CLINICAL TRIAL PROTOCOL

NCT03063541/ PROTECT-U

EudraCT No. 2017-000514-35

Prospective **R**andomized **O**pen-label **T**rial to **E**valuate risk fa**CT**or management in patients with Unruptured intracranial aneurysms (PROTECT-U)

Phase of study:	PHASE III
Study Registry Number:	NCT03063541

GCP Statement: The study will be conducted in compliance with Good Clinical Practices (ICH-GCP) and the Declaration of Helsinki, and in accordance with applicable legal and regulatory requirements, including archiving of essential documents.

CONFIDENTIAL: This protocol contains confidential information and is intended solely for the guidance of the clinical investigation. This protocol may not be disclosed to parties not associated with the clinical investigation or used for any purpose without the prior written consent of the Principal Investigator/ Coordinating Investigator.

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PARTICIPATING SITES
The participating sites are listed in a separate document.

Table of Content

PROTOCOL SYNOPSIS

TITLE	Prospective Randomised Open-label Trial to Evaluate risk faCTor management in patients with Unruptured intracranial aneurysms.
SHORT TITLE	PROTECT-U
CLINICAL TRIAL CODE	PROTECT-U
EUDRACT NO.	2017-000514-35
INDICATION	Intradural saccular unruptured aneurysm
OBJECTIVES	The primary aim of this study is to assess the hypothesis that a strategy with low-dose ASA (81-100mg/day) and intensive blood pressure treatment (targeted systolic blood pressure below 120mmHg) with weekly measurements using a home blood pressure measuring device reduces the risk of aneurysm rupture or growth compared with standard care (i.e. no ASA, blood pressure management according to guidelines which usually advise treatment if systolic blood pressure exceeds 140mmHg, and no home device for weekly blood pressure measurements).
PHASE	III
INVESTIGATIONAL MEDICINAL PRODUCT(S)	Acetylsalicylic acid (ASA), 81-100mg once per day
STUDY DESIGN	Multinational, phase III multicenter, randomised, controlled trial with a PROBE design (prospective, randomised, open-label trial with blinded outcome assessment)
STUDY POPULATION	<u>Inclusion Criteria</u> • Patient with at least one intradural, saccular unruptured aneurysm in whom it is decided not to intervene with preventive neurosurgical or endovascular aneurysm repair and who are monitored on a regular basis for aneurysm growth • 18 years or older • Last aneurysm imaging with either CTA/MRA within the last 3 months • Ability of subject to understand character and individual consequences of clinical trial • Not legally incapacitated • Written informed consent (must be available before enrolment in the trial)

	• For women with childbearing potential adequate contraception
	Exclusion Criteria • All non-saccular UIAs or aneurysms related to arteriovenous malformations • Daily ASA already prescribed for another indication • Use of a vitamin K antagonist or direct oral anticoagulant (DOAC) at baseline • History of hypersensitivity/allergy to ASA or to any other drug with similar chemical structure or to any excipient present in the pharmaceutical form of ASA • History of asthma induced by ASA or other anti-inflammatory drugs • Other contra-indications for low-dose ASA (81 mg - 100 mg per day) not yet mentioned, (e.g. bleeding disorders, , gastric ulcers and/or intestinal ulcers, acute liver failure of kidney failure, severe heart failure, treatment with methotrexate in a dosage 15 mg/week or above) • Use of another platelet aggregation inhibitor, which in combination with ASA would give an unacceptable risk of side effects/complications • Chronic kidney disease stage IV and V (GFR < 30 mL/min/1.73 m^2) • Pregnancy and lactation • Participation in any other interventional clinical trial • Life-expectancy <3 years
SAMPLE SIZE	To be assessed for eligibility: (n = 2500) To undergo screening examination: (n=970) To be assigned to the trial: (n = 776) To be analysed: (n = 705) Assuming a risk reduction of 45% for the primary outcome measure and the risk to have a primary outcome event at three years of 15% in the standard treatment group and 8.25% in the intensive treatment + ASA group, α=0.05 and β=0.20, 353 patients are needed in each group. Assuming a dropout rate of 10%, we will need to assign 776 patients to the trial so that 705 patients can be analysed.
TRIAL DURATION	Total trial duration: [162 months] Duration of clinical phase: [144 months] Beginning of the preparation phase: [Q2 2017] FSI (first subject in): [Q3 2017] LSI (last subject in): [Q2 2026]

	LSO (last subject out): [Q2 2029] DBL (database lock): [Q3 2029] Statistical analyses completed: [Q4 2029] Trial report completed: [Q2 2030]
STATISTICAL ANALYSIS	<u>Primary endpoints:</u> Aneurysm rupture (i.e. aneurysmal subarachnoid hemorrhage, SAH) or growth (increase in any aneurysm diameter by ≥1mm) on serial imaging (either two MR or CT angiographies) within 36±6 months from randomization <u>Secondary endpoints:</u> • Any growth or rupture of aneurysm during follow-up irrespective of the duration of trial participation • Difference of aneurysm volume (defined as increase of aneurysm volume in computerized measurements from source images by >10% and >3mm^3 or aneurysm shape (e.g. development of daughter sac) • Development of de novo aneurysm on serial imaging • Clipping/coiling during the study period • Any ischemic or haemorrhagic stroke, defined as clinical symptoms of stroke AND a compatible lesion on imaging (either plain head CT / CT perfusion / MRI) • Myocardial infarction defined as increase of Troponin, CKMB and/or presence of new significant Q waves obtained in ECG • Vascular death (including fatal stroke, fatal myocardial infarction, sudden death) • Death from all other causes • Major spontaneous bleeding requiring hospitalisation defined as substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating the transfusion of at least 2 units of erythrocyte concentrates achieved • Blood pressure; any data on blood pressure management used • Safety aspects (adverse and serious adverse events, including those mentioned above) • Quality of life We will compare the occurrence of outcome events in the two groups in terms of the risk ratio (RR), which will be obtained by means of a Poisson model. The precision of the RR estimates will be described with 95% confidence intervals obtained from the Poisson model. Our primary analyses will be based on the intention-to-treat principle. We plan subgroup analyses according to

	age, sex, history of previous rupture of another aneurysm, aneurysm size, location and morphology.
NUMBER OF CENTRES	up to 30 (Germany, the Netherlands, Canada, Finland, other countries)
FINANCING	Non-commercial: Dr. Rolf M. Schwiete Foundation (Mannheim, Germany), Dutch Heart Foundation (Netherlands), Phoenix foundation
Other support	Blood pressure measurement devices made available for the time of the trial by Omron Healthcare Europe B.V., Scorpius 33, 2132 LR Hoofddorp, Netherlands

ABBREVIATIONS

AE	Adverse Event
AMG	German Drug Law (Deutsches Arzneimittelgesetz)
ASA	Acetylsalicylic acid
ATC	Anatomical-Therapeutic-Chemical Code, part of WHO-DRL (Drug Reference List)
BDSG	Bundesdatenschutzgesetz
BfArM	Bundesinstitut für Arzneimittel und Medizinprodukte (Federal Institute for Drugs and Medical Devices, Germany)
BMBF	Bundesministerium für Bildung und Forschung
BP	Blood pressure
CCMO	Centrale Commissie Mensgebonden Onderzoek
CRF	Case Report Form
CTA	Computer Tomography Angiogram
CV	Curriculum Vitae
DBL	Data Base Lock
DFG	Deutsche Forschungsgemeinschaft
DSA	Digital Subtraction Angiogram
DSMB	Data Safety Monitoring Board
DOAC	Direct oral anticoagulant
DSUR	Development Safety Update Report
EC	Ethics Committee
EQ-5D-5L	EuroQol – 5 dimensions – 5 levels
FD	Financial Disclosure
FSI	First Subject In
FPI	First Patient In
GCP	Good Clinical Practice
GCP-V	Good Clinical Practice Ordinance (GCP-Verordnung)
GFR	Glomerular filtration rate
GP	General practitioner, family doctor
IB	Investigator´s Brochure
ICH	International Council on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ICH GCP	ICH harmonised tripartite guideline on GCP
ICMJE	International Committee of Medical Journal Editors
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
INN	International Nonproprietary Name
ISF	Investigator Site File
ITT	Intention To Treat
KKS	Coordination Centre for Clinical Trials (Koordinierungszentrum für Klinische Studien)

LKP	Coordinating Investigator according to AMG (Leiter der Klinischen Prüfung)
LPO	Last Patient Out
LSI	Last Subject In
LSO	Last Subject Out
MedDRA	Medical Dictionary for Regulatory Activities
MRA	Magnetic Resonance Angiogram
NL	The Netherlands
PHASES-score	Score based on Population, Hypertension, Age, Size of aneurysm, Earlier haemorrhage from another aneurysm, Site of aneurysm
PI	Principal Investigator
PP	Per-Protocol
PROBE	Prospective randomised open-label trial with blinded outcome assessment
SAE	Serious Adverse Event
SAH	Subarachnoid haemorrhage
SC	Steering Committee
SmPC	Summary of Product Characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMF	Trial Master File
UIA	Unruptured intracranial aneurysm
WBP	Wet Bescherming Persoonsgegevens (Data protection law of the Netherlands)
WHO	World Health Organisation
WMO	Wet Medisch-Wetenschappelijk Onderzoek met Mensen (Clinical Trials Law of the Netherlands)

CLINICAL TRIAL SCHEDULE

Visit No.	Visit 0	Visit 1	Visit 2	Visit 3 - 20	Visit 21	Visit 22
	Screening*	Baseline	Treatment phase		End of treatment/ study	Follow-up[4]
Day / Procedure	0 – 30 days prior to visit 1	Day 0	6 months +/- 30 days	every 6 months +/- 30 days	Month 36 +/- 30 days or month120 +/- 30 days	30 +/- 10 days after end of treatment visit (or after withdrawal)
Written informed consent	● (S)**					
Inclusion/ exclusion criteria	● (S)	●				
Demographic data, vital signs	●					
Medical history	● (R)**					
Smoking status and alcohol consumption	●	●	●	●	●	●
Randomization		●				
Pregnancy test	●[2] (S)	●[2]				
Concomitant medication	● (R)	●	●	●	●	●
AE		●	●	●	●	●
Aneurysm/ baseline characteristics		●				
IMP accountability[1 / 5]		●	●	●	●	
Blood pressure (bp), seated		●	●	●	●	●
Supply with bp device[5]		●				
Clinical chemistry[3]	●	●	●	●	●	●
Cardiovascular outcome			●	●	●	●
EQ-5D-5L		●	●	●	●	●
Check for imaging***/ upload if available		●		● (at least once a year)	●	●

*# Screening and baseline visit may be combined at just one visit, if verification of all inclusion and exclusion can be ensured at this visit, and the patient has ample time to consider participation.
** (S) = study specific / (R) = Clinical routine

*** Either CTA or MRA as per standard of care (SOC), if new imaging is available
1 application of trial medication by patient at home once daily from day 0 to end of treatment; patients of intervention group only
2 applicable for females of childbearing potential only. Test must be repeated on Day 0 if result of initial test is not valid on Day 0 (depending on period/ menstrual cycle)
3 data on GFR and blood sodium in patients with pre-existing, compensated chronic renal failure, or other parameter such as INR, thrombocytes count, haemoglobin, if needed to confirm inclusion/exclusion criteria and/or if perceived necessary by investigator. Data not older than 6 months from certified labs may be used.
4 applicable only if any SAEs have not been resolved at previous visits
5 applicable only for patients of intervention group

1 INTRODUCTION

1.1 Scientific Background

Unruptured intracranial aneurysms (UIAs) are dilated weak spots at major brain arteries. The prevalence in adults is 3%, which means that in Europe and North America alone there are 36 million persons with UIAs. [7] Most UIAs are detected incidentally, for example if head imaging is performed because of headache, ischemic stroke, or trauma. Aneurysms can remain clinically silent for long periods or rupture, which is often preceded by aneurysm growth. Aneurysm rupture results in subarachnoid haemorrhage (SAH), a type of stroke with a poor prognosis: 40% of patients die and most survivors have long-term disability or cognitive impairment. [8]

Preventive treatment of an UIA is an attractive option to eliminate the risk of SAH and hereby increase the number of life years with high quality of life. Presently, the two available treatment options are neurosurgical or endovascular treatment. Unfortunately, both treatment modalities carry a risk of serious treatment complications, with permanent disability or death in more than 6% of patients undergoing preventive aneurysm treatment. [9-11]

The risk of rupture can be estimated based on patient- and aneurysm-related risk factors and the 5-year risk of rupture varies between <0.5 to >15%.[12] If the risk of rupture does not outweigh the risk of treatment complications (mean 6-8% for permanent disability or death) patients often remain untreated. [13, 14] These patients are usually followed over time with repeated angiography to detect possible aneurysm growth. Only if substantial aneurysm growth occurs, which is a marker of aneurysm instability and a predictor of rupture, these aneurysms are treated to prevent rupture.

Since low-risk UIAs are much more prevalent than large-risk UIAs, most UIAs remain untreated and therefore at risk of future haemorrhage. In the end, most instances of SAH derive from small aneurysms. It is therefore important to identify new treatment strategies with a low risk of complications for patients with small UIAs. There is strong evidence that hypertension and aneurysm wall inflammation are the most important modifiable risk factors of aneurysm growth and rupture.[15] Thus, pharmaceutical strategies which target these modifiable risk factors of UIA growth and rupture especially for low-risk UIAs are an appealing novel treatment option.

