REVACEPT, AN INHIBITOR OF PLATELET ADHESION IN SYMPTOMATIC CAROTID STENOSIS: A PHASE II, MULTICENTRE; RANDOMISED, DOSE-FINDING, DOUBLE-BLIND AND PLACEBO-CONTROLLED SUPERIORITY STUDY WITH PARALLEL GROUPS

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1. SYNOPSIS

This summary reports the results of a prospective, randomized, placebo-controlled, double-blind explorative phase II study in 158 patients with recent ischemic stroke/TIA and carotid artery stenosis. All patients were under guideline conform anti-platelet therapy and underwent carotid artery endarterectomy (CEA; 80.4% of all patients), carotid artery stenting (CAS, 7.6%) or best medical therapy (BMT, 12.0%).

Efficacy endpoints were microembolic signals by transcranial Doppler (MES-TCD), diffusion-weighted imaging magnetic resonance imaging (DWI-MRI) and clinical endpoints for ischemic complications (myocardial infarction and coronary intervention, TIA and stroke). Safety endpoints were bleedings according to the RE-LY criteria and further safety aspects (vital signs, ECG, adverse event, laboratory values and use of concomitant medication), All adverse events were investigated for 90 days and with a 365 day telephone interview follow-up in an explorative manner. 53 patients received 120 mg Revacept, 54 patients 40 mg Revacept and 51 patients placebo by a single IV infusion.

The number of infarctions in the brain (DWI-MRI lesion) was reduced by 46% in the 120 mg Revacept group compared to placebo (10% reduction with Revacept 40 mg). 23% fewer patients suffered from new brain infarcts with 120 mg Revacept compared to placebo-treated patients (no positive effect with 40 mg Revacept). TCD-MES could not be analysed appropriately, because their incidence upon study inclusion was less than 50% in all groups – on the basis of a very small number comparison, there was no effect on MES-TCD number or incidence in patients. The time to any critical event risk (combined any stroke & TIA, myocardial infarction & PCI, death and any bleeding) was significantly reduced by 54% (hazard ratio 0.46, p = 0.047) with 120 mg Revacept and 28% (hazard ratio 0.72, p=0.343) with 40 mg Revacept. In patients with carotid stenosis of > 70% ECST criteria (n=116) the time to combined any critical event risk was significantly reduced by 66% (hazard ratio 0.34, p= 0.027) with 120 mg Revacept and 53% (hazard ratio 0.47, p= 0.081) with 40 mg Revacept. The combined rate of clinically apparent any strokes and TIA trended to be reduced up to 90 days after the intervention: 7.5% of patients treated with 120 mg Revacept experienced a recurrent TIA or any stroke, 11.1% in the Revacept 40 mg group and 11.8% in the placebo group (36% risk reduction 120 mg vs placebo). The combined rate of myocardial infarctions and coronary intervention was not affected at 90 days (5.9% of patients with placebo, 3.7% of patients with 40 mg Revacept, 5.7% with 120 mg Revacept). Any bleeding within 90 days occurred in 9.4 % patients treated with 120 mg Revacept, in 11.1% of those with 40 mg Revacept and in 15.7% of those with placebo. Most of the bleedings were postoperative bleedings which tended to be more frequent in placebo-treated patients compared to Revacept. Major bleeding complications (according to the RE-LY criteria) within 90 days occurred in 4 patients (7.5%) in the 120 mg Revacept group, 6 patients (11.1%) in the 40 mg Revacept group and 5 patients (9.8%) in the placebo group. One patient had intra-cerebral bleeding with 40 mg Revacept, and one with placebo, one patient a sub-arachnoidal bleeding with placebo. Two patients died in the Revacept 120 mg group 88 days and 216 days after study drug exposure. A causality of Revacept with the death of the patients seems highly unlikely (almost 13 times of the half-life of Revacept). There were no signs for alterations in the immune system such as more infections or signs for auto-immune diseases or wound healing complications after surgery. No laboratory value abnormalities and no anti-drug antibodies were measured in any of the patient samples.

The study was evaluated as exploratory study not powered for statistical significance. The overview of the risk ratios for all evaluated parameters showed values of 1 or below 1 which speak in favor of Revacept. There was a strong trend for efficacy for 120 mg Revacept in DWI-MRI lesions/minor strokes and a significant reduction of the combined safety and efficacy endpoint including bleeding in all patients and particularly in patients with more severe carotid disease. In summary, Revacept has the potential to reduce brain

infarctions due to the underlying atherothrombosis and the peri-interventional stroke risk at short term with a prolonged protection after a single IV infusion without increase in bleeding. Revacept might be useful for secondary prophylaxis of ischemic complications in patients with cerebro-vascular disease after stroke especially with surgical or interventional procedures and more severe carotid artery stenosis.

