Analysis System SPSS (release 21 SPSS Inc. Chicago, Illinois, USA) or any other internationally accepted software (R, Python etc.) or any other internationally used statistical program that are qualified for this analysis, e.g. SAS program.

2.6. Protocol deviations and their Classification in Minor and Major

Prior to locking the trial data base, possible protocol deviations will be listed. The classification in minor or major deviations will be done at the "Blinded Data Review Meeting". The classification into minor or major deviations will be done in cooperation between the leading investigator (LKP), the Sponsor's Project Manager and the responsible monitoring person. Major protocol violations will be protocol deviations, which are considered to interfere with the assessments of efficacy in this trial.

2.7. Definition of Derived Variables and Transformation of Variables

2.7.1. Missing Values

Missing values in the CRF documented as "ND", "NA" or "UNK" will usually not be entered into the database and the field will be blank.

If date parts are missing (the 'day' and/or the 'month') and there are calculations needed, a missing day will be replaced by '01', a missing month will be replaced by '01'. A missing year will not be replaced.

In case of the start date of an AE is missing, the date of first treatment intake (if appropriate) will be used as worst case imputation, otherwise the first day/month instead of the middle will be taken also as a worst case imputation.

Data of patients having withdrawn their consent to study participation at any time point during the study were not accounted for in the respective analyses up to the time point of withdrawal.

2.7.2. Treatment Exposure and Compliance

Compliance by treatment and by visit

Records of changes in medication are to be kept during the study. Throughout the study, subjects will be instructed about the importance of medication adherence and asked to take any required study-defined antihypertensive treatment at approximately 08:00 am daily except on the morning of each office visit when they will be asked to bring their protocol-defined medication with them to the visit.

Adherence to drug therapy will be captured by interviewing patients, checking the patient's BP diary and by urinary toxicological analysis at baseline, 6 month, and 12 month visit.

2.7.3. Efficacy measures

2.7.3.1. Primary and secondary efficacy variables

Office Blood Pressure Measurements

The measurement of office BP was done according the following guidelines based on the 2018 ESH/ESC Guidelines for the management of arterial hypertension. [5]

24-h ambulatory BP Measurements

The measurement of 24-h ambulatory BP will occur at -4, -1, 12, 26, and 52 weeks FU visits with the ambulatory BP system (Mobilograph®, I.E.M. Stolberg, Germany; 90207 or 90217A, Spacelabs Healthcare, Meerbusch, Germany). Only ambulatory BP recordings with a minimum of 28 measurements during the 24 hour period will be considered valid. The measurement of ambulatory BP was done according the following guidelines based on the 2018 ESH/ESC Guidelines for the management of arterial hypertension. [5]

Home BP Measurements

Home BP measurements are introduced to increase safety for the patients, not for efficacy. After education on the use of the Home BP system, all subjects will be provided with a Home BP monitor (aponorm® Professional Touch, microlife, Widnau, Switzerland).

eGFR Calculation

eGFR calculations for inclusion will be standardized using the currently used estimation formulas (MDRD, CKD-EPI).

Laboratory Assessments

All subjects will have blood collected at every visit. In addition, all subjects will have urine samples collected at -4, -1, 12, 26, and 52 week follow-up visits for urine analysis. Females of child bearing potential will have a urine or blood plasma pregnancy test up to 7 days prior to the procedure.

Laboratory Data	
Blood Chemistry	urea, creatinine, eGFR, cystatin C, uric acid, sodium, potassium, calcium, γ-GT, GOT, GPT, alkaline phosphatase, total cholesterol, LDL-cholesterol, HDL-cholesterol, triglycerides, total serum protein Fasting blood glucose, HbA1c
Hematology	hemoglobin, hematocrit, erythrocyte count, platelet count, white blood count
Urin analysis	Spot urine (urinary creatinine, protein, albumin, sodium and potassium), Urine pregnancy testing (applicable females only)

HP LC-MS/MS of Antihypertensive Adherence

HP LC-MS/MS is a recognized method with good to excellent sensitivity and specificity to detect many pharmacological agents in urine. Urine collected at -1 and 26 and 52 weeks FUs will be sent for analysis.

