STATISTICAL ANALYSIS PLAN

Effect of renal denervation in hypertensive patients with autosomal dominant polycystic kidney disease

Investigational products: Renal Denervation

Study code: RDN2021ADPKD

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Statistical Analysis Plan (V1.0)

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List of abbreviations

AE	Adverse Event
AP	Alkaline Phosphatase
BMI	Body Mass Index
BP	Blood Pressure
CK	Creatinine Kinase
CRC	Clinical Research Center
CRF	Case Report Form
cSBP	Central Systolic Blood Pressure
ECG	Electrocardiogram
eGFR	Estimated Glomerular Filtration Rate
γ-GT	Gamma-Glutamyl-Transferase
HbA1c	Glycosylated Hemoglobin
HDL	High-Density Lipoproteins
HR	Heart Rate
IIT	Intention-to-treat
IP	Investigational Product
MI	Myocardial Infarction
PAD	Peripheral Artery Disease
PPP	Per Protocol Population
PP	Per Protocol
PT	Premature Termination
RAS	Renin Angiotensin System
RBC	Red Blood Cell Count
SAE	Serious Adverse Event
SAF	Safety
SC	Subcutaneous
SCR	Screened

SFU	Safety Follow-Up
SGOT	Serum Glutamate-Oxaloacetate-Transaminase
SGPT	Serum Glutamate-Pyruvate-Transaminase
TSH	Thyroid-Stimulating Hormone
UV	Unscheduled Visit
WBC	White Blood Cell count
WHO	World Health Organization

1. Protocol summary

1.1. Study Objectives

The purpose of the RDN-ADPKD is to demonstrate the ability of the ReCor catheter system to effectively reduce systolic and diastolic ambulatory BP in hypertensive patients with ADPKD. The objective of the RDN-ADPKD study is to demonstrate efficacy and verify safety of RDN with the Paradise System in hypertensive patients with ADPKD.

Pre-treatment values ware defined as follows:

Screening value (S) = screening visit (week -4) value

Baseline value (B) = baseline visit (week -1) value

Pre-treatment value (P) = average of the baseline visit (week -1) value and screening visit (week -4) value

1.1.1. Safety

- Safety endpoints and adverse effects for the duration of the study in the whole study group

1.1.2. Primary objective

The primary efficacy parameter is:

- Change in systolic 24-h ambulatory BP at 3 months post-procedure from pre-treatment (including S, B and P) in the whole study group (irrespective whether treated immediate [I-RDN-group] or delayed [D-RDN-group]).

1.1.3. Key Secondary objectives

Key BP Related Secondary Endpoints

Ambulatory BP changes

Group	Parameter
Whole study group	Change in diastolic 24-h ambulatory BP at 3 months post-procedure in the whole study group (irrespective whether treated immediate [I-RDN-group] or delayed [D-RDN-group]) compared to pre-treatment (including S, B and P).
	Change in systolic and diastolic 24-h ambulatory BP at 6, 12, 18, 24, 30 and 36 months post-procedure in the whole study group compared to pre-treatment (including S, B and P).
	These analyses of ambulatory BP changes will be repeated for daytime and nighttime BP changes identical to the 24h ambulatory BP changes.
I-RDN versus D-RDN	Change in systolic and diastolic 24-h ambulatory BP at 3 months post-procedure from pre-treatment (including S, B and P) in the I-RDN-group versus the change in systolic and diastolic 24-h ambulatory BP from pre-treatment (including S, B and P) to 3 months

	later in D-RDN-group.
	Responder rate in BP (systolic office BP ≥ 5 mmHg, or 24-h systolic ambulatory BP ≥ 3 mmHg) at 3 months pre-treatment (including S, B and P) in the I-RDN-group versus responder rate in BP from pre-treatment (including S, B and P) to 3 months later in the D-RDN-group.

Office BP changes

Group	Parameter and Description
Whole study group	Change in systolic and diastolic office BP at 3, 6, 12, 18, 24, 30 and 36 months post-procedure in the whole study group compared to pre-treatment (including S, B and P).
I-RDN versus D-RDN	Change in systolic and diastolic office BP at 3 months post-procedure from pre-treatment (including S, B and P) in the I-RDN-group versus the change in systolic and diastolic office BP pre-treatment (including S, B and P) to 3 months later in D-RDN-group.

Home BP changes

Group	Parameter and Description
Whole study group	Change in systolic and diastolic home BP (IEM-Tel-O-Graph-GSM) at 3, 6, 12, 24 and 36 months post-procedure in the whole study group compared to pre-treatment (including S, B and P).
I-RDN versus D-RDN	Change in systolic and diastolic home BP at 3 months post-procedure from pre-treatment (including S, B and P) in the I-RDN-group versus the change in systolic and diastolic home BP from pre-treatment (including S, B and P) to 3 months later in D-RDN-group.

