Clinical Study Report

Study title:	Prevention of Silent Cerebral Thromboembolism by Oral Anticoagulation with Dabigatran after Pulmonary Vein Isolation for Atrial Fibrillation
Shorttitle:	The ODIn-AF Study
Sponsor´s Protocol Code	MED2-201301
EudraCT No.:	2013-003492-35
Sponsor:	Rheinische Friedrich-Wilhelm-University of Bonn, represented by the Faculty of Medicine of the University of Bonn, represented by the Dean of the Medical Faculty, Venusberg-Campus 1, 53127 Bonn, Germany
Date of Report	30.09.2022
Version of Report:	1.0

UNIVERSITÄT BONN

ukb universitäts klinikumbonn

SZB Studienzentrum Bonn
Studienzentrale und Phase I Einheit

1. Signatures Clinical Study Report

By their signature, the authors confirm that they agree to the content of this Clinical Study Report. The clinical trial reported on has been conducted in compliance with the Declaration of Helsinki, the ICH-GCP guidelines, and the national laws and regulations.

Sponsor Delegated Person (SDP) and Principal Investigator:

Prof. Dr. Georg Nickenig	30.09.2022		
(SDP and Principal Investigator)	Date	Signature	

Responsible Biometrician:

Dr. Robert Németh	04-Oct-2022		
(Statistician)	Date	Signature	

2. Synopse

Sponsor:	Rheinische Friedrich-Wilhelms-University of Bonn, represented by the Faculty of Medicine of the University of Bonn, represented by the Dean of the Medical Faculty, Sigmund-Freud-Str. 25, D-53127 Bonn, Germany
Investigational product (IMP):	Trade name: Pradaxa® Substance name: Dabigatran etexilate Name of manufacturer: Boehringer Ingelheim International GmbH
Dose and Route of Administration, Batch number of IMP:	Dose per unit: 110 mg and 150 mg Route of administration: oral
Duration of treatment:	12 months
Reference therapy:	no treatment
Reference therapy (dose, route of administration, batch number):	n. a.
Study title:	Prevention of Silent Cerebral Thromboembolism by Oral Anticoagulation with Dabigatran after Pulmonary Vein Isolation for Atrial Fibrillation
Trial history:	Trial protocol version 2.0 (11.05.2015) Amendment 1: Trial protocol version 5.0 (11.03.2016) ⇨ Inclusion after PVI allowed, laser ablation added, additional site added (Cologne) Amendment 2: Trial protocol version 6.0 (01.07.2016) ⇨ Prolongation of interval until screening-TEE, additional sites added (Bielefeld, Ludwigshafen, Göttingen), sites removed (Rostock, Lübeck), prolongation of recruitment period Amendment 3: Trial protocol version 7.0 (03.11.2016) ⇨ Re-PVI can be included, linear ablation procedures for makro-reentry tachycardia allowed, electroanatomical mapping not compulsory anymore, MRI for exclusion contraindications for OAC at randomization added, additional site added (Wuppertal)

	Amendment 4: Trial protocol version 8.0 (26.01.2017) ⇨ Analysis of dispensable laboratory parameters removed (ANP, BNP, NTproBNP, CRP), additional sites added (Munich, Karlsruhe) Amendment 5: Trial protocol version 9.0 (11.09.2017) ⇨ Prolongation of time between Holter and randomization from 7 to 14 days, new sIMPD (changed colour of IMP-capsules), new SmPC (17.01.2013), site removed (Frankfurt) Amendment 6: new SmPC (January 2018) Amendment 7: new SmPC (May 2019)
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Indication studied:	Atrial fibriallation
Main criteria for inclusion:	Inclusion criteria: 1. Written informed consent 2. Patients undergoing circumferential antral PV ablation for non-valvular (mitral regurgitation less than moderate- severe mitral insufficiency; no relevant mitral stenosis with a mean pressure gradient >5mmHg) symptomatic, paroxysmal AF or persistent AF (duration ≤ 12 months) with risk factors resulting in a CHA_2DS_2VASc score ≥2, using a cooled tip RF-, laser- or cryo-balloon-catheter. 3. CHA_2DS_2VASc score ≥ 2 Randomization criteria

	1. Sinus rhythm (as assessed by 72h Holter ECG) following the 3 months blanking and 3 months observation period after first or second pulmonary vein ablation procedure 2. No clinical evidence of recurrent AF after completing 3 months blanking and 3 months observation period as assessed by symptoms 3. No relevant contraindication for OAC as assessed by randomization MRI of the brain <u>Exclusion criteria:</u> 1. Severe mental retardation or psychiatrical disorders resulting in incapability to adequately estimate the risks-and benefits of study parcipitation (i.e. bipolar disorders, severe depression, suicidal tendencies, among others) as judged by the local physician, ongoing drug or alcohol addiction (> 8 drinks/week) 2. Pregnancy /breast feeding 3. Severely impaired renal function, GFR < 30 ml/min 4. Impaired liver function (ALT/AST transaminase count 3fold higher than normal values) or liver disease with reduced life expectancy <1 year 5. Valvular AF (than moderate- severe mitral insufficiency; relevant mitral stenosis with a mean pressure gradient >5mmHg) 6. Long standing persistent (>12 months) and permanent AF 7. NSTEMI/STEMI/implantated drug eluting stent with indication for dual antiplatelet therapy within 12 months before enrolment 8. History of complex left atrial ablation procedures. One previous PVI allowed. 9. Clinical indication for extended left atrial ablation procedures (CFAE-, rotor-ablation) 10. History or presence of left atrial or ventricular thrombus 11. History of stroke / TIA independent from etiology

	12. Acute major bleedings 13. Lesion or condition, if considered a significant risk factor for major bleeding. This may include current or recent gastrointestinal ulceration, presence of malignant neoplasms at high risk of bleeding, recent brain or spinal injury, recent brain, spinal or ophthalmic surgery, recent intracranial haemorrhage, known or suspected oesophageal varices, arteriovenous malformations, vascular aneurysms or major intraspinal or intracerebral vascular abnormalities 14. Need for concomitant anitcoagulation in addition to dabigatran 15. History of previous surgery resulting in contraindication for OAC 16. History of malignoma resulting in contraindication for OAC 17. Mechanical prosthetic heart valve or other indication for permanent OAC 18. Contraindication for MRI (i.e. metallical surgical implants, cerebral port systems, uncontrollable claustrophobia, etc.). Pacemaker and ICD-patients may be included at the discretion of the local investigators/radiologists if MRI is warranted 19. Hypersensitivity against dabigatran or other ingredients of the medical product 20. Concomitant medication with dronedarone, ketoconazole, itraconazole, cyclosporine, tacrolimus or other interacting drugs as specified in the drug information 21. Simultaneous participation in any clinical trial involving administration of an investigational medicinal product within 30 days prior to clinical trial beginning 22. Females of childbearing potential, who are not using or not willing to use medically reliable methods of contraception for the entire study duration (such as oral, injectable, or implantable contraceptives, or intrauterine contraceptive devices) unless they are surgically sterilized /

	hysterectomized or there are any other criteria considered sufficiently reliable by the investigator in individual cases 23. Conditions which interfere with the study treatment at the discretion of the investigator
Brief description (design, comparison, duration, dose and population):	Multi-center randomized clinical trial with 1:1-randomized PROBE design (Prospective, Randomized, Open-label, Blinded-Endpoint)
Phase of study:	III
Study initiation date (FPI):	07.09.2015
Study completion/early termination date (LPO):	LPFV: 09.01.2019 LPO: 15.09.2020
Objectives:	The purpose of the ODIn-AF study is to demonstrate that the continued administration of dabigatran for 12 months is superior in the prevention of silent cerebral embolism to discontinuation of OAC in patients free from symptomatic AF-episodes with an elevated stroke risk (CHA_2DS_2VASc score ≥2) 6 months after successful antral pulmonary vein ablation (and re-ablation if necessary) for paroxysmal and persistent AF.
Methodology	Primary Endpoint: Incidence of new micro- and macro-embolic lesions on cerebral MRI incl. flare and diffusion weighted imaging 12 months after randomization compared to baseline MRI at randomization. Secondary Endpoints: are assessed during a 12 months follow-up after randomization, also as time-to-event analysis: - Location, size and number of new micro- and macro-embolic lesions on cerebral MRI - Incidence of clinically evident cardio-embolic events (stroke, TIA, systemic embolism) - Incidence of clinically apparent neurological deficits - Severeness neurological deficits - Severeness of neurological deficits (modified ranking severity scale (mRS))

	- Incidence of other thrombotic or thrombo-embolic events (myocardial infarction, deep vein thrombosis, pulmonary embolism) - Life-threatening / major / minor bleedings - Hemorrhagic cerebral infarctions - All-cause mortality - Cardiovascular mortality - Correlation of cardio-embolic events to method used for PVI (cryoballoon versus RF versus laser) - Correlation of cardio-embolic events with arrhythmia recurrence (atrial fibrillation or atrial flutter post ablation with ECG documentation or symptoms) - Correlation of cardio-embolic events with echocardiographic parameters (i.e. LA-size, LV function, LAA velocities) - Quality of life questionnaire (AF-specific symptoms, EQ-5D) - Neuropsychological questionnaire and assessment of neurocognitive deficits (MoCA test)
Number of patients:	Planned: 630 Analyzed: 200 (ITT), 169 (PP)
Analysis population:	• Intention-to-treat population (ITT): defined as set of the patients who were randomized. For the ITT-analysis patients will be analyzed as belonging to the treatment group they were randomized to. • Per-protocol population (PP): defined as the patients treated and observed according to protocol. • Safety (SAF) population: defined as set of the patients who were treated. For the SAF-analysis patients will be analyzed as treated (rather than according to the randomisation)
Statistical methods:	Primary Analysis: The primary efficacy analysis will be based on the occurrence of the primary endpoint at 12 months after the randomization visit, which is performed 6 months after PVI. The rate of occurrence of one of the events, which define the endpoint, will be compared between the treatment groups with a Mantel-Haenszel test stratified for centres, at a level of 5%. The primary analysis will be done for the intention-to-treat population (ITT), which is defined as the set of patients who were randomized. For the ITT-analysis, patients

	will be analyzed as belonging to the treatment group they were randomized to. Missing data concerning the endpoint at 12 months will be counted as a failure for the primary analysis. In addition an overall odds ratio with 95% confidence limits will be estimated using the Mantel-Haenszel method. Safety Analysis: Safety analysis will include all patients who have been treated. Tables of adverse event incidence and individual incidence will be produced. A complementary analysis of adverse events by severity of event and by relationship to trial treatment will also be performed. Laboratory parameters will be analysed descriptively.

3. Summary of Study Results

Efficacy Results:

A total of 200 patients were screened for the study. All patients were randomized into the two study arms (with or without dabigatran), 200 (Experimental n=99, Control n=101) were treated. Number of subjects completing the study (providing assessments 12 months after randomization (V3)) were comparable in both arms (Experimental n=87 (87.9%), Control n=91 (90.1 %)).

Demographics and baseline characteristics were well-balanced in the study arms.

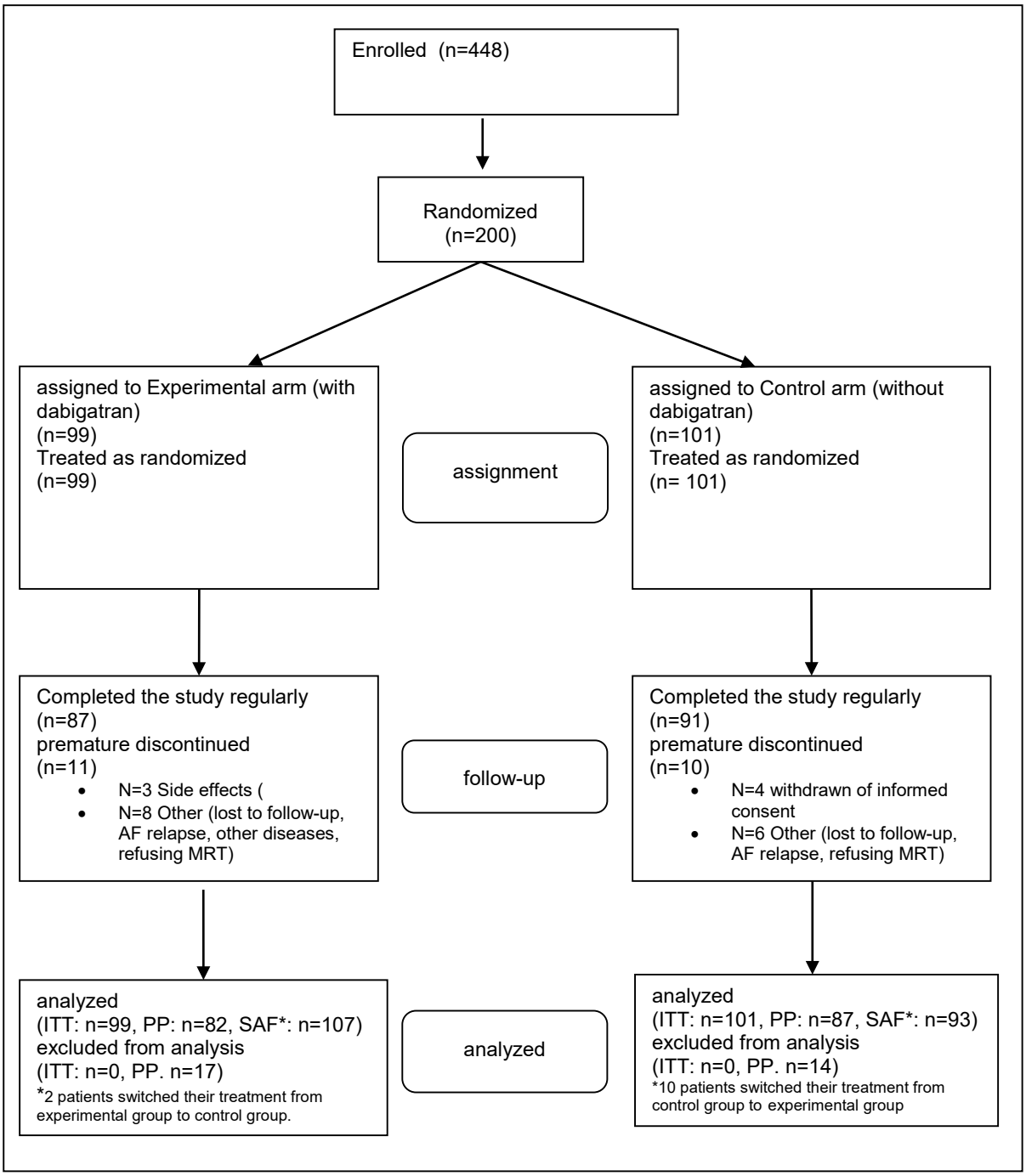
Occurrence of new micro- and macro-embolic lesions 12 months after randomization was analyzed on ITT and PP. There was no significant difference between the experimental and control arm. Missing data were counted as failure (i.e. occurrence of lesions will be set to “YES”). As sensitivity analysis, missing data were ignored. There was also no significant difference between the experimental and control arm.

No patient died during the trial. All other secondary endpoints showed no significant differences between the experimental and control arm.

Safety Results:

Safety results were presented in the Safety population. In this study, there were 10 patients who switched their treatment from control group to experimental group. These patients were counted for experimental group for safety analyses.
Additionally, there were 2 patients who switched their treatment from experimental group to control group. These patients were counted for control group for safety analyses.
Adverse events were reported by 108 patients (Experimental n=72 (67.3%), Control n=46 (49.5%)). There was a notable difference between the experimental and control arm.
9 patients (Experimental n=6 (5.6%), Control n=3 (3.2%)) had drug-related AEs.
The percentage of patients with SAEs were higher in the experimental arm compared to the control arm (Experimental n=34 (31.8%), Control n=18 (19.4%)).
Most affected AE System Organ Classes were: cardiac disorders (Experimental: 35.5%, Control: 10.8%), Infections and infestations (Experimental: 8.4%, Control: 11.8%), Injury, poisoning and procedural complications (Experimental: 9.3%, Control: 9.7%), Nervous system disorders (Experimental: 9.3%, Control: 7.5%), Gastrointestinal disorders(Experimental: 9.3%, Control: 6.5%) and Surgical and medical procedures (Experimental: 8.4%, Control: 6.5%).
Most-frequent AE Preferred terms were Atrial fibrillation (Experimental: 25.2%, Control: 7.5%), Palpitations (Experimental: 4.7%, Control: 3.2%) and Atrial flutter (Experimental: 4.7%, Control: 0.0%).

