TREAT-SVDs

EffecTs of Amlodipine and other Blood PREssure Lowering Agents on Microvascular FuncTion in Small Vessel Diseases

Phase III b clinical trial

Investigational Medicinal Products: amlodipine, losartan, atenolol

Study Code: TRE-1486--0105-I

EudraCT Number: 2016-002920-10

First Patient First Visit: 22.02.2018 – **Last Patient Last Visit:** 28.07.2022

Termination of Clinical Trial: 21.12.2022

Sponsor
Klinikum der Universität München (KUM) – "Anstalt öffentlichen Rechts"
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Synopsis

1.	**Sponsor:** Klinikum der Universität München (KUM) – "Anstalt öffentlichen Rechts" Marchioninistr. 15, D-81377 Munich, Germany **Sponsor Delegated Person (SDP):** Prof. Dr. med. Martin Dichgans Klinikum der Universität München (KUM), Institute for Stroke and Dementia Research Feodor-Lynen-Str. 17, D-81377 Munich, Germany
2.	**Name of Finished Product:** The IMPs have a marketing authorisation in the Member States concerned by this trial. The trade name and marketing authorisation holders are not fixed in the protocol.
3.	**Name of Active Ingredient:** amlodipine (ATC Code: C08CA01), losartan (ATC Code: C09CA01), atenolol (ATC Code: C07AB03)
4.	**Individual Study Table:** (only required for submissions) n.a.
5.	**Study Title:** Effec**T**s of Amlodipine and other Blood P**RE**ssure Lowering **A**gents on Microvascular Func**T**ion in **S**mall **V**essel **D**isease**s**
	Study Design: multicentre, multinational, prospective randomised, open-label, 3 sequence crossover clinical trial with blinded endpoint assessment (PROBE design)
	Study (Protocol) Code Number: TRE-1486--0105-I
	Eudra-CT Number: 2016-002920-10
6.	**Investigator(s):** - Prof. Martin Dichgans, Ludwig-Maximilians-Universität München (LMU), Institute for Stroke and Dementia Research - Prof. Joanna Wardlaw/ Dr. Fergus Doubal, University of Edinburgh (UEDIN), Neuroimaging Sciences and Brain Research Imaging Centre, - Prof. Robert van Oostenbrugge, Maastricht University Medical Center (UM), Department of Neurology - Prof. Geert Jan Biessels, UMC Utrecht Brain Center Robert Magnus (UMCU) - Prof. Alastair Webb, University of Oxford (UOXF), Nuffield Department of Clinical Neurosciences
7.	**Participating Study Centres:** The study was planned and conducted as a multicentre, multinational study. <u>Participating Study Centre in Germany</u>: Ludwig-Maximilians-Universität München (LMU) Klinikum der Universität München (KUM), Institute for Stroke and Dementia Research Feodor-Lynen-Str. 17, D-81377 Munich, Germany <u>Participating Study Centres in the UK</u>: University of Edinburgh (UEDIN) Centre for Clinical Brain Sciences and UK Dementia Research Institute Crewe Rd S, Edinburgh EH4 2HY, United Kingdom

	University of Oxford (UOXF) Wolfson Centre for Prevention of Stroke and Dementia, Nuffield Department of Clinical Neurosciences John Radcliffe Hospital, Oxford OX3 9DU, United Kingdom Participating Study Centres in the Netherlands: University of Maastricht Maastricht University Medical Center (UM), Department of Neurology P. Debyelaan 25, 6229 HX Maastricht, The Netherlands University of Utrecht Brain Center Rudolf Magnus, Department of Neurology University Medical Center Utrecht Universiteitsweg 100, 3584 CG Utrecht, The Netherlands
8.	**Publication:** Kopczak et al. "The EffecTs of Amlodipine and other Blood PREssure Lowering Agents on Microvascular FuncTion in Small Vessel Diseases (TREAT-SVDs) trial: Study protocol for a randomised crossover trial" *Eur Stroke J.* 2023 Mar;8(1):387–397. Kopczak et al. "Effect of blood pressure-lowering agents on microvascular function in people with small vessel diseases (TREAT-SVDs): a multicentre, open-label, randomised crossover trial" *Lancet Neurol.* 2023 Nov; 22(11):991–1004.
9.	**Study period:** First patient first visit (FPFV): 22.02.2018; Last patient out: 28.07.2022 Due to recruitment problems of patients with cerebral autosomal dominant arteriopathy with subcortical infarcts and leukoencephalopathy (CADASIL), the study was terminated early on the 21th December 2022. At this time, 26 out of 30 patients with CADASIL were recruited. The recruitment aim for patients with sporadic small vessel disease (SVD) was reached; all 75 participants with sporadic SVD were recruited.
	Approvals and Amendments **Approval**: Bundesinstitut für Arzneimittel und Medizinprodukte (BfArM): 14.09.2016, clinical study protocol (CSP) version 1.0, 18.07.2016; Ethics Committee (EC): 29.09.2016, CSP Version 2.0, 20.09.2016 **Amendment 1**:The following major changes were included in AM 1: - Adaptation of TREAT-SVDs to the comments of the EC (after BfArM approval for CSP Version 1.0 was obtained) ➔ Exclusion of patients with uncontrolled hypertension and further operationalization of exclusion criteria Approval AM1: BfArM: 02.11.2016; EC: 29.09.2016, CSP Version 2.0, 20.09.2016 **Amendment 2**:The following major changes were included in AM 2:

