TRIAL PROTOCOL

VIPER STUDY: **VI**TRECTOMY **P**LUS **E**NCIRCLING BAND VS. VITRECTOMY ALONE FOR THE TREATMENT OF PSEUDOPHAKIC **R**ETINAL DETACHMENT

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Trial protocol code: VIPER

ISRCTN: wird nachgetragen

EudraCT number: n/a

VIPER Study Protocol, Version V5-11 of 24.03.2011

The information in this trial protocol is strictly confidential. It is for the use of the Principal Coordinating Investigator, investigators, trial personnel, ethics committees, the authorities, and trial subjects only. This trial protocol may not be passed on to third parties without the express agreement of the Principal Coordinating Investigator.

This protocol was written based on the template provided by G. Grass (Ethics Committee University of Cologne, guido.grass@uni-koeln.de) and C. Weiß (Center for clinical trials Cologne / Retina.net Coordination, claudia.weiss@zks-koeln.de)

Signatures

Prof. Dr. P. Walter		
Principal Coordinating Investigator	Signature	Date
PD Dr. Martin Hellmich		
Statistician	Signature	Date
Institute for Medical Statistics, Informatics and Epidemiology, University of Cologne		
Dr. Claudia Weiß		
Scientific Advice	Signature	Date
Dr. Endrik Limburg		
Scientific Advice / support of trial management	Signature	Date
Clinical Trials Center, University of Cologne		

I. Synopsis

Sponsor:	Not applicable
Principal Coordinating Investigator:	Prof. Dr. P. Walter Department of Ophthalmology University Hospital Aachen RWTH Aachen University Pauwelsstr. 30 D-52074 Aachen
Title of the clinical trial:	VIPER Study: Vitrectomy plus encircling band vs. vitrectomy alone for the treatment of pseudophakic retinal detachment
Indication:	Treatment of pseudophakic retinal detachment
Phase:	Phase IIb/III (non AMG / non MPG)
Type of trial, trial design, methodology:	Multicentre, multinational randomised controlled trial: (C) 20 gauge vitrectomy with encircling band versus (E1) 20 gauge vitrectomy without encircling band versus (E2) 23/25 gauge vitrectomy.
Number of subjects:	100 patients in groups (C) and (E1), 33 in group (E2).

Primary trial objective:	To investigate the efficacy of an encircling band in addition to a 20 gauge vitrectomy with gas in the treatment of pseudophakic retinal detachments. The primary endpoint is the absence of any situation leading to an additional retina re-attaching surgical procedure during the follow-up.
Study endpoints:	Primary endpoint: • Absence of an indication for any retina reattaching procedure during the follow-up of 26 weeks; such procedures are additional gas injections, additional vitrectomy or additional buckling procedure Secondary endpoints: • Visual acuity at the end of follow-up as measured by ETDRS charts • Refractive status • Anatomical situation of the anterior and posterior segment • Retina reattachment rate • Occurrence of PVR • Occurrence of adverse events • Number of retina specific procedures to achieve a stable retinal attachment Other variables: • Operation time (time between cut and suture) • Postoperative pain

Criteria for evaluation:

Efficacy:

- Documentation of surgical procedures, visual acuity, refraction status, slitlamp examination and fundus appearance as documented by fundus photography.

Safety:

- Iatrogenic breaks / macular hole, macular edema, macular pucker, ocular hypertony (at week 26), diplopia, choroidal hemorrhage, pain medication, enucleation, death.
- Other adverse events reported by the patients or observed by the investigators.

Medical condition and principal inclusion criteria:	Medical condition or disease to be investigated: • Pseudophakic retinal detachment Principal inclusion criteria: • Age: 18 years or older • Pseudophakic rhegmatogenous retinal detachment not suitable for buckling surgery • Agreement of the patient to participate in the trial • Written informed consent of the patient Principal exclusion criteria: • Manifest uveitis • Uncontrolled glaucoma • Active retinal vascular disease • Malignant intraocular eye tumours • History of cataract surgery less than 3 months ago • History of any other intraocular surgery other than cataract surgery • Giant retinal tears • PVR grade B or C • Inability to understand the rationale of this trial or the study aim • Participation in another clinical trial (less than 3 months ago) • Aphakia • Systemic disorders preventing the participation of control examinations during the follow-up • Systemic disorders not compatible with the local periocular or general anesthesia

Treatments under investigation:	(E1) Surgical therapy of pseudophakic retinal detachment with encircling band and 20 gauge vitrectomy with gas; (E2) Comparison with small gauge (23 or 25G) vitrectomy.
Comparator:	(C) Surgical therapy of pseudophakic retinal detachments by 20 gauge vitrectomy with gas without encircling band
Duration of treatment:	The treatments under investigation have a mean duration of 70 minutes, the comparator a mean duration of 60 minutes.
Time plan:	First patient first visit (FPFV): *03/2011* Last patient first visit (LPFV): *03/2012* Last patient last visit (LPLV): *9/2012* Final study report: *12/2012*
Statistician:	PD Dr. Martin Hellmich Institute for Medical Statistics, Informatics and Epidemiology University of Cologne Kerpener Str. 62 50937 Cologne Germany

Statistical methods:	*Randomisation will be stratified by surgeon (permuted blocks of varying length) implemented using a 24/7-Internet-service. As fallback procedure sequentially numbered opaque envelopes may be provided containing the allocation details.*The primary (superiority) and secondary (non-inferiority) objectives will be evaluated by Cochran-Mantel-Haenszel methods stratified by surgeon. For the exploratory comparison of (C) and (E2) a non-inferiority margin of 1.25 (odds ratio) will be employed. All randomised patients will be analysed (intention-to-treat principle). A missing primary endpoint is considered a treatment failure.
GCP conformance:	The present trial will be conducted in accordance with the valid versions of the trial protocol and the internationally recognised Good Clinical Practice Guidelines (ICH-GCP), including archiving of essential documents.
Financing:	The present trial is performed under the auspices of the retina.net and therefore supported by the retina.net coordination office at the Clinical Trials Center Cologne. Financial support for the retina.net coordination office is given by Jackstaedt Stiftung, Retinologische Gesellschaft and Deutsche Ophthalmologische Gesellschaft. There is no financial support for the trial.