Surprisingly, no bleeding alterations for any bleeding, major bleeding and intracranial bleeding occurred despite Revacept was given on top of treatment to the basal guideline conform anti-platelet medication and during surgical and catheter-based vascular intervention. Therefore, Revacept seems the first plaque-specific thrombus inhibitor without general impairment of haemostasis.

2. TABLE OF CONTENTS

4. LIST OF ABBREVIATIONS

ADP	Adenosine Diphosphate
AE	Adverse event
ASA	Acetyl-Salicylic Acid
aPTT	Activated partial thromboplastin time
BMI	Body Mass Index
BMT	Best Medical Treatment
BP	Blood Pressure
CAS	Carotid Artery Stenting
CCT	Cranial Computed Tomography
CK-MB	Creatine Kinase Myocardial Band
CRF	Case Report Form
CT	Computed Tomography
CV	Curriculum Vitae
dl	decilitre
DWI	Diffusion-Weighted Imaging
ECST	European Carotid Surgery Trial
ECG	Electrocardiogram
GCP	Good Clinical Practice
GPVI	GlycoProtein VI
HbA1c	Haemoglobin A1c
Hr or hrs	hour or hours
IMP	Investigational Medicinal Product
INR	International normalisation ratio
ITT	intention-to-treat
IV	IntraVenous
kg	kilogram
l	litre
LDL	Low-Density Lipoprotein
MES	MicroEmbolic Signals
µmol	micromole
MI	Myocardial Infarction
mmHg	millimetre of mercury
MRI	Magnetic Resonance Imaging
MRS	Modified Rankin Skale
NIHSS	National Institute of Health Stroke Scale
NMR	Nuclear Magnetic Resonance
NOAC	Novel Anti-Coagulant
NRES	National Research Ethics Service
p	Probability
PCI	Percutaneous Coronary Intervention
PFA	Platelet Function Analyser
PK	PharmacoKinetics
PP	Per Protocol
PTT	partial thromboplastin time
SAE	Serious adverse event
SAH	SubArachnoid Haemorrhage
SD	Standard Deviation
STEMI	ST-Elevation Myocardial Infarction
SUSAR	Suspected Unexpected Serious Adverse Reaction
TCD	TransCranial Doppler
TIA	Transient Ischaemic Attack
TRAP	Thrombin Receptor-Activating Peptide
TUM	Technische Universität München
V	Visit

5. ETHICS

This study was conducted in accordance with the ethical principles that have their origins in the Declaration of Helsinki and that are consistent with Good Clinical Practices and applicable regulatory requirements.

The study and all substantial amendments were reviewed by an Independent Ethics Committee in the United Kingdom: NRES Committee East of England – Cambridge South, The Old Chapel, Royal Standard Court, Nottingham, NG16FS and the lead Ethics Committee Germany: Ethikkommission der Fakultät für Medizin der Technischen Universität München, Ismaninger Straße 22, 81675 München.

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7. INTRODUCTION

Patients suffering from TIA or stroke because of relevant carotid artery stenosis are at 30-35 % risk of experiencing recurrent strokes within the following 5 years and are advised to undergo vascular surgery in order to reduce the risk of future brain infarction[1]. In addition to surgical carotid endarterectomy (CEA) or carotid stenting (CAS), administration of antiplatelet agents also favours event free survival in patients undergoing carotid endarterectomy (CEA) [2] and in patients with symptomatic carotid stenosis [3].

Additional risk is due to the intervention at the carotid artery stenosis with ischemic events caused by the iatrogenic thrombogenic surface (stent or surgical neointima). Risk of peri-procedural ischemic stroke was 5.8% after CEA and 8.9 % after CAS in a meta analysis of EVA-3S, SPACE and ICSS studies [4]. Although current anti-platelet agents do reduce the risks for recurrent stroke during and after CEA and CAS, their use is associated with potentially life-threatening bleeding complications. It is therefore highly desirable to develop novel therapeutic strategies that selectively inhibit thromboembolisation at the site of vascular stenosis whilst not compromising systemic haemostasis.

Such selectivity can be achieved by targeting structures that differ between healthy and atherosclerotic vasculature. Collagen is an important component of the extracellular

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matrix of arterial walls and thus shielded from the blood stream by the vascular endothelium under normal conditions. Upon vascular injury or atherosclerotic transformation, however, collagen becomes increasingly exposed to the arterial lumen where it triggers platelet aggregation by activating the GPVI receptor on thrombocytes [5]. By masking collagen exposure to the blood stream at the site of atherosclerotic plaques rather than directly inhibiting thrombocytes, one could prevent local thrombosis without jeopardising systemic platelet functions and coagulation. This is the strategy investigated in this clinical trial. Revacept is a protein that is made up of an Fc (fragment crystallisable) fragment fused to the GPVI receptor (an endogenous platelet collagen receptor). Consequently, Revacept binds to its ligand (collagen) on atherosclerotic plaques preventing circulating thrombocytes from binding to collagen exposed by the injured plaque. In addition, Revacept inhibits binding of von Willebrand factor (vWF) to collagen, thus impacting on local platelet activation via glycoprotein Ib [6]. Most importantly, Revacept does not impair general thrombocyte activity in animal models [7] and in healthy humans in a phase I study [8].