	- Adaptation of TREAT-SVDs to revised guidelines of the European Society of Hypertension for arterial hypertension, in which a combination therapy of several low-dose antihypertensive drugs is preferred to single high-dose drugs ➔ Modification of an exclusion criterion, so patients with a low-dose combination therapy of three drugs could be included into the study - Adaptation of TREAT-SVDs to clinical routine because not all stroke patients received a magnetic resonance imaging (MRI) scan or a repeated cranial computed tomography (CCT) scan in the acute stage due to limited capacity and for logistic reasons ➔ Modification of an inclusion criterion with an option for an additional MRI during the screening visit to enable patients without MRI or repeated CCT study participation - Adaptation of TREAT-SVDs to clinical routine and for practical reasons because the clinical dementia rating (CDR) score did not always reflect vascular cognitive impairment. ➔ Modification of an inclusion criterion allowing for more flexibility within the validated measurement tool of vascular cognitive impairment, for example but not limited to CDR, Montreal Cognitive Assessment (MoCA) or Cambridge Cognition Examination (CAMCOG) - Adding the University of Leiden, The Netherlands, and the University of Glasgow, UK, as participant information centers (PIC) for patients with CADASIL Approval AM2: BfArM: 15.04.2019; EC: 14.03.2019, CSP Version 3.0, 25.02.2019 **Amendment 3**:The following major changes were included in AM 3: - Adaptation of TREAT-SVDs to the European Commission implementing decision from 28th June 2021, stating that there is an adequate protection of personal data by the United Kingdom where the UK GDPR applies that has been incorporated under the European Union (Withdrawal) Act 2018 ➔ Modification of the study protocol and patient information sheet stating that pseudonymized MRI data will be transferred and analysed in the UK (outside the EU, where the UK GDPR applies) Approval AM3: BfArM: 25.08.2022; EC: 18.07.2022, CSP Version 4.0, 03.06.2022
10.	**Phase of development** Phase III b
11.	**Objectives:** **Primary Objective:** To test the hypothesis that the calcium channel blocker amlodipine has a superior beneficial effect on cerebrovascular reactivity in patients with symptomatic SVDs when compared to either the Angiotensin II type 1 (AT1) receptor blocker losartan or the beta-blocker atenolol. **Secondary Objectives:** To test the hypothesis that losartan has a superior beneficial effect on cerebrovascular reactivity when compared to atenolol.
12.	**Methodology** The study was conducted as a multinational, prospective, randomised, open-label, three sequence three period crossover study with blinded endpoint assessment (PROBE design).

13. **Sample size (planned/analysed):**

Planned: 105 patients

Included / analysed: 101 patients

14. **Patient Population (Diagnosis):**

In TREAT-SVDs, 101 patients were enrolled and randomized (75 patients with sporadic SVDs, 26 CADASIL patients). The characterisation of the patients subgroups by age and sex are provided below:

SPORADIC SVD Group

No. of patients	sex	age
20	female	50-59: (5) 60-69: (7) 70-79: (6) 80-89: (2)
55	male	30-39: (1) 40-49: (1) 50-59 (18) 60-69: (18) 70-79: (12) 80-89: (5)

CADASIL Group

No. of patients	sex	age
16	female	40-49: (4) 50-59: (8) 60-69: (4)
10	male	30-39 (1) 40-49: (3) 50-59: (5) 60-69: (1)

Intention-to-treat population: 79 patients, 62/75 sporadic SVD and 17/26 CADASIL patients, were included in the intention-to-treat analysis defined as all study participants randomised who had at least one valid assessment for the endpoint.