Win ratio analysis

Win ratio analysis will also be conducted, with the criteria 24h ambulatory systolic BP change > 3 mmHg, and office systolic BP change > 5 mmHg at 3 months from pre-procedure (including P and B) in the I-RDN compared to the D-RDN group.(1)

Group	Parameter and Description
I-RDN versus D-RDN	Win ratio analysis will be conducted, with the criteria 24h ambulatory systolic BP change > 3 mmHg, office systolic BP change > 5 mmHg, and decrease of medication number from pre-treatment (including S, B and P) to 3 month post procedure in the I-RDN group versus pre-treatment (including S, B and P) to 3 months later in D-RDN-group.
	Win ratio analysis will be conducted, with the criteria 24h ambulatory systolic BP change > 3 mmHg, office systolic BP change > 5 mmHg, and any decrease of drug burden index from pre-treatment (including S, B and P) to 3 month post procedure in the I-RDN group versus pre-treatment (including S, B and P) to 3 months later in D-RDN-group.

	Win ratio analysis will be conducted, with the criteria 24h ambulatory systolic BP change > 3 mmHg, office systolic BP change > 5 mmHg, and any decrease of antihypertensive load index from pre-treatment (including S, B and P) to 3 month post procedure in the I-RDN group versus pre-treatment (including S, B and P) to 3 months later in D-RDN-group

Key Renal Related Secondary Endpoints

Group	Parameter and Description
Whole study group	Change in serum creatinine, cystatin C and derived estimated glomerular filtration rate (eGFR) at 3, 6, 12, 18, 24, 30 and 36 months post-procedure in the whole study group compared to pre-treatment (including S and B).
	Change in total kidney volume (assessed by magnetic resonance imaging) at 6, 12, 24 and 36 months post-procedure in the whole study group compared to pre-treatment (including B).
	Change in measured GFR (assessed by single-shot iohexol clearance) at 6, 12, 24 and 36 months post-procedure in the whole study group compared to pre-treatment (including B).
	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, 12, 18, 24, 30 and 36 months post-procedure from pre-treatment (including S and B).
	Change of the slope of eGFR (derived from creatinine; CKD-epi formula) after 3, 6, 12, 18, 24, 30 and 36 months post-procedure from pre-treatment (including S and B) compared to the historical slope the year before in the total study group.
I-RDN versus D-RDN	Change in serum creatinine, cystatin C and derived eGFR at 3 months post-procedure from pre-treatment (including S and B) in the I-RDN-group versus the change serum creatinine, cystatin C and derived eGFR from pre-treatment (including S and B) to 3 months later in D-RDN-group.
	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 from pre-procedure pre-treatment (including S and B) in the I-RDN-group versus the change from pre-treatment (including S and B) to 3 months later in the D-RDN-group.
	Change of the slope of eGFR (derived from creatinine; CKD-epi formula) after 3 month post-procedure from pre-treatment (including S and B) eGFR values) in the I-RDN group compared to change after 3 month FU from pre-treatment (including S and B) in the D-RDN group.

1.1.4. Observational Efficacy Assessment

group	parameter	description
Whole study	Level of pain	Level of pain (related to ADPKD) determined by the use

group		of a visual analogue scale at 3, 6, 12, 24 and 36 months post-procedure in the whole study group compared to pre-treatment (including B).
	Quality of life	Change in Quality of life (QoL) (e.g. ADPKD Impact Scale or EQ-5D-5L) at 3, 6, 12, 24 and 36 months post-procedure in the whole study group compared to compared to pre-treatment (including B).
	Biomarkers	Change in plasma and urinary biomarkers (e.g. albumin, copeptin) at 6, 12 months post-procedure in the whole study group compared to pre-treatment (including B).
	Medication/Drug burden	Change in number of antihypertensive drugs at 3, 6, 12, 18, 24, 30 and 36 months post-procedure from pre-treatment (including B) in the whole study group.
	Medication/Drug burden	Change in drug burden index at 3, 6, 12, 18, 24, 30 and 36 months post-procedure from pre-treatment (including B) in the whole study group.
	Medication/Drug burden	Change in antihypertensive load index at 3, 6, 12, 18, 24, 30 and 36 months post-procedure from pre-treatment (including B) in the whole study group.
I-RDN versus D-RDN	Medication/Drug burden	Change in number of antihypertensive drugs from pre-treatment (including S, B and P) to 3 month post procedure in the I-RDN group versus pre-treatment (including S, B and P) to 3 months later in D-RDN-group.
	Medication/Drug burden	Change in drug burden index from pre-treatment (including S, B and P) to 3 month post procedure in the I-RDN group versus pre-treatment (including S, B and P) to 3 months later in D-RDN-group.
	Medication/Drug burden	Change in antihypertensive load index from pre-treatment (including S, B and P) to 3 month post procedure in the I-RDN group versus pre-treatment (including S, B and P) to 3 months later in D-RDN-group.
Whole study group	Heart rate	Change in average 24 hour ambulatory heart rate at 3, 6, 12, 18, 24, 30 and 36 months post-procedure from pre-treatment (including S, B and P) in the whole study group.
	Heart rate	Change in office heart rate at 3, 6, 12, 18, 24, 30 and 36 months post-procedure from pre-treatment (including S, B and P) in the whole study group.
I-RDN versus D-RDN	Heart rate	Change in average 24 hour ambulatory heart rate at 3 month post procedure from pre-treatment (including S, B and P) in the I-RDN group versus pre-treatment (including S, B and P) to 3 months later in D-RDN-group.
	Heart rate	Change in office heart rate at 3 month post procedure from pre-treatment (including S, B and P) in the I-RDN group versus pre-treatment (including S, B and P) to 3 months later in D-RDN-group.
I-RDN versus D-	BP control	Incidence of ambulatory systolic BP (daytime/24-