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III. Abbreviations

abbreviation	meaning
AE	Adverse Event
BfArM	Federal Institute for Drugs and Medical Devices (Bundesinstitut für Arzneimittel und Medizinprodukte)
BSS	Balanced salt solution
C	Control Group
CRF	Case Report Form
DMC	Data Monitoring Committee
E1	Experimantal Group 1
E2	Experimantal Group 2
ETDRS	Early treatment of diabetic retinopathy study
GCP	Good Clinical Practice
IOL	Intraocular lens
IOP	Intraocular pressure
LKP	Principal Coordinating Investigator (PCI, Leiter der klinischen Prüfung)
n/a	Not applicable
PEI	Paul-Ehrlich-Institut
PPV	Pars plana vitrectomy
PVR	Proliferative vitreoretinopathy
PRD	Pseudophacic retinal detachment
RD	Retinal Detachment

RPE	Retinal pigment epithelium
RWTH	Rheinisch Westfälische Technische Hochschule
SAE	Serious Adverse Event
SPR trial	Primary vitrectomy vs. scleral buckling for rhegmatogenous RD
SUSAR	Suspected Unexpected Serious Adverse Reaction

1. Introduction

Pseudophakic retinal detachment (PRD) can be treated either by scleral buckling alone or by primary vitrectomy. The SPR trial showed that the outcome of patients with PRD treated with primary vitrectomy is better than those treated with scleral buckling. However, it remains unclear whether the use of an additional encircling band improves the outcome of the vitrectomy for PRD. With the broader use of transconjunctival small incision vitrectomy techniques an encircling band is not anymore possible. It is not known if the outcome of small gauge vitrectomy in the treatment of patients with PRD is comparable to the “older” technique. These two questions are addressed in this multicentre randomised controlled trial. The control group (C) consists of PRD patients treated with 20 gauge vitrectomy alone whereas the experimental group 1 (E1) consists of PRD patients treated with 20 gauge vitrectomy plus encircling band. The experimental group 2 (E2) consists of PRD patients treated with 23 or 25 gauge vitrectomy without encircling band. The outcome of both experimental groups will be compared with the outcome of the control group. Primary outcome parameter is the absence of any situation leading to further retina re-attaching procedures during the follow up of 26 weeks. Secondary outcome parameters are visual acuity, retinal re-attachment rates, complications, and adverse events.

2. Objectives of the clinical trial

2.1. Rationale for the clinical trial

The incidence of retinal detachment in pseudophakic eyes after phacoemulsification is on average about 1% in the first year (*Lois & Wong*: Surv Ophthalmol 48; 467-87, 2003). With 600,000 cataract procedures per year in Germany it could be estimated that 6,000 cases of retinal detachment do occur. Three treatment options are currently used: Scleral buckling, primary vitrectomy or a combination of both. These methods have their specific risk and complication profiles and have mostly been compared in retrospective non-randomised trials. Brazitikos and co-authors published data of a prospective randomised trial comparing vitrectomy alone with scleral buckling for pseudophakic retinal detachment in 150 patients with a postoperative follow-up of 1 year (*Brazitikos et al*: Retina 25; 957-64, 2005). They found that with vitrectomy alone the retina was attached in 94% after one procedure and with scleral buckling in 82%. The difference was statistically significant. In a large retrospective series of 524 cases the success rate of scleral buckling was significantly worse for pseudophakic detachments compared to phakic patients (*Haritoglu et al*: Ophthalmologica 224(5); 312-318, 2010). The SPR trial (Primary vitrectomy vs. scleral buckling for rhegmatogenous retinal detachment) was a multicentre randomised trial funded by the German Research Council (DFG) in which both methods were compared with respect to efficacy. The re-attachment rate in pseudophakic eyes after one procedure was 73% in the vitrectomy group and 56% in the scleral buckling cohort which was statistically significant. It has been further shown that the risk to develop proliferative vitreoretinopathy (PVR) as a typical negative outcome of the disease is statistically less after primary vitrectomy than after scleral buckling in this condition (*Heimann et al*: Ophthalmology 114; 2142-54, 2007). However, in the SPR trial primary vitrectomy was sometimes combined with a circumferential scleral buckle (encircling band) depending on the choice of the surgeon. A subgroup analysis of the data did not show conclusive results (i.e. non-randomised comparison): In pseudophakic eyes 10/88 showed a re-detachment when vitrectomy was combined with a circumferential buckle whereas in 18/44 eyes a re-detachment occurred when no buckle was placed. In contrast, in phakic eyes this difference was not seen. In case series it was

reported that with primary vitrectomy without scleral buckling retinal re-attachment is achieved in 64 – 94 % of cases. In series where vitrectomy was combined with an encircling band the primary re-attachment rates vary between 89% and 100% suggesting also a superiority of the combined method. In several non-randomised studies vitrectomy was compared with vitrectomy plus encircling band as treatment for pseudophakic retinal detachment. In the series of Pournaras and Kapetanios with both techniques excellent reattachment rates were reported which were statistically not different suggesting that the encircling band is not necessary (*Pournaras & Kapetanios*: Eur J Ophthalmol 13; 298-306, 2003). Wickham and co-authors retrospectively compared vitrectomy alone with vitrectomy and scleral buckling in cases with inferior breaks. In both groups about half of the patients were pseudophakic. The primary re-attachment rate was 89% in the vitrectomy alone group and 73% in the vitrectomy plus buckle group. The difference was statistically not significant (*Wickham et al*: Br J Ophthalmol 88; 1376-9, 2004). Stangos and co-authors published a prospective non-randomised trial in which they compared vitrectomy alone with vitrectomy plus scleral buckling for pseudophakic retinal detachment. The reattachment rate was 97% in the vitrectomy alone group and 92% in the vitrectomy plus buckle group. However, the groups differed considerably in size and the choice of the treatment was assigned to the patient (*Stangos et al*: Am J Ophthalmol 138; 952-8, 2004).