2.8. Safety and Tolerability Measures

Term	Definition
Adverse Event (AE) *Ref: ISO 14155-2011*	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. NOTE 1: This definition includes events related to the investigational medical device or the comparator. NOTE 2: This definition includes events related to the procedures involved NOTE 3: For users or other persons, this definition is restricted to events related to the investigational medical device.
Adverse Device Effect (ADE) *Ref: ISO 14155-2011*	AE related to the use of an investigational medical device NOTE 1: This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device. NOTE 2: This definition includes any event resulting from use error or from intentional misuse of the investigational medical device.
Serious Adverse Event (SAE) *Ref: Ordinance on Medical Devices Vigilance (MPSV)*	Adverse event that directly or indirectly have led, might have led, or might lead to death or to a serious deterioration in the health of a subject, user, or other person, whether or not related to the investigational medical device,
Serious Adverse Device Effect (SADE) *Ref: ISO 14155-2011*	Adverse device effect that has resulted in any of the consequences characteristic of a SAE.
Unanticipated Serious Adverse Device Effect (USADE) *Ref: ISO 14155-2011*	Serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. **NOTE 1**: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.
Device Deficiency *Ref: ISO 14155-2011*	Inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety or performance. NOTE: Device deficiencies include malfunctions, use errors, and inadequate labelling.

Definitions of Adverse Events and Device Deficiency

Assessment of Severity

The clinical severity of an AE will be classified as:

Mild: asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated.

Moderate: minimal, local or non-invasive intervention indicated; limiting age-appropriate instrumental activities of daily living.

Severe: severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self care activities of daily living.

Life-threatening: Life-threatening consequences; urgent intervention indicated

Fatal: Death related to AE

The definitions above are difficult to apply for some data (e.g. clinically relevant laboratory values that are documented and evaluated on the CRF AE report form). In such situations, the investigator made a judgment based on personal experience.

Assessment of Seriousness

The seriousness were assessed by the investigator and the Sponsor.

Assessment of Causality

The relationship between the use of the investigational medical device (including the medical-surgical procedure) and the occurrence of each adverse event were assessed and classified according to five different levels of causality:

Not related: relationship to the device or procedures can be excluded when:

- the event is not a known side effect of the product category the device belongs to or of similar devices and procedures;

- the event has no temporal relationship with the use of the medical device or the procedures;

- the event does not follow a known response pattern to the medical device (if the response pattern is previously known) and is biologically implausible;

- the discontinuation of medical device application or the reduction of the level of activation/exposure - when clinically feasible - and reintroduction of its use (or increase of the level of activation/exposure), do not impact on the event;

- the event involves a body-site or an organ not expected to be affected by the device or procedure;

- the event can be attributed to another cause (e.g. an underlying or concurrent illness/ clinical condition, an effect of another device, drug, treatment or other risk factors);

- the event does not depend on a false result given by the medical device used for diagnosis, when applicable;

- harms to the subject are not clearly due to use error;

- In order to establish the non-relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.

Unlikely: the relationship with the use of the device seems not relevant and/or the event can be reasonably explained by another cause, but additional information may be obtained

Possibly related: the relationship with the use of the medical device is weak but cannot be ruled out completely. Alternative causes are also possible (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment). Cases were relatedness cannot be assessed or no information has been obtained should also be classified as possible.

Probably related: the relationship with the use of the investigational device seems relevant and/or the event cannot reasonably explained by another cause, but additional information may be obtained.

Causal relationship: the adverse event is associated with the investigational device or with procedures beyond reasonable doubt when:

- the event is a known side effect of the product category the device belongs to or of similar devices and procedures;

- the event has a temporal relationship with device use/application or procedures;

- the event involves a body-site or organ that the medical device or procedures are applied to or the medical device or procedures have an effect on;

- the event follows a known response pattern to the medical device (if the response pattern is previously known);

- the discontinuation of medical device application (or reduction of the level of activation/exposure) and reintroduction of its use (or increase of the level of activation/exposure), impact on the event (when clinically feasible);

- other possible causes (e.g. an underlying or concurrent illness/clinical condition or/and an effect of another device, drug or treatment) have been adequately ruled out;

- harm to the subject is due to error in use;

- the event depends on a false result given by the medical device used for diagnosis , when applicable;

- In order to establish the relatedness, not all the criteria listed above might be met at the same time, depending on the type of device/procedures and the event.