4. CONSORT Flow Diagram



5. Overall Conclusion

Oral anticoagulation treatment following catheter ablation of atrial fibrillation (AF) is controversial. Even in case of clinically successful ablation therapy and no evidence of atrial fibrillation recurrences, recent guidelines recommend a lifelong continuation of oral anticoagulation in all patients with a relevant risk factor profile (CHA_2DS_2VASc score ≥2 for me; ≥3 for women). The net clinical benefit of perpetuated oral anticoagulation (OAC) in these patients remained unclear as prospective data was missing. As oral anticoagulation bears the risk of severe bleeding events, the ODIn-AF study aimed to prospectively evaluate the effect of OAC on the incidence of silent cerebral embolic events, clinically relevant cardioembolic events und safety, particularly regarding bleeding events, in patients with an intermediate to high risk for embolic events, but free from symptomatic atrial fibrillation after successful pulmonary vein ablation.

Medication with OAC (vitamin K antagonists and novel oral anticoagulants (NOAC)) following the $CHADS_2$- and CHA_2DS_2VASc-scores, is the predominant therapeutic intervention that improves survival in paroxysmal, persistent and permanent AF patients. The expert consensus of the most recent update of the AF guidelines from the ESC and EHRA advise to continue OAC in patients with elevated stroke risk (patients older than 65 years of age and/or have one additional risk factor for thromboembolic complications) after catheter ablation for AF with, but also without detected AF recurrences, as stroke rate and rate of silent embolisms might persistently be elevated in this cohort due to asymptomatic, short lasting AF relapses.

Data from prospective randomized studies supporting a benefit of ongoing OAC treatment after successful AF ablation bearing the associated bleeding-risk, are missing. The ODIn-AF study is the first large scale prospective study to systematically evaluate the necessity to continue OAC for prevention of silent cerebral microembolism and clinical events in patients with paroxysmal or short lasting persistent AF and relevant risk for cerebral embolic events, as assessed by a CHA_2DS_2-VASc-score ≥2, after successful pulmonary vein ablation (PVI) for AF.

Former studies concentrated on clinically significant embolic events as endpoint for the estimation of cardioembolic events. The primary endpoint of ODIn-AF was the incidence of new microembolic lesions in cerebral MR, as it is known that microvascular lesions might be predictor of significant stroke events and predispose to neurodegenerative disease. There was no significant difference in the patient group treated with OAC as compared without OAC. Only two patients exhibited cerebral lesions, both in the experimental OAC group. Clinically significant embolisms were evaluated in secondary endpoint analyses between the treatment group with dabigatran and the patients without OAC. There were no such events found in both groups. Hence, cessation of OAC was not associated to elevated cardioembolic risk in this patient population, as compared to OAC. Before ODIn-AF,

prospective data was missing on discontinuation of OAC after ablation therapy and it was unclear, whether the patient population after successful AF-Ablation and without clinical or ECG documented AF recurrences exhibits the same risk for cardioembolic events as patients not ablated or before ablation procedure. ODIn-AF shows that the embolic risk in a well-controlled population might be lower compared to patients with AF and without successful ablation. These results point toward a different stroke risk after successful AF-Ablation in patients free from AF recurrences and towards the fact that risk stratification in such patients after AF-ablation might not be reliably assessed by the risk scores available.

It has been shown, that in many cases general practice already does not follow guidelines recommendation to continue OAC after PVI, mainly to avoid bleeding events. The ODIn-AF study is the first study to prospectively investigate cessation of OAC after AF ablation in a safety strategy setup with regular clinical und ECG screenings for freedom of AF, thus warranting best patient guidance for a valid discontinuation strategy, based on absence of AF relapses and clinical presentation. In ODIn-AF, only regular Holter ECGs and clinical presentation/symptoms and validation by ECG were utilized for screening for AF recurrences, as practicably conductable in clinical outpatient practice. No cardiac monitors were allowed. Yet, 10% of patients were identified in the control group with AF recurrence and switched to OAC therapy experimental arm, but were analysed in IIT fashion. None of the switchers showed erelevant events regarding primary and secondary endpoints, pointing towards the fact that the practicable and successive Holter-ECGs and clinical evaluation are sufficient to monitor these patients and to safely change therapy regime to OAC, when AF relapses are present.

Even in the era of NOAC, bleeding complications remain the main cause of morbidity and mortality caused by (N)OAC. From the RE-LY study, we can estimate a risk for major bleeding events under OAC with dabigatran up to 3.32% (150 mg dabigatran bid) per year, sometimes resulting in major complications and difficult emergency management. Life-threatening bleeding occurred in up to 1.45%. Thus, even with NOAC use there is a risk of relevant and life threatening bleedings under OAC in AF free patients after AF-ablation, substantiating the need to evaluate the clinical benefit of continuing OAC in these patients. In ODIn-AF, bleeding rates evaluated in the safety and as secondary endpoint analyses were, even under OAC with dabigatran, comparatively low, and with the patient number investigated no significant benefit from OAC cessation as compared to continued OAC therapy after ablation regarding bleeding events was seen. This might be additionally caused to the low number of patients and short 1 year follow up under OAC therapy. As secondary endpoint analysis, no hemorrhagic cerebral infarction as most severe bleeding event under (N)OAC therapy occurred in both groups.

All other secondary endpoints, among those and including mortality, all-cause mortality, systemic embolism, neurological deficits, modified ranking score and MOCA testing for neurological deficits and thrombotic events such as myocardial infarction showed no differences among the groups, supporting the thesis that both therapeutic regimes do not differ regarding severe clinical events and MACE. On the other hand, quality of life also was not different among the groups, so there was no benefit of cessation of OAC on patient´s life-quality, as on could have expected. Despite that, the OAC group exhibited more adverse events, mainly caused by side effects of the medication.

Limitations of the ODIn-AF trial are the comparatively low patient numbers (randomized and IIT analysed 100 patients) per group. As potential bias, patients were not blinded (side effects of medication) and the follow up periods was only one year, encouraging future larger randomized trials with prolonged follow up to proof effectiveness and safety of OAC after successful AF-ablation. On the other hand, the low bleeding rates seen in ODIn-AF might diminish the benefit of OAC cessation, also warranting trials with longer follow up periods.

Before ODIn-AF, there was no reliable prospective data on the incidence of silent cerebral microembolism in a high risk population for thromboembolic events (CHA_2DS_2VASc-score >=2) free from AF after apparently successful AF ablation. The individual cardioembolic risk after successful PVI catheter ablation remained uncertain due to lack of prospective randomized data in this patient cohort. ODIn-AF is the first brick to close this gap. Cessation of OAC in patients with standard clinical follow up regarding AF relapses showed feasible and safe. On the other hand, there was no excess bleeding in the OAC cohort but a higher rate of adverse events.

6. Publication

In preparation.

7. Appendix – Analysis results

7.1 Demography and baseline characteristics

Table 14.1.1: Disposition
Population: Randomised

	Arm	
	A (Experimental) *N=99*	*B (Control)* *N=101*
Number of subjects randomized	99 (100.0%)	101 (100.0%)
Number of subjects in treatment phase	99 (100.0%)	101 (100.0%)
Number of subjects completing the study	87 (87.9%)	91 (90.1%)
Number of subjects withdrawn from the study	11 (11.1%)	10 (9.9%)
Reason for premature discontinuation:		
Other	8 (8.1%)	6 (5.9%)
side effects	3* (3.0%)	0 (0.0%)
withdrawn informed consent	0 (0.0%)	4 (4.0%)

Note: Percentage based on number of randomized patients.
Other reason are: lost to follow-up, AF relapse, other diseases, refusing MRT

*2/3 of these patients had visits after discontinuation of study treatment (Switcher from Arm A to Arm B)
T_Disposition.sas 07MAR22 13:29

Listing: Specification of other reasons for discontinuation
Population: Randomised

Arm	*Site No.*	*Pat-ID*	*Specification for other reasons for discontinuation*	*ITT*	*PP*
A (Experimental)	1	194	Studienabbruch bei Unverträglichkeit von Dabigatran.	yes	no
		208	Gesicherte Alzheimer-Krankheit mit spätem Beginn (R00.1/ G30.1 G)	yes	no
	8	53	Re-PVI	yes	no
	9	171	Hörsturz/Drehschwindel	yes	no
		199	Verärgerung wg. langer Wartezeit	yes	no
	13	44	2x täglich, regelmäßige Einnahme von Pradaxa ist nicht sicher gestellt.	yes	no
		73	Lost to follow up	yes	no
	17	112	Pat. ist nicht bereit ins MRT zu gehen	yes	no
B (Control)	1	4	MRT wurde abgebrochen	yes	no
		104	Patient wurde in den Kontrollarm randomisiert (kein Verzicht auf OAK seitens des Pat.) am 30.09.2017 Einverständniserklärung zurückgezogen.	yes	no
	5	67	Patient nicht mehr zu Visiten erschienen, keine Reaktion auf zahlreiche Anrufe und einen Brief	yes	no
	7	41	Rezidiv VHF	yes	no
	13	231	einmaliges VHF-Rezidiv	yes	no
	18	160	Rezidiv Vorhofflattern	yes	no

Table 14.1.1-2: Study population by site
Population: Randomised

		Arm	
Site	*Population*	*A (Experimental) N=99*	*B (Control) N=101*
Total	Randomized	99	101
	Safety	99	101
	ITT	99	101
	PP	82	87
01	Randomized	25	23
	Safety	25	23
	ITT	25	23
	PP	22	20
05	Randomized	7	9
	Safety	7	9
	ITT	7	9
	PP	6	6
07	Randomized	3	3
	Safety	3	3
	ITT	3	3
	PP	3	2
08	Randomized	6	6
	Safety	6	6

		Arm	
Site	*Population*	*A (Experimental) N=99*	*B (Control) N=101*
	ITT	6	6
	PP	3	6
09	Randomized	11	11
	Safety	11	11
	ITT	11	11
	PP	9	9
10	Randomized	2	1
	Safety	2	1
	ITT	2	1
	PP	1	1
11	Randomized	3	2
	Safety	3	2
	ITT	3	2
	PP	3	2
12	Randomized	3	5
	Safety	3	5
	ITT	3	5
	PP	2	5
13	Randomized	16	17
	Safety	16	17

		Arm	
Site	*Population*	*A (Experimental) N=99*	*B (Control) N=101*
	ITT	16	17
	PP	13	14
14	Randomized	2	1
	Safety	2	1
	ITT	2	1
	PP	2	1
15	Randomized	0	2
	Safety	0	2
	ITT	0	2
	PP	0	2
16	Randomized	2	4
	Safety	2	4
	ITT	2	4
	PP	1	4
17	Randomized	7	8
	Safety	7	8
	ITT	7	8
	PP	6	8
18	Randomized	2	3
	Safety	2	3

		Arm	
Site	*Population*	*A (Experimental) N=99*	*B (Control) N=101*
	ITT	2	3
	PP	2	2
19	Randomized	1	1
	Safety	1	1
	ITT	1	1
	PP	1	1
20	Randomized	3	1
	Safety	3	1
	ITT	3	1
	PP	3	0
21	Randomized	3	3
	Safety	3	3
	ITT	3	3
	PP	3	3
22	Randomized	3	1
	Safety	3	1
	ITT	3	1
	PP	2	1

		Arm	
Site	*Population*	*A (Experimental)* *N=99*	*B (Control)* *N=101*

Safety population not involved treatment switcher. Including switchers mean: A – N=107, B – N=93
T_Popul.sas 07MAR22 13:24

Table 14.1.2: Demography - quantitative parameter - ITT Population
Population: ITT

Variable	*Arm*	*n*	*Mean*	*S.D.*	*Median*	*Range*	*95%-CI*	*P-value**
Age (years)								
	A (Experimental)	99	67.3	7.2	67.0	47- 81	(65.81 ; 68.69)	0.8629
	B (Control)	101	67.1	7.7	67.0	43- 82	(65.54 ; 68.60)	
						.		
	Total	200	67.2	7.5	67.0	43- 82	(66.12 ; 68.20)	
Height (cm)								
	A (Experimental)	99	173.5	9.1	173.0	**-192	(171.70 ; 175.32)	0.7665
	B (Control)	101	173.1	8.3	174.0	**-192	(171.49 ; 174.79)	
						.		
	Total	200	173.3	8.7	173.5	**-192	(172.11 ; 174.53)	
Weight (kg)								
	A (Experimental)	98	86.4	18.9	85.0	51-137	(82.65 ; 90.22)	0.2098
	B (Control)	101	89.7	17.3	88.0	50-138	(86.25 ; 93.07)	
						.		
	Total	199	88.1	18.1	87.0	50-138	(85.54 ; 90.60)	
BMI (kg/m^2)								
	A (Experimental)	98	28.7	6.1	27.4	19- 52	(27.49 ; 29.94)	0.1600
	B (Control)	101	29.8	4.8	29.8	19- 42	(28.86 ; 30.76)	

Variable	*Arm*	*n*	*Mean*	*S.D.*	*Median*	*Range*	*95%-CI*	*P-value**
	Total	199	29.3	5.5	29.0	. 19- 52	(28.50 ; 30.04)	

*by Student's t-test
T_DEMOG.sas 06JUL22 08:57

Table 14.1.3: Demography - qualitative parameter - ITT Population
Population: ITT

Parameter - n (%)		*Arm A (Experimental) N=99*	*B (Control) N=101*	*Total N=200*	*p-Value**
Sex	male	56 (56.6%)	56 (55.4%)	112 (56.0%)	0.8876
	female	43 (43.4%)	45 (44.6%)	88 (44.0%)	
Cardinal point	NORDEN	9 (9.1%)	7 (6.9%)	16 (8.0%)	.
	OSTEN	16 (16.2%)	17 (16.8%)	33 (16.5%)	
	SÜDEN	34 (34.3%)	36 (35.6%)	70 (35.0%)	
	WESTEN	40 (40.4%)	41 (40.6%)	81 (40.5%)	
Federated state	Nordrhein-Westfalen	40 (40.4%)	41 (40.6%)	81 (40.5%)	.
	Baden Würtemberg	25 (25.3%)	28 (27.7%)	53 (26.5%)	
	Rheinland-Pfalz	3 (3.0%)	2 (2.0%)	5 (2.5%)	
	Sachsen	16 (16.2%)	17 (16.8%)	33 (16.5%)	
	Bayern	6 (6.1%)	6 (5.9%)	12 (6.0%)	
	Niedersachen	9 (9.1%)	7 (6.9%)	16 (8.0%)	

*by Fisher's exact test
T_DEMOG.sas 06JUL22 08:57

Table 14.1.4: Baseline characteristics - quantitative parameter - ITT Population
Population: ITT

Variable	*Arm*	*n*	*Mean*	*S.D.*	*Median*	*Range*	*95%-CI*	*P-value**
CHA2DS2VASc Score								
	A (Experimental)	99	2.6	0.8	2.0	2- 5	(2.44 ; 2.77)	0.7346
	B (Control)	101	2.6	0.7	2.0	2- 4	(2.50 ; 2.79)	
						.		
	Total	200	2.6	0.8	2.0	2- 5	(2.52 ; 2.73)	
HAS-BLED-Score								
	A (Experimental)	59	1.3	0.7	1.0	0- 3	(1.15 ; 1.53)	0.2135
	B (Control)	58	1.5	0.7	2.0	0- 3	(1.33 ; 1.67)	
						.		
	Total	117	1.4	0.7	1.0	0- 3	(1.29 ; 1.55)	
ECG - Heart rate [bpm]								
	A (Experimental)	99	71.3	20.7	65.0	42-142	(67.18 ; 75.45)	0.6725
	B (Control)	100	70.0	22.7	63.5	39-180	(65.52 ; 74.50)	
						.		
	Total	199	70.7	21.7	65.0	39-180	(67.63 ; 73.69)	
TTE - LVEF [%]								
	A (Experimental)	80	58.0	9.4	60.0	10- 76	(55.87 ; 60.08)	0.8623