Despite numerous studies on the importance of these risk factors, to date no randomised controlled trial targeting their modification has been initiated for UIA patients:

The recent Systolic Blood Pressure Intervention Trial (SPRINT) on intensive versus standard blood pressure reduction in a total of 9,361 patients at increased risk for cardiovascular disease was stopped prematurely at 3.3 years of median follow-up because of a lower incidence of the primary outcome event (myocardial infarction, other coronary syndromes, stroke or death from other cardiovascular causes) in the intensive treatment group (hazard ratio 0.75%; 95% CI 0.64-0.89), without an effect on overall incidence of adverse events (Level IB evidence). [16]

The relevance of aneurysm wall inflammation in the pathogenesis of aneurysm rupture has been underlined by data on the anti-inflammatory effect of acetylsalicylic acid (ASA) on aneurysm wall inflammation and thus protective effect on aneurysm rupture in a nested case-control study of UIA patients: In 1,691 patients with UIAs, those treated with ASA for other indications had lower odds for UIA rupture in the multivariable analysis (OR 0.27; 95% CI 0.27-0.67) (Level IIB evidence). [17] A small Phase I trial randomising patients to ASA treatment or treatment as usual showed a reduction of radiological and histological aneurysm wall inflammation as surrogates for rupture. (Level IIb evidence).[18] ASA use is not associated with more severe haemorrhage or worse outcomes in case of aneurysmal rupture. [19]

In view of the similarity of risk factors between UIAs and cardiovascular diseases, there is a strong rationale to investigate the beneficial effect of intensive blood pressure treatment and ASA on aneurysm growth or rupture.

1.2 Trial Rationale

At present, the current guidelines on management of patients with UIAs do not recommend any medical treatment or low-risk measures to reduce the rupture risk of UIAs in patients in whom the benefits of preventive endovascular or neurosurgical treatment do not outweigh the risk of treatment complications. [20, 21] In these patients, no randomised, phase II or III clinical studies have been conducted to study the modification of hypertension, smoking and aneurysm wall inflammation, even though many data on the detrimental effects of these risk factors are available. We performed a systematic MEDLINE search (July 2016) using the PubMed database for relevant articles between 1990 and 2015 in 'English'. We used the search terms 'intracranial aneurysm' OR 'subarachnoid haemorrhage' combined with the individual search terms for each aspect, highlighted below.

1.3 Risk-benefit Assessment

Risk of rupture versus risk of preventive treatment

According to the largest pooled analysis of 6 prospective cohort studies on 8,382 patients and 10,272 UIAs on the risk of aneurysm rupture, the 1-year risk of aneurysm rupture is 1.4% (95% CI 1.1–1.6), and the 5-year risk 3.4% (2.9–4.0) (Level IIA and IIB evidence). Since patients with UIAs with a large risk of rupture are usually treated with preventive endovascular or neurosurgical aneurysm treatment, this trial focuses on patients with low-intermediate risk UIAs where the benefits of preventive endovascular or neurosurgical treatment are considered not to outweigh the risk of treatment complications. In these patients, the 5-year risk of rupture is usually <3%. These patients are usually followed over time with serial aneurysm to detect possible aneurysm growth.

A meta-analysis on a total of 60 studies including 9,845 patients and 10,845 UIAs undergoing surgical repair reported an overall morbidity and mortality of 6.7% (99% CI 4.9- 9.0%; I^2=85%). [9] The most recent meta-analysis for endovascular UIA repair reported data from 71 studies with 5,044 patients harboring 5,771 UIAs.[22] Treatment-related unfavourable outcome including death was reported in 4.8% (99% CI 3.9-6.0%) of patients. These data underline that for the overall population the mid-term risk of rupture is often distinctly lower than the risk of preventive treatment.

Although large aneurysms have a higher risk of rupture than small aneurysms, the proportion of patients with a small aneurysm is much larger than those with a large aneurysm in cohorts of patients with aneurysmal subarachnoid haemorrhage. This results from the much higher prevalence of small aneurysms. In order to decrease the incidence of aneurysmal subarachnoid haemorrhage, it is of utmost importance that treatment strategies are developed with a low risk of complications for patients with small aneurysms.

Protective versus detrimental effects effect of risk factor management

Blood pressure treatment

The most recent pooled analysis of 6 prospective cohort studies on 8,382 patients and 10,272 UIAs identified hypertension as a significant and independent modifiable risk factor (hazard ratio 1.4; 95% CI 1.1-1.8) for UIA rupture (Level IIA evidence).[12] Additionally, different studies also reported the relevance of hypertension on UIA growth (Level IIA and IIB evidence). [23-25]

No randomized studies have investigated the protective effect of intensive blood pressure treatment in the setting of UIAs. In the setting of cardiovascular disease, a recent randomised, open-label trial on intensive versus standard blood pressure reduction in a total of 9361 patients was stopped prematurely at 3.3 years of median follow up because of a lower incidence of the primary outcome event (myocardial infarction, other coronary syndromes, stroke or death from other cardiovascular causes) in the intensive treatment group (1.65% versus 2.19% per year, hazard ratio 0.75%; 95% CI 0.64-0.89). [16] The overall incidence of serious adverse events did not differ between the two groups (hazard ratio with intensive treatment, 1.04; P=0.25). However, serious adverse events of hypotension, syncope, electrolyte abnormalities, and acute kidney injury or acute renal failure, but not injurious falls or bradycardia, occurred more often in the intensive treatment group than in the standard-treatment group. Orthostatic hypotension as assessed during a clinic visit was less common in the intensive-treatment group. A total of 220 participants in the intensive-treatment group (4.7%) and 118 participants in the standard treatment group (2.5%) had serious adverse events that were classified as possibly or definitely related to the intervention (hazard ratio 1.88; P<0.001).

Inflammation of aneurysm wall

Aneurysm wall inflammation is the other major risk factor amenable for risk factor modification. A nested case-control study of 1,691 UIA patients suggested that patients treated with ASA for other indications had a lower odds of UIA rupture in the multivariable analysis (OR 0.27; 95% CI 0.27-0.67) (Level IIB evidence).[17] Additionally, a small Phase I trial randomising patients to ASA treatment or treatment as usual showed a reduction of radiological and histological aneurysm wall inflammation as surrogates for rupture (Level IIb evidence). [18] A recent meta-analysis showed that the role of long-term ASA in reducing the risk of aSAH remains unclear and suggested that the significant heterogeneity across the studies included underlined the need for an appropriately designed randomized controlled trial. [26]

In a study analyzing 305 patients with subarachnoid hemorrhage, the outcome of patients using acetylsalicylic acid was slightly better compared to the patients not using acetylsalicylic acid, even though they were older on average. [27]

In another study, 747 consecutive patients with cerebral aneurysms were studied (both ruptured and unruptured aneurysms). [28] The rate of hemorrhagic presentation was significantly greater in patients not taking ASA, although the patients taking ASA were about 10 years older in average and were more often diagnosed with hypertension. In addition, in 305 patients with aneurysmal SAH a comparison was made between patients with and without long-term use of acetylsalicylic

acid. It was found that patients with and without use of acetylsalicylic acid did not differ with respect to clinical condition on admission as measured by Hunt and Hess grade and neurological outcomes, which underlines that patients using acetylsalicylic acid do not have more severe hemorrhages in case of aneurysm rupture. [28]

Finally, in one study, 245 out of 11,549 patients with aneurysmal subarachnoid hemorrhage had long-term acetylsalicylic acid use prior to hospital admission.[19] Although patients using acetylsalicylic acid were significantly older and had more comorbidities than patients without acetylsalicylic acid, they did not differ regarding in-hospital mortality and in-hospital complications. In addition, patients using acetylsalicylic acid, had a shorter length of hospital stay and the odds of a non-routine discharge was lower (OR 0.63, 95% CI 0.48-0.83). Furthermore, ASA use was associated with decreased odds of a cardiac complication (OR 0.57, 95% CI 0.36-0.91) or of venous thromboembolic events (OR 0.53, 95% CI 0.30-0.94).

Cardiovascular benefits:

A meta-analysis on randomized controlled trials of ASA therapy in participants without cardiovascular disease that reported data on myocardial infarction (MI), stroke, and cardiovascular mortality trials identified six major prospective trials with a total of 95,456 individuals: 3 trials included only men, 1 included only women, and 2 included both sexes. [29] Based on the absolute risk reduction of 0.30% in men and 0.37% in women, the number needed to treat to prevent one cardiovascular event over the mean follow-up of 6.4 years was 333 women and 270 men. In other words, ASA therapy for an average of 6.4 years results in an average absolute benefit of approximately 3 cardiovascular events prevented per 1000 women and 4 cardiovascular events prevented per 1000 men. Of note, the population studied had a low risk of fatal or nonfatal vascular events. It has been shown that the cardioprotective benefit of ASA is related to the cardiovascular risk in the population studied. As a result, the absolute risk reduction for these events was small. In women, ASA therapy was associated with a 17% reduction in the odds of stroke (OR 0.83; 95% CI 0.70-0.97). With respect to stroke subtypes in women, ASA was associated with a 24% reduction in ischemic stroke (OR 0.76; 95% CI 0.63-0.93), but had no effect on hemorrhagic stroke (OR 1.07; 95% CI 0.42-2.69). In men with ASA, the odds ratio for stroke was 1.13; 95% CI 0.96-1.33. With respect to stroke subtypes in men, ASA had no effect on ischemic stroke (OR 1.00; 95% CI 0.72-1.41), but was associated with an increased risk of hemorrhagic stroke (OR 1.69; 95% CI 1.04-2.73). The risk of MI was significantly reduced in men (and not in women) receiving ASA, corresponding to an average absolute benefit of approximately 8 MI events prevented per 1000 men treated for 6.4 years. In addition to cardiovascular effects, long term ASA use is likely to prevent cancer. [30]

Extracranial risks

ASA is associated with an increased risk of major (gastrointestinal) bleeding. [29] Based on an absolute risk increase of 0.25% in women and 0.33% in men, the number needed to harm over 6.4 years of ASA treatment by causing 1 major (gastrointestinal) bleeding event was 400 for women and for 303 men. In other words, ASA therapy for an average of 6.4 years results in an average absolute increase of approximately 2.5 major bleeding events caused per 1000 women and 3 major bleeding events caused per 1000 men.

In a clinical trial, 39,876 initially healthy women 45 years of age or older were randomly assigned to receive 100 mg of acetylsalicylic acid on alternate days or placebo and were then monitored for 10 years for a first major cardiovascular event (i.e., nonfatal myocardial infarction, nonfatal stroke, or death from cardiovascular causes). [31] Reports of gastrointestinal bleeding and peptic ulcer were confirmed by means of follow-up questionnaires. These side effects were significantly more common among women in the acetylsalicylic acid group than among women in the placebo

group. There were 127 episodes of gastrointestinal bleeding requiring transfusion in the acetylsalicylic acid group, as compared with 91 in the placebo group (relative risk 1.40; 95% CI 1.07-1.83). Self-reported haematuria, easy bruising, and epistaxis were frequent among women in both groups, with small but statistically significant excesses among those in the acetylsalicylic acid group. The proportion of women reporting any symptoms suggestive of gastric upset was virtually identical in the two groups. There were five fatal gastrointestinal haemorrhages, two in the acetylsalicylic acid group and three in the placebo group.

Means to avoid and/ or take care of unforeseen/ unwanted events

Blood pressure will be checked at all visits in both study arms and we will ask for presence of severe orthostatic hypotension. Patients randomized to the study arm with intensive blood pressure lowering and ASA will be instructed on potential side effects of the drugs. If any of these side effects occur, patients will be advised to visit their general practitioner or the treating physician can decide to halt ASA or adjust (some) blood pressure lowering drugs.

Overall, the trial intervention causes only moderate risks for the patients enrolled, which are largely outweighed by the potential benefits of the trial intervention.

Benefit for the trial subjects

The trial subjects will be closely followed according to a strict trial protocol.

Prospective benefit for patients (possible gain in knowledge to be obtained in the trial and its importance)

This trial will be the first ever phase III trial to study the potential protective effect of risk factor modification in patients with UIAs that are chosen for observation only. Even though such patients are usually at a low risk of rupture, the risk of growth is approximately 14-18% over 2-3 years and patients with growing aneurysms have a 12-fold higher risk of rupture. [15, 25, 32] In addition, a subpopulation of UIA patients does not have a low risk of aneurysm rupture but they may have complex aneurysms and thereby a higher risk of treatment complications than risk of rupture. This underlines the unmet need for any low-risk strategy to decrease the risk of aneurysm instability. Thus, in case of successful completion of our trial and evidence that the experimental treatment is efficacious and safe, this may result in an immediate and worldwide change in clinical practice.

The risk benefit ratio is expected to be identical for the 81 and 100 mg daily doses. For pragmatic reasons (availability) it has been decided to use two different doses various countries.

1.4 Data Safety Monitoring Board (DSMB)

Ensuring the ethical conduct of the trial and protecting the rights and welfare of the patients are the tasks of the DSMB.

The DSMB consists of five international clinical experts on epidemiology, stroke, and intracranial aneurysms, who are not involved in the conduct of the trial. The task of the DSMB is to oversee the safety of the trial subjects in the clinical trial by periodically assessing the safety and efficacy of the trial therapy, and to monitor the integrity and validity of the data collected and the conduct of the clinical trial in accordance to CHMP/EWP/5872/03 Corr (EMEA 2005). Since interim analyses

are planned, an external biometrician is involved in the DSMB. The DSMB will meet on a regular basis. The exact timing will be scheduled by the DSMB. After reviewing the data on the study conduct (recruitment, protocol adherence/ protocol deviations) and on safety issues the DSMB provides the sponsor with recommendations with regard to continuing the trial (e.g. termination, continuation, or modification) based on the data collected. The data necessary for the DSMB to fulfil this function are provided by the sponsor as determined by the DSMB. Amongst other datasets, these must include listings providing information on serious adverse events and further variables that the DSMB considers necessary and when formal interim analyses are conducted. The DSMB may define stopping rules in addition to the rule described in chapter 9.4 (page 46) and inform the coordinating investigator about which data and which documents (e.g. monitoring plan) need to be provided at which time schedule (e.g. annually, twice per year etc.).