The mode of action of Revacept was studied in animal models in great detail [7, 9, 10]. When arterial lesions were induced in mice models of atherosclerosis, Revacept was effective at preventing platelet adhesion and thrombus formation at these sites without affecting bleeding time. Furthermore, bleeding times were not additionally increased when Revacept was combined with conventional antiplatelet agents such as ASA, clopidogrel and heparin. Further preclinical investigation showed that Revacept strongly inhibits human plaque-induced thrombosis in ex vivo superfusion models using human patient blood and plaques taken during carotid surgery [11].
Furthermore, Revacept is characterised by a promising pharmacovigilance profile with no toxicities or signs of aberrant immune activation detected in preclinical animal studies even after repeated dosing.

Following these encouraging preclinical studies, safety and tolerability of Revacept was investigated in a first-in-man study [8]. In a phase I clinical trial, 30 human volunteers received a single intravenous dose of Revacept ranging between 10-160 mg. All investigated doses were well tolerated, no drug-related side effects occurred and no bleeding complications. Moreover, no anti-Revacept antibodies were produced and favourable pharmacokinetic and pharmacodynamic profiles were observed.

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8. STUDY OBJECTIVES

It was the aim of the present study to evaluate safety and efficacy of Revacept in patients with high risk of arterial thrombosis with unstable or ruptured atherosclerotic plaques. Patients with symptomatic carotid artery stenosis undergo surgical, endovascular interventions or best medical therapy as a guideline-conform treatment to reduce future ischemic events.
It was the hypothesis of this study that Revacept can reduce the generation of naturally occurring arterial thromboses by the underlying cerebro-vascular disease. Moreover, during CEA and CAS iatrogenic ischemic events occur by additional platelet thrombi arising from the thrombogenic surface of either the stent or the neointima generated by the surgical procedure. The safety of Revacept should be established and particularly the bleeding complications in patients with extensive cerebro-vascular disease should be closely monitored. Especially bleedings with the combinations of guideline conform anti-platelet and anticoagulant medications in the context of surgical interventions should be evaluated.

Therefore, Revacept was tested as a secondary prophylaxis for arterial thrombosis and consecutive ischemic events with the aim of developing a plaque-selective platelet inhibitor without additional bleeding complications.

9. INVESTIGATIONAL PLAN

9.1 Overall study design

Number of centers:	16 active centers
Randomized:	Yes
Blinded:	double-blinded
Design:	Phase II study
Dosing:	Dose-finding - 2 doses
Placebo controlled:	Yes
Strata:	Yes - anti-platelet therapy prior to screening - statin therapy prior to screening - 50-70% or > 70% ECST carotid stenosis
Treatments:	Placebo 40 mg Revacept 120 mg Revacept

This was a prospective, double-blind, placebo-controlled, randomised phase II study. Eligible subjects were randomised 1:1:1 to one of three treatment groups, placebo, Revacept 40 and Revacept 120 mg as a single IV infusion and underwent endpoint evaluations. Follow ups were scheduled one and three days after treatment, and 3 and 12 months after treatment.

9.2 Discussion of study design and choice of control groups

Patients had a more than 50% carotid artery stenosis according to ECST and suffered from ischemic stroke, transitory ischemic attack or intermittent blindness (amaurosis

fugax) within the last 30 days. All patients were on standard medication with aspirin or clopidogrel and received heparin for thrombosis prophylaxis. Carotid endarterectomy (CEA), carotid stenting (CAS) or best medical therapy for treatment of the carotid stenosis and prevention of secondary thrombo-emboli was performed according to guidelines. Additional treatment with Revacept or placebo was done on top of the standard therapy. Therefore the control group receiving placebo was already on the standard medical therapy for patients with symptomatic carotid stenosis and received also the guideline conform interventions CEA, CAS or best medical therapy.

Secondary prophylaxis of thrombo-embolic ischemic events by Revacept should be investigated. Therefore microemboli were detected by transcranial Doppler and ischemic brain lesions were investigated by diffusion weighted imaging magnetic resonance imaging (DWI-MRI) scan as exploratory endpoints. Moreover clinical endpoints such as stroke, TIA, myocardial infarction, coronary intervention and death were investigated at 1 week, 3 months and 12 months follow-up. Safety was closely monitored with emphasis on bleeding complications as bleeding is the most dreaded complication of anti-thrombotic agents especially in patients with cerebral strokes.