Assessment of Expectedness

The expectedness was assessed by the Sponsor for SADEs only:

An Unanticipated Serious Adverse Device Defect is a Serious Adverse Device Effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

Categories of Patient Outcome

The reportable outcomes and/or sequelae of an AE are as follows:

- Resolved

- Resolved with sequelae

- Ongoing

- Death

Recording and Reporting of Adverse Events

The period of observation for AEs extends from Study Screening/Baseline Eligibility

Visit 1 (Week -4) until Visit 10 (Week +52). New AEs reported to the investigator during the observational period, after the study procedure must be documented, treated, and followed up like all other AEs.

AEs will not be followed up after the final investigation visit which is scheduled 12 months after the treatment with the investigational medical device.

Underlying diseases/pre-existing conditions that do not worsen during the course of the investigation are not reportable as AEs. To determine whether a condition has worsened, it is compared to the condition of the subject at baseline.

Elective treatments planned before screening and which are documented in the subject's source data are usually not regarded as AEs.

Data pertaining to AEs will be collected during each investigation visit based through the investigators inquiry or discovered in the course of examinations done during the visit. The investigators will assess and record any AE in detail in the subject file and on the CRF AE report form.

The following information were recorded:

- AE diagnosis or main symptom.

- Date of event onset.

- Severity

- Investigational medical device (blinded)

- Causal relationship (causal related, probably related, possibly related, unlikely related, not related).

- Serious (yes or no).

- Patient outcome

- Action taken /treatment.

- AE falling under the definition of an AESI (yes or no)

- AE leading to discontinuation of the investigation (yes or no)

- AE due to a device deficiency (yes/no)

- Date of event resolution

After completion of all scheduled visit assessments the investigator must document any AEs arising from these assessments. In case of an SAE, the investigator must also complete an SAE report form.

Recording and Reporting of Serious Adverse Events

Statistical Analysis Plan (V1.0, 01.09.2023)

All SAEs that occur during the investigation period, whether considered to be related to the investigational medical device/procedures or not, were reported by the investigator to the Sponsor within 24 hours of knowledge.

SAE report forms are provided in the ISF. Completed reports were signed by an investigator and transferred by fax to:

Medical Device Vigilance Office
Center for Clinical Studies (CCS Erlangen)
Universitätsklinikum Erlangen
Krankenhausstaße 12

91054 Erlangen
Fax: 09131 / 85 35120
email: ams.ccs@uk-erlangen.de

Although all information required for completion of an SAE report form may not be available within the specified time period, an initial report were submitted if the following minimal information is available:

- An identifiable subject (subject ID).

- An identifiable reporting source (investigator/investigation site identification).

- An event or outcome that can be identified as serious.

The investigator must supply further supporting information within 3 days of knowledge of the SAE, and a detailed SAE description is an integral part of this supporting information. Follow-up reports should be sent without delay to the addressee mentioned above as an SAE report form (marked as a "follow-up" report) and accompanied by appropriate supporting documentation (e.g., hospital reports). The SAE has to be followed up until a final outcome and date are available.

SAEs occurring after the end of the observational period need only be reported if the investigator considers the event to be related to the investigational medical device or procedures. These reports generally will not be entered into the study database.