Variable	*Arm*	*n*	*Mean*	*S.D.*	*Median*	*Range*	*95%-CI*	*P-value**
	B (Control)	84	57.7	8.6	60.0	35- 76	(55.86 ; 59.60)	
						.		
	Total	164	57.8	9.0	60.0	10- 76	(56.46 ; 59.24)	
TTE - Left atrial diameter [mm]								
	A (Experimental)	45	40.6	11.2	40.0	1- 74	(37.22 ; 43.94)	0.5000
	B (Control)	49	42.0	8.8	41.0	6- 67	(39.44 ; 44.52)	
						.		
	Total	94	41.3	10.0	41.0	1- 74	(39.26 ; 43.36)	
TTE - Left atrial volume [mL]								
	A (Experimental)	40	60.1	22.1	54.0	30-108	(53.01 ; 67.14)	0.2795
	B (Control)	43	66.5	31.4	65.0	16-156	(56.86 ; 76.21)	
						.		
	Total	83	63.4	27.4	60.0	16-156	(57.45 ; 69.40)	

*by Student's t-test
T_BL_characteristics.sas 07JUL22 08:04

Table 14.1.5: Baseline characteristics - qualitative parameter - ITT Population
Population: ITT

Parameter - n (%)		*A (Experimental) N=99*	*B (Control) N=101*	*Total N=200*	*p-Value**
NYHA-class	missing	1 (1.0%)	2 (2.0%)	3 (1.5%)	0.6502
	I	18 (18.2%)	21 (20.8%)	39 (19.5%)	
	II	30 (30.3%)	30 (29.7%)	60 (30.0%)	
	III	13 (13.1%)	8 (7.9%)	21 (10.5%)	
	IV	0 (0.0%)	1 (1.0%)	1 (0.5%)	
	Not evaluated	37 (37.4%)	39 (38.6%)	76 (38.0%)	
EHRA-class	missing	4 (4.0%)	4 (4.0%)	8 (4.0%)	0.1048
	I	0 (0.0%)	6 (5.9%)	6 (3.0%)	
	II	30 (30.3%)	33 (32.7%)	63 (31.5%)	
	III	31 (31.3%)	33 (32.7%)	64 (32.0%)	
	IV	2 (2.0%)	1 (1.0%)	3 (1.5%)	
	Not evaluated	32 (32.3%)	24 (23.8%)	56 (28.0%)	
CHA2DS2VASc Score	2	58 (58.6%)	51 (50.5%)	109 (54.5%)	0.1551
	3	25 (25.3%)	35 (34.7%)	60 (30.0%)	
	4	13 (13.1%)	15 (14.9%)	28 (14.0%)	
	5	3 (3.0%)	0 (0.0%)	3 (1.5%)	
HAS-BLED-Score	missing	40 (40.4%)	43 (42.6%)	83 (41.5%)	0.5401
	0	7 (7.1%)	3 (3.0%)	10 (5.0%)	
	1	27 (27.3%)	25 (24.8%)	52 (26.0%)	
	2	23 (23.2%)	28 (27.7%)	51 (25.5%)	
	3	2 (2.0%)	2 (2.0%)	4 (2.0%)	

Parameter - n (%)		*A (Experimental) N=99*	*B (Control) N=101*	*Total N=200*	*p-Value**
ECG - rhythem	atrial fibrillation	26 (26.3%)	29 (28.7%)	55 (27.5%)	0.7460
	atrial fibrillation, other	1 (1.0%)	0 (0.0%)	1 (0.5%)	
	missing	2 (2.0%)	2 (2.0%)	4 (2.0%)	
	other	2 (2.0%)	1 (1.0%)	3 (1.5%)	
	pacemaker	1 (1.0%)	0 (0.0%)	1 (0.5%)	
	sinus rhythm	67 (67.7%)	68 (67.3%)	135 (67.5%)	
	sinus rhythm, other	0 (0.0%)	1 (1.0%)	1 (0.5%)	
TTE - Aortic valve stenosis	ND/NA	19 (19.2%)	19 (18.8%)	38 (19.0%)	0.7241
	none	77 (77.8%)	78 (77.2%)	155 (77.5%)	
	mild	3 (3.0%)	4 (4.0%)	7 (3.5%)	
TTE - Aortic valve insufficiency	ND/NA	19 (19.2%)	19 (18.8%)	38 (19.0%)	0.3955
	none	61 (61.6%)	68 (67.3%)	129 (64.5%)	
	mild	18 (18.2%)	14 (13.9%)	32 (16.0%)	
	moderate	1 (1.0%)	0 (0.0%)	1 (0.5%)	
TTE - Mitral valve insufficiency	ND/NA	19 (19.2%)	20 (19.8%)	39 (19.5%)	0.5751
	none	17 (17.2%)	23 (22.8%)	40 (20.0%)	
	mild	54 (54.5%)	50 (49.5%)	104 (52.0%)	
	moderate	9 (9.1%)	8 (7.9%)	17 (8.5%)	
TTE - Tricuspid valve insufficiency	ND/NA	19 (19.2%)	20 (19.8%)	39 (19.5%)	0.7656
	none	30 (30.3%)	30 (29.7%)	60 (30.0%)	
	mild	47 (47.5%)	46 (45.5%)	93 (46.5%)	
	moderate	3 (3.0%)	4 (4.0%)	7 (3.5%)	

Parameter - n (%)		*A (Experimental)* *N=99*	*B (Control)* *N=101*	*Total* *N=200*	*p-Value**
	severe	0 (0.0%)	1 (1.0%)	1 (0.5%)	

*by Chi square test
T_BL_characteristics.sas 07JUL22 08:04

Table: Selected anamnestic data - qualitative parameter - ITT Population
Population: ITT

Parameter - n (%)		*A (Experimental) N=99*	*B (Control) N=101*	*Total N=200*	*p-Value**
Arterial hypertension	no	13 (13.1%)	12 (11.9%)	25 (12.5%)	0.8332
	yes	86 (86.9%)	89 (88.1%)	175 (87.5%)	
Coronary heart disease	no	83 (83.8%)	81 (80.2%)	164 (82.0%)	0.5821
	yes	16 (16.2%)	20 (19.8%)	36 (18.0%)	
CHD - if yes: specify	.	85 (85.9%)	81 (80.2%)	166 (83.0%)	.
	1-Gefäßerkrankung	7 (7.1%)	9 (8.9%)	16 (8.0%)	
	2-Gefäßerkrankung	5 (5.1%)	6 (5.9%)	11 (5.5%)	
	3-Gefäßerkrankung	2 (2.0%)	5 (5.0%)	7 (3.5%)	
Heart insufficiency	no	87 (87.9%)	90 (89.1%)	177 (88.5%)	0.8275
	yes	12 (12.1%)	11 (10.9%)	23 (11.5%)	
Pacemaker	no	96 (97.0%)	100 (99.0%)	196 (98.0%)	0.3662
	yes	3 (3.0%)	1 (1.0%)	4 (2.0%)	
PM - if yes - specify	.	96 (97.0%)	100 (99.0%)	196 (98.0%)	.
	2-Kammer	3 (3.0%)	1 (1.0%)	4 (2.0%)	
ICD	no	99 (100.0%)	101 (100.0%)	200 (100.0%)	0.3662
ICD - if yes - specify	.	99 (100.0%)	101 (100.0%)	200 (100.0%)	.
Peripheral arterial disease (pAVK)	no	95 (96.0%)	100 (99.0%)	195 (97.5%)	0.2094
	yes	4 (4.0%)	1 (1.0%)	5 (2.5%)	
COPD	no	89 (89.9%)	97 (96.0%)	186 (93.0%)	0.1030
	yes	10 (10.1%)	4 (4.0%)	14 (7.0%)	

Parameter - n (%)		*A (Experimental)* *N=99*	*B (Control)* *N=101*	*Total* *N=200*	*p-Value**
OSAS	no	92 (92.9%)	93 (92.1%)	185 (92.5%)	1.0000
	yes	7 (7.1%)	8 (7.9%)	15 (7.5%)	
Diabetes mellitus	no	78 (78.8%)	81 (80.2%)	159 (79.5%)	0.8618
	yes	21 (21.2%)	20 (19.8%)	41 (20.5%)	
Diabetes - if yes - specify	.	78 (78.8%)	81 (80.2%)	159 (79.5%)	.
	nicht Insulin-abhängig	17 (17.2%)	15 (14.9%)	32 (16.0%)	
	Insulin-abhängig	4 (4.0%)	5 (5.0%)	9 (4.5%)	
Renal failure (GFR<60 mL/min)	no	93 (93.9%)	93 (92.1%)	186 (93.0%)	0.7830
	yes	6 (6.1%)	8 (7.9%)	14 (7.0%)	

*by Fisher's exact test
T_BL_characteristics2.sas 28JUN22 08:46

Table: AF history - qualitative parameter - ITT Population
Population: ITT

Parameter - n (%)		*A (Experimental) N=99*	*B (Control) N=101*	*Total N=200*	*p-Value**
current AF	missing	1 (1.0%)	1 (1.0%)	2 (1.0%)	0.7774
	no	44 (44.4%)	47 (46.5%)	91 (45.5%)	
	yes	54 (54.5%)	53 (52.5%)	107 (53.5%)	
AF classification	missing	3 (3.0%)	0 (0.0%)	3 (1.5%)	0.5815
	paroxysmal	65 (65.7%)	68 (67.3%)	133 (66.5%)	
	persistent	30 (30.3%)	33 (32.7%)	63 (31.5%)	
	permanent	1 (1.0%)	0 (0.0%)	1 (0.5%)	
Number of non-effective Antiarrhythmic agents	0	40 (40.4%)	37 (36.6%)	77 (38.5%)	0.9267
	1	48 (48.5%)	50 (49.5%)	98 (49.0%)	
	2	6 (6.1%)	6 (5.9%)	12 (6.0%)	

*current AF - by Fisher's exact test, others - by Chi square test
T_BL_characteristics3.sas 28JUN22 08:46

Table: Procedural 1st ablation - quantitative parameter - ITT Population
Population: ITT

Variable	*Arm*	*n*	*Mean*	*S.D.*	*Median*	*Range*	*95%-CI*	*P-value**
Transseptal duration (min)								
	A (Experimental)	93	80.5	52.5	78.0	5-306	(69.72 ; 91.33)	0.3626
	B (Control)	95	74.1	43.3	75.0	2-191	(65.30 ; 82.95)	
						.		
	Total	188	77.3	48.1	75.5	2-306	(70.38 ; 84.21)	
Total duration of procedure (min)								
	A (Experimental)	99	125.1	57.1	111.0	30-413	(113.70 ; 136.48)	0.2464
	B (Control)	100	116.8	41.7	110.0	51-240	(108.57 ; 125.11)	
						.		
	Total	199	120.9	50.0	110.0	30-413	(113.95 ; 127.94)	
Fluoroscopy time (min)								
	A (Experimental)	95	24.5	76.7	15.0	2-756	(8.89 ; 40.15)	0.3629
	B (Control)	100	17.0	25.4	13.0	1-251	(11.92 ; 22.00)	
						.		
	Total	195	20.6	56.5	14.0	1-756	(12.66 ; 28.63)	
Before Ablation - systolic BP (mmHg)								
	A (Experimental)	95	132.7	21.0	135.0	75-180	(128.46 ; 137.01)	0.5135

Variable	*Arm*	*n*	*Mean*	*S.D.*	*Median*	*Range*	*95%-CI*	*P-value**
	B (Control)	92	134.8	21.1	134.0	85-195	(130.39 ; 139.11)	
						.		
	Total	187	133.7	21.0	135.0	75-195	(130.70 ; 136.76)	
Before Ablation - diastolic BP (mmHg)								
	A (Experimental)	95	75.0	14.8	75.0	35-115	(72.02 ; 78.06)	0.8566
	B (Control)	92	74.6	15.5	75.0	40-131	(71.44 ; 77.84)	
						.		
	Total	187	74.8	15.1	75.0	35-131	(72.67 ; 77.02)	

*by Student's t-test
T_PVI.sas 07JUL22 08:04

Table: Procedural 1st ablation - qualitative parameter - ITT Population
Population: ITT

Parameter - n (%)		*A (Experimental) N=99*	*B (Control) N=101*	*Total N=200*	*p-Value**
Ablation mode		1 (1.0%)	0 (0.0%)	1 (0.5%)	0.8249
	Anpressdruckmessung	0 (0.0%)	1 (1.0%)	1 (0.5%)	
	Cryo-Ballon	13 (13.1%)	13 (12.9%)	26 (13.0%)	
	Cryo-Ballon / ACHIEVE	11 (11.1%)	16 (15.8%)	27 (13.5%)	
	Cryo-Ballon / ACHIEVE, Oesophagustemperatur	7 (7.1%)	9 (8.9%)	16 (8.0%)	
	Cryo-Ballon / ACHIEVE, RF cooled tip	3 (3.0%)	1 (1.0%)	4 (2.0%)	
	Cryo-Ballon / ACHIEVE, RF cooled tip, Anpressdruckmessung	1 (1.0%)	1 (1.0%)	2 (1.0%)	
	Cryo-Ballon, Cryo-Ballon / ACHIEVE	3 (3.0%)	3 (3.0%)	6 (3.0%)	
	Cryo-Ballon, Cryo-Ballon / ACHIEVE, Oesophagustemperatur	5 (5.1%)	2 (2.0%)	7 (3.5%)	
	Cryo-Ballon, Cryo-Ballon / ACHIEVE, RF cooled tip	0 (0.0%)	2 (2.0%)	2 (1.0%)	
	Cryo-Ballon, Oesophagustemperatur	14 (14.1%)	13 (12.9%)	27 (13.5%)	
	Laser, Oesophagustemperatur	1 (1.0%)	0 (0.0%)	1 (0.5%)	
	Oesophagustemperatur	13 (13.1%)	17 (16.8%)	30 (15.0%)	
	RF cooled tip	12 (12.1%)	13 (12.9%)	25 (12.5%)	

Parameter - n (%)		*A (Experimental) N=99*	*B (Control) N=101*	*Total N=200*	*p-Value**
	RF cooled tip, Anpressdruckmessung	11 (11.1%)	7 (6.9%)	18 (9.0%)	
	RF cooled tip, Anpressdruckmessung, Oesophagustemperatur	3 (3.0%)	3 (3.0%)	6 (3.0%)	
	RF cooled tip, Oesophagustemperatur	1 (1.0%)	0 (0.0%)	1 (0.5%)	
3D mapping	CARTO	26 (26.3%)	27 (26.7%)	53 (26.5%)	0.7521
	NAVX	28 (28.3%)	24 (23.8%)	52 (26.0%)	
	No 3D Mapping	45 (45.5%)	50 (49.5%)	95 (47.5%)	
Additional Ablation of cavotrikuspidal isthmus	no	89 (89.9%)	85 (84.2%)	174 (87.0%)	0.2275
	yes	10 (10.1%)	16 (15.8%)	26 (13.0%)	

*by Chi square test
T_PVI.sas 07JUL22 08:04

Procedural 2nd ablation was conducted in 6 patients (Pat. Nos. 80, 199 of Arm A and Pat. Nos. 85, 126, 154, 229 of Arm B).