RDN		h/night-time) reductions of ≥ 3 mmHg, ≥ 5 mmHg at 3 months post-procedure from pre-treatment (including S, B and P) in the I-RDN group compared to 3 months later from pre-treatment (including S, B and P) in the D-RDN group.
	BP control	Percentage of subjects who are controlled in the absence of changes in hypertensive medication at 3 months post-procedure in the I-RDN compared to 3 month after pre-treatment (including S, B and P) in the D-RDN group. (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)
	BP control	Percentage of subjects who are controlled irrespective of any changes in hypertensive medication at 3 months post-procedure in the I-RDN compared to 3 month after pre-treatment (including S, B and P) in the D-RDN group. (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)
Whole study group	Arterial stiffness	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, 12, 18, 24, 30 and 36 months post-procedure from pre-treatment (including B) in the total study group. • Pulse pressure, central systolic pressure, central diastolic pressure, augmentation index at 75 beats per minute, heart minute volume (HMV), peripheral resistance, reflexion coefficient, pulse wave velocity (PWV)
	Arterial stiffness	Change in office and 24 hour ambulatory pulse pressure at 3, 6, 12, 18, 24, 30 and 36 months post-procedure from pre-treatment (including B) in the total study group.

- 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
    - 1) comparing the treatment values at 3, 6, 12, 18, 24, 30 and 36 months with 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 total study group.
    - 2) comparing the difference between treatment values at 3 months post procedure and pre-procedure values in the I-RDN group with the difference between follow up values at 3 month and pre-procedure values in the D-RDN group.

1.1.5. Procedure details in both groups (I-RDN and D-RDN group)

Procedure and renal denervation details in both groups 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)
- 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)
- Renal denervation in close proximity to a renal cyst (yes or no)

1.1.6. Safety analysis

- Safety endpoints and adverse effects during 3 months post-procedure in the I-RDN group compared to 3 months follow up in the D-RDN group.
    - Comparison of number / percentages of SAE, AE, AESI, escape rate between the 2 groups
- Safety endpoints and adverse effects 3, 6, 12, 18, 24, 30 and 36 months post-procedure in the total study 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
- Increase of serum creatinine / eGFR (calculated based on CKD-epi) between visit 2 (week -1) and visit 6 (week +13) between the 2 groups (I-RDN and D-RDN group) and in each group separately
- Change in hematuria determined by urine dipstick at 3, 6, 12, 18, 24, 30 and 36 months post-procedure from pre-procedure (pre-procedure visit (week -1) value and screening visit (week -4)) in the whole study cohort.
- Safety endpoints and adverse effects in patient group with renal denervation in close proximity to a renal cyst compared to safety endpoints and adverse effects in patient group with no renal denervation in close proximity to a renal cyst.

The following events will be presented at all-time points post-procedure comparing the I-RDN and D-RDN group:

- 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

The following AESIs will be presented as a table at all time points post-procedure comparing the I-RDN and D-RDN group:

- 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 the I-RDN and D-RDN group

- 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

1.1.7. Design of the Trial

RDN-ADPKD is a prospective, randomized (1:1, central randomization), single-center, hypothesis-generating, feasibility study.

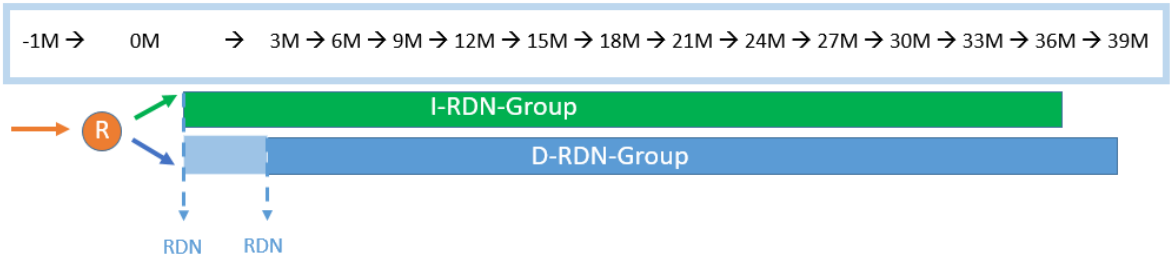
If the patient fulfils inclusion criteria and in the absence of exclusion criteria at visit 1, the patient has been enrolled into the trial, and the study visits were scheduled. All subjects have their office BP measured, a limited medical history review, physical exam and current medication review and a safety laboratory evaluation. Furthermore, an ABP measurement was conducted.