Up to now there is no randomised controlled trial comparing vitrectomy alone with vitrectomy plus encircling band in a sufficient number of patients for the treatment of pseudophakic retinal detachment, leaving the decision on the best technique to treat the pseudophakic retinal detachment up to the surgeon and his individual experience. The success rate of retinal detachment surgery is not getting better. Success rates of about 70-80% were already achieved 30 years ago. A subgroup analysis of the SPR trial in which the results of vitrectomy alone were compared with vitrectomy plus encircling band was inconclusive however contrary to the expectations of many surgeons. Because the use of an encircling band strongly effects the outcome of the surgery at least in inducing a myopic shift of about 2 D but also by possibly causing complications such as infection, prolonged surgical time, strabism, explant intrusion, and others, it is important to determine whether the use of it is of any benefit.

2.2. Primary objective

The primary objective is to investigate the efficacy of an encircling band in addition to a 20 gauge vitrectomy with gas in the treatment of pseudophakic retinal detachments. The main endpoint criterion is the absence of any situation leading to additional retina re-attaching surgical procedure during the follow-up.

2.3. Secondary and other objectives

The secondary objective is to investigate if 23/25 gauge transconjunctival vitrectomy with gas is not inferior to 20 gauge vitrectomy with gas in the treatment of pseudophakic retinal detachment without encircling band.

3. Organisational and administrative aspects of the trial

3.1. Sponsor

Sponsor : n/a

Represented by: n/a

3.2. Principal Investigator

Principal Coordinating Investigator:

Prof. Dr. P. Walter
Department of Ophthalmology
University Hospital Aachen
RWTH Aachen University
Pauwelsstr. 30

3.3. Statistics

Statistician:

PD Dr. Martin Hellmich
Institute for Medical Statistics, Informatics and Epidemiology
University of Cologne
Kerpener Str. 62
50937 Cologne
Germany

Data Monitoring Committee:

For this clinical trial, no Data Monitoring Committee will be set up.

3.4. Further committees

3.4.1. Steering Committee

For this clinical trial, no Steering Committee will be set up.

3.4.2. Advisory Committee

For this clinical trial, no Advisory Committee will be set up.

3.4.3. Review Board

For this clinical trial, no Review Board will be set up.

Decisions concerning evaluation of potential protocol violations in the context of definition of the study populations (intention-to-treat, ITT; per-protocol, PP, as treated / valid for safety, VFS / full analysis set, FAS) will be agreed between the Principal Coordinating Investigator and the responsible Statistician. Further clinical experts will be involved if necessary.

3.5. Study laboratories and other technical services

There are no further tasks that will be performed by other service providers.

3.6. Central organisation units

Trial and safety management:	Prof. Dr. P. Walter Department of Ophthalmology University Hospital Aachen RWTH Aachen University Pauwelsstr. 30
Monitoring:	central quality assurance (see also 4.8.1) will be perfomed by Data Management

Data management: Andrea Pfeiffer
Cologne Centre for Clinical Trials (ZKS Köln)
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Germany
Tel.: +49 221 478 88133
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Email: Andrea.Pfeiffer@zks-koeln.de

Scientific advice and support of trial management: Dr. Endrik Limburg
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3.7. Investigators and trial sites

This clinical trial will be carried out as a multicentre trial in Germany and the United Kingdom. If necessary, further qualified trial sites may be recruited to the trial.

A list of trial sites involved, including information on the principal investigators, further investigators, and trial staff, will be continuously updated. A list of the trial sites with names of the principal investigators is given in Appendix 11.1.

Requirements for investigators and trial sites

Surgeons must confirm that they had treated at least 100 cases of retinal detachment with primary vitrectomy using a 20 gauge approach of which at least 20 must be combined

surgery vitrectomy plus encircling band. For surgeons included in the 1:1:1 randomisation scheme, 20 surgical procedures for retinal detachment with 23 or 25 gauge vitrectomy are required in addition to the 100 cases with 20 gauge vitrectomy and the surgeon has to state that he or she feels safe and comfortable with the transconjunctival technique.

3.8. Financing

The present trial is performed under the auspices of the retina.net and therefore supported by the retina.net coordination office at the Clinical Trials Center Cologne. Financial support for the retina.net coordination office is given by Jackstaedt Stiftung, Retinologische Gesellschaft and Deutsche Ophthalmologische Gesellschaft. There is no financial support for the trial.

4. Trial conduct

4.1. General aspects of trial design

This study is conducted as a multicentre, multinational, randomised controlled clinical trial with three parallel treatment arms.