Table: Procedural 2nd ablation - quantitative parameter - ITT Population
Population: ITT

Variable	*Arm*	*n*	*Mean*	*S.D.*	*Median*	*Range*	*95%-CI*	*P-value**
Transseptal duration (min)								
	A (Experimental)	1	35.0		35.0	35- 35		
	B (Control)	4	91.5	80.3	87.5	7-184	(-36.26 ; 219.26)	
	Total	5	80.2	74.0	45.0	7-184	(-11.66 ; 172.06)	
Total duration of procedure (min)								
	A (Experimental)	2	84.5	29.0	84.5	64-105	(-176.0 ; 344.98)	0.2627
	B (Control)	4	179.0	95.3	197.5	55-266	(27.37 ; 330.63)	
	Total	6	147.5	89.4	130.0	55-266	(53.65 ; 241.35)	
Fluoroscopy time (min)								
	A (Experimental)	2	18.0	15.6	18.0	7- 29	(-121.8 ; 157.77)	0.4398
	B (Control)	3	10.0	5.0	10.0	5- 15	(-2.42 ; 22.42)	
	Total	5	13.2	9.6	10.0	5- 29	(1.28 ; 25.12)	
Before Ablation - systolic BP (mmHg)								
	A (Experimental)	2	138.0	12.7	138.0	129-147	(23.64 ; 252.36)	0.0747
	B (Control)	4	108.3	14.8	105.5	96-126	(84.63 ; 131.87)	

Variable	*Arm*	*n*	*Mean*	*S.D.*	*Median*	*Range*	*95%-CI*	*P-value**
						.		
	Total	6	118.2	20.0	120.5	96-147	(97.16 ; 139.17)	
Before Ablation - diastolic BP (mmHg)								
	A (Experimental)	2	86.5	29.0	86.5	66-107	(-174.0 ; 346.98)	0.2813
	B (Control)	4	66.5	13.4	64.5	53- 84	(45.21 ; 87.79)	
						.		
	Total	6	73.2	19.5	67.5	53-107	(52.65 ; 93.68)	

*by Student's t-test
T_PVI.sas 07JUL22 08:04

Table: Procedural 2nd ablation - qualitative parameter - ITT Population
Population: ITT

Parameter - n (%)		*A (Experimental) N=99*	*B (Control) N=101*	*Total N=200*	*p-Value**
Ablation mode	Cryo-Ballon / ACHIEVE, RF cooled tip	1 (1.0%)	0 (0.0%)	1 (0.5%)	0.4409
	Cryo-Ballon, Cryo-Ballon / ACHIEVE	0 (0.0%)	1 (1.0%)	1 (0.5%)	
	Oesophagustemperatur	0 (0.0%)	1 (1.0%)	1 (0.5%)	
	RF cooled tip	1 (1.0%)	1 (1.0%)	2 (1.0%)	
	RF cooled tip, Anpressdruckmessung, Oesophagustemperatur	0 (0.0%)	1 (1.0%)	1 (0.5%)	
3D mapping	CARTO	0 (0.0%)	3 (3.0%)	3 (1.5%)	0.1534
	NAVX	1 (1.0%)	0 (0.0%)	1 (0.5%)	
	No 3D Mapping	1 (1.0%)	1 (1.0%)	2 (1.0%)	
Additional Ablation of cavotrikuspidal isthmus	no	1 (1.0%)	3 (3.0%)	4 (2.0%)	0.5403
	yes	1 (1.0%)	1 (1.0%)	2 (1.0%)	

*by Chi square test
T_PVI.sas 07JUL22 08:04

Table 14.1.8-1: Compliance by category - ITT population
Population: ITT

			Arm	
Visit	*Parameter - n (%)*		*A (Experimental) N=99*	*B (Control) N=101*
Visit 1 (3 months after Rand.)	Compliance category	missing	3 (3.0%)	101 (100.0%)
		good	89 (89.9%)	0 (0.0%)
		modrate	3 (3.0%)	0 (0.0%)
		poor	4 (4.0%)	0 (0.0%)
Visit 2 (9 months after Rand.)	Compliance category	missing	10 (10.1%)	98 (97.0%)
		good	76 (76.8%)	1 (1.0%)
		modrate	7 (7.1%)	0 (0.0%)
		poor	6 (6.1%)	2 (2.0%)
Visit 3 (12 months after Rand.)	Compliance category	missing	15 (15.2%)	96 (95.0%)
		good	70 (70.7%)	4 (4.0%)
		modrate	13 (13.1%)	1 (1.0%)
		poor	1 (1.0%)	0 (0.0%)

Percentage based on patients in the ITT population
Compliance in Arm B due to treatment switch.
good - > 80%, poor - < 50%, moderate - not good or poor
T_COMPLIANCE 07MAR22 13:30

Table 14.1.8-2: Number of switcher - ITT Population
Population: ITT

		Arm	
Parameter - n (%)		*A (Experimental) N=99*	*B (Control) N=101*
Switcher	yes	2 (2.0%)	10 (9.9%)
	no	97 (98.0%)	91 (90.1%)

T_SWITCHER.sas 18MAY22 08:50

Table 14.1.8-3: Number of switcher per visit - ITT Population
Population: ITT

Visit	*Parameter - n (%)*		*A (Experimental)*	*B (Control)*
Visit 1 (3 months after Rand.)	Switcher	missing	96 (98.0%)	0 (0.0%)
		yes	2 (2.0%)	3 (3.2%)
		no	0 (0.0%)	90 (96.8%)
Visit 2 (9 months after Rand.)	Switcher	missing	93 (100.0%)	0 (0.0%)
		yes	0 (0.0%)	7 (7.8%)
		no	0 (0.0%)	83 (92.2%)
Visit 3 (12 months after Rand.)	Switcher	missing	90 (100.0%)	0 (0.0%)
		yes	0 (0.0%)	8 (8.7%)
		no	0 (0.0%)	84 (91.3%)

Percentage based on patients per visit in the ITT population.
Mutliple citations possible.
T_SWITCHER.sas 18MAY22 08:50

7.2 Efficacy - Primary endpoint

Table 14.2.1-1: Occurrence of new micro- and macro-embolic lesions 12 months after randomization – ITT population
Population: ITT

		Arm			
Parameter - n (%)		*A (Experimental) N=99*	*B (Control) N=101*	*Total N=200*	*P-value*
Occurence of lesions after 12 months	no	84 (84.8%)	90 (89.1%)	174 (87.0%)	0.4545
	yes	15 (15.2%)	11 (10.9%)	26 (13.0%)	

Percentage based on patients in the ITT population
Missing values will be counted as failure (occurence of lesion=YES).
p-value according to Cochran-Mantel Haenzel test stratified by site. Breslow-Day Statistic not computed--the data are too sparse.
T_MRT_Corelab 07MAR22 13:25

Table: Difference in occurrence of lesions
Population: ITT

Diff. in occurrence of lesions Arm A minus Arm B	*95% CI**	*CI Type*
4.3 %	(-9.362 , 18.230)	Exact
	(-5.056 , 13.577)	Wald

*for occurence of lesions YES.
Missing values will be counted as failure (occurence of lesion=YES).
T_MRT_Corelab_CI.sas 17MAY22 12:05

Table 14.2.1-2: Occurrence of new micro- and macro-embolic lesions 12 months after randomization – PP population
Population: PP

		Arm			
Parameter - n (%)		*A (Experimental) N=82*	*B (Control) N=87*	*Total N=169*	*P-value*
Occurence of lesions after 12 months	no	80 (97.6%)	87 (100.0%)	167 (98.8%)	0.1591
	yes	2 (2.4%)	0 (0.0%)	2 (1.2%)	

Percentage based on patients in the PP population
Missing values will be counted as failure (occurence of lesion=YES).
p-value according to Cochran-Mantel Haenzel test stratified by site. Breslow-Day Statistic not computed--the data are too sparse.
T_MRT_Corelab 07MAR22 13:25

Table: Difference in occurrence of lesions
Population: PP

Diff. in occurrence of lesions Arm A minus Arm B	*95% CI**	*CI Type*
2.4 %	(-12.734 , 17.464)	Exact
	(-0.900 , 5.778)	Wald

*for occurence of lesions YES.
Missing values will be counted as failure (occurence of lesion=YES).
T_MRT_Corelab_CI.sas 17MAY22 12:05

Table 14.2.1-1: Occurrence of new micro- and macro-embolic lesions 12 months after randomization – ITT population
Population: ITT

		Arm			
Parameter - n (%)		*A (Experimental) N=99*	*B (Control) N=101*	*Total N=200*	*P-value*
Occurence of lesions after 12 months	missing	13 (13.1%)	11 (10.9%)	24 (12.0%)	
	no	84 (84.8%)	90 (89.1%)	174 (87.0%)	0.1517
	yes	2 (2.0%)	0 (0.0%)	2 (1.0%)	

Percentage based on patients in the ITT population
Missing values due to premature discontinuation or MRT refuse at V3 will be ignored.
p-value according to Cochran-Mantel Haenzel test stratified by site. Breslow-Day Statistic not computed--the data are too sparse.
T_MRT_Corelab 07MAR22 13:25

Table: Difference in occurrence of lesions
Population: ITT

Diff. in occurrence of lesions Arm A minus Arm B	*95% CI**	*CI Type*
2.3** %	(-12.590 , 17.207)	Exact
	(-0.860 , 5.511)	Wald

*for occurence of lesions YES.
**2/86=2.3%
Missing values due to premature discontinuation or MRT refuse at V3 will be ignored.
T_MRT_Corelab_CI.sas 17MAY22 12:05

7.3 Efficacy - Secondary endpoints

- Location, size and number of new micro- and macro-embolic lesions

Listing 14.2.2-1: Location, size and number of new micro- and macro-embolic lesions on cerebral MRI
Population: Randomised

Arm	*Site No.*	*Pat-ID*	*No. new lesions*	*No. unchanged lesions*	*Total Volume all lesions (ml)*	*Total Volume new lesions (ml)*	*ITT*	*PP*
A (Experimental)	1	107	1	20	4.68	0.01	yes	yes
	13	211	2	0	0.04	0.04	yes	yes

Listing 14.2.2-2: New lesions
Population: Randomised

Arm	*Site No.*	*Pat-ID*	*Lesion No.*	*Size (Volume in mL)*	*Side*	*Aterial blood stream area*	*ITT*	*PP*
A (Experimental)	1	107	1	0.01	left	MCA	yes	yes
	13	211	1	0.02	right	MCA	yes	yes
			2	0.02	right	ACA	yes	yes

- **Incidence of clinically evident cardio-embolic events**

Table 14.2.3-1: Incidence of clinically evident cardio-embolic events -ITT population
Population: ITT

			Arm	
Visit	*Parameter - n (%)*		*A (Experimental) N=99*	*B (Control) N=101*
1	Stroke	no	98 (99.0%)	94 (93.1%)
	TIA	no	98 (99.0%)	94 (93.1%)
	Systemic embolism	no	98 (99.0%)	94 (93.1%)
	Cardio-embolic event	no	98 (99.0%)	94 (93.1%)
2	Stroke	no	94 (94.9%)	90 (89.1%)
	TIA	no	94 (94.9%)	90 (89.1%)
	Systemic embolism	no	94 (94.9%)	90 (89.1%)
	Cardio-embolic event	no	94 (94.9%)	90 (89.1%)
3	Stroke	no	90 (90.9%)	91 (90.1%)
	TIA	no	90 (90.9%)	91 (90.1%)
	Systemic embolism	no	90 (90.9%)	91 (90.1%)
	Cardio-embolic event	no	90 (90.9%)	91 (90.1%)

Percentage based on number of patients in the ITT population

T_SecEP 07MAR22 13:23

Table 14.2.3-2: Incidence of clinically evident cardio-embolic events -PP population
Population: PP

			Arm	
Visit	*Parameter - n (%)*		*A (Experimental) N=82*	*B (Control) N=87*
1	Stroke	no	82 (100.0%)	87 (100.0%)
	TIA	no	82 (100.0%)	87 (100.0%)
	Systemic embolism	no	82 (100.0%)	87 (100.0%)
	Cardio-embolic event	no	82 (100.0%)	87 (100.0%)
2	Stroke	no	82 (100.0%)	86 (98.9%)
	TIA	no	82 (100.0%)	86 (98.9%)
	Systemic embolism	no	82 (100.0%)	86 (98.9%)
	Cardio-embolic event	no	82 (100.0%)	86 (98.9%)
3	Stroke	no	82 (100.0%)	86 (98.9%)
	TIA	no	82 (100.0%)	86 (98.9%)
	Systemic embolism	no	82 (100.0%)	86 (98.9%)
	Cardio-embolic event	no	82 (100.0%)	86 (98.9%)

Percentage based on number of patients in the PP population

T_SecEP 07MAR22 13:23

- **Incidence of clinically apparent neurological deficits**

Table 14.2.4-1: Incidence of clinically apparent neurological deficits -ITT population
Population: ITT

			Arm	
Visit	*Parameter - n (%)*		*A (Experimental) N=99*	*B (Control) N=101*
1	Clinical apparent neurological deficits	no	98 (99.0%)	94 (93.1%)
		yes	0 (0.0%)	0 (0.0%)
2	Clinical apparent neurological deficits	no	94 (94.9%)	89 (88.1%)
		yes	0 (0.0%)	1 (1.0%)
3	Clinical apparent neurological deficits	no	90 (90.9%)	90 (89.1%)
		yes	0 (0.0%)	1 (1.0%)

Percentage based on number of patients in the ITT population
Multiple citation possible
T_SecEP 07MAR22 13:23

Table 14.2.4-2: Incidence of clinically apparent neurological deficits -PP population
Population: PP

			Arm	
Visit	*Parameter - n (%)*		*A (Experimental) N=82*	*B (Control) N=87*
1	Clinical apparent neurological deficits	no	82 (100.0%)	87 (100.0%)
		yes	0 (0.0%)	0 (0.0%)
2	Clinical apparent neurological deficits	no	82 (100.0%)	85 (97.7%)
		yes	0 (0.0%)	1 (1.1%)
3	Clinical apparent neurological deficits	no	82 (100.0%)	85 (97.7%)
		yes	0 (0.0%)	1 (1.1%)

Percentage based on number of patients in the PP population
Multiple citation possible
T_SecEP 07MAR22 13:23

Listing: Clinically apparent neurological deficits

	Site	*Pat-ID*	*Visit*	*Clinical apparent neurological deficits*	*neurological deficit - Date*	*neurological deficit - mRS*	*neurological deficit-confirmation*	*EP - Comment - 1*	*EP - Comment - 2*
A (Experimental)	1	208	2	yes	11/09/2019	.	Not confirmed	Kriterium des neurologischen Defizits nicht erfüllt	1. CEC am 12.06.2020: kein EP. 2. CEC am 11.06.2021: trotzt zusätzlicher Infos weiterhin kein EP
B (Control)	1	26	2	yes	11/06/2020	.	Confirmed		Okulo Motorinsparese (??) neurologisch bestätigt, im CT keine Bedeutung, keine Thrombose

- **Severeness of neurological deficits**

There is only 1 patient in Arm B who had clinically apparent neurological deficits. Severeness was not judged (missing mRS assessment).