At Visit 2 patients are randomized into (immediate) I-RDN-group and (delayed) D-RDN-group, respectively. Patients in the I-RDN group will undergo RDN-procedure within one week after randomization. Patients in the D-RDN-group will undergo RDN-procedure within three month. Patients in both groups will be followed for additional 36 months.

At Visit 2 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. Subjects of child bearing potential must have a documented negative pregnancy test dated within a maximum of 7 days prior to the procedure.

FU Visits took place 3 weeks, 7 weeks and 3, 6, 12, 18, 24, 30 and 36 months post-procedure.

Hence, study design allows several comparisons both of whole study group (at same time-point of follow-up) as well as between I-RDN-group and D-RDN-group.



Escape Criteria

Enrolled subjects will be excluded:

- if home BP increases to ≥160 systolic or ≥100 mmHg diastolic pre-randomization, confirmed by office (attended) BP ≥170/105mmHg
- if office (attended) BP exceeds ≥170/105 mmHg pre-randomization, confirmed by 7-day average of home BP measurements ≥ 160/100 mmHg (excluding white coat effect) or confirmed by office (attended) 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

1.1.8. 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[I]	V4[I]	V5[I]	V6	V7[D]	V8[D]	V9	V10	V11[D]	V12[D]
Week	-4	-1	0	3	7	13	13	16	20	26	33	39
Informed consent	X											
Inclusion/exclusion criteria	X											
Medical history	X											
Randomization		X										
RDN			X				X					
Physical exam	X	X	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	X	X
Home BP[3]	X	X		X	X	X				X		X
Safety and efficacy lab	X	X	X	X	X	X	X	X	X	X	X	X
AEs/ADEs	X	X	X	X	X	X	X	X	X	X	X	X
Questionaire (Pain, QoL)		X				X				X		X
Urinalysis (hematuria, UACR)	X	X	X	X	X	X	X	X	X	X	X	X
Biomarkers (plasma and urine)		X[I]				X[D]				X[I]		X[D]
eGFR, Cystatin C	X	X				X				X		X
Urinary toxicological analyses[4]		X				X				X		X
MRA of Renal Arteries[5]		X[I]				X[D]						
Medication review	X	X	X	X	X	X	X	X	X	X	X	X
MRI (total kidney volume)		X[I]				X[D]				X[I]		X[D]
Iohexol clearance		X[I]				X[D]				X[I]		X[D]

Table 2. Visit schedule; note: visits V1 – V12 can be scheduled +/-5days; Visits V4, V5, V8, V9 and V11 can be done by the (referring) physician

[I] only in patients of the I-RDN-group; [D] only in patients of the D-RDN-group

[1] 24-h ambulatory BP measurements will be conducted by Mobil-O-Graph (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] Home BP measurments will be conducted by IFM-Tel-O-Graph-GSM

4To assess adherence to prescribed medication (the CCC 2017[31] suggest to perform adherence measurements by urine toxicological measurements. In Germany, the forensic institutes in Homburg (the master) and in Frankfurt (the scholar) have performed these measurements in the SPYRAL MED OFF and ON trials by analyzing all antihypertensive drugs thereby detecting drop-ins and drop-outs qualitatively.[only dihydralazine cannot be detected]. We will use the experienced center in Frankfurt (Prof Tönnes) or in Homburg (Prof. Meyer) and the result will be used for the adherence per protocol study population analysis.
Please note that no specific storage or shipment (e.g. no dry ice or immediate need to froze samples is necessary)
5MRA has only to be performed if no images (previous MRI, previous CT, previous angiogram) of anatomy of renal artery supply is available

Visit #	V13[I]	V14[D]	V15[I]	V16[D]	V17[I]	V18[D]	V19[I]	V20[D]	V21[I]	V22[D]
Week	52	65	78	91	104	117	130	143	156	169
Informed consent										
Inclusion/exclusion criteria										
Medical history										
Randomization										
RDN										
Physical exam	X	X	X	X	X	X	X	X	X	X
24-h ABP measurement[1]	X	X			X	X			X	X
Office (attended) BP[2]	X	X	X	X	X	X	X	X	X	X
Home BP[3]	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
Questionaire (Pain, QoL)	X	X			X	X			X	X
Urinalysis (hematuria, UACR)	X	X	X	X	X	X	X	X	X	X
Biomarkers (plasma and urine)	X	X			X	X			X	X
eGFR, Cystatin C	X	X	X	X	X	X	X	X	X	X
Urinary toxicological analyses[4]	X	X			X	X			X	X
Medication review	X	X	X	X	X	X	X	X	X	X
MRI (total kidney volume)	X	X			X	X			X	X
Iohexol clearance	X	X			X	X			X	X

Table 3. Visit schedule; note: visits V13 – V22 can be scheduled +/- 4 weeks

[I] only in patients of the I-RDN-group; [D] only in patients of the D-RDN-group.
[1] 24-h ambulatory BP measurements will be conducted by Mobil-O-Graph (IEM, Aachen) allowing also the assessment of central systolic BP in addition to brachial BP readings.