4.1.1. Time plan

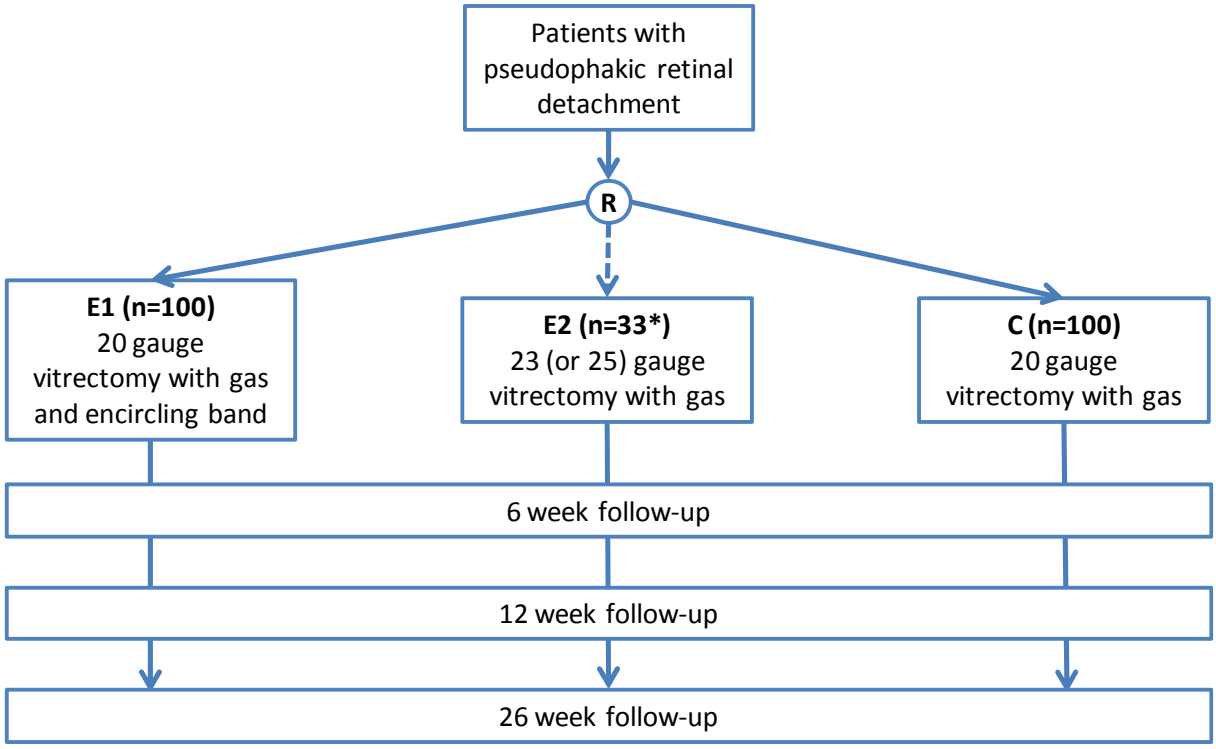
Table 1: Time plan of the trial

First patient first visit (FPFV):	*03/2011*
Last patient first visit (LPFV):	*03/2012*
Last patient last visit (LPLV):	*9/2012*
Final study report:	*12/2012*

End of the clinical trial

The end of this clinical trial is defined as the last visit of the last patient (LPLV).

Figure 2: Trial Flowchart



*E2 will only be performed by selected (experienced) study surgeons

4.2. Discussion of trial design

Pseudophakic retinal detachment can be treated either by scleral buckling alone or by primary vitrectomy. The SPR trial showed that the outcome of patients with PRD treated with primary vitrectomy is better than those treated with scleral buckling. However, it remains unclear whether the use of an additional encircling band improves the outcome of the vitrectomy for PRD. With the broader use of transconjunctival small incision vitrectomy techniques an encircling band is not anymore possible. It is not known if the outcome of small gauge vitrectomy in the treatment of patients with PRD is comparable to the “older” technique. These two questions are addressed in this multicentre randomised controlled trial. The control group (C) consists of PRD patients treated with 20 gauge vitrectomy alone whereas the experimental group 1 (E1) consists of PRD patients treated with 20 gauge

vitrectomy plus encircling band. The experimental group 2 (E2) consists of PRD patients treated with 23 or 25 gauge vitrectomy without encircling band. The outcome of both experimental groups will be compared with the outcome of the control group.

Randomisation will be stratified by surgeon. The ratio is either 1:1:1 or 1:1 depending on individual experience/training in 23/25 G vitrectomy (E2). The individual ratio may be switched (i.e. from 1:1 to 1:1:1) while the trial is ongoing (i.e. when sufficient experience/training has been gained outside the trial).

4.3. Selection of trial population

4.3.1. Inclusion criteria

- Pseudophakic retinal detachment
- pseudophakic rhegmatogenous retinal detachment not suitable for buckling surgery
- Age: 18 years or older
- Agreement of the patient to participate in the trial
- Written consent of the patient

4.3.2. Exclusion criteria

- Manifest uveitis
- Uncontrolled glaucoma
- Active retinal vascular disease
- Malignant intraocular eye tumours
- History of cataract surgery less than 3 months ago
- History of any other intraocular surgery other than cataract surgery
- Giant retinal tears
- PVR grade B or C

- Inability to understand the rationale of this trial or the study aim
- participation in another, potentially interfering interventional clinical trial (less than 3 months ago)
- Aphakia
- Systemic disorders preventing the participation of control examinations during the follow-up
- Systemic disorders not compatible with the local periocular or general anesthesia
- legally incapacitated

4.4. Withdrawal of trial subjects after trial start

An individual patient will only be withdrawn from the trial in case of withdrawal of consent to the trial (nonretention). In case of withdrawal it has to be clarified whether the patient only refuses study treatment and / or additional treatment or if he refuses follow-up investigation and documentation as well. This has to be documented in the eCRF and patients original chart.

In order to assure analysis of the intention-to-treat (ITT) population, it is intended to complete follow-up of all patients, even in case of occurrence of protocol violations which will be documented as well.

No replacement of drop-out patients is planned.

4.4.1. Procedures for premature withdrawal from treatment during the trial

Premature withdrawal from study treatment is not applicable. Study treatment consists of the initial surgery only. Further surgeries as well as any modification of the randomised treatment are to be performed in case of medical indication only.

4.5. Closure of trial sites/Premature termination of the clinical trial

4.5.1. Closure of trial sites

Closure of a trial site will be considered by the Principal Coordinating Investigator in case of serious concerns regarding safety of the patients or data validity (plausibility, completeness). Decisions will be made after consulting the retina.net board.