1.5 Steering Committee (SC)

The steering committee is comprised of the coordinating investigators and their supporting co-investigators, clinical experts not directly involved in the clinical trial, and the responsible biometrician. The steering committee is responsible for the scientific integrity of the study protocol, the quality of the study conduct as well as for the quality of the final study report. The Steering committee will decide on the recommendations made by the DSMB.

2 TRIAL OBJECTIVES AND ENDPOINTS

2.1 Primary Objective and Primary Endpoint

The main purpose of this study is to assess the hypothesis that a strategy with a daily intake of low-dose ASA (81mg/day - 100 mg/day) and intensive blood pressure treatment (targeted systolic blood pressure below 120mmHg) with advice to patients to do weekly measurements using a home blood pressure measuring device reduces the risk of aneurysm rupture or growth compared with standard care (i.e. no ASA, blood pressure management according to guidelines which usually advise treatment if systolic blood pressure exceeds 140mmHg, and no home device for weekly blood pressure measuring.

The primary outcome measure will be aneurysm rupture or growth on serial imaging (MR- or CT-angiography). Aneurysm growth is defined as an increase in any aneurysm diameter by ≥ 1mm within 36±6 months from randomization. Aneurysm rupture or growth will be assessed centrally by two independent trial radiologists, who will be blinded to the treatment allocation. Events suspicious for SAH but negative CT-imaging will be reviewed centrally by the adjudication committee. Instances of sudden death of patients who died before reaching a hospital will be reviewed centrally by one neurosurgeon and two neurologists who are blinded to the treatment allocation to assess the (un)likelihood of SAH as cause of the sudden death.

2.2 Secondary Objectives and Secondary Endpoints

Secondary objectives of the study are:

A) To assess whether ASA reduces the risk of aneurysm rupture or growth compared with no ASA treatment.
B) To assess whether intensive blood pressure lowering therapy reduces the risk of aneurysm rupture or growth compared with no intensive blood pressure lowering therapy.

C) To assess whether intensive blood pressure treatment plus ASA reduces the incidence of cardiovascular events compared with standard BP treatment alone.
D) To assess whether beneficial effects of the intervention with intensive blood pressure treatment and ASA are not negated by side effects of the intervention.
E) To assess the effect of the intervention on quality of life
F) To investigate if the intervention is cost-effective

Secondary endpoints of the study are:

1. Any growth or rupture of aneurysm during follow-up irrespective of the duration of trial participation
2. Difference of aneurysm volume (defined as increase of aneurysm volume in computerized measurements from source images by >10% and >3mm^3) or aneurysm shape (e.g. development of daughter sac)
3. Development of de novo aneurysm on serial imaging
4. If a second aneurysm is present: Growth in diameter or volume and alteration of shape of this second aneurysm.
5. Clipping/coiling during the study period
6. Any ischemic or haemorrhagic stroke, defined as clinical symptoms of stroke AND a compatible lesion on imaging
7. Myocardial infarction defined as increase of Troponin, CKMB and/or presence of new significant Q waves obtained in ECG
8. Vascular death (including fatal stroke, fatal myocardial infarction, sudden death)
9. Death from all other causes
10. Major spontaneous bleeding requiring hospitalisation defined as substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating the transfusion of at least 2 units of erythrocyte concentrates
11. Blood pressure; any data on blood pressure management used
12. Safety aspects (adverse and serious adverse events, including those mentioned above, see also 8.1.6 and 8.2)
13. Quality of life (as determined by completion of the paper-based EQ-5D-5L form by patient)

2.3 Additional Research

Participants in the intervention group will receive a blood pressure measurement device to perform blood pressure home-measurements, as an additional measure of blood pressure control and to increase compliance, thus quality assurance. At the time of follow-up during the study visits, participants will provide the local investigators of each study site the blood pressure measurement device for download of the blood pressure data onto a tablet. A graph comprising mean systolic and diastolic blood pressure values obtained over the past 6 months will enable the local investigators to assess whether or not study participants have reached their assigned blood pressure target. Additionally, blood pressure data will be transmitted in a pseudonymized fashion via a secure online connection to a central database at the sponsor's institution. The uploaded data may be used for further analysis of achieved blood pressures in the intervention group at the end of the trial. The uploaded data will not be used for a diagnostic or therapeutic intervention if the blood pressure is outside the normal range.

3 TRIAL DESIGN AND DESCRIPTION

3.1 Trial design and justification of design aspects

This phase III multicenter, randomised, controlled trial with a PROBE design (prospective, randomised, open-label trial with blinded outcome assessment) is designed to assess whether a strategy with low dose ASA (81 mg/ day - 100mg/day) and intensive blood pressure treatment (targeted systolic blood pressure below 120mmHg) with weekly measurements using a home blood pressure measuring device reduces the risk of intracranial aneurysm rupture or growth, which is an established surrogate for the risk of rupture, compared with standard care (i.e. no ASA and blood pressure management according guidelines, which usually advise treatment if systolic blood pressure exceeds 140mmHg). [33]

We will perform a phase III trial instead of a phase I/II trial since the protective effect of ASA on aneurysm inflammation or rupture was highlighted in a nested case-control study of UIA patients (n=1691) as well as in a small phase I trial randomising patients to ASA treatment or treatment as usual, which showed a significant reduction of radiological and histological aneurysm wall inflammation as surrogates for rupture. [17, 18] Further, the recent SPRINT study randomising 9361 patients to intensive versus standard BP treatment demonstrated a reduction of the primary composite outcome (myocardial infarction, other acute coronary syndromes, stroke, heart failure, or death from cardiovascular causes) without affecting the overall incidence of adverse or serious adverse events. [16]

We chose an open-label design with observer-blinded outcome adjudication (by two independent neuroradiologists), because: a) a double or single-blinded study with predefined blood pressure targets would not be feasible, irrespective of the concomitant ASA treatment, b) to allow inclusion of UIA patients who are already treated for hypertension; and c) for pragmatic reasons, e.g. to not having to unblind treatment allocation for patients, who require a medical procedure potentially under ASA during the duration of the study (for at least 36±6 months after randomization). Also, due to very specific and well-known effects of ASA, it would be very likely to un-blind the patient by side effects.

Because the 5-year risk of rupture is usually <3% in patients with small aneurysms, a randomized trial with rupture as the main primary outcome measure is unfeasible. We therefore combine aneurysm rupture with aneurysm growth as the primary outcome measurement, since UIA growth occurs more often and is a predictor of aneurysm rupture (see also above). The risk of growth is approximately 15% in 3 years, and approximately 18% in 5 years.[15, 25, 32]

From a scientific perspective it would be important to understand the individual protective effects of both factors, i.e. intensive blood pressure reduction and ASA treatment, on aneurysm growth or rupture. We decided on a two-arm trial (i.e. concomitant ASA treatment plus intensive blood pressure treatment) instead of a three-arm trial (i.e. ASA treatment or intensive blood pressure management or standard of care), because in a three-arm trial investigating the protective effect of each component separately, the effect size for each treatment component would be smaller than for the combined effect. Hereby, the number of patients would not only increase as a result of adding an additional arm, but also because the effect size for each component was smaller.

We assume that combined ASA and intensive blood pressure lowering will reduce 3-year incidence of the primary outcome (aneurysm rupture or growth) from 15% to 8.25%, thus a relative risk reduction of 45%. We previously considered a trial with ASA only (without blood pressure reduction). For such a trial we assumed that the risk reduction to be attributed to ASA is 22.5%. Then the reduction by ASA monotherapy would be from 15% to 11.625% and the subsequent number for the a trial with two arms and with such a contrast would be 2 x 1597 for a total of 3194 patients who are available for the analysis. Even if we assume that the risk reduction contributed

to ASA would be as large as 30% (15% down to 10.5%) a two-armed trial would require 2 x 864 = 1728 patients. Based on these calculations we decided against such a design.

We also considered a 2 x 2 factorial design (ASA vs. no ASA and intensive vs. regular blood pressure control). Since such a trial would need at least 1,728 patients, we also considered this design unfeasible.

For more details about Randomisation see section 5.5 “Randomisation .

Feasibility

The trial will be performed worldwide in up to 30 medical centers that see at least 50 new patients with unruptured aneurysms per year per center in addition to existing patients with unruptured aneurysms who are already managed conservatively at each center. These patients will be screened for study eligibility. If patients had an MRA or CTA scan 3 months prior to eligibility assessment, they are also eligible.

3.2 Trial Duration and Schedule

The duration of the trial for each subject is expected to be at least 36 months intervention and one-month follow-up. For those subjects enrolled early in the trial, the intervention will be continued until the last subject enrolled completed the 36 months of intervention (maximum duration of treatment 120 months ± 30 days).

The overall duration of the trial is expected to be approximately 162 months. Recruitment of subjects has been started in in Q3 2017 in Germany. The actual overall or recruitment duration may vary. Based on a planned interim analysis, the DSMB can recommend modifying the duration of the trial. The study end is defined as “last patient out” (LPO), this may apply as well to a follow-up visit, if appropriate.

Duration of the clinical phase for each patient:	[up to 120 months]
Total trial duration:	[162 months]
Duration of clinical phase:	[144 months]
Beginning of the preparation phase:	[Q2 2017]
FSI (first subject in):	[Q3 2017]
LSI (last subject in):	[Q2 2026]
LSO (last subject out):	[Q2 2029]
DBL (database lock):	[Q3 2029]
Statistical analyses completed:	[Q4 2029]
Trial report completed:	[Q2 2030]

4 SELECTION OF SUBJECTS AND CENTRES

4.1 Number of Subjects

As calculated in section 9.1, Sample Size Calculation, 776 subjects should be enrolled in the clinical trial, i.e. 388 subjects per treatment group.

4.2 Sites

The study will be conducted on a multinational and multicenter basis. It is intended that the study will take place at approximately 30 sites.

4.3 General Criteria for Subjects' Selection

All adult patients with unruptured saccular aneurysms will be considered for trial inclusion, if it is decided that the risk of preventive aneurysm repair outweighs the risk of aneurysm rupture, based on the individual centres' policy. Irrespective of this management decision, there will be no further selection based on all other patient- or aneurysm-characteristics.

4.4 Inclusion Criteria

Subjects meeting all of the following criteria will be considered for admission to the trial:

- Patient with at least one intradural, saccular unruptured aneurysm in whom it is decided not to intervene with preventive neurosurgical or endovascular aneurysm repair and who are monitored on a regular basis for aneurysm growth
- 18 years or older
- Last aneurysm imaging with either CTA/MRA within the last 3 months
- Ability of subject to understand character and individual consequences of clinical trial
- Not legally incapacitated
- Written informed consent (must be available before enrolment in the trial)
- For women with childbearing potential adequate contraception.

4.5 Exclusion Criteria

Subjects presenting with any of the following criteria will not be included in the trial:

- All non-saccular UIAs or aneurysms related to arteriovenous malformations
- Daily ASA already prescribed for another indication
- Use of a vitamin K antagonist or direct oral anticoagulant (DOAC) treatment at baseline
- History of hypersensitivity/allergy to ASA or to any other drug with similar chemical structure or to any excipient present in the pharmaceutical form of ASA
- History of asthma induced by salicylates or other anti-inflammatory drugs
- Other contra-indications for ASA not yet mentioned in the dosage of 81-100 mg/day (e.g. bleeding disorders, gastric ulcers and/or intestinal ulcers, acute liver failure of kidney failure, severe heart failure, treatment with methotrexate in a dosage 15 mg/week or above)
- Use of another platelet aggregation inhibitor, which in combination with ASA would give an unacceptable risk of side effects/complications
- Chronic kidney disease stage IV and V (GFR <30mL/min/1.73m2)
- Pregnancy and lactation
- Participation in another interventional clinical trial
- Life-expectancy <3 years

No subject will be allowed to enrol in this trial more than once.

4.6 Criteria for Withdrawal

4.6.1 Withdrawal of Patients from Treatment

Any patient can withdraw from the treatment at any time without personal disadvantages and without having to give a reason. Patients who discontinue participation in the clinical study on their own or patients who are withdrawn by the investigator, for reasons other than disease progression (i.e. in case of AEs, protocol violations), will be defined as premature withdrawals. Withdrawn patients will be asked to attend a final follow-up visit and to return unused trial medication. Premature withdrawals will not be replaced. The time of treatment discontinuation must be documented in the patient file and on the CRF.

The investigator can also discontinue the participation of a patient in the study after considering the risk-to-benefit ratio, if he/she no longer considers the further treatment of the patient according to study protocol justifiable. The date of and the primary reason for the withdrawal, as well as the observations available at the time of withdrawal, are to be documented on the CRF. Reasons leading to the withdrawal of a patient can include the following (**one primary reason must be determined**):

- **Lack of efficacy** of the experimental intervention
- **Intolerable adverse events** from **both** components of the intervention (intensive blood pressure control **and** ASA-medication), e.g.
  - Any bleeding that results in hospital inpatient treatment
  - Severe skin reaction and/or asthma requiring treatment with medication exceeding a single dose
  - Gastric ulcer, if not possible to manage by gastroprotective co-medication
  - Severe orthostatic hypotension
- Disease progression
  - In patients with 1 intracranial aneurysm, end of treatment applies if aneurysm rupture (SAH) occurs or interventional treatment of the aneurysm (endovascular or neurosurgical). Patients who have multiple aneurysms can stay in the trial if growth, rupture or preventive treatment of 1 aneurysm occurs
- **Lack of patient's cooperation**, e.g.
  - Patient's request to withdraw
  - Lack of compliance, patient fails to attend the interim visits as agreed or perform self-medication according to schedule
- **Other reasons** (noting reason), e.g.
  - Other diagnosis than study disease
  - Did not meet major in-/exclusion criteria (coming to light after randomisation)
  - Existing or intended pregnancy, lactation in patients of the intervention group. If patients in the control group become subsequently pregnant and/or need to breastfeed after randomisation, they will not be excluded from the trial.