SPORADIC SVD Group

No. of patients	sex	age
17	female	50-59: (5) 60-69: (5) 70-79: (5) 80-89: (2)
45	male	30-39: (1) 40-49: (1) 50-59 (16) 60-69: (15) 70-79: (9) 80-89: (3)

CADASIL Group

No. of patients	sex	age
11	female	40-49: (3) 50-59: (6) 60-69: (2)
6	male	30-39 (1) 40-49: (2) 50-59: (3)

Per-protocol population: The per-protocol population was identical with the intention-to-treat population, but the number of observations differed from the intention-to-treat analysis.

Safety population: 71/75 sporadic SVD patients and 23/26 CADASIL patients were included in the safety population defined as all participants who received at least one dose of study drug.

SPORADIC SVD Group

No. of patients	sex	age
18	female	50-59: (5) 60-69: (5) 70-79: (6) 80-89: (2)
53	male	30-39: (1) 40-49: (1) 50-59 (18) 60-69: (17) 70-79: (11) 80-89: (5)

CADASIL Group

No. of patients	sex	age
14	female	40-49: (3) 50-59: (7) 60-69: (4)
9	male	30-39 (1) 40-49: (2) 50-59: (5) 60-69: (1)

Main criteria for inclusion

- Symptomatic SVD defined as
  - History of clinical lacunar stroke in the last 5 years with a corresponding small subcortical infarct visible on MRI scan or CT scan compatible with the clinical syndrome.
  - or cognitive impairment defined as visiting a memory clinic with cognitive complaints, objective cognitive impairment, and capacity to consent, and with confluent deep white matter hyperintensities (WMH) on MRI (defined on the Fazekas scale as deep WMH score ≥ 2)

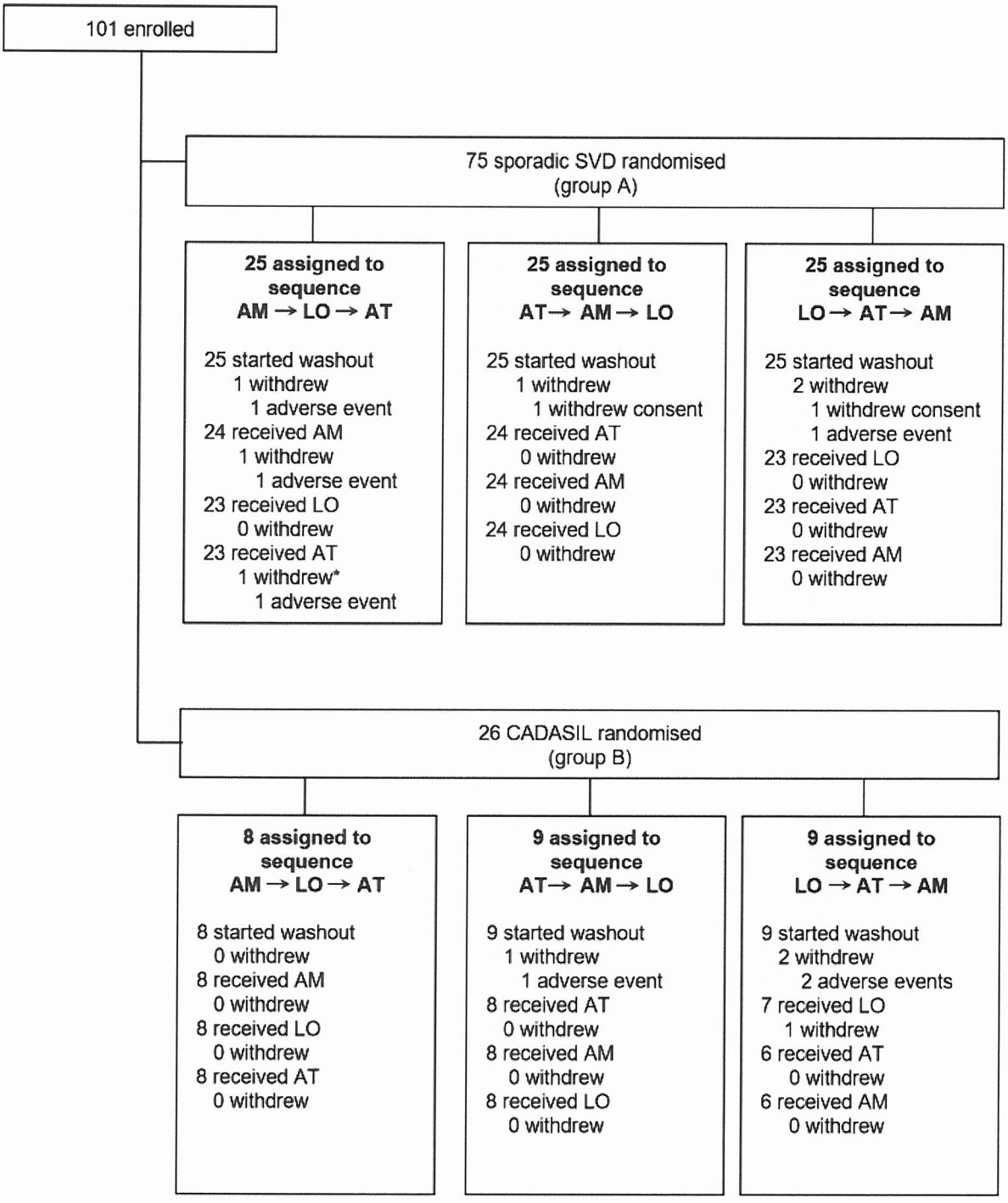
	○ or a diagnosis of CADASIL established by molecular genetic testing of the *NOTCH3* gene (presence of an archetypical, cysteine-affecting mutation) or the presence of granular osmiophilic material in ultrastructural, electron microscopy analysis of skin biopsy • Indication for antihypertensive treatment as defined by meeting one of the following: ○ Hypertension defined as SBP ≥140mmHg or diastolic BP (DBP) ≥90mmHg without antihypertensive treatment or use of an antihypertensive drug for previously diagnosed hypertension ○ Prior history of stroke or transient ischaemic attack (TIA) • Age 18 years or older • Written informed consent
15.	**Test product, dose and mode of administration** **Study treatment:** Trial medications were amlodipine, losartan, and atenolol. Antihypertensive treatment was administered as open-label oral medication in standard dose. Amlodipine: CAS number: 88150-42-9; EV Substance code: SUB05467MIG Losartan CAS number: 114798-26-4; EV Substance code: SUB08593MIG Atenolol CAS number: 29122-68-7; EV substance code: SUB05590MIG All study drugs used were approved for the treatment of hypertension, were recommended in national and international guidelines, and were not under patent protection. **Batch-No. (Ch.-B):** Local pharmacies purchased commercially available products, and study participants received open-label medications.
16.	**Duration of administration** Trial drugs were taken each one for 4 weeks of monotherapy according to the randomised sequence of drug intake resulting.
17.	**Background therapy:** standard of care, but no other antihypertensive treatment except for thiazide and thiazide-like diuretics were allowed **Comparator:** n.a.
	Blinding: n.a., open-label study medication