9.3 Selection of study population

9.3.1 Inclusion criteria

- Signed written informed consent
- Extracranial carotid artery stenosis (diagnosed by vascular duplex ultrasound peak flow or angiography)

  Lesions with ≥ 50 % stenosis according to the European Carotid Surgery Trial (ECST) criteria
- TIA, amaurosis fugax or stroke within the last 30 days
- Age and sex: Men and women aged >18 years

9.3.2 Main Exclusion Criteria

- Women who were unwilling or unable to use an acceptable method to avoid pregnancy for up to 4 weeks after receiving investigational product, were pregnant or breastfeeding
- NIHSS score > 18
- Recent intracerebral haemorrhage by X-ray computed tomography (CT) or nuclear magnetic resonance (NMR)
- Cardiac cause of embolisation (atrial fibrillation or other cardiac source e.g. artificial heart valves)
- History of hypersensitivity, contraindication or serious adverse reaction to inhibitors of platelet aggregation, hypersensitivity to related drugs (cross-allergy) or to any of the excipients in the study drug
- History or evidence of thrombocytopenia (<30.000/µl), bleeding diathesis or coagulopathy (pathological international normalised ratio (INR) or activated partial thrompoplastin time (aPTT))
- Thrombolysis within the last 48 hours
- Relevant haemorrhagic transformation as determined by CT, NMR or anamnesis
- Oral anticoagulation or dual anti-platelet therapy with aspirin or clopidogrel and

other P2Y inhibitors at screening (3 days for dipyridamole extended release; 8 hours for tirofiban/Aggrastat)

- Sustained hypertension (systolic BP >179 mmHg or diastolic BP >109 mmHg), hypertensive patients shall be treated in accordance with current guidelines for the management of arterial hypertension
- History of severe systemic disease such as terminal carcinoma, renal failure (or current creatinine >200 µmol/l), cirrhosis, severe dementia, or psychosis
- Current severe liver dysfunction (transaminase level greater than 5-fold over upper normal range limit)
- Active autoimmune disorder such as systemic lupus erythematosus, rheumatoid arthritis, vasculitis or glomerulonephritis
- Known atrial fibrillation or other clinically significant ECG abnormalities (at present)

Other Exclusion criteria

- Inability to provide informed consent (except for patient's legally responsible representative)
- Acoustic window that did not allow for TCD recording
- Participation in any other interventional study within less than 30 days prior to screening
- Suspected poor capability to follow instructions and cooperate
- Prisoners or subjects who were involuntarily incarcerated
- Subjects who were compulsorily detained for treatment of either a psychiatric or physical illness (e.g. infectious disease)
- Ongoing drug or alcohol abuse

10. STUDY SCHEDULE

							Follow Up	
	Screening	Randomisation	Treatment (T)	T +24 hrs (±22 hrs)	CEA T + 3 d (-69 hrs/+5d)	CEA + 24 hrs (±12 hrs)	T+ 3 m (±1 m)	T + 12 m (±1 m)
Procedure Visit	1	-	2	3	4	5	6	7
Informed consent	x							
Randomisation		x						
Study medication (Revacept or placebo)			X					
CEA or other intervention					x^r			
CEA / intervention outcome						x^r		
Assessment of wound healing Complications						x^r	x	
Anamnesis	x							
Concomitant medication	x		X	x	X	x	x	
Physical examination	x^r		X	x	x^r	x^r	x	

Adverse events		X	x	X	x	x	
MRS, Barthel Index		x^r				x	
NIH Stroke Scale		x^r			x^r	x	
Clinical outcome						x	x
TCD	x		x				
Electrocardiogram	x^r		x		x^r	x	
DWI-MRI	$x^{a,r}$				x		
Laboratory Tests	Biochemistry	x^r		x^r		x^r	x	
	Haematology / Bleeding	x^r		x^r		x^r	x	
	Coagulation	x^r		x^r		x^r	x	
	Urinalysis	x^r		x^r		x^r	x	
	In vitro bleeding time (PFA100) and aggregation		x*	x*	x*		x*	
	Pregnancy test	x						
	Pharmacokinetics (selected patients)		x^b	x^c	x^c		x^e	
	Anti-drug antibodies		X				x	

[r]routine assessment / blood sampling
* where feasible
[a]eligible patients only
[b]drawing times: t0 prior to IMP administration, t 0.5h 30 mins (±5 mins) after start of IMP infusion, t 6h: 6 h (±1 hr) after start of IMP infusion
[c]drawing time: t24h (±4 hrs) after start of IMP infusion
[d]drawing time: t3d (±48hrs) after start of IMP infusion
[e]drawing time: t3m (±1month) after start of IMP infusion