- If a causal relationship between the SAE and the investigational medical device, a comparator device, diagnostic or therapeutic procedures performed as part of the clinical trial or other conditions of the trial conduct cannot be excluded:

SAE report immediately, as a single report on the German SAE report form to MPSAE@bfarm.de

- If A causal relationship between the SAE and the investigational medical device, a comparator device, diagnostic or therapeutic procedures performed as part of the clinical trial or other conditions of the trial conduct can be excluded:

SAE reports quarterly, as a summary table on the MEDDEV 2.7/3 SAE report table to MPSAE@bfarm.de

- In addition all SAE reports quarterly together with a SAE summary evaluation

Recording and Reporting of Device deficiencies

Device deficiencies are defined as inadequacy of a medical device with respect to its identity, quality, durability, reliability, safety and performance. The investigator will record and assess any device deficiency in detail on the CRF Device Deficiency Form.

Recording and Reporting of Pregnancies

Each pregnancy that becomes known during the investigation in a female participant must be reported by the investigator to the addressee mentioned above (see 13.3.2) within 24 hours of learning of its occurrence and followed up until 8 post partum. Pregnancies and pregnancy follow-up should be reported on a Pregnancy Monitoring Form. Pregnancy follow-up should describe the outcome of the pregnancy, including any voluntary or spontaneous discontinuation; details of the birth; the presence or absence of any congenital abnormalities, birth defects, maternal or newborn complications, and their relation to the investigational medical device/procedures. Each pregnancy has to be reported as a non-serious AE (device exposure before or during pregnancy) as well.

2.9.   General Analysis

2.9.1.   General Methodology

Descriptive statistics will be displayed for all documented and derived variables. For continuous variables, number of observations, number of missing values, mean, standard deviation, minimum, median and maximum will be calculated. For categorical variables, number of patients, absolute and relative frequencies will be calculated.

In this parallel, controlled study, data analysis will be performed using unadjusted analysis, i.e. simple paired an unpaired t-test under the assumption of a normal distribution for the difference of interest.

2.9.2. General Information about the Conduct of the Study

General information about the conduct of the trial will be displayed as follows:

The date of first subject in, last subject out and trial duration (duration in days between the first subject in and the last subject out) will be described.

The patient disposition (accounting of patients) will be presented by displaying the number of patients belonging to the different analysis populations.

The number of discontinued subjects and the reasons for discontinuation, on the screened population will be described.

2.9.3. Analysis of Demographic and other Baseline Characteristics

Demographic and patient characteristics will be summarized in tables and listings for the SAF, ITT, modified ITT, PPP, modified PPP, Bavarian population, separated by treatment groups and for the total population.

The demographic characteristics are: age and gender etc.

Summary of medical history and prior or concomitant medication will be presented.

The summary of medical history and current medical conditions including all previous and current medical conditions will be presented by preferred term and by body system of the system.

Baseline values of the efficacy measures will be presented in the efficacy section.

Baseline laboratory values will be presented.

Data from patients who were enrolled into the study, but not treated renal denervation or sham, will be presented in listings. No further analyses will be done with these patients' data.

2.9.4. Analysis of Efficacy

The primary analysis will be conducted on the ITT population.

2.9.4.1. Primary efficacy variable

Primary variable is the change in systolic 24-h ambulatory BP at 6 months post-procedure compared between the 2 groups.

Hence, (e.g.) the following null hypotheses H_0, will be tested against their alternative hypotheses H_1 using unpaired t-test:

H0: There is no significant difference in systolic 24-h ambulatory BP at 6 months post-renal denervation compared between the 2 groups. (RDN group vs. sham group)

H1: There is a significant difference in systolic 24-h ambulatory BP at 6 months post-renal denervation compared between the 2 groups (RDN group vs. sham group).

The overall significance level of the trial is defined as α = 0.05 (two-sided).