18.	**Criteria for evaluation:** **Primary endpoint:** Change in cerebrovascular reactivity (ΔCVR) in normal appearing white matter from end of washout to end of treatment. **Secondary questions:** 1. ΔCVR in white matter hyperintensities from end of washout to end of treatment 2. ΔCVR in subcortical grey matter from end of washout to end of treatment 3. change in mean central systolic blood pressure (Δmean SBP) from end of washout to treatment 4. change in blood pressure variability (ΔBPv) from end of washout to treatment
	Efficacy: BP was assessed by daily telemetric monitoring. CVR was determined by brain MRI signal response to hypercapnic challenge.
	Safety assessments - BP was monitored by the investigators remotely with alarms for extreme values. - Adherence to the trial drug was assessed by pill counts at each visit. - Adverse events were assessed at each visit after study inclusion.
19.	**Statistical methods:** A linear mixed effects (LME) model was employed to analyse the repeated measurements during cross-over, to assess sequence effects in the crossover, and corresponding treatment effects. The primary analysis followed a hierarchical test principle (closed testing procedure) by assessing a global effect between atenolol, amlodipine, and losartan. In case of a significant difference, the analysis assessed the three pairs of differences. The analysis was stratified by patients with sporadic SVDs (group A) and patients with CADASIL (group B).
20.	**Summary - Conclusions:** **Patient demographics**

	Sporadic SVD n=75	CADASIL n=26
Age, years	64.9 (9.9)	53.1 (7.0)
Sex		
Female	20 (27%)	16 (62%)
Male	55 (73%)	10 (38%)

Ethnicity		
White	74 (99%)	26 (100%)
Asian	1 (1%)	0 (0%)

Patient disposition:



Abbreviations: AM, amlodipine; LO, losartan; AT, atenolol.

Compliance:

There was one violation of the exclusion criterion "use of >2 antihypertensive drugs for an appropriate BP control", which was modified in amendment 2 to "use of >2 antihypertensive drugs at maximum dose or equivalent (one drug at the maximum dose and two drugs at half of the maximum dose) for an appropriate BP control".

At the time of study inclusion, the ethical approval was already in place for amendment 2 that allowed study inclusion of patients with a low-dose combination therapy of three drugs. As agreed in the data review meeting, this patient was included in the analysis set.