4.5.2. Premature termination of trial

The PCI has the right to terminate the trial prematurely if there are any relevant medical or ethical concerns, or if completing the trial is no longer practicable. If such action is taken, the reasons for terminating the trial must be documented in detail. All trial subjects still under treatment at the time of termination must undergo a final examination which has to be documented. The PCI must be informed without delay if any investigator has ethical concerns about continuation of the trial.

Premature termination of the trial will be considered if:

- The risk-benefit balance for the trial subject changes markedly
- other reasons reducing ethical justification
- an unacceptable high number of serious adverse events
- The PCI considers that the trial must be discontinued for safety reasons
- relevant superiority of one group (therapy) in a comparable clinical trial
- a novel therapy, developed in the meantime, superior to the investigated therapy modalities
- It is no longer practicable to complete the trial
- a high number of drop-outs (> 20 %)

The PCI decides on whether to discontinue the trial in consultation with the ZKS project manager, the advisory board of retina.net and the trial statistician.

4.6. Treatment

4.6.1. Treatments to be given

Control group (C): Patients who are randomised to the control group will receive 20 gauge vitrectomy without encircling band.

Surgery is performed with an operating microscope and a wide field viewing system. The conjunctiva is opened at the limbus to expose the sclera. Three sclerotomies are made with a distance of 3-4 mm to the limbus. The sclerotomies are 20 gauge wide. A full vitrectomy is performed. If the vitreous is not fully detached a complete vitreous detachment should be obtained. Heavy liquids may be used to drain subretinal fluid. After full re-attachment of the retina under heavy liquids or under air, each retinal break is treated with endolaser or cryopexy. High risk degenerations should be treated as well. A prophylactic circumferential laser treatment is not allowed. The surgery is completed with a gas fill using non expandable gases such as SF6 20%,C2F6 14% or C3F8 14% and the closure of the conjunctiva. Ocular pressure must be monitored at least once within 8h after surgery and the day after surgery. If the intraocular pressure rises to more than 40 mmHg, gas should be released via the pars plana using sterile techniques.

Experimental group 1 (E1): Patients in this group receive 20 gauge vitrectomy with encircling band.

Surgery starts with a circumferential opening of the conjunctiva at the limbus. A 2 to 4 mm encircling band is placed underneath the recti muscles and fixated in all four quadrants. The encircling band is positioned onto the equator of the globe. At the end of surgery no folding of choroidal tissue adjacent to the impression of the encircling band should be visible. The 20 gauge vitrectomy is perfomed as described for the control group (C).

Experimental group 2 (E2): Patients in this group receive 23 or 25 gauge vitrectomy without encircling band.

A 23 or 25 gauge vitrectomy is performed using transconjunctival trokar systems. Trokars are inserted tangentially after displacement of the conjunctiva. A full vitrectomy is performed. If not yet present a full vitreous detachment should be achieved. Endodrainage of the subretinal fluid is achieved with the use of heavy liquids and/or air. After full re-attachment of the retina, breaks and high-risk degenerations are treated with the endolaser probe or with exocryo. A circumferential prophylactic laser treatment is not allowed. After full fluid air exchange the eye is filled with a non expandable air/gas mixture. Trokars are removed. If the sclerotomies are not tight they have to be sutured either transconjunctivally or after opening of the conjunctiva.

4.6.2. Treatments not allowed:

- Use of Triamcinolone or other means to visualize the vitreous
- Use of silicone oil
- Prophylactic circumferential laser/cryo
- Peeling of the internal limiting membrane

4.6.3. Description of investigational medicinal product

not applicable

4.6.4. Compliance with treatment / Dispensing and return of investigational medicinal product

Surgical procedures will be performed following a center specific standard procedure (for all of the three or for two out of three procedures) which will be documented and handed out to the PCI before start of recruitment.

4.6.5. Assignment of trial subjects to treatment groups

Rhegmatogeneous retinal detachment is an emergency situation. Therefore sophisticated screening examinations are not possible. During the initial examination, inclusion and exclusion criteria are considered, the patient is informed in detail and written consent of the patient to participate in the trial is obtained. The results of this initial examination are documented as the first examination of the trial. After including the patient, he will be randomised to one of three treatment groups. Randomisation is 1:1:1 or 1:1, depending on experience/training of the surgeon. A central Internet 24/7 randomisation service is used for randomisation. Sealed opaque envelopes containing allocation details may be prepared as a fallback procedure.

Control group (C): Patients, assigned to the control group, will receive 20 gauge vitrectomy without encircling band.

Experimental group 1 (E1): Patients assigned to receive 20 gauge vitrectomy with encircling band.

Experimental group 2 (E2): Patients assigned to receive 23 or 25 gauge vitrectomy without encircling band.

4.6.6. Selection of dosage of investigational medicinal product

not applicable

4.6.7. Time of administration and adjustments to dosage of the investigational medicinal product in the individual trial subject

not applicable

4.6.8. Blinding

As the study treatments are different surgical procedures, blinding of the study surgeons is not possible. Taking into account the described possible effects of the additional encircling

band, such as myopic shift of about 2 D and possible complications such as infection, strabism, explant intrusion, and others, patient blinding it is not possible either.

4.6.8.1. Unblinding

not applicable

4.6.9. Previous and concomitant medication

4.6.9.1. Rescue therapy for emergencies

not applicable

4.7. Efficacy and safety variables

4.7.1. Measurement of efficacy and safety variables

4.7.1.1. Primary target variable

The primary endpoint is defined as the absence of an indication for any retina reattaching procedure during the follow-up.

Retina re-attaching procedures are additional gas injections, additional vitrectomy or additional buckling procedure.