2. Outcome Measures and Target Parameters

2.1. Efficacy

Pre-treatment values ware defined as follows:

Screening value (S) = screening visit (week -4) value

Baseline value (B) = pre-procedure visit (week -1) value

Pre-treatment value (P) = average of the baseline visit (week -1) value and screening visit (week -4) value

The primary efficacy parameter is:

- Change in systolic 24-h ambulatory BP at 3 months post-procedure from pre-treatment (including S, B and P) in the whole study group (irrespective whether treated immediate [I-RDN-group] or delayed [D-RDN-group]).

2.1.1. Key Secondary objectives

Key BP Related Secondary Endpoints

Ambulatory BP changes

Group	Parameter
Whole study group	Change in diastolic 24-h ambulatory BP at 3 months post-procedure in the whole study group (irrespective whether treated immediate [I-RDN-group] or delayed [D-RDN-group]) compared to pre-treatment (including S, B and P).
	Change in systolic and diastolic 24-h ambulatory BP at 6, 12, 18, 24, 30 and 36 months post-procedure in the whole study group compared to pre-treatment (including S, B and P).
	These analyses of ambulatory BP changes will be repeated for daytime and nighttime BP changes identical to the 24h ambulatory BP changes.
I-RDN versus D-RDN	Change in systolic and diastolic 24-h ambulatory BP at 3 months post-procedure from pre-treatment (including S, B and P) in the I-RDN-group versus the change in systolic and diastolic 24-h ambulatory BP from pre-treatment (including S, B and P) to 3 months later in D-RDN-group.
	Responder rate in BP (systolic office BP ≥ 5 mmHg, or 24-h systolic ambulatory BP ≥ 3 mmHg) at 3 months pre-treatment (including S, B and P) in the I-RDN-group versus responder rate in BP from pre-treatment (including S, B and P) to 3 months later in the D-RDN-group.

Office BP changes

Group	Parameter and Description
Whole study group	Change in systolic and diastolic office BP at 3, 6, 12, 18, 24, 30 and 36 months post-procedure in the whole study group compared to pre-treatment (including S, B and P).
I-RDN versus D-RDN	Change in systolic and diastolic office BP at 3 months post-procedure from pre-treatment (including S, B and P) in the I-RDN-group versus the change in systolic and diastolic office BP pre-treatment (including S, B and P) to 3 months later in D-RDN-group.

Home BP changes

Group	Parameter and Description
Whole study group	Change in systolic and diastolic home BP (IEM-Tel-O-Graph-GSM) at 3, 6, 12, 24 and 36 months post-procedure in the whole study group compared to pre-treatment (including S, B and P).
I-RDN versus D-RDN	Change in systolic and diastolic home BP at 3 months post-procedure from pre-treatment (including S, B and P) in the I-RDN-group versus the change in systolic and diastolic home BP from pre-treatment (including S, B and P) to 3 months later in D-RDN-group.

Win ratio analysis

Win ratio analysis will also be conducted, with the criteria 24h ambulatory systolic BP change > 3 mmHg, and office systolic BP change > 5 mmHg at 3 months from pre-procedure (including P and B) in the I-RDN compared to the D-RDN group.(1)

Group	Parameter and Description
I-RDN versus D-RDN	Win ratio analysis will be conducted, with the criteria 24h ambulatory systolic BP change > 3 mmHg, office systolic BP change > 5 mmHg, and decrease of medication number from pre-treatment (including S, B and P) to 3 month post procedure in the I-RDN group versus pre-treatment (including S, B and P) to 3 months later in D-RDN-group.
	Win ratio analysis will be conducted, with the criteria 24h ambulatory systolic BP change > 3 mmHg, office systolic BP change > 5 mmHg, and any decrease of drug burden index from pre-treatment (including S, B and P) to 3 month post procedure in the I-RDN group versus pre-treatment (including S, B and P) to 3 months later in D-RDN-group.
	Win ratio analysis will be conducted, with the criteria 24h ambulatory systolic BP change > 3 mmHg, office systolic BP change > 5 mmHg, and any decrease of antihypertensive load index from pre-treatment (including S, B and P) to 3 month post procedure in the I-RDN group versus pre-treatment (including S, B and P) to 3 months later in D-RDN-group

Key Renal Related Secondary Endpoints

Group	Parameter and Description
Whole study group	Change in serum creatinine, cystatin C and derived estimated glomerular filtration rate (eGFR) at 3, 6, 12, 18, 24, 30 and 36 months post-procedure in the whole study group compared to pre-treatment (including S and B).
	Change in total kidney volume (assessed by magnetic resonance imaging) at 6, 12, 24 and 36 months post-procedure in the whole study group compared to pre-treatment (including B).
	Change in measured GFR (assessed by single-shot iohexol clearance) at 6, 12, 24 and 36 months post-procedure in the whole study group compared to pre-treatment (including B).
	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, 12, 18, 24, 30 and 36 months post-procedure from pre-treatment (including S and B).
	Change of the slope of eGFR (derived from creatinine; CKD-epi formula) after 3, 6, 12, 18, 24, 30 and 36 months post-procedure from pre-treatment (including S and B) compared to the historical slope the year before in the total study group.
I-RDN versus D-RDN	Change in serum creatinine, cystatin C and derived eGFR at 3 months post-procedure from pre-treatment (including S and B) in the I-RDN-group versus the change serum creatinine, cystatin C and derived eGFR from pre-treatment (including S and B) to 3 months later in D-RDN-group.
	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 from pre-procedure pre-treatment (including S and B) in the I-RDN-group versus the change from pre-treatment (including S and B) to 3 months later in the D-RDN-group.
	Change of the slope of eGFR (derived from creatinine; CKD-epi formula) after 3 month post-procedure from pre-treatment (including S and B) eGFR values) in the I-RDN group compared to change after 3 month FU from pre-treatment (including S and B) in the D-RDN group.