Protocol Violation (PV):

245 PVs were reported in 85/101 patients:
- 202/245 PV were rated as minor. They were related to study inclusion although taking a low-dose combination of three drugs (1), study drug intake (59), CVR measurement (10), BP measurements (8), timing of study visits or study assessments (42) and others (82) such as missing laboratory values.
- 43/245 PV were classified as major since they affected either safety of study participants or the validity of the study results. They were related to a low heart rate (1), study drug intake (6), CVR measurement (17), BP measurements (13), timing of study visits or study assessments (3) and others (3).
- There was no serious breach.

Study medication:

All patients received the treatment they were assigned to. There was no misrandomisation. Compliance to trial drug intake was assessed at each study visit by pill counts.

Two visits were excluded from the per protocol analysis. The reasons for exclusion were a singular intake of another antihypertensive drug than the trial drug and a too short period of trial drug intake of less than 21 days.

Safety Results

Adverse events were reported by 79 participants of the safety population (94 participants).

	washout	amlodipine	losartan	atenolol
Adverse event	57	92	65	118
Drug-related adverse event	0	58	33	87
Serious adverse event	0	1	0	1
Drug-related serious adverse event	0	0	0	0
Death	0	0	0	0
Adverse event leading to discontinuation of trial treatment	1	1	1	1
Drug-related adverse event leading to discontinuation of trial treatment	0	0	0	1

	Two serious adverse events (SAEs) were reported. One occurred while taking amlodipine and the other one while taking atenolol. Neither of the two SAEs was related to study drug intake, and neither led to discontinuation of trial treatment. There were no suspected unexpected serious adverse reactions (SUSAR).
	Efficacy Results In patients with sporadic SVD, change in cerebrovascular reactivity (ΔCVR) in normal appearing white matter from end of washout to end of treatment did not differ statistically between trial drugs ($p_{overall}$=0.39). In CADASIL patients, there was a statistically significant difference in ΔCVR in normal appearing white matter between trial drugs ($p_{overall}$=0.019). Mean ΔCVR [standard error] was 15.7 [27.5] x 10^{-4} %/mmHg for amlodipine, 19.4 [27.9] x 10-4 %/mmHg for losartan, and -23.9 [27.5] x 10^{-4} %/mmHg for atenolol. Pairwise comparisons showed that CVR improved with amlodipine when compared with atenolol (p=0.019) and improved with losartan when compared with atenolol (p=0.0061). There was no statistically significant difference between amlodipine and losartan in ΔCVR in normal appearing white matter. Results were confirmed in the per protocol analysis. Similar to the efficacy analysis, per protocol analysis showed no significant difference in ΔCVR between trial drugs in sporadic SVD patients ($p_{overall}$=0.29), while there was a significant differential treatment effect in CADASIL patients ($p_{overall}$=0.019). All trial drugs lowered mean central systolic BP (SBP) to a similar extend. There was no statistically significant difference in the reduction in SBP (Δmean SBP) from end of washout to end of treatment between trial drugs in sporadic SVD patients ($p_{overall}$=0.075) and in CADASIL patients ($p_{overall}$=0.79). Change in BP variability (ΔBPv) from end of washout to end of treatment differed between trial drugs in sporadic SVD patients ($p_{overall}$<0.0001). ΔBPv [standard error] was -0.7 [0.4] for amlodipine, 0.3 [0.4] for losartan, and 1.3 [0.4] for atenolol. Pairwise comparisons showed that BPv decreased with amlodipine when compared with atenolol (p<0.0001) and decreased with losartan when compared with atenolol (p=0.0030). In CADASIL patients, there was a similar pattern. However, it did not reach statistical significance ($p_{overall}$=0.11).
	Overall Conclusion: A 4-week treatment with amlodipine, losartan, or atenolol did not reveal statistically significant differential effects on cerebrovascular reactivity in patients with sporadic SVD, but such differential effects were observed in the younger cohort of CADASIL patients with amlodipine and losartan having both a beneficial effect on CVR when compared to atenolol. All trial drugs lowered mean systolic blood pressure to a similar extend but blood pressure variability differed between trial drugs. Amlodipine and losartan had both a beneficial effect on BPv when compared to atenolol in sporadic SVD patients. Again, a similar pattern was observed in CADASIL patients that did not reach statistical difference. Whether these different treatment effects have an impact on clinical outcomes in patients with SVD requires further research.

21.	**Date of report:** **Date: 20.10.2023** **Signature:** _____ SDP **Date: 20.10.2023** **Signature:** _____ Statistician