4.7.1.2. The release of gas after a gas fill with a postoperative intraocular pressure of more than 40 mmHg, laser- or cryotreatment for new or overseen breaks or to demarcate persistant areas of retinal detachment anterior to the equator are not regarded as failure indicating procedures.Secondary and other target variables

- Visual acuity at the end of follow-up as measured by ETDRS charts
- Refractive status
- Retina reattachment rate
- Rate of occurrence of PVR, Grade C according to Machemer

- The number of retina specific procedures to achieve a stable retinal attachment
- Operation time (time between cut and suture)
- Postoperative pain will be evaluated
- Anatomical situation of the anterior and posterior segment

4.7.1.3. Safety data

- Iatrogenic breaks / macular hole
- Macular edema
- Macular pucker
- Ocular hypertony (at week 26)
- Diplopia
- Choroidal hemorrhage
- Pain medication
- Enucleation
- Death

4.7.1.4. Description of visits

Visits will be conducted at the following times and must fall between the ‘first day possible’ and the ‘last day possible’ (measured in trial weeks) given in Table 2.

Table 3: Overview on data acquisition and timing of examination

Time (weeks)	0	6	12	26
first and last week possible	0	5-7	10-14	23-29
Inclusion and exclusion criteria	X			
Informed consent	X			
Medical history	X	X	X	X
AEs/SAEs		X	X	X
Best corrected visual acuity (ETDRS)	X	X	X	X
Refraction	X	X	X	X
Tonometry	X	X	X	X
Slitlamp	X	X	X	X
Funduscopy	X	X	X	X
Fundus drawing	X	X	X	X
Fundus photography				X
End of study				X

Duration of the clinical trial in the individual subject

Trial duration of an individual patient consists of the initial surgery and a follow-up of 26 weeks.

4.7.2. Pharmacokinetics/Determination of drug levels

not applicable

4.8. Data quality assurance

4.8.1. Monitoring

In this trial, three standard treatments are compared, which are part of daily routine in the participating study sites. Therefore there are very low study specific riscs. For this reason, central quality assurance measures are regarded sufficient and will be applied and performed by data management personnel. There will be no on site monitoring in the respective study centers.

4.8.2. Audits/Inspections

As part of quality assurance, the PCI has the right to audit the trial sites and any other institutions involved in the trial. The aim of an audit is to verify the validity, accuracy and completeness of data, to establish the credibility of the clinical trial, and to check whether the trial subject's rights and trial subject safety are being maintained. The PCI may assign these activities to persons otherwise not involved in the trial (auditors). These persons are allowed access to all trial documentation (especially the trial protocol, case report forms, trial subjects' medical records, drug accountability documentation, and trial-related correspondence).

The PCI and all trial sites involved undertake to support auditors at all times and to allow the persons charged with these duties access to the necessary original documentation.

All persons conducting audits undertake to keep all trial subject data and other trial data confidential.

4.9. Documentation

All data relevant to the trial are documented soon after measurement by the investigator responsible in the electronic case report form supplied. Entering data may be delegated to members of the trial team. The eCRFs are electronically signed by the investigator.

4.9.1. Data management

The IT infrastructure and data management staff will be supplied by the ZKS Cologne. The trial database will be developed and validated before data entry based on standard operating procedures at the ZKS Cologne. The data management system is based on commercial trial software and stores the data in a database. All changes made to the data are documented in an audit trail. The trial software has a user and role concept that can be adjusted on a trial-specific basis. The database is integrated into a general IT infrastructure and safety concept with a firewall and backup system. The data are backed up daily. After completion and cleaning of data, the database is locked and the data exported for statistical analysis.

The data will be entered online at the trial sites via the Internet. Plausibility checks are run during data entry, thereby detecting many discrepancies immediately. The ZKS Cologne Data Management will conduct further checks for completeness and plausibility and will clarify any questions with the trial sites electronically via the trial software. These electronic queries have to be answered by the trial site without unreasonable delay. Further details will be specified in the data management manual.

4.9.2. Archiving

All CRFs, informed consent forms and other important trial materials will be archived for at least 10 years in accordance with §13 Sec. 10 of the GCP Regulations. Trial subject identification lists at each trial site will be stored separately from trial documentation.

5. Ethical and regulatory aspects

5.1. Independent ethics committee

In each trial site, the clinical study will not be started before approval of the competent local ethics committee concerning the suitability of the trial site and the qualifications of the investigators.

5.2. Ethical basis for the clinical trial

The present trial protocol and any amendments were and will be prepared in accordance with the Declaration of Helsinki in the version of October 1996 (48th General Assembly of the World Medical Association, Somerset West, Republic of South Africa).

5.2.1. Legislation and guidelines used for preparation

The present clinical trial will be conducted in accordance with the published principles of the guidelines for Good Clinical Practice (ICH-GCP) and applicable legislation (especially the GCP-V). These principles cover, amongst other aspects, ethics committee procedures, the obtaining of informed consent from trial subjects, adherence to the trial protocol, administrative documentation, documentation regarding the IMP, data collection, trial subjects' medical records (source documents), documentation and reporting of adverse events (AEs), preparation for inspections and audits, and the archiving of trial documentation. All investigators and other staff directly concerned with the study will be informed that domestic and foreign supervisory bodies, the competent federal authorities and authorised representatives of the sponsor have the right to review trial documentation and the trial subjects' medical records at any time.

5.3. Notification of the authorities, approval and registration

As the regulations of federal drug law (Arzneimittelgesetz, AMG) or Medical Products Act (Medizinproduktegesetz, MPG) do not apply to this trial, notification is not applicable.

Before the trial is started, it will be registered under Current Controlled Trials (www.controlled-trials.com) or another trial register approved by the World Health Organisation (WHO) (http://www.who.int/ictrp/en/). The trial protocol will be submitted for publication.