- **Incidence of other thrombotic or thrombo-embolic events**

Table 14.2.6-1: Incidence of other thrombotic or thrombo-embolic events -ITT Population
Population: ITT

			Arm	
Visit	*Parameter - n (%)*		*A (Experimental) N=99*	*B (Control) N=101*
1	Myocardial infarction	no	98 (99.0%)	94 (93.1%)
	Deep vein thrombosis	no	98 (99.0%)	94 (93.1%)
	Pulmonary embolism	no	98 (99.0%)	94 (93.1%)
	Thrombo-embolic event	no	98 (99.0%)	94 (93.1%)
2	Myocardial infarction	no	94 (94.9%)	90 (89.1%)
	Deep vein thrombosis	no	94 (94.9%)	90 (89.1%)
	Pulmonary embolism	no	94 (94.9%)	90 (89.1%)
	Thrombo-embolic event	no	94 (94.9%)	90 (89.1%)
3	Myocardial infarction	no	90 (90.9%)	91 (90.1%)
	Deep vein thrombosis	no	90 (90.9%)	91 (90.1%)
	Pulmonary embolism	no	90 (90.9%)	91 (90.1%)
	Thrombo-embolic event	no	90 (90.9%)	91 (90.1%)

Percentage based on number of patients in the ITT population

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Table 14.2.6-2: Incidence of other thrombotic or thrombo-embolic events -PP Population
Population: PP

			Arm	
Visit	*Parameter - n (%)*		*A (Experimental) N=82*	*B (Control) N=87*
1	Myocardial infarction	no	82 (100.0%)	87 (100.0%)
	Deep vein thrombosis	no	82 (100.0%)	87 (100.0%)
	Pulmonary embolism	no	82 (100.0%)	87 (100.0%)
	Thrombo-embolic event	no	82 (100.0%)	87 (100.0%)
2	Myocardial infarction	no	82 (100.0%)	86 (98.9%)
	Deep vein thrombosis	no	82 (100.0%)	86 (98.9%)
	Pulmonary embolism	no	82 (100.0%)	86 (98.9%)
	Thrombo-embolic event	no	82 (100.0%)	86 (98.9%)
3	Myocardial infarction	no	82 (100.0%)	86 (98.9%)
	Deep vein thrombosis	no	82 (100.0%)	86 (98.9%)
	Pulmonary embolism	no	82 (100.0%)	86 (98.9%)
	Thrombo-embolic event	no	82 (100.0%)	86 (98.9%)

Percentage based on number of patients in the PP population

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- **Life-threatening/major/minor bleedings**

Table 14.2.7-1: Bleeding - ITT population
Population: ITT

			Arm	
Visit	*Parameter - n (%)*		*A (Experimental) N=99*	*B (Control) N=101*
1	Bleeding	no	97 (98.0%)	93 (92.1%)
		yes	1 (1.0%)	1 (1.0%)
2	Bleeding	no	92 (92.9%)	90 (89.1%)
		yes	2 (2.0%)	0 (0.0%)
3	Bleeding	no	88 (88.9%)	90 (89.1%)
		yes	2 (2.0%)	1 (1.0%)

Percentage based on number of patients in the ITT population
Multiple citation possible
T_SecEP 07MAR22 13:23

Table 14.2.7-3: Bleeding - PP population
Population: PP

			Arm	
Visit	*Parameter - n (%)*		*A (Experimental) N=82*	*B (Control) N=87*
1	Bleeding	no	81 (98.8%)	86 (98.9%)
		yes	1 (1.2%)	1 (1.1%)
2	Bleeding	no	80 (97.6%)	86 (98.9%)
		yes	2 (2.4%)	0 (0.0%)
3	Bleeding	no	80 (97.6%)	85 (97.7%)
		yes	2 (2.4%)	1 (1.1%)

Percentage based on number of patients in the PP population
Multiple citation possible
T_SecEP 07MAR22 13:23

Listing: Bleeding

	Site	*Pat-ID*	*Visit*	*Bleeding*	*Bleeding Date*	*Bleeding grade*	*Bleeding confirmation*	*EP - Comment - 1*	*EP - Comment - 2*
A (Experimental)	5	70	3	yes	11/05/2018	minor	Confirmed	Patient berichtet Ã¼ber vermehrtes Zahnfleischbluten an Zahnimplantaten	Gingivabluten, Endpunkte bestätigt. VHF durch Patienten bestätigt
		71	1	yes	15/10/2017	minor	Confirmed	Patient berichtet von vermehrtem Zahnfleischbluten, deshalb wurde die Dosis reduziert.	Gingivabluten, Babigatrandosis erhöht

	Site	Pat-ID	Visit	Bleeding	Bleeding Date	Bleeding grade	Bleeding confirmation	EP - Comment - 1	EP - Comment - 2
B (Control)	8	54	1	yes	18/09/2017	minor	Confirmed		Keine Unterlagen, Endpunkt nicht bestätigt (CEC 11.06.2020). Endpunkt doch bestätigt durch Augenschein Visite 25.09.2017 (CEC 11.06.2021)

- **Hemorrhagic cerebral infarctions**

Table 14.2.8-1: Hemorrhagic cerebral infarctions - ITT population
Population: ITT

			Arm	
Visit	*Parameter - n (%)*		*A (Experimental) N=99*	*B (Control) N=101*
1	Hemorrhagic cerebral infarctions	no	98 (99.0%)	94 (93.1%)
2	Hemorrhagic cerebral infarctions	no	94 (94.9%)	90 (89.1%)
3	Hemorrhagic cerebral infarctions	no	90 (90.9%)	91 (90.1%)

Percentage based on number of patients in the ITT population
Multiple citation possible
T_SecEP 07MAR22 13:23

Table 14.2.8-2: Hemorrhagic cerebral infarctions -PP population
Population: PP

			Arm	
Visit	*Parameter - n (%)*		*A (Experimental) N=82*	*B (Control) N=87*
1	Hemorrhagic cerebral infarctions	no	82 (100.0%)	87 (100.0%)
2	Hemorrhagic cerebral infarctions	no	82 (100.0%)	86 (98.9%)
3	Hemorrhagic cerebral infarctions	no	82 (100.0%)	86 (98.9%)

Percentage based on number of patients in the PP population
Multiple citation possible
T_SecEP 07MAR22 13:23

- **All-cause mortality**

Table 14.2.9-1: All-cause mortality - ITT population
Population: ITT

			Arm	
Visit	*Parameter - n (%)*		*A (Experimental) N=99*	*B (Control) N=101*
1	Death	no	98 (99.0%)	94 (93.1%)
2	Death	no	94 (94.9%)	90 (89.1%)
3	Death	no	90 (90.9%)	91 (90.1%)

Percentage based on number of patients in the ITT population
Multiple citation possible
T_SecEP 07MAR22 13:23

Table 14.2.9-2: All-cause mortality - PP population
Population: PP

			Arm	
Visit	*Parameter - n (%)*		*A (Experimental) N=82*	*B (Control) N=87*
1	Death	no	82 (100.0%)	87 (100.0%)
2	Death	no	82 (100.0%)	86 (98.9%)
3	Death	no	82 (100.0%)	86 (98.9%)

Percentage based on number of patients in the PP population
Multiple citation possible
T_SecEP 07MAR22 13:23

- **Cardiovascular mortality**

No patient died during the trial.

- **Cardio-embolic events subgroup analyses**

No cardio-embolic events occurred during the trial.

- **QoL-EQ-5D**

Table 14.2.12-1: QoL-EQ-5D - ITT population
Population: ITT

Visit	*Arm*	*n*	*Mean*	*S.D.*	*Range*	*Median*	*95%-CI*	*P-value**
Randomisation	A (Experimental)	96	76.1	17.1	5-100	80.0	(72.59 ; 79.53)	
	B (Control)	99	81.2	13.8	20-100	85.0	(78.46 ; 83.98)	
Visit 3 (12 months after Rand.)	A (Experimental)	89	77.1	18.5	5-101	80.0	(73.17 ; 80.97)	
	B (Control)	91	79.3	15.6	30-100	80.0	(76.10 ; 82.58)	
Changes from day 0					.			
Visit 3 (12 months after Rand.)	A (Experimental)	89	3.0	20.7	-40- 90	0.0	(-1.36 ; 7.36)	0.1888
	B (Control)	91	-0.7	16.9	-50- 95	0.0	(-4.24 ; 2.81)	

*by Student's t-test
T_MOCA_QoL.sas 07JUL22 08:04

Table 14.2.12-2: QoL-EQ-5D - PP Population
Population: PP

Visit	*Arm*	*n*	*Mean*	*S.D.*	*Range*	*Median*	*95%-CI*	*P-value**
Randomisation	A (Experimental)	79	77.2	16.9	5-100	80.0	(73.39 ; 80.97)	
	B (Control)	86	82.0	12.8	40-100	85.0	(79.26 ; 84.74)	
Visit 3 (12 months after Rand.)	A (Experimental)	82	77.4	18.5	5-101	80.0	(73.32 ; 81.46)	
	B (Control)	86	80.2	14.9	30-100	80.0	(76.99 ; 83.36)	
Changes from day 0					.			
Visit 3 (12 months after Rand.)	A (Experimental)	82	3.0	21.5	-40- 90	0.0	(-1.69 ; 7.77)	0.2213
	B (Control)	86	-0.7	17.2	-50- 95	0.0	(-4.34 ; 3.01)	

*by Student's t-test
T_MOCA_QoL.sas 07JUL22 08:04

- **MOCA test**

Table 14.2.13-1: MOCA test - ITT population
Population: ITT

Visit	*Arm*	*n*	*Mean*	*S.D.*	*Range*	*Median*	*95%-CI*	*P-value**
Randomisation	A (Experimental)	95	25.2	3.5	12- 30	26.0	(24.46 ; 25.90)	
	B (Control)	96	25.7	3.5	16- 31	26.0	(24.95 ; 26.36)	
Visit 3 (12 months after Rand.)	A (Experimental)	84	26.0	3.3	17- 30	27.0	(25.33 ; 26.77)	
	B (Control)	87	26.5	2.8	17- 30	27.0	(25.93 ; 27.13)	
Changes from day 0					.			
Visit 3 (12 months after Rand.)	A (Experimental)	84	1.2	5.2	-11- 28	1.0	(0.08 ; 2.32)	0.5145
	B (Control)	87	0.8	3.2	-8- 8	1.0	(0.08 ; 1.46)	

*by Student's t-test
T_MOCA_QoL.sas 07JUL22 08:04

Table 14.2.13-2: MOCA test - PP Population
Population: PP

Visit	*Arm*	*n*	*Mean*	*S.D.*	*Range*	*Median*	*95%-CI*	*P-value**
Randomisation	A (Experimental)	79	25.3	3.3	16- 30	25.0	(24.55 ; 26.01)	
	B (Control)	83	25.8	3.3	17- 31	26.0	(25.04 ; 26.48)	
Visit 3 (12 months after Rand.)	A (Experimental)	79	26.0	3.3	17- 30	27.0	(25.29 ; 26.76)	
	B (Control)	82	26.5	2.9	17- 30	27.0	(25.89 ; 27.15)	
Changes from day 0					.			
Visit 3 (12 months after Rand.)	A (Experimental)	79	1.4	5.1	-8- 28	1.0	(0.23 ; 2.53)	0.3795
	B (Control)	82	0.8	3.3	-8- 8	1.0	(0.06 ; 1.50)	

*by Student's t-test
T_MOCA_QoL.sas 07JUL22 08:04

7.4 Safety

- Adverse Events

Table 14.3.2-1: Overview of AEs - SAF population
Population: Safety

	Arm		
Number of treated subjects - n (%)	*A (Experimental) N=107*	*B (Control) N=93*	*p-Value**
with any AE	72 (67.3%)	46 (49.5%)	0.0106
with drug-related AE	6 (5.6%)	3 (3.2%)	0.5078
With severe AE	10 (9.3%)	8 (8.6%)	0.8546
with SAE	34 (31.8%)	18 (19.4%)	0.0458

Note: Calculation of percentages based on number of patients in SP
*by Chi-Square test. If any category has a cell count less than 5, then the Fisher exact test will be used
T_AE_overview.sas 28SEP22 09:07

Table 14.3.2-2: Incidence of AEs by SOC and PT - SAF population
Population: Safety

		Arm		
System Organ Class	*Preferred term*	*A (Experimental) N= 107*	*B (Control) N= 93*	*P-Value* (Chi-Square/Fisher Exact)*
Allgemeine Erkrankungen und Beschwerden am Verabreichungsort	Total	9 (8.4%)	3 (3.2%)	0.1458
	Brustkorbbeschwerden	1 (0.9%)	0 (0.0%)	1.0000
	Brustkorbschmerz	2 (1.9%)	0 (0.0%)	0.4999
	Chemische Unvertraeglichkeit von Medikamenten	1 (0.9%)	0 (0.0%)	1.0000
	Ermuedung	1 (0.9%)	0 (0.0%)	1.0000
	Granulom	0 (0.0%)	1 (1.1%)	0.4650
	Oedem peripher	2 (1.9%)	2 (2.2%)	1.0000
	Schmerzen an der Punktionsstelle	1 (0.9%)	0 (0.0%)	1.0000
	Unerwuenschte Arzneimittelwirkung	1 (0.9%)	0 (0.0%)	1.0000
	Zyste	1 (0.9%)	0 (0.0%)	1.0000
Augenerkrankungen	Total	1 (0.9%)	3 (3.2%)	0.3396
	Augenblutung	0 (0.0%)	1 (1.1%)	0.4650
	Doppeltsehen	0 (0.0%)	1 (1.1%)	0.4650
	Entropium	1 (0.9%)	0 (0.0%)	1.0000
	Makulaoedem	0 (0.0%)	1 (1.1%)	0.4650
Chirurgische und medizinische Eingriffe	Total	9 (8.4%)	6 (6.5%)	0.5997
	Cholezystektomie	1 (0.9%)	0 (0.0%)	1.0000

System Organ Class	Preferred term	Arm A (Experimental) N= 107	 B (Control) N= 93	P-Value* (Chi-Square/Fisher Exact)
	Dentaloperation	0 (0.0%)	1 (1.1%)	0.4650
	Einsetzen eines Herzschrittmachers	0 (0.0%)	1 (1.1%)	0.4650
	Gelenkplastik	1 (0.9%)	0 (0.0%)	1.0000
	Intraokulaeres Linsenimplantat	1 (0.9%)	0 (0.0%)	1.0000
	Katarakt-Operation	1 (0.9%)	1 (1.1%)	1.0000
	Katheterablation	1 (0.9%)	0 (0.0%)	1.0000
	Krankenhausaufenthalt	1 (0.9%)	0 (0.0%)	1.0000
	Operation zur Wiederherstellung des Fingers	0 (0.0%)	1 (1.1%)	0.4650
	Operativer Eingriff	2 (1.9%)	0 (0.0%)	0.4999
	Transurethrale Blasenresektion	0 (0.0%)	1 (1.1%)	0.4650
	Varizenoperation	1 (0.9%)	0 (0.0%)	1.0000
	Zahnwurzelentfernung	0 (0.0%)	1 (1.1%)	0.4650
Endokrine Erkrankungen	Total	0 (0.0%)	3 (3.2%)	0.0988
	Hypothyreose	0 (0.0%)	2 (2.2%)	0.2150
	Struma	0 (0.0%)	1 (1.1%)	0.4650
Erkrankungen der Atemwege, des Brustraums und Mediastinums	Total	9 (8.4%)	5 (5.4%)	0.4015
	Asthma	0 (0.0%)	1 (1.1%)	0.4650
	Belastungsdyspnoe	1 (0.9%)	2 (2.2%)	0.5984
	Diaphragmalaehmung	1 (0.9%)	0 (0.0%)	1.0000

System Organ Class	Preferred term	Arm A (Experimental) N= 107	 B (Control) N= 93	P-Value* (Chi-Square/Fisher Exact)
	Dyspnoe	1 (0.9%)	1 (1.1%)	1.0000
	Epistaxis	3 (2.8%)	0 (0.0%)	0.2499
	Pleuraerguss	1 (0.9%)	1 (1.1%)	1.0000
	Pulmonale arterielle Hypertonie	1 (0.9%)	0 (0.0%)	1.0000
	Schlafapnoe-Syndrom	1 (0.9%)	2 (2.2%)	0.5984
Erkrankungen der Geschlechtsorgane und der Brustdruese	Total	1 (0.9%)	0 (0.0%)	1.0000
	Kruemmung des Penis	1 (0.9%)	0 (0.0%)	1.0000
Erkrankungen der Haut und des Unterhautgewebes	Total	3 (2.8%)	1 (1.1%)	0.6249
	Akne	1 (0.9%)	0 (0.0%)	1.0000
	Ausschlag	0 (0.0%)	1 (1.1%)	0.4650
	Kalter Schweiss	1 (0.9%)	0 (0.0%)	1.0000
	Psoriasis	1 (0.9%)	0 (0.0%)	1.0000
Erkrankungen der Nieren und Harnwege	Total	5 (4.7%)	1 (1.1%)	0.2186
	Nichtinfektioese Zystitis	1 (0.9%)	1 (1.1%)	1.0000
	Nierenfunktionsbeeintraechtigung	2 (1.9%)	0 (0.0%)	0.4999
	Nierenversagen	2 (1.9%)	0 (0.0%)	0.4999
Erkrankungen des Gastrointestinaltrakts	Total	10 (9.3%)	6 (6.5%)	0.4518
	Bauch aufgetrieben	1 (0.9%)	0 (0.0%)	1.0000
	Chronische Gastritis	1 (0.9%)	0 (0.0%)	1.0000
	Diarrhoe	2 (1.9%)	0 (0.0%)	0.4999