All patients who finish the study prematurely will be asked to attend a follow-up visit and to return unused trial medication. The patient must be asked to consent to this last examination. The withdrawal examination will be documented in the CRF.

If a patient does not come to a visit, the patient will be contacted and asked for information. If the patient wants to withdraw and agrees to give explaining reasons, the reason should be documented in the patients file and in the CRF.

In case of early withdrawal, the last aneurysm imaging will be used for the primary outcome analysis *(last observation carried forward).*

If a patient has severe side effects from one component of the intervention only, (e.g. severe orthostatic hypotension from intensive blood pressure control or major gastrointestinal bleeding from ASA), it can be decided to adjust or stop the component of the intervention causing the side effects, while continuing the other component of the intervention.

For documentation of AEs and SAEs see 8.1.6 and 8.2.

Term	**Definition**	**Comment/ Sample**
Drop-out, study	Participation terminated completely, including follow-up Possible reasons: • Patient withdraws consent: **Withdrawal** • Patient moved/cannot be contacted • Interventions cannot be performed due to medical reasons • Non-compliance of patient Drop-out after completion of study intervention: **Lost to follow-up** Final examination will be performed, if patient agrees. Study-Completion/ Withdrawal-form will be completed.	ITT-sample ITT-sample (if study intervention completed)
Drop-out, study intervention	Termination of study intervention, follow-up once as per protocol.	ITT
Screening-failure	Exclusion criteria given prior to screening / enrolment: Patient will be recorded at screening list, but will not be provided with a patient number.	-
Protocol deviation	Drop-out to study and drop-out to study intervention are both protocol deviations. <u>Major deviations:</u> If exclusion criteria become evident after enrollment, and safety of the participant is affected, or if the diagnosis does not any more relate to the indication listed in the protocol affecting the benefit/risk negatively, the participant has to be excluded from study intervention. FU-examinations may still be performed. <u>Minor deviations:</u>	ITT (assessment of protocol deviations by LKP/ PI together with Biometrician) ITT-analysis (if minor deviations)

	Other protocol deviations (errors in timing of visits/ missing samples/ missing examinations) do not result in exclusion	

4.6.2 Premature Closure of the Clinical Trial or a Centre

If new information on the risk-to-benefit ratio of the drug or on the treatment methods used in the study is obtained in the meantime and safety concerns arise, the sponsor reserves the right to interrupt or terminate the project according to the recommendation of the DSMB and after consultation of the steering committee. Premature termination is also possible if the sponsor or steering committee notices and agrees upon that patient recruitment is insufficient and that this cannot be expedited by appropriate measures.

The DSMB can recommend interruption or termination of the study or of treatment arms based on the results of the intermittent SAE evaluation or of accumulating information on the above mentioned reasons.

Premature termination of a single centre is also possible if the sponsor notices that the conduction of the trial is not compliant with ICH-GCP and / or is not according to the protocol, the patient recruitment and / or the quality of the data is insufficient.

The ethics committee (EC) and the competent authorities must be informed about the premature closure of the trial or one of the treatment arms. Furthermore, the ethics committee(s) and competent authorities themselves may decide to stop or suspend the trial.

All involved investigators have to be informed immediately about a cessation / suspension of the trial. The decision is binding to all trial centres and investigators.

When the trial is closed, all study materials (e.g. blood pressure devices) must be sent to the sponsor.

5 INVESTIGATIONAL MEDICINAL PRODUCT (IMP)

5.1 Study medication

5.1.1 General Information

The sponsor (UMM) will provide the quantity of trial medication required for the clinical trial sites in Germany and the Netherlands.

Supply of IMP in additional countries will be managed by the national coordinators in accordance with the national regulations.

The medication provided must be used only in the context of this clinical trial. Careful records will be kept of the trial medication supplied to the centres and distributed to the patients. If deficiencies of the trial medication are noticed, the monitor and the project manager must be informed immediately.

Blood pressure lowering drugs will not be part of the IMP. The general practitioner will control the blood pressure target and prescribe blood pressure lowering drugs. The general practitioner can decide himself/herself on the type of antihypertensive drug(s) he/she wants to use to decrease the blood pressure.

5.1.2 Characterisation of study medication

The study medication is:

International Nonproprietary Name (INN):	Acetylsalicylic acid
ATC code:	B01AC06
Pharmaceutical formulation:	Tablets
Dose	Daily, 81 – 100 mg (depending on country)
Mode of administration:	Oral
Storage instructions:	Store below 30°C / 86° F, protected from humidity

5.2 Packaging and Labelling

The trial medication will be used in the original packaging, and labelled specifically for the clinical trial. Labelling in accordance to local regulations may be performed by qualified/authorized pharmacies.

5.3 Supplies and Drug Accountability

Supply with trial medication and blood pressure measurement devices in Germany and the Netherlands will be performed by the Pharmacy of the University Hospital Heidelberg by ordering using the IMP order form. Shipment of study medication and blood pressure measurement devices in Germany and the Netherlands will be without temperature control to each site. The investigator will confirm correct receipt of the trial medication in writing and ensure that the medication is stored safely and correctly. The trial medication must be carefully stored in accordance with manufacturer's instructions at the study sites and at the patients` home, in a locked area with restricted access, separately from other drugs, and kept out of the reach and sight of children. The investigator will document the distribution and return of the trial medication

to the patient with the date, recording the quantity distributed and used on the forms provided for this purpose. The site monitor will periodically check the supplies of trial medication held by the investigator to ensure the correct accountability of all trial medication used. Documented destruction of used and unused IMP will take place locally at the sites. It will be assured that a final report of the drug accountability is prepared and maintained by the investigator.

National regulations will be observed regarding provision, handling and labelling of trial medication. Blood pressure devices may be obtained locally.

Study medication handed to patients during a visit must not have an expiry date prior to the date of the next scheduled visit for this patient. Stored study medication will be destroyed at the centres as soon as the durability no longer exceeds 6 months.

5.4 Administration of study medication

5.4.1 Assignment of Identification Codes

All patients who seem suitable for study participation and take part in the screening will receive a screening number. At the end of the screening phase the eligibility of the patient is assessed finally.

When the patient is included in the study (all inclusion criteria fit and none of the exclusion criteria), he/she will be given a patient study number. This will consist of a number coding the trial centre and the randomisation number generated by the online randomising tool. Patients withdrawn from the study retain their patient number. New patients must always be allocated a new randomisation number.

For allocation to a treatment arm (randomisation) see 5.5.

5.4.2 Dosage Schedule

The study medication is given only to patients who have consented to study participation and who are randomized to the intervention group.

Maximum duration of treatment: 120 months
Maximum dose allowed: 100mg ASA daily, orally

IMP Compliance

IMP accountability (supply and return) will be documented at each visit, according to the trial schedule. Respective numbers will be transferred in the CRF. Additionally, investigators must provide a statement regarding patients` over-all compliance at the end of the treatment.

5.4.3 Prior and Concomitant Diseases

Relevant additional diseases present at the time of informed consent are regarded as concomitant diseases and will be documented on the appropriate pages of the case report form (CRF). Included are conditions that are seasonal, cyclic, or intermittent (e.g. seasonal allergies; intermittent headache).

Abnormalities which appear for the first time or worsen (intensity, frequency) during the trial are adverse events (AEs) and must be documented on the appropriate pages of the CRF.

5.4.4 Prior and Concomitant Medication

The treatment of accompanying illnesses not subject to the exclusion criteria is permissible if this is not expected to have any effect on the outcome measures used in this study and to interfere with the trial medication.

In particular, the following drug groups are **not permitted** as concomitant medication:

- Concomitant treatment with Vitamin-K antagonists or DOACs
- Platelet-inhibitors, if it is perceived that the potential benefit of this combination does not outweigh the risk of complications (for example: caution with combination of ASA with clopidogrel, while combination of ASA with dipyridamole is permitted)

The following drug groups are **permitted under restriction** as concomitant medication:

- Acetylsalicylic acid for other indications (e.g. short term use for a migraine attack).

If concomitant drugs are administered, these must be recorded in the patient file and in the CRF, stating

- The type (preferably the generic name / INN, or trade name)
- The route of administration
- The regimen including: dosage schedule, daily dose (if not indicated by the type), and form of application
- The indication
- The duration

Existing, permitted concomitant treatments are not to be changed during the course of this study.

5.4.5 Adjustments to dosage of the IMP in the individual trial subject

A) The use of ASA may be interrupted, if a patient needs surgery during the course of the clinical trial. It will be resumed as soon as possible after surgery.
B) No changes in IMP dosage are intended or permitted, even in case patients require a higher dose of ASA for other indications. However, if patients are medically required to be treated with higher doses of ASA (e.g. due to cardiovascular event) while being on treatment with the IMP, the treating physician can prescribe ASA as required and the IMP will be stopped for the time in which ASA is prescribed.
C) For safety data, patients of the intervention group, who received concomitant long-term ASA will be analysed as per protocol, patients of the control group as ITT.

No further adjustments are planned.

5.5 Randomisation

5.5.1 Randomisation method

For randomisation an online tool (https://www.randomizer.at/) will be used. Any patient included will be 1:1 randomised into one of the two study arms: 1) a strategy with ASA 81 - 100mg/day and intensive blood pressure treatment (targeted systolic blood pressure below 120mmHg) with weekly measurements using a home blood pressure measuring device; or 2) standard of care.

There is no placebo group. Each study centre will be provided with an access code to perform the randomisation independently. Stratification will occur according to centre.

5.6 Blinding

This is an open trial, in which patients and investigators are not blinded. However, there will be an examiner-blinded assessment of images, therefore no information of patient allocation using patient ID-numbers or other data that would unblind the allocation of a patient to one of the two trial arms should be made available prior to the imaging analysis.

6 DESCRIPTION OF TRIAL VISITS

The study period for an individual patient consists of a minimum treatment period of 36 months and a maximum treatment period of 120 months (all patients stay on intervention until 3 years of the last patients' enrolment, even if the primary endpoint has occurred for the purpose of the secondary endpoint analyses).

Overview of trial visits

6.1 Screening Visit

A patient with an unruptured saccular intracranial aneurysm will be considered for participation in PROTECT-U if the benefits of preventive aneurysm treatment (by means of clipping or an endovascular procedure) do not outweigh the procedural risks, preferably according to a multidisciplinary team of physicians (which at least includes a neurosurgeon, an interventional neuroradiologist and a neurologist). The management decision is discussed with the patient at the outpatient clinic and is part of regular care. If the patient may be eligible for PROTECT-U, he/she will be informed and asked to provide informed consent (IC). To sign the IC form, the patient will be given sufficient time. During the screening visit, the patient will be screened for eligibility (in-and exclusion criteria) for PROTECT-U. The following are key elements of the screening visit:

- The trial will be explained to the patient and written information regarding the trial will be provided.
- Demographic data are collected as well as vital signs (blood pressure, height, weight).
- Medical history is obtained regarding inclusion- and exclusion criteria, concomitant medication, smoking status and alcohol consumption.
- If necessary, a blood sample for verification of inclusion/exclusion criteria is taken (pregnancy test for women with childbearing capacity, creatinine to permit a GFR-estimation as described above, see 4.5). The investigator may decide to include other parameters, if needed (e.g. INR, thrombocytes count, hemoglobin).
- Depending on the cycle and the time between the visits, this test should be repeated at the baseline visit.
- Screening logs will be collected at the trial centres which will include all patients screened for study participation. Reasons for non-eligibility will be collected.

Patients may be contacted prior to the visit to inform them about the PROTECT-U trial. Written information will then be mailed. In these situations, patients have sufficient time to consider participation in the trial, in case the multidisciplinary team decides against preventive

endovascular or neurosurgical treatment of the aneurysm. At their visit to the tertiary care facility, remaining questions will be answered. If the patient is interested in participation, they will be randomized at their first visit to the tertiary care facility (see 6.2) after informed consent has been obtained. Patients may also be provided with information about the trial and asked screening questions when scheduled for a standard of care visit, e.g. for imaging. If the informed consent has already been signed by patient at the time of the screening visit, blood samples (see 6.2) may be taken at this visit.