2.1.2. Observational Efficacy Assessment

group	parameter	description
Whole study group	Level of pain	Level of pain (related to ADPKD) determined by the use of a visual analogue scale at 3, 6, 12, 24 and 36 months post-procedure in the whole study group compared to pre-treatment (including B).
	Quality of life	Change in Quality of life (QoL) (e.g. ADPKD Impact Scale or EQ-5D-5L) at 3, 6, 12, 24 and 36 months post-procedure in the whole study group compared to compared to pre-treatment (including B).
	Biomarkers	Change in plasma and urinary biomarkers (e.g.

		albumin, copeptin) at 6, 12 months post-procedure in the whole study group compared to pre-treatment (including B).
	Medication/Drug burden	Change in number of antihypertensive drugs at 3, 6, 12, 18, 24, 30 and 36 months post-procedure from pre-treatment (including B) in the whole study group.
	Medication/Drug burden	Change in drug burden index at 3, 6, 12, 18, 24, 30 and 36 months post-procedure from pre-treatment (including B) in the whole study group.
	Medication/Drug burden	Change in antihypertensive load index at 3, 6, 12, 18, 24, 30 and 36 months post-procedure from pre-treatment (including B) in the whole study group.
I-RDN versus D-RDN	Medication/Drug burden	Change in number of antihypertensive drugs from pre-treatment (including S, B and P) to 3 month post procedure in the I-RDN group versus pre-treatment (including S, B and P) to 3 months later in D-RDN-group.
	Medication/Drug burden	Change in drug burden index from pre-treatment (including S, B and P) to 3 month post procedure in the I-RDN group versus pre-treatment (including S, B and P) to 3 months later in D-RDN-group.
	Medication/Drug burden	Change in antihypertensive load index from pre-treatment (including S, B and P) to 3 month post procedure in the I-RDN group versus pre-treatment (including S, B and P) to 3 months later in D-RDN-group.
Whole study group	Heart rate	Change in average 24 hour ambulatory heart rate at 3, 6, 12, 18, 24, 30 and 36 months post-procedure from pre-treatment (including S, B and P) in the whole study group.
	Heart rate	Change in office heart rate at 3, 6, 12, 18, 24, 30 and 36 months post-procedure from pre-treatment (including S, B and P) in the whole study group.
I-RDN versus D-RDN	Heart rate	Change in average 24 hour ambulatory heart rate at 3 month post procedure from pre-treatment (including S, B and P) in the I-RDN group versus pre-treatment (including S, B and P) to 3 months later in D-RDN-group.
	Heart rate	Change in office heart rate at 3 month post procedure from pre-treatment (including S, B and P) in the I-RDN group versus pre-treatment (including S, B and P) to 3 months later in D-RDN-group.
I-RDN versus D-RDN	BP control	Incidence of ambulatory systolic BP (daytime/24-h/night-time) reductions of ≥ 3 mmHg, ≥ 5 mmHg at 3 months post-procedure from pre-treatment (including S, B and P) in the I-RDN group compared to 3 months later from pre-treatment (including S, B and P) in the D-RDN group.
	BP control	Percentage of subjects who are controlled in the absence of changes in hypertensive medication at 3 months post-procedure in the I-RDN compared to 3 month after pre-treatment (including S, B and P) in the

		D-RDN group. (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)
	BP control	Percentage of subjects who are controlled irrespective of any changes in hypertensive medication at 3 months post-procedure in the I-RDN compared to 3 month after pre-treatment (including S, B and P) in the D-RDN group. (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)
Whole study group	Arterial stiffness	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, 12, 18, 24, 30 and 36 months post-procedure from pre-treatment (including B) in the total study group. • Pulse pressure, central systolic pressure, central diastolic pressure, augmentation index at 75 beats per minute, heart minute volume (HMV), peripheral resistance, reflexion coefficient, pulse wave velocity (PWV)
	Arterial stiffness	Change in office and 24 hour ambulatory pulse pressure at 3, 6, 12, 18, 24, 30 and 36 months post-procedure from pre-treatment (including B) in the total study group.

- 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
    - 1) comparing the treatment values at 3, 6, 12, 18, 24, 30 and 36 months with 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 total study group.
    - 2) comparing the difference between treatment values at 3 months post procedure and pre-procedure values in the I-RDN group with the difference between follow up values at 3 month and pre-procedure values in the D-RDN group.