System Organ Class	Preferred term	Arm A (Experimental) N= 107	 B (Control) N= 93	P-Value* (Chi-Square/Fisher Exact)
	Dyspepsie	1 (0.9%)	0 (0.0%)	1.0000
	Erosive Gastritis	0 (0.0%)	1 (1.1%)	0.4650
	Gastritis	2 (1.9%)	1 (1.1%)	1.0000
	Gastrooesophageale Refluxerkrankung	0 (0.0%)	1 (1.1%)	0.4650
	Leistenbruch	2 (1.9%)	0 (0.0%)	0.4999
	Oesophagitis	1 (0.9%)	0 (0.0%)	1.0000
	Pankreatitis	0 (0.0%)	1 (1.1%)	0.4650
	Parotisvergroesserung	0 (0.0%)	1 (1.1%)	0.4650
	Schmerzen Oberbauch	0 (0.0%)	2 (2.2%)	0.2150
	Stuhl weich	1 (0.9%)	0 (0.0%)	1.0000
	Uebelkeit	1 (0.9%)	0 (0.0%)	1.0000
Erkrankungen des Immunsystems	Total	0 (0.0%)	1 (1.1%)	0.4650
	Ueberempfindlichkeit	0 (0.0%)	1 (1.1%)	0.4650
Erkrankungen des Nervensystems	Total	10 (9.3%)	7 (7.5%)	0.6455
	Demenz vom Alzheimertyp	1 (0.9%)	0 (0.0%)	1.0000
	Hypoaesthesie	0 (0.0%)	1 (1.1%)	0.4650
	Karpaltunnelsyndrom	1 (0.9%)	0 (0.0%)	1.0000
	Kopfschmerzen	2 (1.9%)	0 (0.0%)	0.4999
	Myasthenia gravis	0 (0.0%)	1 (1.1%)	0.4650
	Neuralgie	1 (0.9%)	0 (0.0%)	1.0000

System Organ Class	Preferred term	Arm A (Experimental) N= 107	 B (Control) N= 93	P-Value* (Chi-Square/Fisher Exact)
	Schwindel orthostatisch	0 (0.0%)	1 (1.1%)	0.4650
	Schwindelgefuehl	3 (2.8%)	2 (2.2%)	1.0000
	Stenose der Arteria carotis	1 (0.9%)	0 (0.0%)	1.0000
	Synkope	2 (1.9%)	2 (2.2%)	1.0000
	Zerebrale Mikroembolie	1 (0.9%)	0 (0.0%)	1.0000
Erkrankungen des Ohrs und des Labyrinths	Total	1 (0.9%)	1 (1.1%)	1.0000
	Hoersturz	1 (0.9%)	0 (0.0%)	1.0000
	Lagerungsvertigo	0 (0.0%)	1 (1.1%)	0.4650
	Tinnitus	1 (0.9%)	0 (0.0%)	1.0000
	Vertigo	1 (0.9%)	0 (0.0%)	1.0000
Gefaesserkrankungen	Total	6 (5.6%)	5 (5.4%)	0.9430
	Haematom	1 (0.9%)	1 (1.1%)	1.0000
	Hitzewallung	0 (0.0%)	1 (1.1%)	0.4650
	Hypertensive Krise	2 (1.9%)	1 (1.1%)	1.0000
	Hypertensiver Notfall	0 (0.0%)	1 (1.1%)	0.4650
	Hypertonie	0 (0.0%)	1 (1.1%)	0.4650
	Hypotonie	1 (0.9%)	0 (0.0%)	1.0000
	Kreislaufkollaps	1 (0.9%)	0 (0.0%)	1.0000
	Lymphoedem	0 (0.0%)	1 (1.1%)	0.4650
	Periphere Venenerkrankung	1 (0.9%)	0 (0.0%)	1.0000

System Organ Class	Preferred term	Arm A (Experimental) N= 107	 B (Control) N= 93	P-Value* (Chi-Square/Fisher Exact)
Gutartige, boesartige und nicht spezifizierte Neubildungen (einschl. Zysten und Polypen)	Total	2 (1.9%)	5 (5.4%)	0.2539
	Basalzellkarzinom	0 (0.0%)	1 (1.1%)	0.4650
	Boesartiges Melanom	0 (0.0%)	1 (1.1%)	0.4650
	Enchondromatose	0 (0.0%)	1 (1.1%)	0.4650
	Karzinom der Bronchien	0 (0.0%)	1 (1.1%)	0.4650
	Lipom der Brustdruese	1 (0.9%)	0 (0.0%)	1.0000
	Prostatakarzinom	1 (0.9%)	1 (1.1%)	1.0000
Herzerkrankungen	Total	38 (35.5%)	10 (10.8%)	<0.0001
	Aortenklappeninsuffizienz	1 (0.9%)	0 (0.0%)	1.0000
	Bradyarrhythmie	0 (0.0%)	1 (1.1%)	0.4650
	Bradykardie	1 (0.9%)	0 (0.0%)	1.0000
	Diastolische Dysfunktion	1 (0.9%)	0 (0.0%)	1.0000
	Herzinsuffizienz	3 (2.8%)	0 (0.0%)	0.2499
	Mitralklappeninsuffizienz	1 (0.9%)	0 (0.0%)	1.0000
	Myokarditis	1 (0.9%)	0 (0.0%)	1.0000
	Palpitationen	5 (4.7%)	3 (3.2%)	0.7265
	Perikarderguss	2 (1.9%)	0 (0.0%)	0.4999
	Sinusbradykardie	0 (0.0%)	1 (1.1%)	0.4650
	Supraventrikulaere Extrasystolen	1 (0.9%)	0 (0.0%)	1.0000
	Tachyarrhythmia	1 (0.9%)	0 (0.0%)	1.0000

System Organ Class	Preferred term	Arm A (Experimental) N= 107	 B (Control) N= 93	P-Value* (Chi-Square/Fisher Exact)
	Tachykardie	2 (1.9%)	0 (0.0%)	0.4999
	Tachykardie ventrikulaer	1 (0.9%)	0 (0.0%)	1.0000
	Trikuspidalklappeninsuffizienz	2 (1.9%)	0 (0.0%)	0.4999
	Vorhofflattern	5 (4.7%)	0 (0.0%)	0.0624
	Vorhofflimmern	27 (25.2%)	7 (7.5%)	0.0009
Infektionen und parasitaere Erkrankungen	Total	9 (8.4%)	11 (11.8%)	0.4218
	Bakterielle Infektion	0 (0.0%)	1 (1.1%)	0.4650
	Bronchitis	1 (0.9%)	1 (1.1%)	1.0000
	Erysipel	0 (0.0%)	1 (1.1%)	0.4650
	Gastrointestinalinfektion	0 (0.0%)	1 (1.1%)	0.4650
	Grippe	3 (2.8%)	1 (1.1%)	0.6249
	Harnwegsinfektion	0 (0.0%)	1 (1.1%)	0.4650
	Herpes zoster	0 (0.0%)	2 (2.2%)	0.2150
	Konjunktivitis	1 (0.9%)	0 (0.0%)	1.0000
	Nasopharyngitis	1 (0.9%)	0 (0.0%)	1.0000
	Pneumonie	2 (1.9%)	1 (1.1%)	1.0000
	Sinusitis	0 (0.0%)	2 (2.2%)	0.2150
	Zahnfistel	0 (0.0%)	1 (1.1%)	0.4650
	Zystitis	2 (1.9%)	0 (0.0%)	0.4999
Leber- und Gallenerkrankungen	Total	0 (0.0%)	1 (1.1%)	0.4650

System Organ Class	Preferred term	Arm A (Experimental) N= 107	 B (Control) N= 93	P-Value* (Chi-Square/Fisher Exact)
	Leberzyste	0 (0.0%)	1 (1.1%)	0.4650
Psychiatrische Erkrankungen	Total	2 (1.9%)	1 (1.1%)	1.0000
	Depression	0 (0.0%)	1 (1.1%)	0.4650
	Panikattacke	2 (1.9%)	0 (0.0%)	0.4999
Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen	Total	7 (6.5%)	4 (4.3%)	0.5488
	Arthralgie	0 (0.0%)	1 (1.1%)	0.4650
	Bandscheibenprotrusion	1 (0.9%)	0 (0.0%)	1.0000
	Bursitis	1 (0.9%)	0 (0.0%)	1.0000
	Haematom des Muskels	0 (0.0%)	1 (1.1%)	0.4650
	Osteoarthrose	2 (1.9%)	1 (1.1%)	1.0000
	Rueckenschmerzen	0 (0.0%)	1 (1.1%)	0.4650
	Schleimbeutelerkrankung	1 (0.9%)	0 (0.0%)	1.0000
	Schmerz in einer Extremitaet	1 (0.9%)	0 (0.0%)	1.0000
	Schmerzen des Muskel- und Skelettsystems	1 (0.9%)	0 (0.0%)	1.0000
	Spinalstenose	1 (0.9%)	0 (0.0%)	1.0000
Stoffwechsel- und Ernaehrungsstoerungen	Total	3 (2.8%)	1 (1.1%)	0.6249
	Dehydratation	1 (0.9%)	0 (0.0%)	1.0000
	Gicht	2 (1.9%)	1 (1.1%)	1.0000
Untersuchungen	Total	6 (5.6%)	2 (2.2%)	0.2889
	Arthroskopie	1 (0.9%)	0 (0.0%)	1.0000

System Organ Class	Preferred term	Arm A (Experimental) N= 107	 B (Control) N= 93	 P-Value* (Chi-Square/Fisher Exact)
	Auswurffraktion verkleinert	0 (0.0%)	1 (1.1%)	0.4650
	C-reaktives Protein anomal	1 (0.9%)	0 (0.0%)	1.0000
	Endoskopie des oberen Gastrointestinaltrakts	1 (0.9%)	0 (0.0%)	1.0000
	Glykolisiertes Haemoglobin erhoeht	1 (0.9%)	0 (0.0%)	1.0000
	Leberfunktionstest anomal	1 (0.9%)	0 (0.0%)	1.0000
	N-terminales Prohormon von BNP	0 (0.0%)	1 (1.1%)	0.4650
	N-terminales Prohormon von BNP erhoeht	1 (0.9%)	1 (1.1%)	1.0000
	Natriuretisches Peptid Typ B erhoeht	0 (0.0%)	1 (1.1%)	0.4650
Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen	Total	10 (9.3%)	9 (9.7%)	0.9364
	Arthropodenbiss	1 (0.9%)	0 (0.0%)	1.0000
	Baenderzerrung	0 (0.0%)	1 (1.1%)	0.4650
	Blutung nach einem Eingriff	1 (0.9%)	0 (0.0%)	1.0000
	Fraktur der Hand	1 (0.9%)	1 (1.1%)	1.0000
	Fraktur des Fusses	1 (0.9%)	1 (1.1%)	1.0000
	Fraktur des Schluesselbeins	1 (0.9%)	0 (0.0%)	1.0000
	Fraktur einer oberen Extremitaet	1 (0.9%)	0 (0.0%)	1.0000
	Fraktur eines Brustwirbels	1 (0.9%)	0 (0.0%)	1.0000
	Frakturen von Gesichtsknochen	1 (0.9%)	0 (0.0%)	1.0000

System Organ Class	Preferred term	Arm A (Experimental) N= 107	 B (Control) N= 93	 P-Value* (Chi-Square/Fisher Exact)
	Gestoerte Wundheilung an der Inzisionsstelle	1 (0.9%)	0 (0.0%)	1.0000
	Haematurie nach einem Eingriff	0 (0.0%)	1 (1.1%)	0.4650
	Hauteinriss	0 (0.0%)	1 (1.1%)	0.4650
	Humerusfraktur	0 (0.0%)	2 (2.2%)	0.2150
	Nervenverletzung	0 (0.0%)	1 (1.1%)	0.4650
	Serom	0 (0.0%)	1 (1.1%)	0.4650
	Sturz	2 (1.9%)	1 (1.1%)	1.0000
	Vaskulaeres Pseudoaneurysma	1 (0.9%)	0 (0.0%)	1.0000
	Verkehrsunfall	1 (0.9%)	0 (0.0%)	1.0000

Note: Calculation of percentages based on number of patients in SP
Note: A patient with more than one AE within a PT was counted once in PT
*If any category has a cell count less than 5, then the Fisher exact test will be used
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Table 14.3.1-3: Incidence of AEs by maximum severity - SAF Population
Population: Safety

			Arm	
System Organ Class	*Preferred term*	*Severity*	*A (Experimental) N= 107*	*B (Control) N= 93*
Allgemeine Erkrankungen und Beschwerden am Verabreichungsort	Total	mild	4 (3.7%)	3 (3.2%)
		moderate	5 (4.7%)	0 (0.0%)
	Brustkorbbeschwerden	moderate	1 (0.9%)	0 (0.0%)
	Brustkorbschmerz	mild	1 (0.9%)	0 (0.0%)
		moderate	1 (0.9%)	0 (0.0%)
	Chemische Unvertraeglichkeit von Medikamenten	mild	1 (0.9%)	0 (0.0%)
	Ermuedung	mild	1 (0.9%)	0 (0.0%)
	Granulom	mild	0 (0.0%)	1 (1.1%)
	Oedem peripher	mild	1 (0.9%)	2 (2.2%)
		moderate	1 (0.9%)	0 (0.0%)
	Schmerzen an der Punktionsstelle	mild	1 (0.9%)	0 (0.0%)
	Unerwuenschte Arzneimittelwirkung	moderate	1 (0.9%)	0 (0.0%)
	Zyste	moderate	1 (0.9%)	0 (0.0%)
Augenerkrankungen	Total	mild	0 (0.0%)	2 (2.2%)
		severe	1 (0.9%)	1 (1.1%)
	Augenblutung	mild	0 (0.0%)	1 (1.1%)
	Doppeltsehen	mild	0 (0.0%)	1 (1.1%)

			Arm	
System Organ Class	*Preferred term*	*Severity*	*A (Experimental) N= 107*	*B (Control) N= 93*
	Entropium	severe	1 (0.9%)	0 (0.0%)
	Makulaoedem	severe	0 (0.0%)	1 (1.1%)
Chirurgische und medizinische Eingriffe	Total	mild	2 (1.9%)	3 (3.2%)
		moderate	6 (5.6%)	2 (2.2%)
		severe	1 (0.9%)	1 (1.1%)
	Cholezystektomie	moderate	1 (0.9%)	0 (0.0%)
	Dentaloperation	mild	0 (0.0%)	1 (1.1%)
	Einsetzen eines Herzschrittmachers	severe	0 (0.0%)	1 (1.1%)
	Gelenkplastik	severe	1 (0.9%)	0 (0.0%)
	Intraokulaeres Linsenimplantat	moderate	1 (0.9%)	0 (0.0%)
	Katarakt-Operation	moderate	1 (0.9%)	1 (1.1%)
	Katheterablation	mild	1 (0.9%)	0 (0.0%)
	Krankenhausaufenthalt	mild	1 (0.9%)	0 (0.0%)
	Operation zur Wiederherstellung des Fingers	mild	0 (0.0%)	1 (1.1%)
	Operativer Eingriff	moderate	2 (1.9%)	0 (0.0%)
	Transurethrale Blasenresektion	moderate	0 (0.0%)	1 (1.1%)
	Varizenoperation	moderate	1 (0.9%)	0 (0.0%)
	Zahnwurzelentfernung	mild	0 (0.0%)	1 (1.1%)
Endokrine Erkrankungen	Total	mild	0 (0.0%)	3 (3.2%)
	Hypothyreose	mild	0 (0.0%)	2 (2.2%)

System Organ Class	Preferred term	Severity	Arm A (Experimental) N= 107	Arm B (Control) N= 93
	Struma	mild	0 (0.0%)	1 (1.1%)
Erkrankungen der Atemwege, des Brustraums und Mediastinums	Total	mild	5 (4.7%)	2 (2.2%)
		moderate	4 (3.7%)	1 (1.1%)
		severe	0 (0.0%)	2 (2.2%)
	Asthma	mild	0 (0.0%)	1 (1.1%)
	Belastungsdyspnoe	mild	0 (0.0%)	2 (2.2%)
		moderate	1 (0.9%)	0 (0.0%)
	Diaphragmalaehmung	moderate	1 (0.9%)	0 (0.0%)
	Dyspnoe	mild	1 (0.9%)	0 (0.0%)
		moderate	0 (0.0%)	1 (1.1%)
	Epistaxis	mild	3 (2.8%)	0 (0.0%)
	Pleuraerguss	mild	0 (0.0%)	1 (1.1%)
		moderate	1 (0.9%)	0 (0.0%)
	Pulmonale arterielle Hypertonie	moderate	1 (0.9%)	0 (0.0%)
	Schlafapnoe-Syndrom	mild	1 (0.9%)	0 (0.0%)
		severe	0 (0.0%)	2 (2.2%)
Erkrankungen der Geschlechtsorgane und der Brustdruese	Total	moderate	1 (0.9%)	0 (0.0%)
	Kruemmung des Penis	moderate	1 (0.9%)	0 (0.0%)
Erkrankungen der Haut und des Unterhautgewebes	Total	mild	2 (1.9%)	0 (0.0%)
		moderate	1 (0.9%)	0 (0.0%)