6.2 Baseline Visit

The following are key elements of the baseline visit:

- Confirmation that all inclusion- / exclusion criteria are satisfied
- If a recent (<6 months) GFR (determined at the lab of the trial center or at another lab that provides a copy of the appropriate lab certificate) is not available, a blood test will be done to measure GFR after informed consent has been obtained.
- Verification of participant contact information
- Completion of the study randomization procedure using an online randomization tool, as soon as lab values needed for inclusion (e.g. negative pregnancy testing) are available.
- Collection of the following baseline characteristics by history taking: history of hypertension / ischemic stroke / intracerebral hemorrhage / subarachnoid hemorrhage / myocardial infarction / peripheral vascular disease / polycystic kidney disease, tobacco smoking history including number of packyears of smoking and current number of cigarettes per day, medication use, alcohol consumption, number of first degree and second degree relatives with an intracranial aneurysm (either unruptured or ruptured), and an EQ-5D-5L questionnaire is completed by the patient.
- Collection of aneurysm characteristics based on reviewing medical data: 1) number of intracranial aneurysms; 2) anatomical site(s) of the UIA; 3) maximum UIA diameter; and 4) aneurysm shape.
- A blood pressure will be measured in sitting position.
- If the time between screening visit and baseline visit exceeds so much time (depending on the cycle of the patient) that another pregnancy test is necessary, an additional rapid test will be performed.
- Clinical chemical parameter may be controlled, if the investigator decides they are necessary.
- A baseline assessment for symptoms of potential adverse effects of ASA is performed prior to beginning the therapy.
- Trial medication is provided to patients randomized to the intervention group.
- Patients in the intervention arm will be provided with a letter to the treating physician explaining the study in detail and the blood pressure limits aimed for (120 mmHg systolic). Also a device for blood pressure measurements at home will be handed to the patient. The patient will be explained how to do measurements with this device. Patients provided with an electronic blood pressure measuring device are recommended to use this device to measure blood pressure at home at least once per week and up to 4 times per week, which will ensure that we do not exceed the maximum of 100 measurements at the time of each follow-up. However, if a patient would not do weekly measurements, this would not be defined as protocol deviation.

The last routine imaging of the aneurysm (either CTA or MRA) within 3 months before randomization) will be uploaded to a central server in a pseudonymised manner by using the patient ID number and date of imaging. The pseudonymisation method must not reveal the allocation to intervention group or standard of care, to permit a blinded imaging assessment. Screening and Baseline visit may be performed at one single day.

6.3 Treatment Visits

Treatment visit schedules for data collection do not differ by group assignment. For the purpose of data collection and event ascertainment all participants will have post-randomization visits, at month 6 (+/- 30 days), and every 6 months (+/- 30 days) thereafter. During all treatment visits, blood pressures will be recorded in a sitting position. Patients will be asked for the occurrence of adverse events and (reasons) of admissions to hospitals and visits to outpatient clinics, quality of life (EQ-5D-5L), information regarding concomitant medication, and the cardiovascular outcome are retrieved. All subsequent CTAs/MRAs of the aneurysm which are made as part of standard care will be uploaded in a pseudonymised manner to a central server.

Patients of the intervention group will be asked to have the blood-pressure device with them, to permit a readout of the blood-pressure values to a tablet computer at the trial centre. In case patients did not yet transfer the blood pressure measurements to the central database using their own smartphone, the investigator can transmit available measurements in a pseudonymized fashion via a secure online connection to the central database at the sponsor's institution (University Medicine Mannheim). The investigator will see a displayed graph at the tablet computer and will categorize the findings into one of these three classifications:

- The blood pressure is satisfactory or lower,
- The blood pressure is higher than recommended,
- The blood pressure is not checked at least once a week

Based on the available blood pressure data, the investigator will decide whether or not the patient should see a GP for optimisation of blood pressure treatment. If the blood pressure is not checked at least once a week, patients are reinstructed how to use the device.

Blood pressure data obtained by the electronic device are not subject to clinical monitoring.

For the control group, a visit could be replaced by a telephone visit, if the previous visit was performed at the trial center.

In the event that the Covid-19 pandemia would cause circumstances in which the treatment visits need to be cancelled, the scheduled trial visit can be replaced by a telephone visit. The blood pressure readout of the devices of the intervention group would be skipped then until the next visit at the center.

CTAs/MRAs beyond this time point will also be uploaded to the central server. We will collect data on GFR and blood sodium in patients with pre-existing, compensated chronic renal failure (stage III: GFR <60 mL/min/1.73 m^2), who are monitored for these parameters by their treating physicians. During all trial visits the investigators will stress that smoking cessation is pivotal and inform patients who smoke about possible options for help in smoking cessation. The number of cigarettes per day and alcohol consumption per day will be recorded. The investigator will collect data on GFR and blood sodium in patients with pre-existing, compensated chronic renal failure (stage III), who are monitored for these parameters by their treating physicians.

Any subsequent imaging during the study period will be uploaded to the core lab. Timing and frequency of subsequent CT- or MR examinations vary in clinical practice. In case the 36 (±6) months' time point is not sampled in a particular patient, the latest CTA/MRA prior to this date will be analysed. Patients with imaging using different imaging modalities (e.g. initial MRA vs. subsequent CTA) will be excluded from assessing the images for the primary endpoint and considered to be dropouts in the statistical analysis. However, for patients with several images of the same modality, an analysis for the time span between these two identical modalities may be permitted by the adjudication committee.
At each treatment visit, remaining trial medication will be collected, the number documented and the blisters will be sent back for disposal. New trial medication is provided for the next period.

End of treatment visit will be planned 36 months after inclusion of the last patient. The same procedures are performed as in treatment visits. Patients should be asked to continue study participation/ treatment until month 120 (±30 days) or end of study (whatever comes first).

In case of intolerable AEs/ SAEs, new visits will be planned by the investigator until the findings have been clarified or became stable.

All patients will have a CTA/MRA at least 36 (±6) months after randomization and preferably around the last follow-up visit as per standard of care. All images will be uploaded in a pseudonymised manner to a central server. Patients will be told to stop the IMP if there is no indication to continue (indications to continue are for example myocardial infarction, TIA, ischemic stroke), and be advised to visit a general practitioner for future blood pressure regulation. A letter will be sent to the general practitioner that the study has ended.

6.4 Follow-up visit

30 days after end of treatment (+/- 10 days) patients return for a follow-up visit. At this visit, blood pressure is measured (as described above); data on smoking, alcohol use, concomitant medication and AEs/SAEs are collected. A blood sample is taken only if there has previous blood parameters at earlier visits required follow-up. If trial medication was left at the patients home after the end of treatment visit, the remaining tablets will be collected, the number documented and the blisters will be sent back for disposal. The status of uploaded images will be double-checked; missing images will be retrieved and also uploaded. The investigator will continue to follow-up on all patients (also withdrawals) with AEs/ SAEs until the findings have been clarified or became stable. The follow-up visit may be waived if there was no unresolved SAE at time point end of treatment visit.

6.5 Planned treatment after study end

After the subject has ended participation in the trial, the primary responsible physician (either a neurosurgeon, neurologist, or neuroradiologist) at the treating hospital will continue with standard care. The IMP does not need to be tapered off. The general physician will be responsible for blood pressure management after study end.

7 METHODS OF DATA COLLECTION

Please refer to the CLINICAL TRIAL SCHEDULE for parameters and time points captured.

7.1 Safety Parameters

Adverse Events:
For definition see 8.1.1.

Adverse events will be interrogated for at each contact between the responsible investigator and the study subject. Furthermore, all pathological and clinically relevant findings in physical examinations, blood pressure, clinical chemistry, hematology, and clotting will be documented as adverse events.

Wherever possible, adverse events will be reported on the basis of CTCAE v5.

Adverse events will be reported with subject ID, start and end date, description, grading, seriousness, relationship, action taken and outcome.

Blood pressure:
Systolic and diastolic blood pressure determined on all study days will be documented as numerical values on appropriate CRF-pages.

12-lead ECG

12-lead ECG may be recorded at any time at discretion of the responsible investigator, but only if medically imperative for clarification of clinical signs and symptoms. Pathological and clinically relevant findings will be documented as adverse events/ serious adverse events.

Clinical chemistry, hematology and clotting:
Following parameters will be determined on the predefined study days:

Clinical chemistry: We will collect data on GFR and blood sodium in patients with pre-existing, compensated chronic renal failure (stage III), who are monitored for these parameters by their treating physicians.

After collection, the samples will immediately be delivered to the laboratory of the participating institution for respective determinations. All parameters will be documented on appropriate CRF-pages.

Further laboratory parameters may be determined at any time during the study at discretion of the responsible investigator. Pathological and clinically relevant findings will be documented as adverse events/ serious adverse events.

7.2 Efficacy Parameters

Primary efficacy endpoint:

- Aneurysm rupture (i.e. aneurysmal subarachnoid hemorrhage, SAH) or growth (increase in any aneurysm diameter by ≥1mm) on serial imaging (either two MR or CT angiographies) within 36 +/- 6 months from randomization.

Secondary efficacy endpoints:

1. Any growth or rupture of aneurysm during follow-up irrespective of the duration of trial participation
2. Difference of aneurysm volume (defined as increase of aneurysm volume in computerized measurements from source images by >10% and >3mm^3) or aneurysm shape (e.g. development of daughter sac)
3. Development of de novo aneurysm on serial imaging

4. If a second aneurysm is present: Growth in diameter or volume and alteration of shape of this second aneurysm.
5. Clipping/coiling during the study period
6. Any ischemic or haemorrhagic stroke, defined as clinical symptoms of stroke AND a compatible lesion on imaging
7. Myocardial infarction defined as increase of Troponin, CKMB and/or presence of new significant Q waves obtained in ECG
8. Vascular death (including fatal stroke, fatal myocardial infarction, sudden death)
9. Death from all other causes
10. Major spontaneous bleeding requiring hospitalisation defined as substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating the transfusion of at least 2 units of erythrocyte concentrates
11. Blood pressure; any data on blood pressure management used
12. Safety aspects (adverse and serious adverse events, including those mentioned above, see also 8.1.6 and 8.2)
13. Quality of life, as determined by completion of the paper-based EQ-5D-5L form by patient.

7.2.1 Progression-free Survival

Progression-free survival, defined as the time from randomization to the first observation of aneurysm growth or rupture, will be assessed every 12 months, based on available data such as subsequent imaging, until study end. During the course of the study, timing of subsequent imaging of the intracranial aneurysm will be at the discretion of the treating physician, since there are currently no guidelines in this respect. However, we anticipate that many centers will perform imaging every one or two years. If a patient is lost to follow up, progression-free survival is censored at the time of last imaging. No x-ray or other radiation is used for trial purposes only. However, if the patient undergoes examinations for medical reasons (such as routine control of aneurysm) such examinations may be used for a second assessment for trial purposes.

7.2.2 Overall Survival

Survival data will be collected continuously during the study period (treatment phase) until study end. If a patient is lost to follow up, overall survival time is censored at the time of last contact.

8 ADVERSE EVENTS

8.1 Definitions

8.1.1 Adverse Event

According to GCP, an adverse event (AE) is defined as follows: Any untoward medical occurrence in a subject administered a pharmaceutical product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal (investigational) product, whether or not related to the medicinal (investigational) product.

An AE may be:

- New symptoms/ medical conditions
- New diagnosis
- Changes of laboratory parameters

The criteria that should be considered when determining whether an abnormal test finding should be reported as adverse event are as follows:

- Test result is associated with accompanying symptoms, and/or
- Test result require diagnostic testing or medical/surgical intervention, and/or
- Test result lead to a change in trial dosing outside the protocol-stipulated dose adjustments, or discontinuation from the trial, significant additional concomitant drug treatment, or other therapy, and/or
- Test result is considered clinically relevant at the discretion of the investigator or sponsor

- Intercurrent diseases and accidents

- Worsening of medical conditions/ diseases existing before clinical trial start

- Recurrence of disease

- Increase of frequency or intensity of episodic diseases.

A pre-existing disease or symptom will not be considered an adverse event unless there will be an untoward change in its intensity, frequency or quality. This change will be documented by an investigator.

Surgical procedures themselves, including aneurysm surgery, are not AEs; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an AE. Planned surgical measures permitted by the clinical trial protocol and the condition(s) leading to these measures are not AEs, if the condition leading to the measure was present prior to inclusion into the trial. In the latter case the condition should be reported as medical history.

AEs are classified as "non-serious" or "serious".

8.1.2 Serious Adverse Event

A serious adverse event (SAE) is one that at any dose:

- Results in death

- Is life-threatening (the term life-threatening refers to an event in which the subject was at risk of death at the time of event and not to an event which hypothetically might have caused death if it was more severe)

- Requires hospitalisation or prolongation of existing hospitalisation*

- Results in persistent or significant disability/ incapacity**

- Is a congenital anomaly/ birth defect or

- Is otherwise medically relevant

* Hospitalisation for performing *preventive* aneurysm treatment is not classified as an SAE. Hospitalisations for disease-related procedures (surgery, imaging, laboratory tests) or any procedures planned before entry into the study are not considered SAEs. Hospitalisations for social reasons in the absence of an adverse event are not classified as SAEs either.

** Persistent or significant disability or incapacity means that there is a substantial disruption of a person's ability to carry out normal life functions. The irreversible injury of an organ function (e.g. paresis, diabetes, cardiac arrhythmia) fulfils this criterion.

Medical and scientific judgement will be exercised in deciding whether expedited reporting is appropriate in other situations - such as important medical events that may not be immediately

life threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed above. These should also usually be considered serious (examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm; blood dyscrasias or convulsions that do not result in hospitalisation; or development of drug dependency or drug abuse).

SAE reporting will be coordinated by the KKS pharmacovigilance.

8.1.3 Serious Adverse Reaction

SAEs that potentially may be attributed to the investigational medicinal product (IMP) are classified as Serious Adverse Reactions (SARs).

8.1.4 Expectedness

An 'unexpected' adverse reaction is an adverse reaction of which the nature or severity is not consistent with the applicable product information, (Summary of Product Characteristics, SmPC). Furthermore, reports which add significant information on specificity or severity of a known adverse reaction constitute 'unexpected' events.

8.1.5 Suspected Unexpected Serious Adverse Reaction (SUSAR)

SAEs that are both 'suspected', i.e., possibly related to the study drug (investigational medicinal product (IMP)) and 'unexpected', i.e., the nature and/ or severity of which is not consistent with the applicable product information are to be classified as Suspected Unexpected Serious Adverse Reactions (SUSARs).