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.

Safety assessments will be collected from the time a subject signs the informed consent form until the visit 21 (I-group) and visit 22 (D-group), respectively.

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 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. 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.

All safety aspects mentioned in chapter 1.1.5 will be listed and compared between 1) the I-RDN and D-RDN group and 2) between pre-procedure and all FU time points in the whole study group.

2.3. Analysis populations

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

The **Screened population (SCR population)** included all patients who provided informed consent and any demographic or baseline assessment.

The **Safety population (SAF population)** included all patients who underwent the procedure renal denervation. It thus also includes patients without any efficacy measurements after randomization.

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

The **Per Protocol population (PP population)** included all patients of the ITT population who did not show any major protocol violation. These patients received at least two measurements of 24-h ambulatory BP, one at baseline and one 3 months post-procedure, done in technically high quality.

Use of analysis sets

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

The efficacy data will be displayed on the PP and the SAF population. The PP population will be the basis for the primary analysis, since this is a mechanistic study and not an endpoint trial.

2.4. Analyses

Statistical analyses will be based on the basis of international guidelines (CPMP/ICH/363/96:E9).

Efficacy:

Change of systolic 24-h ambulatory BP at 3 months post-procedure from pre-procedure in the whole study group. (primary efficacy endpoint) will be analyzed in a linear mixed model including the covariates that were significantly different between the time points. 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 between the time points. 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 per protocol population (PP).

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

3. A secondary analysis will be done with the intention to treat population (ITT).

4. A secondary analysis will be done with the modified intention to treat population (mITT) in which study subjects of the ITT 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.

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 by the Study Data Manager. 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 principal investigator, 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

Derivations like change from baseline and/or previous visit are not mentioned in this chapter, but in the corresponding analysis section. Parameters used as objectives of the trial, will not be recalculated by programming as they are already calculated by the devices. Source data, resp. printouts delivered by the devices will be fixed up into the case report form (CRF).

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 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, 3, 6, 12, 24 and 36 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.(2)

24-hour ambulatory blood pressure

The measurement of 24-h ABP will occur at -4, -1 (only I-RDN group), 13, 26, and 39 (only D-RDN group), 52 (only I-RDN group), 65 (only D-RDN group), 104 (only I-RDN group), 117 (only D-RDN group), 156 (only I-RDN group) and 169 (only D-RDN group) weeks visits. Study participants will be trained on the use of the ABP system (Mobilograph®, I.E.M. Stolberg, Germany). Subjects will return the device approximately 24 hours later with the ABP system

to download the ABP data (transport of ABP systems to the clinical center may be arranged at the discretion of the Investigator). 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.(2)

- The ABP system will be provided by the clinical center to the subject with an appropriate cuff size for the person's arm

- The cuff will be attached to the patient's non-dominant arm after they have had their office (attended) BP recorded. System set up (including choice and fitting of BP cuff) subject instructions for use will be included in the Manual of Operations

- The subjects will be instructed that they may not remove the BP cuff during the 24-h period of recording even when washing.

- The subjects will be instructed that they should relax their arm and try not to walk or speak during the period in which measurements occur.

- BP will be measured every 20 minutes during daytime (07:00-22:00) and every 30 min overnight (22:00-07:00).

- Only ABP recordings with a minimum of 28 measurements during the 24 hour period will be considered valid. In case of a non-valid measurement, a new ABP recording can be performed the next day.

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 (Tel-O-Graph® GSM, IEM) during the visit at which they are assigned to either cohort. Subjects will measure their BP at home during the 7 consecutive days prior to each scheduled office FU visit. It is recommended that the clinical site contact the subject to remind them when to begin their 7 day Home BP monitoring. Measurements will be taken in a quiet room with the subject in a seated position, back and arm supported after at least 5 minutes of rest with the adapted cuff placed at the level of the brachial artery

- Two BP measurements will be made after a period of at least 5 minutes rest, 1-2 minutes apart twice daily. The two measurements should be made once in the morning prior to eating and antihypertensive drug intake (if relevant) and once in the evening after eating. The time that BP measurements are made will be immediately documented in the patient diary.

- It will be ensured that the same arm is used for all Home BP measurements.

- Home BP values will be calculated as the mean of all measurements taken after the first day which will be discarded. A minimum of 18 BP measurements are required for a valid reading.

- These instructions follow current guidelines.(2)

eGFR Calculation:

eGFR calculations for inclusion will be standardized using the currently used estimation formulas (MDRD, CKD-EPI, serum creatinine and cystatin c based combined formula)

Laboratory Assessments:

All subjects will have blood and urine samples collected at every visit (see visit scedule). 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 V2 (only I-RDN), V6 (only D-RDN), V10 (only I-RDN) and V12 (only D-RDN group), V13 (only I-RDN group), V14 (only D-RDN group), V17 (only I-RDN group), V18 (only D-RDN group), V21 (only I-RDN group) and V22 (only D-RDN group) will be analyzed.