System Organ Class	Preferred term	Severity	Arm A (Experimental) N= 107	Arm B (Control) N= 93
		severe	0 (0.0%)	1 (1.1%)
	Akne	mild	1 (0.9%)	0 (0.0%)
	Ausschlag	severe	0 (0.0%)	1 (1.1%)
	Kalter Schweiss	moderate	1 (0.9%)	0 (0.0%)
	Psoriasis	mild	1 (0.9%)	0 (0.0%)
Erkrankungen der Nieren und Harnwege	Total	mild	3 (2.8%)	0 (0.0%)
		moderate	2 (1.9%)	1 (1.1%)
	Nichtinfektioese Zystitis	moderate	1 (0.9%)	1 (1.1%)
	Nierenfunktionsbeeintraechtigung	mild	2 (1.9%)	0 (0.0%)
	Nierenversagen	mild	1 (0.9%)	0 (0.0%)
		moderate	1 (0.9%)	0 (0.0%)
Erkrankungen des Gastrointestinaltrakts	Total	mild	8 (7.5%)	4 (4.3%)
		moderate	2 (1.9%)	1 (1.1%)
		severe	0 (0.0%)	1 (1.1%)
	Bauch aufgetrieben	mild	1 (0.9%)	0 (0.0%)
	Chronische Gastritis	mild	1 (0.9%)	0 (0.0%)
	Diarrhoe	mild	2 (1.9%)	0 (0.0%)
	Dyspepsie	mild	1 (0.9%)	0 (0.0%)
	Erosive Gastritis	mild	0 (0.0%)	1 (1.1%)
	Gastritis	mild	2 (1.9%)	1 (1.1%)

System Organ Class	Preferred term	Severity	Arm A (Experimental) N= 107	Arm B (Control) N= 93
	Gastrooesophageale Refluxerkrankung	severe	0 (0.0%)	1 (1.1%)
	Leistenbruch	moderate	2 (1.9%)	0 (0.0%)
	Oesophagitis	mild	1 (0.9%)	0 (0.0%)
	Pankreatitis	mild	0 (0.0%)	1 (1.1%)
	Parotisvergroesserung	moderate	0 (0.0%)	1 (1.1%)
	Schmerzen Oberbauch	mild	0 (0.0%)	2 (2.2%)
	Stuhl weich	mild	1 (0.9%)	0 (0.0%)
	Uebelkeit	mild	1 (0.9%)	0 (0.0%)
Erkrankungen des Immunsystems	Total	mild	0 (0.0%)	1 (1.1%)
	Ueberempfindlichkeit	mild	0 (0.0%)	1 (1.1%)
Erkrankungen des Nervensystems	Total	mild	3 (2.8%)	3 (3.2%)
		moderate	6 (5.6%)	4 (4.3%)
		severe	1 (0.9%)	0 (0.0%)
	Demenz vom Alzheimertyp	moderate	1 (0.9%)	0 (0.0%)
	Hypoaesthesie	moderate	0 (0.0%)	1 (1.1%)
	Karpaltunnelsyndrom	moderate	1 (0.9%)	0 (0.0%)
	Kopfschmerzen	mild	1 (0.9%)	0 (0.0%)
		severe	1 (0.9%)	0 (0.0%)
	Myasthenia gravis	moderate	0 (0.0%)	1 (1.1%)
	Neuralgie	moderate	1 (0.9%)	0 (0.0%)

System Organ Class	Preferred term	Severity	Arm A (Experimental) N= 107	Arm B (Control) N= 93
	Schwindel orthostatisch	mild	0 (0.0%)	1 (1.1%)
	Schwindelgefuehl	mild	1 (0.9%)	1 (1.1%)
		moderate	2 (1.9%)	1 (1.1%)
	Stenose der Arteria carotis	mild	1 (0.9%)	0 (0.0%)
	Synkope	mild	1 (0.9%)	1 (1.1%)
		moderate	1 (0.9%)	1 (1.1%)
	Zerebrale Mikroembolie	mild	1 (0.9%)	0 (0.0%)
Erkrankungen des Ohrs und des Labyrinths	Total	mild	0 (0.0%)	1 (1.1%)
		severe	1 (0.9%)	0 (0.0%)
	Hoersturz	severe	1 (0.9%)	0 (0.0%)
	Lagerungsvertigo	mild	0 (0.0%)	1 (1.1%)
	Tinnitus	severe	1 (0.9%)	0 (0.0%)
	Vertigo	severe	1 (0.9%)	0 (0.0%)
Gefaesserkrankungen	Total	mild	5 (4.7%)	4 (4.3%)
		moderate	1 (0.9%)	1 (1.1%)
	Haematom	mild	1 (0.9%)	1 (1.1%)
	Hitzewallung	mild	0 (0.0%)	1 (1.1%)
	Hypertensive Krise	mild	1 (0.9%)	1 (1.1%)
		moderate	1 (0.9%)	0 (0.0%)
	Hypertensiver Notfall	mild	0 (0.0%)	1 (1.1%)

			Arm	
System Organ Class	*Preferred term*	*Severity*	*A (Experimental) N= 107*	*B (Control) N= 93*
	Hypertonie	mild	0 (0.0%)	1 (1.1%)
	Hypotonie	mild	1 (0.9%)	0 (0.0%)
	Kreislaufkollaps	mild	1 (0.9%)	0 (0.0%)
	Lymphoedem	moderate	0 (0.0%)	1 (1.1%)
	Periphere Venenerkrankung	mild	1 (0.9%)	0 (0.0%)
Gutartige, boesartige und nicht spezifizierte Neubildungen (einschl. Zysten und Polypen)	Total	mild	1 (0.9%)	0 (0.0%)
		moderate	0 (0.0%)	4 (4.3%)
		severe	1 (0.9%)	1 (1.1%)
	Basalzellkarzinom	moderate	0 (0.0%)	1 (1.1%)
	Boesartiges Melanom	moderate	0 (0.0%)	1 (1.1%)
	Enchondromatose	moderate	0 (0.0%)	1 (1.1%)
	Karzinom der Bronchien	moderate	0 (0.0%)	1 (1.1%)
	Lipom der Brustdruese	mild	1 (0.9%)	0 (0.0%)
	Prostatakarzinom	severe	1 (0.9%)	1 (1.1%)
Herzerkrankungen	Total	mild	15 (14.0%)	9 (9.7%)
		moderate	19 (17.8%)	1 (1.1%)
		severe	4 (3.7%)	0 (0.0%)
	Aortenklappeninsuffizienz	mild	1 (0.9%)	0 (0.0%)
	Bradyarrhythmie	mild	0 (0.0%)	1 (1.1%)
	Bradykardie	mild	1 (0.9%)	0 (0.0%)

System Organ Class	Preferred term	Severity	Arm A (Experimental) N= 107	Arm B (Control) N= 93
	Diastolische Dysfunktion	mild	1 (0.9%)	0 (0.0%)
	Herzinsuffizienz	mild	1 (0.9%)	0 (0.0%)
		moderate	2 (1.9%)	0 (0.0%)
	Mitralklappeninsuffizienz	mild	1 (0.9%)	0 (0.0%)
	Myokarditis	moderate	1 (0.9%)	0 (0.0%)
	Palpitationen	mild	3 (2.8%)	3 (3.2%)
		moderate	2 (1.9%)	0 (0.0%)
	Perikarderguss	mild	1 (0.9%)	0 (0.0%)
		severe	1 (0.9%)	0 (0.0%)
	Sinusbradykardie	mild	0 (0.0%)	1 (1.1%)
	Supraventrikulaere Extrasystolen	moderate	1 (0.9%)	0 (0.0%)
	Tachyarrhythmia	moderate	1 (0.9%)	0 (0.0%)
	Tachykardie	mild	2 (1.9%)	0 (0.0%)
	Tachykardie ventrikulaer	moderate	1 (0.9%)	0 (0.0%)
	Trikuspidalklappeninsuffizienz	mild	1 (0.9%)	0 (0.0%)
		moderate	1 (0.9%)	0 (0.0%)
	Vorhofflattern	mild	2 (1.9%)	0 (0.0%)
		moderate	3 (2.8%)	0 (0.0%)
	Vorhofflimmern	mild	10 (9.3%)	6 (6.5%)
		moderate	14 (13.1%)	1 (1.1%)

System Organ Class	Preferred term	Severity	Arm A (Experimental) N= 107	Arm B (Control) N= 93
		severe	3 (2.8%)	0 (0.0%)
Infektionen und parasitaere Erkrankungen	Total	mild	2 (1.9%)	6 (6.5%)
		moderate	7 (6.5%)	5 (5.4%)
	Bakterielle Infektion	mild	0 (0.0%)	1 (1.1%)
	Bronchitis	mild	1 (0.9%)	1 (1.1%)
	Erysipel	moderate	0 (0.0%)	1 (1.1%)
	Gastrointestinalinfektion	mild	0 (0.0%)	1 (1.1%)
	Grippe	mild	1 (0.9%)	0 (0.0%)
		moderate	2 (1.9%)	1 (1.1%)
	Harnwegsinfektion	moderate	0 (0.0%)	1 (1.1%)
	Herpes zoster	mild	0 (0.0%)	1 (1.1%)
		moderate	0 (0.0%)	1 (1.1%)
	Konjunktivitis	moderate	1 (0.9%)	0 (0.0%)
	Nasopharyngitis	moderate	1 (0.9%)	0 (0.0%)
	Pneumonie	moderate	2 (1.9%)	1 (1.1%)
	Sinusitis	mild	0 (0.0%)	1 (1.1%)
		moderate	0 (0.0%)	1 (1.1%)
	Zahnfistel	mild	0 (0.0%)	1 (1.1%)
	Zystitis	moderate	2 (1.9%)	0 (0.0%)
Leber- und Gallenerkrankungen	Total	mild	0 (0.0%)	1 (1.1%)

System Organ Class	Preferred term	Severity	Arm A (Experimental) N= 107	Arm B (Control) N= 93
	Leberzyste	mild	0 (0.0%)	1 (1.1%)
Psychiatrische Erkrankungen	Total	mild	2 (1.9%)	0 (0.0%)
		moderate	0 (0.0%)	1 (1.1%)
	Depression	moderate	0 (0.0%)	1 (1.1%)
	Panikattacke	mild	2 (1.9%)	0 (0.0%)
Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen	Total	mild	3 (2.8%)	3 (3.2%)
		moderate	4 (3.7%)	1 (1.1%)
	Arthralgie	mild	0 (0.0%)	1 (1.1%)
	Bandscheibenprotrusion	moderate	1 (0.9%)	0 (0.0%)
	Bursitis	mild	1 (0.9%)	0 (0.0%)
	Haematom des Muskels	mild	0 (0.0%)	1 (1.1%)
	Osteoarthrose	mild	1 (0.9%)	0 (0.0%)
		moderate	1 (0.9%)	1 (1.1%)
	Rueckenschmerzen	mild	0 (0.0%)	1 (1.1%)
	Schleimbeutelerkrankung	mild	1 (0.9%)	0 (0.0%)
	Schmerz in einer Extremitaet	moderate	1 (0.9%)	0 (0.0%)
	Schmerzen des Muskel- und Skelettsystems	moderate	1 (0.9%)	0 (0.0%)
	Spinalstenose	mild	1 (0.9%)	0 (0.0%)
Stoffwechsel- und Ernaehrungsstoerungen	Total	mild	1 (0.9%)	1 (1.1%)
		moderate	2 (1.9%)	0 (0.0%)

			Arm	
System Organ Class	*Preferred term*	*Severity*	*A (Experimental) N= 107*	*B (Control) N= 93*
	Dehydratation	mild	1 (0.9%)	0 (0.0%)
	Gicht	mild	0 (0.0%)	1 (1.1%)
		moderate	2 (1.9%)	0 (0.0%)
Untersuchungen	Total	mild	4 (3.7%)	0 (0.0%)
		moderate	2 (1.9%)	1 (1.1%)
		severe	0 (0.0%)	1 (1.1%)
	Arthroskopie	mild	1 (0.9%)	0 (0.0%)
	Auswurffraktion verkleinert	severe	0 (0.0%)	1 (1.1%)
	C-reaktives Protein anomal	mild	1 (0.9%)	0 (0.0%)
	Endoskopie des oberen Gastrointestinaltrakts	mild	1 (0.9%)	0 (0.0%)
	Glykolisiertes Haemoglobin erhoeht	moderate	1 (0.9%)	0 (0.0%)
	Leberfunktionstest anomal	mild	1 (0.9%)	0 (0.0%)
	N-terminales Prohormon von BNP	moderate	0 (0.0%)	1 (1.1%)
	N-terminales Prohormon von BNP erhoeht	moderate	1 (0.9%)	0 (0.0%)
		severe	0 (0.0%)	1 (1.1%)
	Natriuretisches Peptid Typ B erhoeht	moderate	0 (0.0%)	1 (1.1%)
Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen	Total	mild	3 (2.8%)	2 (2.2%)
		moderate	5 (4.7%)	5 (5.4%)
		severe	2 (1.9%)	2 (2.2%)

System Organ Class	Preferred term	Severity	Arm A (Experimental) N= 107	Arm B (Control) N= 93
	Arthropodenbiss	mild	1 (0.9%)	0 (0.0%)
	Baenderzerrung	moderate	0 (0.0%)	1 (1.1%)
	Blutung nach einem Eingriff	mild	1 (0.9%)	0 (0.0%)
	Fraktur der Hand	moderate	1 (0.9%)	1 (1.1%)
	Fraktur des Fusses	mild	1 (0.9%)	0 (0.0%)
		severe	0 (0.0%)	1 (1.1%)
	Fraktur des Schluesselbeins	moderate	1 (0.9%)	0 (0.0%)
	Fraktur einer oberen Extremitaet	severe	1 (0.9%)	0 (0.0%)
	Fraktur eines Brustwirbels	severe	1 (0.9%)	0 (0.0%)
	Frakturen von Gesichtsknochen	mild	1 (0.9%)	0 (0.0%)
	Gestoerte Wundheilung an der Inzisionsstelle	moderate	1 (0.9%)	0 (0.0%)
	Haematurie nach einem Eingriff	mild	0 (0.0%)	1 (1.1%)
	Hauteinriss	moderate	0 (0.0%)	1 (1.1%)
	Humerusfraktur	moderate	0 (0.0%)	1 (1.1%)
		severe	0 (0.0%)	1 (1.1%)
	Nervenverletzung	mild	0 (0.0%)	1 (1.1%)
	Serom	moderate	0 (0.0%)	1 (1.1%)
	Sturz	mild	0 (0.0%)	1 (1.1%)
		moderate	1 (0.9%)	0 (0.0%)
		severe	1 (0.9%)	0 (0.0%)

			Arm	
System Organ Class	*Preferred term*	*Severity*	*A (Experimental)* *N= 107*	*B (Control)* *N= 93*
	Vaskulaeres Pseudoaneurysma	moderate	1 (0.9%)	0 (0.0%)
	Verkehrsunfall	moderate	1 (0.9%)	0 (0.0%)

Calculation of percentages based on number of patients in SP
A patient with more than one AE within a PT was counted once in PT
T_AE_maxSev.sas 05JUL22 07:58

Table 14.3.1-4: Incidence of drug-related AEs - SAF Population
Population: Safety

System Organ Class	*Preferred term*	*Arm* *A (Experimental) N= 107*	*B (Control) N= 93*	*P-Value* (Chi-Square/Fisher Exact)*
Allgemeine Erkrankungen und Beschwerden am Verabreichungsort	Total	2 (1.9%)	0 (0.0%)	0.4999
	Chemische Unvertraeglichkeit von Medikamenten	1 (0.9%)	0 (0.0%)	1.0000
	Unerwuenschte Arzneimittelwirkung	1 (0.9%)	0 (0.0%)	1.0000
Erkrankungen der Atemwege, des Brustraums und Mediastinums	Total	1 (0.9%)	0 (0.0%)	1.0000
	Epistaxis	1 (0.9%)	0 (0.0%)	1.0000
Erkrankungen des Gastrointestinaltrakts	Total	2 (1.9%)	2 (2.2%)	1.0000
	Bauch aufgetrieben	1 (0.9%)	0 (0.0%)	1.0000
	Diarrhoe	1 (0.9%)	0 (0.0%)	1.0000
	Schmerzen Oberbauch	0 (0.0%)	2 (2.2%)	0.2150
	Stuhl weich	1 (0.9%)	0 (0.0%)	1.0000
Herzerkrankungen	Total	0 (0.0%)	1 (1.1%)	0.4650
	Vorhofflimmern	0 (0.0%)	1 (1.1%)	0.4650
Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen	Total	1 (0.9%)	0 (0.0%)	1.0000
	Blutung nach einem Eingriff	1 (0.9%)	0 (0.0%)	1.0000