In case, either the investigator who primary reported the SAE or the second assessor, classifies the SAE as 'suspected' *(i.e., either as 'definitely' or 'probable' or 'possible' related to IMP or 'not assessable')* and the SAE is unexpected it will be categorised as a SUSAR.

All SUSARs are subject to an expedited reporting to the responsible ethics committee(s), the competent authorities and to all participating investigators.

Grading of AEs

The grading of AEs in this trial will be carried out on the basis of the 5-grade scale defined in the CTCAE v5.0:

Grade 1:	Mild: signs and symptoms that can be easily tolerated. Symptoms can be ignored or disappear when the subject is distracted.
Grade 2:	Moderate: symptoms cause discomfort but are tolerable, they cannot be ignored and affect normal activity.
Grade 3:	Severe: symptoms strongly affect normal activity.
Grade 4:	Life threatening or causing disablement
Grade 5:	Death

The grading of all AEs listed in the CTCAE v5.0 will be based on the information contained therein. The grading of all other AEs, i.e., those which are not listed in the CTCAE v5.0 will be performed by a responsible investigator, based on definitions given above.

Clarification of the difference in meaning between "serious" and "severe":

The terms “serious” and “severe” are not synonymous. The term ‘severe’ should be used to describe the intensity (severity) of a specific event; the event itself, however, may be of relatively minor significance (such as severe headache). This is not the same as “serious”, which is based on the existence of one of the above mentioned seriousness criteria.

8.1.6 Relationship and Outcome of AEs

The investigator will evaluate each AE that occurred after randomisation. Regarding the **relationship** with the administration of the IMP it will be assessed:

Definitely related:	There is a reasonable possibility that the event may have been caused by the IMP. A certain event has a **strong temporal relationship** and an alternative cause is unlikely.
Probable:	An AE that has a reasonable possibility that the event is likely to have been caused by the IMP. The AE has a **timely relationship** and **follows a known pattern of response**, but a potential alternative cause may be present.
Possible:	An AE that has a reasonable possibility that the event may have been caused by the IMP. The AE has a **timely relationship** to the IMP; **however, the pattern of response is untypical**, and an alternative cause seems more likely, or there is significant uncertainty about the cause of the event.
Unlikely:	Only a remote connection exists between the IMP and the reported adverse event. Other conditions including concurrent illness, progression or expression of the disease state or reaction of the concomitant medication appear to explain the reported adverse event.
Not related:	An AE that does not follow a reasonable temporal sequence related to the IMP and is likely to have been produced by the subject’s clinical state, other modes of therapy or other known aetiology.
Not assessable:	There is insufficient or incomplete evidence to make a clinical judgement of the causal relationship.

All subjects who have reportable AEs, whether considered associated with the use of the trial medication or not, must be monitored to determine the **outcome**. The clinical course of the AE will be followed up until resolution or normalisation of changed laboratory parameters or until it has changed to a stable condition. This also holds for on-going AEs/SAEs of withdrawn subjects.

The outcome of an AE at the time of the last observation will be classified as:

Recovered / resolved:	All signs and symptoms of an AE disappeared without any sequels at the time of the last interrogation.
Recovering / resolving:	The intensity of signs and symptoms has been diminishing and / or their clinical pattern has been changing up to the time of the last interrogation in a way typical for its resolution.
Not recovered/not resolved:	Signs and symptoms of an AE are mostly unchanged or worsened at the time of the last interrogation.

Recovered / resolved with sequel:	Actual signs and symptoms of an AE disappeared but there are sequels related to the AE.
Fatal:	Resulting in death. If there is more than one adverse event, only the adverse event leading to death (possibly related) will be characterised as 'fatal'.
Unknown	The outcome is unknown or implausible and the information cannot be supplemented or verified.

The action taken with the IMP will be assigned to one of the following categories:

Dose not changed:	No change in the dose of the IMP.
Dose reduced:	Reduction in the dose of the IMP.
Dose increased:	Increase in the dose of the IMP.
Drug withdrawn:	Discontinuation (temporary or permanent) of the IMP.
Unknown:	The information is unknown or implausible and it cannot be supplemented or verified
Not applicable:	The question is implausible (e.g. the subject is dead).

The term "countermeasures" refers to the specific actions taken to treat or alleviate adverse events or to avoid their sequels. Following categories will be used to categorise the countermeasures to adverse events:

None:	No action taken.
Drug treatment:	Newly-prescribed medication or change in dose of a medication.
Others:	Other countermeasures, e.g. an operative procedure.

8.2 Period of Observation and Documentation

Adverse events (AEs) will be ascertained by the investigators using non-leading questions, noted as spontaneously reported by the patients to the medical staff or observed during any measurements on all study days. The observation period begins with the randomisation and ends with the last study visit, 30 days +/-10 days after end of treatment visit (or after withdrawal) (i.e. follow-up-visit). AEs will be documented in the patient file and in the CRF. All subjects who present AEs, whether considered associated with the use of the trial medication or not, will be monitored by the responsible investigator to determine their outcome; this applies to withdrawals too (see also 8.1.7).

The end date of the SAE is defined typically the same as for AEs. The end date of the SAE must not be later than the end date of the corresponding AE.

AEs and SAEs that are on-going at the time of death are considered not resolved or resolving.

The patients should report any AEs occurring during the outpatient part to the study centre by phone.

All SAEs and their relevance for the benefit/risk assessment of the study will be evaluated continuously during the study and for the final report. All SAEs will be documented in the "Serious Adverse Event" form (see 8.3).

8.3 Reporting of Serious Adverse Events by Investigator

All SAEs must be reported by the investigator to the responsible Safety Officer at the KKS Heidelberg within 24 hours after the SAE becomes known using the "Serious Adverse Event" form. The initial report must be as complete as possible including details of the current illness and (serious) adverse event and an assessment of the causal relationship between the event and the trial medication.

The reporting will be performed by sending a completed ‘SAE Form’ to the KKS Heidelberg.

Fax no.:

+49-(0)6221-56-33725

Only in case of technical faults the SAE Form can be also submitted by e-mail:

Email: Pharmakovigilanz.KKS@med.uni-heidelberg.de

8.4 Reporting of Pregnancies

Female patients taking the IMP prior to knowing about a pregnancy will only be reported if the daily dose at least once was higher than one tablet during the time span of undetected pregnancy. Reporting will be made within 24 hours by using the SAE-form.

8.5 Expedited Reporting

SUSARs are to be reported to the responsible ethics committees, the competent authorities, if applicable other institutions according to national regulations and to all participating investigators within defined timelines, i.e. they are subject to an expedited reporting.

All SAEs will be subject to a second assessment by a designated person. Procedures and responsibilities regarding second assessment are described in a separate document (Safety manual).

The second assessor will fill out a ‘Second Assessment Form’ for each SAE and send it back per fax to the responsible person at the KKS Heidelberg within 48 hours, fax-number:

+49-(0)6221 – 56 – 33725

The ‘Second Assessment Form’ will contain the following information:

I) Assessment of relationship between SAE and IMP (causality)
II) Assessment of expectedness of SAE (derived from SmPC)
III) Assessment of relationship between SAE and the underlying disease
IV) Statement if the benefit/ risk assessment for the trial did change as a result of SAE.

The expedited reporting (to competent authorities, responsible ethics committees and investigators) will be carried out by a responsible Safety Officer at KKS Heidelberg. Only SUSARs/ SAEs occurring after administration of IMP will undergo expedited reporting. Details concerning the reporting of SUSARs will be described in a separate document “Safety Manual”.

9 STATISTICAL PROCEDURES

9.1 Sample Size Calculation

The test of the primary hypothesis is outlined in paragraph 9.4 (Statistical Methods). The sample size calculation is based on the following assumptions:

Previously a hazard ratio of 1.3 (95%CI 1.0-1.9) for hypertension as a risk factor for aneurysm rupture (PHASES cohort) and an odds ratio of 0.27 (95% CI 0.27-0.67) for risk of rupture in patients with unruptured intracranial aneurysms using ASA was reported. [12, 17] If we conservatively assume a risk reduction of 45% for the primary outcome measure and the risk to have a primary outcome event at three years of 15% in the standard treatment group and 8.25% in the intensive treatment + ASA group, an alpha of 0.05 and a power of 80%, 353 patients are needed in each group. Assuming a dropout rate of 10%, we will need to assign 776 patients to the trial so that 706 patients can be analyzed. [15, 25, 32]

Analysis Variables
Primary analysis variable:

- Aneurysm rupture (i.e. aneurysmal subarachnoid hemorrhage, SAH) or growth (increase in any aneurysm diameter by ≥1mm) on serial imaging (either two MR or CT angiographies) within 36 +/- 6 months from randomization.

Secondary analysis variables:

- Any growth or rupture of aneurysm during follow-up irrespective of the duration of trial participation
- Difference of aneurysm volume (defined as increase of aneurysm volume in computerized measurements from source images by >10% and >3mm^3 or aneurysm shape (e.g. development of daughter sac)
- Development of de novo aneurysm on serial imaging.
- If a second aneurysm exists at baseline, this aneurysm will be defined for its localization and analyzed for growth in diameter, growth in volume, and alteration of shape.
- Clipping/coiling during the study period
- Any ischemic or haemorrhagic stroke, defined as clinical symptoms of stroke AND a compatible lesion on imaging
- Myocardial infarction defined as increase of Troponin, CKMB and/or presence of new significant Q waves obtained in ECG
- Vascular death (including fatal stroke, fatal myocardial infarction, sudden death)
- Death from all other causes
- Major spontaneous bleeding requiring hospitalisation defined as substantially disabling bleeding, intraocular bleeding leading to the loss of vision, or bleeding necessitating the transfusion of at least 2 units of erythrocyte concentrates achieved
- Blood pressure; any data on blood pressure management used
- Safety aspects (adverse and serious adverse events, including those mentioned above)
- Quality of life

9.2 Definition of Trial Population to be analysed

The primary analysis will be performed for the full analysis set which comprises all patients randomised into the trial. In this set, every patient is analysed according to the group randomised into. Exceptions to this rule can be made for patients for whom non-eligibility became apparent after randomisation, provided all three of the following conditions hold:

- The entry criterion was measured prior to randomisation;
- The detection of the relevant eligibility violations can be made completely objectively;
- All subjects receive equal scrutiny for eligibility violations; (This may be difficult to ensure in an open-label study, or even in a double-blind study if the data are unblinded prior to this scrutiny, emphasising the importance of the blind review.)

The safety set will comprise all patients who have received study medication at least once, and will allocate the patients to the treatment they actually received, regardless of randomisation.

For definition of “premature withdrawal”, “screening failure” and “drop-out” see 4.6.1.

9.3 Statistical Methods

Baseline characteristics will be summarized as means with standard deviations or proportions, as appropriate. In the primary analysis we will quantify the treatment effect of a strategy aimed at risk factor modification by intensive blood pressure treatment, monitoring with a blood pressure measuring device, and acetylsalicylic acid (ASA) on the risk of aneurysm rupture or growth, which is an established surrogate for the risk of rupture, compared with standard blood pressure treatment and no ASA.

We will compare the occurrence of outcome events in the two groups in terms of the risk ratio (RR), which will be obtained by means of a Poisson model. The precision of the RR estimates will be described with 95% confidence intervals obtained from the Poisson model. Our primary analyses will be based on the intention-to-treat principle. Patients will be censored in case of death from causes other than aneurysm rupture. In addition to crude analyses, we will do an analysis adjusted for the main risk factors of the primary outcome: aneurysm size, shape, location, age and smoking status. For our secondary analyses in which the timing of the outcome event is not prespecified but all follow-up data are taken into account, we will calculate hazard ratios using Cox regression analyses. Final details will be specified in the Statistical Analysis Plan.

We plan the following subgroup analyses: age (≤55 versus >55 years), sex, and type (with or without previous rupture of another aneurysm), size (1.0-4.0 mm versus ≥4.1 mm), aneurysm location (posterior communicating artery / anterior communicating artery / posterior circulation versus all other aneurysms) and morphology of aneurysm (regular versus irregular shape).

In addition to our main research question on the effect of combined ASA and blood pressure lowering therapy, a secondary aim is to study the effect of the blood pressure component of the combination therapy. For this aim we will accurately record who is using intensive blood pressure lowering therapy. Data of both the intervention and the control arms of PROTECT-U can be used for this purpose. For this research aim we will relate the intensive blood pressure lowering therapy usage percentage to the primary outcome. As this analysis pertains to a non-randomized comparison we need to adjust for potential confounding by other determinants of the primary outcome, including the other component (acetylsalicylic acid) of the combined treatment. Analyses will be done with multivariable Poisson regression in which we will model cumulative incidence of the primary outcome at three years.

We will do an additional analysis restricted to the patients randomized to the intervention group, because within this group detailed data on achieved blood pressure will be available obtained with a device that transmits blood pressure to a central post. For each patient we will calculate the percentage of time that systolic blood pressure is below 120 mm Hg. Then we will do an

analysis similar as described above in which we will relate the percentage of time that systolic blood pressure is below 120 mm Hg to the primary outcome, also adjusted for other determinants of the outcome.

Another secondary aim is to study the effect of ASA treatment alone. For these analyses, we will use data on drug accountability (for acetylsalicylic acid use). As these analyses pertain to non-randomized comparisons, we need to adjust for potential confounding by other determinants of the primary outcome, including the other component of the combined treatment. Analyses will be done with multivariable Poisson regression in which we will model cumulative incidence of the primary outcome at three years. These data will not be subject to an interim analysis.