2.9.4.2. Secondary efficacy variables

- 24-hour, daytime and nighttime ambulatory variables (Mobil-O-Graph):
    - Mean systolic and diastolic 24-hour ambulatory BP
    - Daytime mean systolic and diastolic ambulatory BP
    - Nighttime mean systolic and diastolic ambulatory BP
    - Mean 24-hour, daytime and nighttime heart rate
    - Mean systolic and diastolic dipping, dipping type
    - Mean 24-hour, daytime and nighttime pulse pressure
    - Mean 24-hour, daytime and nighttime central systolic BP
    - Mean 24-hour, daytime and nighttime central diastolic BP
    - Mean 24-hour, daytime and nighttime augmentation index at 75 bpm
    - Mean 24-hour, daytime and nighttime heart minute volume
    - Mean 24-hour, daytime and nighttime peripheral resistance
    - Mean 24-hour, daytime and nighttime reflexion coefficient
    - Mean 24-hour, daytime and nighttime pulse wave velocity
    - 24 hour central BP and pulse pressure
    - Dipping status

- o 24h hour , daytime and nighttime heart rate

- Office variables

    - o Systolic and diastolic office BP

    - o Pulse pressure

    - o Heart rate

- Home BP (aponorm® Professional Touch)

    - o Systolic and diastolic Home BP
    - o Pulse pressure
    - o Heart rate

- Antihypertensive Medication

    - o medication number, drug burden index, antihypertensive load index

- Renal parameters

    - o Serum creatinine, estimated glomerular filtration rate (eGFR)with serum creatinine (CKD-epi formula) and serum cystatin separately, eGFR derived from the combined creatinine/Cystatin-C formula
    - o Proteinuria, albuminuria, urine sodium, urine potassium, urine creatinine (all parameters in mg/g creatinine)

- Safety endpoints and adverse effects

- Body composition parameters (BCM)

    - o Weigth

    - o Height

    - o Body mass index

    - o Overhydration (OH)

    - o Overhydration in percent (OH%) of extracellular water (ECW)

2.9.5.   Analysis of Safety and Tolerability

All safety analyses will be performed on the SAF population.

2.9.5.1. Adverse Events

Frequency tables for the preferred terms will be compiled, based on patients experiencing an AE and based on the number of AEs. The AE will also be analysed with regard to system organ class. They will be displayed with regard to severity and relationship to study drug. All AEs will be listed.

2.9.5.2. Criteria for clinically notable laboratory abnormalities

Please note: Normal ranges are given by the central laboratory of the University Hospital Erlangen-Nuremberg

Liver parameters:

Serum SGOT, SGPT, γ-GT, AP > 30% of upper normal range

Renal parameters:

decrease of eGFR (CKD-Epi) >30%, serum potassium above normal range, serum sodium under normal range

Hematological parameters:

Abnormal blood cell counts at baseline and changes of ≥ 20% of blood cell counts

Descriptive statistics of all laboratory values will be given.

2.9.6. Vital signs

Descriptive statistics of all vital signs will be produced.

2.9.7. Electrocardiogram

Descriptive statistics will be produced, if applicable.

2.9.8. Physical examination

Descriptive statistics will be displayed, if applicable.

2.9.9. Subgroup analysis

Will be defined once the baseline characteristics and discrepancies are known. Most important subgroup analysis would be to compare all primary and secondary objectives (1.1.1 – 1.1.5) between patients with CKD 3a (eGFR=45-59; creatinine derived eGFR calculated based on CKD-epi formula) and 3b (eGFR=30-44; creatinine derived eGFR calculated based on CKD-epi formula)

2.9.10. Interim analysis

No interim analyses are planned.

3. Literature

1.   Inker, L.A., et al., *New Creatinine- and Cystatin C-Based Equations to Estimate GFR without Race.* N Engl J Med, 2021. **385**(19): p. 1737-1749.
2.   Cheuiche, A.V., et al., *Performance of Cystatin C-Based Equations for Estimation of Glomerular Filtration Rate in Diabetes Patients: A Prisma-Compliant Systematic Review and Meta-Analysis.* Sci Rep, 2019. **9**(1): p. 1418.
3.   Inker, L.A., et al., *Estimating glomerular filtration rate from serum creatinine and cystatin C.* N Engl J Med, 2012. **367**(1): p. 20-9.
4.   Kandzari, D.E., et al., *Prioritised endpoints for device-based hypertension trials: the win ratio methodology.* EuroIntervention, 2021. **16**(18): p. e1496-e1502.
5.   Williams, B., et al., *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.* J Hypertens, 2018. **36**(10): p. 1953-2041.