System Organ Class	Preferred term	Arm A (Experimental) N= 107	 B (Control) N= 93	 P-Value* (Chi-Square/Fisher Exact)

Calculation of percentages based on number of patients in SP
A patient with more than one AE within a PT was counted once in PT
Relation to study drug was judged with YES
*If any category has a cell count less than 5, then the Fisher exact test will be used
T_ae_studmed.sas 27SEP22 09:25

Table 14.3.1-5: SAE - SAF Population
Population: Safety

		Arm		
System Organ Class	*Preferred term*	*A (Experimental) N= 107*	*B (Control) N= 93*	*P-Value* (Chi-Square/Fisher Exact)*
Allgemeine Erkrankungen und Beschwerden am Verabreichungsort	Total	2 (1.9%)	0 (0.0%)	0.4999
	Brustkorbbeschwerden	1 (0.9%)	0 (0.0%)	1.0000
	Brustkorbschmerz	1 (0.9%)	0 (0.0%)	1.0000
Augenerkrankungen	Total	1 (0.9%)	1 (1.1%)	1.0000
	Doppeltsehen	0 (0.0%)	1 (1.1%)	0.4650
	Entropium	1 (0.9%)	0 (0.0%)	1.0000
Chirurgische und medizinische Eingriffe	Total	5 (4.7%)	2 (2.2%)	0.4530
	Cholezystektomie	1 (0.9%)	0 (0.0%)	1.0000
	Einsetzen eines Herzschrittmachers	0 (0.0%)	1 (1.1%)	0.4650
	Gelenkplastik	1 (0.9%)	0 (0.0%)	1.0000
	Katheterablation	1 (0.9%)	0 (0.0%)	1.0000
	Operativer Eingriff	2 (1.9%)	0 (0.0%)	0.4999
	Transurethrale Blasenresektion	0 (0.0%)	1 (1.1%)	0.4650
Endokrine Erkrankungen	Total	0 (0.0%)	1 (1.1%)	0.4650
	Struma	0 (0.0%)	1 (1.1%)	0.4650
Erkrankungen der Atemwege, des Brustraums und Mediastinums	Total	2 (1.9%)	1 (1.1%)	1.0000
	Dyspnoe	0 (0.0%)	1 (1.1%)	0.4650
	Pleuraerguss	1 (0.9%)	0 (0.0%)	1.0000

System Organ Class	Preferred term	Arm A (Experimental) N= 107	 B (Control) N= 93	P-Value* (Chi-Square/Fisher Exact)
	Schlafapnoe-Syndrom	1 (0.9%)	0 (0.0%)	1.0000
Erkrankungen der Geschlechtsorgane und der Brustdruese	Total	1 (0.9%)	0 (0.0%)	1.0000
	Kruemmung des Penis	1 (0.9%)	0 (0.0%)	1.0000
Erkrankungen der Haut und des Unterhautgewebes	Total	0 (0.0%)	1 (1.1%)	0.4650
	Ausschlag	0 (0.0%)	1 (1.1%)	0.4650
Erkrankungen der Nieren und Harnwege	Total	1 (0.9%)	0 (0.0%)	1.0000
	Nierenversagen	1 (0.9%)	0 (0.0%)	1.0000
Erkrankungen des Gastrointestinaltrakts	Total	4 (3.7%)	3 (3.2%)	1.0000
	Diarrhoe	1 (0.9%)	0 (0.0%)	1.0000
	Gastritis	1 (0.9%)	0 (0.0%)	1.0000
	Gastrooesophageale Refluxerkrankung	0 (0.0%)	1 (1.1%)	0.4650
	Leistenbruch	2 (1.9%)	0 (0.0%)	0.4999
	Pankreatitis	0 (0.0%)	1 (1.1%)	0.4650
	Parotisvergroesserung	0 (0.0%)	1 (1.1%)	0.4650
Erkrankungen des Nervensystems	Total	3 (2.8%)	1 (1.1%)	0.6249
	Demenz vom Alzheimertyp	1 (0.9%)	0 (0.0%)	1.0000
	Kopfschmerzen	1 (0.9%)	0 (0.0%)	1.0000
	Myasthenia gravis	0 (0.0%)	1 (1.1%)	0.4650
	Synkope	1 (0.9%)	0 (0.0%)	1.0000
Erkrankungen des Ohrs und des Labyrinths	Total	0 (0.0%)	1 (1.1%)	0.4650

System Organ Class	Preferred term	Arm A (Experimental) N= 107	 B (Control) N= 93	P-Value* (Chi-Square/Fisher Exact)
	Lagerungsvertigo	0 (0.0%)	1 (1.1%)	0.4650
Gefaesserkrankungen	Total	0 (0.0%)	1 (1.1%)	0.4650
	Hypertensive Krise	0 (0.0%)	1 (1.1%)	0.4650
	Hypertensiver Notfall	0 (0.0%)	1 (1.1%)	0.4650
Gutartige, boesartige und nicht spezifizierte Neubildungen (einschl. Zysten und Polypen)	Total	1 (0.9%)	3 (3.2%)	0.3396
	Boesartiges Melanom	0 (0.0%)	1 (1.1%)	0.4650
	Karzinom der Bronchien	0 (0.0%)	1 (1.1%)	0.4650
	Prostatakarzinom	1 (0.9%)	1 (1.1%)	1.0000
Herzerkrankungen	Total	18 (16.8%)	2 (2.2%)	0.0006
	Herzinsuffizienz	2 (1.9%)	0 (0.0%)	0.4999
	Myokarditis	1 (0.9%)	0 (0.0%)	1.0000
	Palpitationen	2 (1.9%)	0 (0.0%)	0.4999
	Perikarderguss	1 (0.9%)	0 (0.0%)	1.0000
	Supraventrikulaere Extrasystolen	1 (0.9%)	0 (0.0%)	1.0000
	Tachyarrhythmia	1 (0.9%)	0 (0.0%)	1.0000
	Tachykardie	1 (0.9%)	0 (0.0%)	1.0000
	Vorhofflattern	3 (2.8%)	0 (0.0%)	0.2499
	Vorhofflimmern	10 (9.3%)	2 (2.2%)	0.0384
Infektionen und parasitaere Erkrankungen	Total	2 (1.9%)	2 (2.2%)	1.0000
	Erysipel	0 (0.0%)	1 (1.1%)	0.4650

System Organ Class	Preferred term	Arm A (Experimental) N= 107	 B (Control) N= 93	P-Value* (Chi-Square/Fisher Exact)
	Grippe	1 (0.9%)	0 (0.0%)	1.0000
	Harnwegsinfektion	0 (0.0%)	1 (1.1%)	0.4650
	Pneumonie	1 (0.9%)	0 (0.0%)	1.0000
Skelettmuskulatur-, Bindegewebs- und Knochenerkrankungen	Total	1 (0.9%)	2 (2.2%)	0.5984
	Haematom des Muskels	0 (0.0%)	1 (1.1%)	0.4650
	Osteoarthrose	1 (0.9%)	1 (1.1%)	1.0000
Stoffwechsel- und Ernaehrungsstoerungen	Total	1 (0.9%)	0 (0.0%)	1.0000
	Dehydratation	1 (0.9%)	0 (0.0%)	1.0000
Untersuchungen	Total	1 (0.9%)	0 (0.0%)	1.0000
	Arthroskopie	1 (0.9%)	0 (0.0%)	1.0000
Verletzung, Vergiftung und durch Eingriffe bedingte Komplikationen	Total	3 (2.8%)	6 (6.5%)	0.3082
	Fraktur des Fusses	0 (0.0%)	1 (1.1%)	0.4650
	Fraktur einer oberen Extremitaet	1 (0.9%)	0 (0.0%)	1.0000
	Fraktur eines Brustwirbels	1 (0.9%)	0 (0.0%)	1.0000
	Frakturen von Gesichtsknochen	1 (0.9%)	0 (0.0%)	1.0000
	Gestoerte Wundheilung an der Inzisionsstelle	1 (0.9%)	0 (0.0%)	1.0000
	Haematurie nach einem Eingriff	0 (0.0%)	1 (1.1%)	0.4650
	Hauteinriss	0 (0.0%)	1 (1.1%)	0.4650
	Humerusfraktur	0 (0.0%)	2 (2.2%)	0.2150
	Serom	0 (0.0%)	1 (1.1%)	0.4650

System Organ Class	Preferred term	Arm A (Experimental) N= 107	 B (Control) N= 93	 P-Value* (Chi-Square/Fisher Exact)

Calculation of percentages based on number of patients in SP
A patient with more than one AE within a PT was counted once in PT
*If any category has a cell count less than 5, then the Fisher exact test will be used
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- Selected laboratory data

Table 14.3.6: Selected laboratory data - SAF Population
Population: Safety

Variable	*Visit*	*Arm*	*n*	*Mean*	*S.D.*	*Median*	*Range*	*95%-CI*
Serum creatinine [mg/dL]	Randomisation	A (Experimental)	104	0.9	0.2	0.9	1- 2	(0.90 ; 0.99)
		B (Control)	91	0.9	0.2	0.9	0- 2	(0.87 ; 0.96)
	Visit 1	A (Experimental)	101	0.9	0.2	0.9	1- 2	(0.91 ; 0.99)
		B (Control)	82	2.1	10.6	0.9	1- 97	(-0.23 ; 4.43)
	Visit 2	A (Experimental)	99	1.8	8.1	0.9	1- 81	(0.21 ; 3.43)
		B (Control)	82	0.9	0.2	0.9	1- 2	(0.88 ; 0.97)
	Visit 3	A (Experimental)	97	0.9	0.2	0.9	1- 2	(0.88 ; 0.96)
		B (Control)	84	0.9	0.2	0.9	1- 2	(0.86 ; 0.94)
	Changes from day 0						.	
	Visit 1	A (Experimental)	101	0.0	0.2	0.0	-1- 1	(-0.01 ; 0.07)
		B (Control)	82	1.2	10.6	0.0	-0- 96	(-1.12 ; 3.53)
	Visit 2	A (Experimental)	99	0.9	8.1	0.0	-1- 80	(-0.70 ; 2.52)
		B (Control)	82	0.0	0.2	0.0	-0- 1	(-0.00 ; 0.09)
	Visit 3	A (Experimental)	97	0.0	0.2	0.0	-1- 1	(-0.04 ; 0.05)
		B (Control)	84	0.0	0.2	-0.0	-0- 1	(-0.02 ; 0.06)

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Table 14.3.6: Selected laboratory data - SAF Population
Population: Safety

Variable	*Visit*	*Arm*	*n*	*Mean*	*S.D.*	*Median*	*Range*	*95%-CI*
GFR [mL/min]	Randomisation	A (Experimental)	102	71.7	16.1	70.0	44- 120	(68.59 ; 74.91)
		B (Control)	89	74.5	16.2	70.0	42- 108	(71.13 ; 77.95)
	Visit 1	A (Experimental)	102	70.4	15.0	70.0	41- 121	(67.49 ; 73.38)
		B (Control)	82	74.2	16.7	70.0	39- 137	(70.52 ; 77.84)
	Visit 2	A (Experimental)	98	71.1	15.0	70.0	33- 112	(68.14 ; 74.13)
		B (Control)	80	74.7	16.0	70.0	37- 126	(71.12 ; 78.23)
	Visit 3	A (Experimental)	96	72.6	14.8	70.0	35- 115	(69.63 ; 75.61)
		B (Control)	84	74.4	16.0	70.0	37- 132	(70.95 ; 77.87)
	Changes from day 0						.	
	Visit 1	A (Experimental)	102	2.8	15.0	0.0	-22- 73	(-0.19 ; 5.71)
		B (Control)	82	3.0	17.2	0.0	-39- 95	(-0.74 ; 6.84)
	Visit 2	A (Experimental)	98	2.8	17.1	0.0	-42- 72	(-0.66 ; 6.20)
		B (Control)	80	3.0	18.8	0.0	-39- 91	(-1.15 ; 7.21)
	Visit 3	A (Experimental)	96	5.0	18.2	0.0	-39- 73	(1.36 ; 8.72)
		B (Control)	84	2.6	18.8	0.0	-39- 91	(-1.47 ; 6.67)

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Table 14.3.6: Selected laboratory data - SAF Population
Population: Safety

Variable	*Visit*	*Arm*	*n*	*Mean*	*S.D.*	*Median*	*Range*	*95%-CI*
CRP [mg/L]	Randomisation	A (Experimental)	99	2.5	3.6	1.0	0- 19	(1.76 ; 3.18)
		B (Control)	87	2.1	2.8	1.2	0- 19	(1.47 ; 2.68)
	Visit 1	A (Experimental)	93	1.9	2.3	1.0	0- 9	(1.39 ; 2.34)
		B (Control)	77	1.7	2.2	0.9	0- 13	(1.21 ; 2.22)
	Visit 2	A (Experimental)	87	2.7	5.3	1.2	0- 41	(1.61 ; 3.88)
		B (Control)	74	1.9	2.5	1.0	0- 13	(1.33 ; 2.49)
	Visit 3	A (Experimental)	90	2.0	2.6	1.1	0- 17	(1.44 ; 2.55)
		B (Control)	76	2.0	2.6	0.9	0- 13	(1.37 ; 2.57)
	Changes from day 0						.	
	Visit 1	A (Experimental)	93	-0.5	3.0	0.0	-14- 9	(-1.12 ; 0.11)
		B (Control)	77	-0.0	2.1	0.0	-9- 12	(-0.48 ; 0.45)
	Visit 2	A (Experimental)	87	0.3	5.7	0.0	-16- 40	(-0.93 ; 1.50)
		B (Control)	74	0.2	1.7	0.0	-3- 9	(-0.18 ; 0.61)
	Visit 3	A (Experimental)	90	-0.4	3.7	0.0	-14- 16	(-1.15 ; 0.40)
		B (Control)	76	0.3	2.0	0.0	-4- 9	(-0.12 ; 0.78)

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Table 14.3.6: Selected laboratory data - SAF Population
Population: Safety

Variable	*Visit*	*Arm*	*n*	*Mean*	*S.D.*	*Median*	*Range*	*95%-CI*
NTproBNP [pg/mL]	Randomisation	A (Experimental)	89	291.9	382.4	179.0	10- 2315	(211.31 ; 372.41)
		B (Control)	79	226.1	191.4	183.0	19- 863	(183.21 ; 268.95)
	Visit 1	A (Experimental)	88	279.1	338.4	150.0	5- 2039	(207.42 ; 350.81)
		B (Control)	73	238.7	258.1	164.0	23- 1571	(178.46 ; 298.89)
	Visit 2	A (Experimental)	84	351.8	656.7	185.0	10- 4797	(209.26 ; 494.31)
		B (Control)	71	213.6	186.6	131.0	21- 798	(169.39 ; 257.71)
	Visit 3	A (Experimental)	89	342.3	607.8	176.0	11- 4329	(214.30 ; 470.39)
		B (Control)	76	298.8	702.5	164.5	20- 6050	(138.29 ; 459.34)
	Changes from day 0						.	
	Visit 1	A (Experimental)	88	9.1	223.1	0.5	-691- 665	(-38.19 ; 56.36)
		B (Control)	73	31.2	202.0	5.0	-159- 1571	(-15.89 ; 78.38)
	Visit 2	A (Experimental)	84	114.0	387.2	25.9	-279- 2482	(29.93 ; 197.99)
		B (Control)	71	21.1	117.2	16.0	-235- 352	(-6.60 ; 48.88)
	Visit 3	A (Experimental)	89	95.9	531.6	5.0	-687- 3290	(-16.03 ; 207.93)
		B (Control)	76	105.9	699.8	11.5	-189- 6050	(-54.00 ; 265.82)

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