Cost-effectiveness analysis

Cost-effectiveness will be studied by relating cost-differences between the intervention and comparator treatment to differences in number of patients who experience the primary outcome, i.e. cost per aneurysm growth or rupture prevented. It is anticipated that the low-cost intervention will prevent high-cost aneurysm ruptures and be cost-saving during the 3 year follow-up period. Furthermore, cost-utility will be assessed by studying cost differences between the two trial arms in relation to quality of life changes in patients. Quality of life will be measured 6-monthly using the EQ5D-5L questionnaire and QALYs will be estimated following the algorithm of Versteegh et al. 2016.[33] Data on health care use, patient cost, and productivity losses will be elicited through the repeated administration (6-monthly) of standard questionnaires. Questionnaires will be distributed during outpatient visits of patients. Separate analyses for the German and Dutch data will be made, following either Dutch (Zorginstituut Nederland) or German (IQWIG) guidelines for economic evaluation. Data will be presented both from a health care and a societal perspective. Bootstrap methods will be used to present uncertainty around cost-effectiveness estimates using cost-effectiveness planes and acceptability curves. The economic evaluation will have a similar timeframe as the clinical study.

Budget Impact Analysis (BIA)

The design of the budget impact analysis (BIA) will be a study of different scenarios of either or not introducing preventive medication for patients with an aneurysm. The BIA will be based on data collected alongside the clinical study. It will allow estimation of the financial consequences of introduction of both ASA treatment and intensive hypertension control from the perspective of different stakeholders involved. All cost items needed for the BIA will be derived directly from our economic data collection, the valuation of those items depends on the perspective taken for the budget impact analysis. The perspectives to be included in the BIA are (1) net-BKZ or government perspective and (2) the health insurance perspective. Substitution effects, i.e. reduced need for expensive health care after aneurysm rupture will be taken into account. Different scenarios with different levels of implementation of preventive treatments will be analysed and compared, ranging from all patients with a known aneurysm, to patients with larger aneurysms only. The time horizon for the BIA will be 3 years. BIA results will be reported separately for each year within the time horizon and indexation will be applied.

Biometric analysis will be defined in the statistical analysis plan, which has to be authorised before opening the database by the biometrician, the sponsor, and the LKP.

The adjudication committee (PIs and another experts) will review protocol deviations and reach consensus on whether these should be regarded as major or minor, using blinded data if possible.

In addition, this committee will review unclear endpoints, such as sudden deaths and subarachnoid haemorrhage of unknown origin.

Subjects to be included in the analyses are all subjects randomised and thus a full intention to treat analysis.

The additional data provided by patients of the intervention group using blood pressure devices may be displayed in tables for descriptive statistics. They may be examined for their relationship with blood pressure values obtained during trial visits, for description of device utilisation, and for their relationships with outcomes as described above.

9.4 Interim Analyses

The DSMB will review data of two interim analyses on the primary outcome to assess the strength of the efficacy data. The first interim analysis will be carried out after 235 patients have had their 3-year outcome assessment; the second one after 470 patients have these outcome data. The DSMB will also check the assumptions for sample size calculations. The DSMB can recommend the Steering Committee of the PROTECT-U trial to:

- Adjust the sample size
- Early terminate the study when there is clear and substantial evidence of benefit, based on a significant (with alpha 0.1%) reduction in aneurysm growth and rupture (according to the Peto approach of interim analysis with alpha 5% at final analysis); a different stopping rule may be suggested by the DSMB.
- Early terminate the study when there is evidence of severe harm based on SAE reporting, outcome, and case fatality
- Early terminate the study in case accrual rates are too low to provide adequate statistical power for identifying the primary endpoint
- The Steering Committee and the DSMB will agree on the approach to early termination (stopping rules) and the statistical methods used for efficacy evaluation beforehand. This approach will be described in a separate DSMB charter.

After the inclusion of 100, 300 and 600 patients, and if needed after later time points, the proportion of patients with aneurysms <3 mm will be analysed. Patients in this subgroup have the lowest risk of aneurysm growth and rupture. Care should be taken that the proportion of patients with aneurysms <3 mm does not exceed 30% of the total study cohort, so that the power calculation is not jeopardized. With 776 patients to be included, no more than 230 patients with aneurysms <3 mm should be included.

Because the first formal interim analysis will take place after 235 patients reached the 36 months visit, an additional two preliminary interim analyses will be done based on the first 235 and 470 patients, at the timepoint 12 months after randomization of subject 235 and 470 respectively, with all routinely obtained follow-up data available. To this end local reports on aneurysm growth will be used.

Interim analysis reports will be prepared and supported by a member of the data management team of the KKS and then forwarded to the DSMB. The results will not be disseminated inside or outside the study team.

Any subarachnoid hemorrhage will be monitored and an expedited notice will be forwarded to local PIs of all centres, national authorities and ethic committees (if required) and the DSMB, including clinical data that may be significant for assessment of the severity of the bleeding. Depending on the requirements of additional participating countries, other regulatory authorities

will be notified on interim results as well. The safety monitoring intervals will be every half year initially and more frequently as the number of person-years of observation will increase non-linearly. If the lower limit of the 95% confidence interval is higher than 2% rupture rate, the DSMB will recommend to stop the study.

10 DATA MANAGEMENT

10.1 Data Collection

A study specific database will be set up using Clincase ™ and validated for this project with coded information of the participants who are included in the study. After informed consent, subjects will be registered in a secured database managed by the KKS using unique participant identification numbers. The patient ID is composed of a site number and the randomization number generated by the online randomizing tool. Only authorized study personnel will have access. Hence, the names and patient numbers of participants will be replaced by a study code for all study related procedures and will not be directly convertible to the participant. This code list is exclusively possessed by PI and investigators at each trial centre, and saved in a separate, secured database. All data will be collected according to the applicable national data protection, privacy and secrecy laws.

Study data collected in the e-CRF will consist of:

- Study characteristics: study number, date of randomization, treatment allocation.
- Data collected at baseline: date of birth, sex, history of hypertension / ischemic stroke / intracerebral hemorrhage / subarachnoid hemorrhage / myocardial infarction / peripheral vascular disease / polycystic kidney disease, medication use, tobacco smoking history including number of packyears of smoking and current number of cigarettes per day, alcohol use, recent (<6 months) GFR, number of first degree and second degree relatives with an intracranial aneurysm (either unruptured or ruptured), date and type of last aneurysm imaging before randomization, seated blood pressure, number of aneurysms, aneurysm size, aneurysm location, aneurysm shape, EQ-5D-5L.
- Data collected during the trial: smoking status, seated blood pressure, drug adherence (by counting unused tables), occurrence of adverse events, concurrent medication, date(s) and type(s) of subsequent imaging, occurrence of aneurysm growth or rupture during trial according to local investigator, occurrence of cardio-/cerebrovascular outcomes during the trial, EQ-5D-5L.

A detailed list of study data that will be collected will be provided in the Investigator Site File. All entries in the eCRF will be verifiable by source documents. In the source documents it will be mentioned that the patient has been included in an investigational study. The data in the CRF will be consistent between eCRF and source documents. The investigator is responsible for ensuring that all sections of the eCRF are completed correctly and that entries can be verified against source data.

All protocol-required information collected during the trial must be entered by the investigator, or a designated representative, in the eCRF. Patient data will be documented pseudonymously. The investigator, or a designated representative, should complete the eCRF pages as soon as possible after the information is collected, preferably on the same day when a trial subject is seen for an examination, treatment, or any other trial procedure. Any pending entries must be completed immediately after the final examination. Explanation should be given for all missing data. In case of data correction, a reason for change needs to be specified.

The data will be analysed by Dr. D. Verbaan, a clinical epidemiologist with ample experience in the analysis of clinical trial data. Archiving of data of the eCRF will be provided by KKS for long term storage by the sponsor (University Medicine Mannheim, Ruprecht-Karls-University Heidelberg). Data will be kept in storage for 15 years.

10.2 Data Handling

Data entries will undergo an automatized online check for plausibility and consistency. In case of implausibilities, 'warnings' will be produced during data entry (edit checks). A responsible investigator or a designated representative will be obliged either to correct the implausible data or to confirm its authenticity and to give appropriate explanation. The responsible data manager will check all explanations and resolves the warnings if the explanation is appropriate. The responsible monitor can generate special questions (monitor query), that will be send back to the responsible investigator. The investigator or a designated representative will have to answer them all. The responsible monitor will check all answers and resolves the monitor query if the answer is appropriate. Also, the data manager can send queries (DM query).

The investigator has to confirm the accuracy of all data by signing electronically online in the eCRF.

All missing data or inconsistencies will be reported back to the centre(s) and have to be clarified by the responsible investigator prior to database lock. If no further corrections are to be made in the database it will be declared locked and used for statistical analysis.

All data management activities will be done according to the current SOPs of the KKS.

10.3 Archiving of Essential Documents

The investigator(s) will archive all trial data (source data and Investigator Site File (ISF) including subject identification list and relevant correspondence according to the section 4.9 of the ICH Consolidated Guideline on GCP (E6) and to local law or regulations.

The sponsor shall retain all Sponsor Trial Master File documentation for at least 10 years according to the §13 of the German GCP-Ordinance. These procedures shall include:

- The protocol including the rationale, objectives and statistical design and methodology of the trial, with conditions under which it is performed and managed, and details of the investigational product used.
- Standard operating procedures
- The statistics analysis plan
- All written opinions on the protocol and procedures,
- Final report,
- Case report forms (not RDE),
- Audit certificate(s), if available.
- All other relevant documents of the trial master file, according to the ICH-GCP guideline

Any change of data ownership shall be documented. All data shall be made available if requested by relevant authorities.

11 ETHICAL AND LEGAL ASPECTS

11.1 Good Clinical Practice

The procedures set out in this trial protocol, pertaining to the conduct, evaluation, and documentation of this trial, are designed to ensure that all persons involved in the trial abide by ICH harmonised tripartite guideline on Good Clinical Practice (ICH-GCP) and the ethical principles described in the applicable version of the Declaration of Helsinki. The trial will be carried out in keeping with local legal and regulatory requirements.

11.2 Legal bases

The study will be conducted in compliance with the protocol, ICH-GCP and the applicable regulatory requirements.

11.2.1 Declaration of Helsinki

The study will be carried out in conformity with the “Ethical principles for medical research involving human subjects” version 1964 including all amendments. The applicable version for the respective country will be taken into consideration.

11.2.2 Other Legal Bases

The other legal bases of this clinical trial are as follows:

- ICH Topic E6, Guideline for Good Clinical Practice, including post Step 4 errata, September 1997
- Directive 2001/20/EC (April 4, 2001)
- Commission Directive 2005/28/EC (April 8, 2005)
- National regulatory requirements/guidelines of the participating countries concerning Clinical Trials [e.g. German federal drug law (AMG), German GCP ordinance (GCP-Verordnung), Wet Medisch-Wetenschappelijk Onderzoek met Mensen (WMO) which also refers to the Wet Geneeskundige Behandelings Overeenkomst (WGBO).]
- General national regulatory requirements, e.g. Bundesdatenschutzgesetz (BDSG), Wet Bescherming Persoonsgegevens (WBP), the relevant legislation of other participating countries.
- For additional trial centres in other states (e.g. Canada, Finland), the appropriate legal bases, equivalent to the regulations mentioned above for the Netherlands and Germany.
- EU general data protection regulation (GDPR)

The Coordinating Investigators and all investigators will be provided with an investigator’s brochure containing full details of the status of the pre-clinical and clinical knowledge of the study medication or SmPCs. As soon as new information is obtained, an updated version will be supplied.

11.3 Approval of Trial Protocol and Amendments

Before the start of the trial, the trial protocol, informed consent document, and any other appropriate documents will be submitted to the independent Ethics Committee (EC) as well as to the national competent authority.

A written favourable vote of the EC and an (implicit) approval by the competent authority are a prerequisite for initiation of this clinical trial. The statement of EC should contain the title of the trial, the trial code, the trial site, and a list of reviewed documents. It must mention the date on which the decision was made and must be officially signed by a committee member. This

documentation must also include a list of members of the EC present on the applicable EC meeting and a GCP compliance statement.

Before the first subject is enrolled in the trial, all ethical and legal requirements must be met.

All substantial changes will be submitted to EC and the competent authorities in writing as protocol amendments. They have to be signed by the sponsor and statistician and approved by the EC and the competent authority.

11.4 Notification of Regulatory Authorities

In addition to the approval by the competent authority (see 11.3) the clinical trial will be notified to the competent authority before recruitment of the first patient, if required by national law.

The local regulatory authorities responsible for each particular investigator will be informed before the beginning, during and at the end of the trial according to and applicable if required by the applicable national regulations. These responsibilities have been delegated to the KKS for all German sites.

Substantial Amendments, interruption or premature end of the trial will be reported, if applicable.

11.5 Subject Information and Informed Consent

Before being admitted to the clinical trial, the patient must consent to participate after being fully informed by the investigator or a designated member of the investigating team about the nature, importance, risks and individual consequences of the clinical trial and their right, to terminate the participation at any time.

The patient will also have the opportunity to consult the investigator, or a physician member of the investigating team about the details of the clinical trial. The informed consent to participate in the clinical trial may be withdrawn by the patient verbally in the presence of, or in written form directed to, the investigator or a physician member of the investigating team at any time during the trial. The patient must not entail any disadvantage therefore or be coerced or unduly influenced to continue to participate. Furthermore, the patient is not obligated to disclose reasons for the withdrawal of the consent.

If the patient has a primary physician, the investigator will inform him or her about the patient’s participation in the trial, provided the patient agrees hereto.

After reading the informed consent document, the patient must give consent in writing. The patient's consent must be confirmed by the personally dated signature of the patient and by the personally dated signature of the physician conducting the informed consent discussion.