5.4. Obtaining informed consent from trial subjects

Trial subjects may not be enrolled into the present trial unless they have consented to take part in the trial after having been informed verbally and in writing in comprehensible language of the nature, scope and possible consequences by a trial investigator. Together with the consent to take part in the trial, the trial subject must also agree to representatives of the sponsor (e.g. monitors or auditors) or the competent supervisory or federal authorities having access to the data recorded within the framework of the clinical trial. The trial subject will be informed of the potential benefit and possible side effects of the study therapy. It must be clear to trial subjects that he or she can withdraw his or her consent at any time without giving reasons and without jeopardizing his / her further course of treatment.

The originally signed consent form is archived in the investigator site file. Trial subjects receive copies of the written information sheet, confirmation of insurance with conditions, and the signed informed consent form. A copy of the written information sheet and the signed informed consent form will be filed in the patient's record.

The patient information sheet and informed consent form are supplied in Appendix 11.3.

The patient information sheet, informed consent form, all other documents handed out to the trial subject and any recruitment advertisements must be submitted for approval before use to the ethics committee

5.5. Insurance of trial subjects

The insurance of trial subjects is provided by the general insurance company of the respected study centre. For the centre of the PCI in Aachen this is Zürich Versicherungs AG No. 813.380.000.270. The

administration of the insurance documents for the PCI centre is provided by Ecclesia Mildenberger Hospital GmbH, Klingenbergstr. 4, 32758 Detmold. The insurance of trial subjects for other participating centers has to be provided by the respective study centers.

5.6. Data protection

The provisions of data protection legislation will be observed. It is assured by the PCI that all investigational materials and data will be pseudonymised in accordance with data protection legislation before scientific processing.

Trial subjects will be informed that their pseudonymised data will be passed on in accordance with provisions for documentation and notification pursuant to § 12 and § 13 of the GCP Regulations to the recipients described there. Subjects who do not agree that the information may be passed on in this way will not be enrolled into the trial.

6. Statistical methods and sample size calculation

6.1. Statistical and analytical plan

The primary analysis will be according to intention to treat, i.e. all patients randomised will be analysed as assigned. A missing primary endpoint is considered a treatment failure. Otherwise (secondary) the last observation may be carried forward and/or multiple imputation may be done. Further details will be layed out in the statistical analysis plan.

6.1.1. Trial populations

All analyses will be conducted in three trial populations:

Intention-to-treat (ITT) population. This dataset includes all trial subjects enrolled into the trial and randomised. Analysis will be as assigned

Per-protocol (PP) population. This dataset includes all trial subjects who were treated and observed according to protocol.

As-treated (AT) population: This dataset includes all trial subjects enrolled into the trial and randomised. Analysis will be as treated.

6.1.2. Description of trial subject groups

Demographic data and baseline values of target variables will be summarised using mean, standard deviation, count and percentage etc.

6.1.3. Primary target variable

Primary endpoint:

The primary target variable is obtained as the number of patients for which is stated

“absence of an indication for any retina reattaching procedure during the follow-up”.

The primary objective will be evaluated for superiority by Cochran-Mantel-Haenszel method stratified by surgeon. For the exploratory comparison of (C) and (E2) a non-inferiority margin of 1.25 (odds ratio) will be employed.

Logistic regression, GEE and multiple imputation methods will be used for sensitivity analysis.

6.1.4. Secondary target variables

Secondary endpoints:

- Visual acuity at the end of follow-up as measured by ETDRS charts
- Refractive status
- Retina reattachment rate
- The occurrence of PVR, Grade C according to Machemer
- The number of retina specific procedures to achieve a stable retinal attachment
- Operation time (time between cut and suture)
- Postoperative pain (medication)
- Anatomical situation of the anterior and posterior segment

The secondary variables will be evaluated by Cochran-Mantel-Haenszel methods (nominal variables) or linear models (metric variables), respectively, stratified by surgeon.

Mixed models for repeated measures (MMRM), GEE and multiple imputations methods will be used for sensitivity analysis.

6.1.5. Subgroup analyses

Men (expected 73%) and women will be analysed together as well as separately.

6.1.6. Interim analysis

No formal interim analysis is planned in this study.

6.2. Sample size calculation

In the SPR study 11.4% (=10/88) of pseudophakic patients who had recieved combined primary vitrectomy and scleral bluckling suffered from a redetachment, in contrast to 40.9% (=18/44) of pseudophakic patients who received primary vitrectomy only. Thus, carefully assuming event fractions of 15% vs. 35%, 82 Patients per group will be required to give the corrected chi-square test 80% power at two-sided significance level 5%. Accounting for stratification and 10% attrition fraction, 100 patients will be allocated to arms (C) and (E1). After reaching this target, recruitment to the whole trial will be stopped, i.e. when, according to expectation, about 33 patients have been allocated to group (E2). Thus, the comparison of (E2) and (C) will/can be explorative only. Note that the number of patients required to yield convincing results with adequate power and precision is about 1400 per group.

7. Safety

7.1. Definitions of adverse events and adverse drug reactions

7.1.1. Adverse event

An adverse event (AE) is any untoward medical occurrence in a trial subject administered an IMP. There does not necessarily have to be a causal relationship with this treatment.

The term 'adverse event' covers any sign, symptom, syndrome, or illness that appears or worsens in a subject during the period of observation in the clinical study and that may impair the well being of the subject. The term also covers laboratory findings or results of other diagnostic procedures that are considered to be clinically relevant (e.g., that require unscheduled diagnostic procedures or treatment measures, or result in withdrawal from the study). The adverse event may be:

- a new illness
- worsening of a sign or symptom of the condition under treatment, or of a concomitant illness
- an effect of the study intervention
- a combination of two or more of these factors.

No causal relationship with the study intervention or with the study itself is implied by the use of the term "Adverse Event". Surgical procedures themselves are not adverse events; they are therapeutic measures for conditions that require surgery. The condition for which the surgery is required may be an adverse event.