MRI (total kidney volume)

Calculation of TKV based on MRI using the ellipsoid formula will be done according the minimal MRI protocol given in the “Recommendations for Diagnostic and Prognostic Evaluation of Autosomal Dominant Polycystic Kidney Disease (ADPKD) with a Focus on Imaging”.(3) Additional images may be done according to the protocols of TEMPO 3:4 trial(4) and TEMPO 4:4 trial.(5)

Single-shot iohexol clearance

Single-shot iohexol clearance (infusion of 5ml of iohexol solution, containing 3235 mg of iohexol [Accupaque, GE Healthcare Buchler, Braunschweig, Germany] administered intravenously into an antecubital, forearm or hand vein, and flushed with 10 mL of saline) with repeatedly blood sample collections up to 5 hours will be applied for assessment of GFR. Iohexol is approved on the German market and the single-shot clearance is a standard diagnostic procedure in nephrology departments to precisely measure GFR, e.g. used in Erlangen to evaluate living donors.

Biomarkers (plasma and urine)

Plasma and urinary biomarkers (e.g. albumin, IgG, α1MG, β2MG, KIM-1, NGAL, MCP-1) will be analyzed according the manual of the individual biomarker, respectively.(6, 7)

Quality of life

Assessment of QoL (e.g. ADPKD Impact Scale50 or EQ-5D-5L) will be done using common questionnaire(s), respectively.

Level of pain

Assessment of “Level of pain” (related to ADPKD) will be done using a visual analogue scale.

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 should make a judgment based on personal experience.

Assessment of Seriousness

The seriousness will be 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 will be 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 risk assessment.

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 22 (D-RDN group, week +169) and Visit 21 (I-RDN-group, week +156) 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 3 years 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

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

- 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 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. 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 and unpaired t-test under the assumption of a normal distribution for the difference of interest.

The statistical analysis will be done on a per protocol study population (The safety analysis includes all randomized patients) including the steps described below (exploratory analysis):

- First, the primary and secondary objectives measured at 3 months, 6, months, 12 months, 18 months, 24 months, 30 months and 36 months (e.g. primary objective: systolic 24-h ambulatory BP at 3 months post-procedure) in the whole study group (irrespective whether treated I-RDN-group or delayed D-RDN-group] are compared to pre-procedure (including P and B). (paired t-test in case of normal distribution)
- Second, Changes of secondary objectives between 3 months and pre-procedure (including P and B). in the I-RDN-group are compared to the change between 3 month FU and pre-procedure (including P and B). in D-RDN-group. (unpaired t-test in case of normal distribution)

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 SCR 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, PP and AS population, separated by treatment group and for the total population.

The demographic characteristics are: age and gender

Clinical characteristics at visit 1 will be described (in a table) for the IIT population. 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 with renal denervation, 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 PP population.

2.9.4.1. Primary efficacy variable

The primary endpoint of this pilot study is the change in systolic 24-h ambulatory BP at 3 months post-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) in the whole study group (irrespective whether treated immediate [I-RDN-group] or delayed [D-RDN-group]).

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

H_0: There is no significant difference in systolic 24-h ambulatory BP at 3 months post-procedure from pre-procedure in the whole study group.

H_1: There is a significant difference in systolic 24-h ambulatory BP at 3 months post-procedure from pre-procedure in the whole study group.

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

2.9.4.2. Secondary efficacy variables

- 24-hour, daytime and nighttime ambulatory variables (Molbil-O-Graph):
    - Mean systolic and diastolic 24-hour ambulatory BP
    - Daytime systolic and diastolic 24-hour ambulatory BP
    - Nighttime systolic and diastolic 24-hour ambulatory BP
    - 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
    - 24h hour , daytime and nighttime heart rate

- Office BP
    - Systolic and diastolic office BP
    - Pulse pressure
    - Heart rate
- Home BP (aponorm ® Professional Touch)
    - Systolic and diastolic Home BP
    - Pulse pressure
    - Heart rate
- Antihypertensive Medication
    - Medication number, drug burden index, antihypertensive load index
- Renal parameters

  - 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
  - Total kidney volume (assessed by magnetic resonance imaging)
  - Proteinuria, albuminuria, urine sodium, urine potassium, urine creatinine (all parameters in mg/g creatinine)

- Safety endpoints and adverse effects
- Level of pain (related to ADPKD) determined by the use of a visual analogue scale
- Change in Quality of life (QoL) (e.g. ADPKD Impact Scale or EQ-5D-5L)
- Change in plasma and urinary biomarkers (e.g. albumin, IgG, KIM-1, NGAL, MCP-1) at 6, 12
- Body composition parameters (BCM)
  - Weigth
  - Height
  - Body mass index
  - Overhydration (OH)
  - 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

Subgroup analyses are planned in an exploratory way, for primary and secondary objectives. Possible subgroups are based on age, baseline eGFR and total kidney volume.

2.9.10. Interim analysis

An interim analyses is planned when 20 patients completed the 6 months FU (irrespective whether I-RDN or D-RDN group) in order to see a signal, whether a larger study should be initiated.

3. Literature

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