If the patient is unable to write, oral presentation and explanation of the content of the informed consent form and of the data protection information must take place in the presence of an impartial witness. The witness and the physician conducting the informed consent discussions must also sign and personally date the consent document. The witness must not be in any way dependent on the sponsor of the trial, the trial site or any member of the investigating team (e. g. an employee at the trial site).

A copy of the signed informed consent document will be given to the subject; the original will be filed by the investigator. The documents will be in a language understandable to the subject and must specify who informed the subject.

The subjects will be informed as soon as possible if new information may influence his/her decision to participate in the trial. The communication of this information should be documented.

Consent by the study participant:
The Investigator will obtain a freely given written consent from each subject after an appropriate explanation of the aims, methods, anticipated benefits, potential hazards and any other aspect of the study which is relevant to the subject's decision to participate. The informed consent form must be signed, with name and date noted by the subject, before the subject is exposed to any study-related procedure, including screening tests for eligibility.

11.6 Insurance

According to § 40 AMG, the sponsor will subscribe to an insurance policy covering, in its terms and provisions, its legal liability for injuries caused to participating persons and arising out of this research performed strictly in accordance with the scientific protocol as well as with applicable law and professional standards. For Germany, the insurance was taken out at HDI Gerling Industrie Versicherung AG, Niederlassung Düsseldorf (insurance number 57 010321 03010). For centres in the Netherlands, a separate insurance was issued due to different legal requirements in the AMG and the WMO, the insurance company for the Netherlands is HDI Global SE (insurance number: V-057-124-194-9).

For the insurance covering patients in additional countries (such as Canada, Finland), an equivalent insurance will be issued in compliance to local regulations.

Any impairment of health which might occur in consequence of trial participation must be notified to the insurance company. The subject is responsible for notification. The insured person will agree with all appropriate measures serving for clarification of the cause and the extent of damage as well as the reduction of damage.

During the conduct of the trial, the subject must not undergo other clinical treatment except for cases of emergency. The subject is bound to inform the investigator immediately about any adverse events and additionally drugs taken. The terms and conditions of the insurance should be delivered to the subject.

The insurance company has to be informed about all amendments that could affect subjects' safety.

In the event of the extension of this trial to other countries, contracts for insurances according to local legislation will be made.

11.7 Continuous Information to the Ethics Committee and the Competent Authority

Pursuant to the local laws and regulations, the responsible ECs and competent authorities and all participating investigators will be informed of all suspected unexpected serious adverse reactions (SUSARs).

All relevant parties also will be notified in case the risk/ benefit assessment did change or any others new and significant hazards for subjects' safety or welfare did occur. Furthermore, a report on the subjects safety will be submitted once a year if requested by law.

The ECs and the regulatory authorities will be informed of the end of the trial, if required.

12 QUALITY CONTROL AND QUALITY ASSURANCE

The sponsor, the investigators, and all involved study personnel agree to conduct this clinical trial in accordance with the ICH Guideline for Good Clinical Practice.

12.1 Direct Access to Source Documents According to ICH GCP

According to ICH-GCP the investigator(s)/institution(s) must provide direct access to source data/documents for trial related monitoring, audits and regulatory inspection. Each subject has consented - via written informed consent - to direct access to his/her original medical records for trial-related monitoring, audit and regulatory inspection. Content of the protocol must be the identification of any data to be recorded directly on the CRFs (i.e., no prior written or electronic record of data), and to be considered to be source data (see 10.1).

In the absence of either an audit-trail or limited access for the monitor the electronic record of data must be printed out.

12.2 Data Protection

The data obtained in the course of the trial will be treated pursuant to the General Data Protection Regulation (GDPR) und Bundesdatenschutzgesetz, BDSG, in Germany and Wet Bescherming Persoonsgegevens (WBP) in the Netherlands). From May 25th 2018 the General Data Protection Regulation of the EU will be applicable. In case of participation of centres outside of the EU, local data protection legislation will be observed there. No patient related data obtained within the EU will be transmitted outside the EU.

During the clinical trial, subjects will be identified solely by means of their individual identification code (subject number, randomisation number). Trial data stored on a computer will be stored in accordance with local data protection law and will be handled in strictest confidence. Distribution of these data to unauthorised persons has to be prevented strictly. The appropriate regulations of local data legislation will be fulfilled in its entirety.

The subject consents in writing to release the investigator from his/her professional discretion in so far as to allow inspection of original data for monitoring purposes by health authorities and authorised persons (inspectors, clinical monitors, auditors). Authorised persons (inspectors, clinical monitors, auditors) may inspect the subject-related data collected during the trial ensuring the data protection laws (specifically: Wet Bescherming Persoonsgegevens (WBP) in the Netherlands, DS-GVO and BDSG in Germany, other legislation may apply in other countries such as Canada or Finland).

The investigator will maintain a subject identification list (subject numbers with the corresponding subject names) to enable records to be identified. Subjects who did not consent to circulate their pseudonymised data will not be included into the trial.

This protocol, the CRFs and other trial-related documents and material must be handled with strict confidentiality and not be disclosed to third parties except with the express prior consent of Sponsor. In particular, it must be ensured that the study medication is kept out of reach of third parties. Staffs of the investigators involved in this study are also bound by this agreement.

12.3 Monitoring

Monitoring will be done by on-site and off-site visits and frequent communication (letters, telephone, fax, e-mail) by a clinical monitor. The monitor will ensure that the trial is conducted according to the protocol and regulatory requirements by review of source documents, entries into the CRFs and essential documents. Therefore, the investigator must allow the monitor to verify these documents (s. also 12.1) and must provide support to the monitor at all times. The

monitor will document the visits in a report for the sponsor. The site will be provided with a follow-up letter of the findings and the necessary actions to be taken.

As the monitoring strategy will consider current aspects of risk based quality management, frequency of monitoring activities per site will vary depending on recruitment, experience, and general performance, e.g. quality of documentation of the individual trial sites. Details of monitoring will be defined in the monitoring manual.

If there are major findings during monitoring or an audit, the investigational site might be closed.

12.4 Inspections and Audits

Regulatory authorities and/ or auditors authorised by the sponsor may request access to all source documents, CRFs, and other trial documentation. Direct access to these documents must be guaranteed by the investigator who must provide support at all times for these activities.

The investigator will inform the sponsor immediately about a planned inspection.

12.5 Responsibilities of the Investigator

The investigator ensures that all team members are informed adequately about the protocol, all amendments to the protocol, the study procedures und study specific duties and tasks.

The investigator will maintain a list to delegate tasks to the team members.

13 ADMINISTRATIVE AGREEMENTS

13.1 Financing of the Trial

The trial will be financed by using funds of the Dr. Rolf M. Schwiete Foundation, Mannheim, Germany, Dutch Heart Foundation, The Netherlands, and the Phoenix Foundation, The Netherlands. Additional funding will be obtained during the course of the trial from local funding institutions in the different states involved. Also, the use of grants from individual contributions will be considered, provided that accepting such contributions will not interfere with the goals of the trial nor the independence of the scientists involved.

Financial Disclosure

Before the start of the trial, the investigator will disclose to the sponsor any proprietary or financial interests he or she might hold in the sponsor/ a funding company, in the investigational product(s) or any commercial organisation being involved in the clinical trial. The investigator has also to confirm that he/she has not entered into any financial arrangement, whereby the value of compensation paid could affect the outcome of the clinical trial.

The investigator agrees to update this information in case of significant changes.

13.2 Reports

Within one year of the completion of the trial, the competent federal authority and the ethics committee will be supplied with a summary of the final report on the clinical trial containing the principle results according to §42 AMG. Similar reports in accordance to local requirements will be issued in other countries, as applicable.

13.3 Registration of the Trial

The trial has been registered at the EudraCT database (2017-000514-35) and at ClinicalTrials.gov (NCT03063541). In the event of approval of trial sites outside the European Union (e.g. Canada), additional registrations required by local law will be carried out. The responsibility for updating data and adding results into these databases lies with the Principal Investigator.

13.4 Publication

All information concerning the trial is confidential before publication.

Results of the study will be submitted for publication in scientific journals and be presented at national and international conferences. Study results will be published and/or presented after appropriate time for review and written agreement by the sponsor. The sponsor will be provided with a draft of the abstract and/or manuscript for review and editorial comments at least 30 days prior to submission and/or presentation. Neither the sponsor nor the Coordinating Investigator has the right to prevent publication, except for patent or copyright purposes.

Study data published or disclosed to third parties must not contain data that allow the identification of a subject.

KKS staff members who gave relevant scientific support to the study design, conductance and/or analysis of results will be included as coauthors or listed in the appendix, if applicable. A copy of all publications will be sent to the KKS.

14 SIGNATURES

The present trial protocol was subject to critical review and has been approved in the present version by the persons undersigned. The information contained is consistent with:

- the current risk-benefit assessment of the investigational medicinal product,
- the moral, ethical, and scientific principles governing clinical research as set out in the latest relevant version of Declaration of Helsinki, the principles of the guidelines of ICH Good Clinical Practices and the applicable legal and regulatory requirements.

The investigator will be supplied with details of any significant or new finding including AEs relating to treatment with the investigational medicinal product.

It will be ensured that the first subject is enrolled only after all ethical and regulatory requirements are fulfilled. Written consent from all subjects is received after detailed oral and written information and according to the requirements of local law. I confirm that all study participants will be informed on the type of encoding their personal data (pseudonymization) and who receives or has access to such data. Subjects who do not agree to this data encoding and transfer will not be enrolled into the trial. In this context it will be assured that all investigational sites comply with the local regulatory requirements for data protection.

Sponsor/ Sponsor representative states that it is not planned to include subjects in a relationship of any dependence to the investigator or sponsor.

Via current versions of the clinical trial protocol and the SmPC it will be ensured that all principal investigators are informed about the pharmacological-toxicological assessments and results regarding the benefits and risks of the clinical trial.

Date:	_____	Signature:	_____
		Name (block letters):	Prof. Dr. Nima Etminan
		Role:	Sponsor Representative delegated by internal IIT contract and LKP according to §40 AMG
Date:	_____	Signature:	_____
		Name (block letters):	Dr. Mervyn Vergouwen
		Role:	Coordinating investigator NL
Date:	_____	Signature:	_____
		Name (block letters):	Dr. Dagmar Verbaan
		Role:	Clinical Epidemiologist, Trial Biometrician

15 DECLARATION OF INVESTIGATOR

I have read the above trial protocol and confirm that it contains all information to conduct the clinical trial. I pledge to conduct the clinical trial according to the protocol.

I will enrol the first subject only after all ethical and regulatory requirements are fulfilled. I will obtain written consent for trial participation from all subjects after detailed oral and written information and according to the requirements of local law I declare that all study participants will be informed on the type of encoding their personal data (pseudonymisation) and who receives or has access to such data. Subjects who do not agree to this data encoding and transfer will not be enrolled into the trial. In this context I confirm that my investigational site complies with all local regulatory requirements for data protection.

Furthermore, I declare that to the best of my knowledge no subjects in a relationship of any dependence to the investigator or sponsor will be included.

I know the requirements for accurate notification of serious adverse events and I pledge to document and notify such events as described in the protocol.

I declare that I am informed about the pharmacological-toxicological assessments and results regarding the benefits and risks of the clinical trial by reading the description in the clinical trial protocol and in the current version of the IB/ SmPC). I ensure that all investigators/ relevant staff at my site will be informed of this results and possibly new risks that are forwarded by the sponsor later on (e.g. via new version of the IB/ SmPC).

I confirm that every staff will be adequately trained to guaranty compliance to the trial protocol incl. subsequent amendments.

I will retain all trial-related documents and source data as described. I will provide a Curriculum Vitae (CV) before trial start. I agree that the CV and Financial Disclosure (FD) may be submitted to the responsible EC.

As the clinical trial and the results have to be published in a clinical trial register and forwarded to the EC and competent authorities I agree that my name and clinic address will be part of this final trial (summary) report/ public register and are disclosed.

Date: _____ Signature: _____

Name (block letters): _____

Role: Principal Investigator (PI)

Investigational Site (location): _____

Date: _____ Signature: _____

Name (block letters): _____

Role: Deputy of the PI (if applicable)

16 REFERENCES

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9. Kotowski, M. et al. Safety and occlusion rates of surgical treatment of unruptured intracranial aneurysms: a systematic review and meta-analysis of the literature from 1990 to 2011. *J.Neurol.Neurosurg.Psychiatry* (2012).

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17 APPENDICES

Highly-effective contraceptive methods

Declaration of Helsinki (applicable Version)

Appendix 1

Highly-effective contraceptive methods (this may also apply to the trial subject's partner depending on the investigational product (IMP)).

The following contraceptive methods with a Pearl Index lower than 1 are regarded as highly-effective:

- Oral hormonal contraception ('pill') (as far as its efficacy is not expected to be impaired during the trial, e.g. with IMPs that cause vomiting and diarrhoea or interfere with hormone metabolism, adequate safety cannot be assumed)
- Dermal hormonal contraception (e.g. contraceptive patch)
- Vaginal hormonal contraception (NuvaRing®)
- Long-acting injectable contraceptives
- Implants that release progesterone (Implanon®)
- Tubal ligation (female sterilisation)
- Intrauterine devices that release hormones (hormone spiral)
- Double barrier methods

This means that the following are not regarded as safe: condom plus spermicide, simple barrier methods (vaginal pessaries, condom, female condoms), copper spirals, the rhythm method, basal temperature method, and the withdrawal method (coitus interruptus).

The obligation to ensure effective contraception is based on Guideline ICH E8 Chapter 3.2.2.1 Selection of subjects together with ICH M3 Note 4.