Possible AE's for example are any newly diagnosed systemic diseases, conjunctivitis, headache, infection of the fellow or of the study eye, late macular edema, macular pucker, optic atrophy, persistent postoperative elevated intraocular pressure (IOP > 22 mmHg), retinal traction detachment, sicca syndrome, unscheduled reoperation of the study eye, uveitis or other diagnoses.

All adverse events that occur after the subject has signed the informed consent document must be documented on the pages provided in the electronic case report form (eCRF) online. Every attempt should be made to describe the adverse event in terms of diagnosis. If only non-specific signs or symptoms are present, then these should be recorded as a diagnosis.

All subjects who have adverse events, whether considered associated with the study intervention or not, must be monitored to determine the outcome. The clinical course of the adverse event will be followed up according to accepted standards of medical practice, even after the end of the period of observation, until a satisfactory explanation is found or the investigator considers it medically justifiable to terminate follow-up.

Concomitant diseases

The deterioration of a preexisting illness is also an AE in the context of a clinical trial. The following, however, is not regarded as an AE: a preexisting disease that led to a planned treatment measure before the start of the clinical trial, e.g. admission to hospital as an inpatient. This should be made clear in the trial subject's medical records and should also be documented in the CRF (see Section 7.1.3).

Pregnancy

For reasons of drug safety, the occurrence of a pregnancy during the conduct of this trial is to be regarded as an AE.

7.1.2. Adverse reaction

The term "adverse drug reaction, ADR" is not applicable. However, adverse events regarded to be related to the study treatment (initial surgery) will be regarded as adverse reaction (AR).

7.1.3. Serious adverse events and serious adverse reactions

A serious AE (SAE) or serious AR (SAR) is any untoward medical occurrence that at any dose

1. Results in death,

2. Is life-threatening at the time of the event
3. Requires inpatient hospitalisation or prolongation of existing hospitalisation
4. results in persistent or significant disability/incapacity
5. is a congenital anomaly or birth defect (1.-4.: § 3(8) GCP Regulations)
6. In the opinion of the investigator, fulfils any other criteria similar to 1.–4.

Inpatient hospitalisation is defined as any stay in hospital on the part of a trial subject that includes at least one night (midnight to 06:00). Admission to hospital as an inpatient planned before the first admission of the IMP are not SAEs, but must be documented in the proper manner in the trial subject's medical records and CRF (see Section 7.1.1).

If an AE is classified as an SAE, this is documented on a separate SAE eform in addition to the standard AE documentation. The PCI must be notified of SAEs (for procedure, see 7.3)

7.1.4. Unexpected adverse reaction

An unexpected AR is an AR which, the nature or severity of which is not consistent with the following:

- iatrogenic breaks

7.1.5. Suspected unexpected serious adverse reactions

A suspected unexpected serious adverse reaction (SUSAR) is an adverse event the nature or severity of which is not consistent with the product information available for the IMP, is regarded as serious, and has at least a possible causal relationship with the IMP.

7.2. Documentation and follow-up of adverse events

The PCI ensures that all persons involved in the treatment of trial subjects are adequately informed of the responsibilities and actions required when AEs occur. Trial subjects will be

asked at each visit whether they have experienced AEs or SAEs. AEs will be documented in the trial subject's medical records and in the eCRF.

For the procedure of SAE-reporting see section 7.3, and section 4.7.1.3 for safety analyses.

7.2.1. Documentation of adverse events and adverse drug reactions

All AEs will be documented in the CRF including all information listed below.

The AE is documented in the CRF including the following information:

- Date and time of onset and resolution
- Severity
- Causal relationship with study treatment
- Seriousness
- measures taken

Regardless of whether a causal relationship between the AE and the IMP is suspected, trial subjects who develop adverse events will be monitored until all symptoms have been subsided, pathological laboratory values have returned to pre-event levels, a plausible explanation is found for the AE, the trial subject has died, or the study has been terminated for the trial subject concerned.

Preexisting diseases are not documented as adverse events but as concomitant diseases. New diseases and preexisting diseases that worsen during the trial are documented as AEs.

7.2.2. Severity of the adverse event

The investigator will classify the severity of AEs as follows:

- Mild: clinical symptoms or signs that are well tolerated
- Moderate: clinical symptoms or signs that are enough to impair everyday activities
- Severe: clinical symptoms or signs that markedly impair the trial subject and result in inability to work or go about everyday activities

7.2.3. Causal relationship between adverse event and investigational medicinal product

The investigator will assess the for every AE whether a causal relationship with the study treatmentcan be assumed or not. The assessment includes consideration of the nature and type of reaction, the temporal relationship with the study treatment, the clinical status of the trial subject, concomitant medication and other relevant clinical factors. If the event is considered due to lack of efficacy or as a symptom or sign of the underlying disorder, no causal relationship will be assumed.

The following definitions are used to assess the causal relationship between all AEs and the IMP (for documentation in CRF, see also Section 7.2.2) (WHO Causality Assessment of Suspected Adverse Reactions):

- Certain: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
- Probable/likely: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

- Conditional/unclassified: A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.

  Unassessable/unclassifiable: A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

An AR is suspected if the causal relationship is at least 'possible' or 'conditional/unclassified' or 'unassessable/unclassifiable'. Events assessed as 'unlikely' are not suspected ARs.

7.3. Reporting of serious adverse events and changes in risk-benefit assessment

Regardless of the assumed causal relationship, every SAE that occurs during a trial must be documented in the appropriate part of the eCRF. With immediate online-documentation without unreasonable delay, the investigators fulfill their obligation of reporting SAEs to the PCI.

The principle investigator of each study Centre is responsible for reporting SAEs to the local ethics committee if required.

7.3.1. Reports from the investigator to the PCI

The investigators ensure immediate online-documentation of the occurrence or receipt of knowledge of the occurrence of an SAE without delay, at the latest within 24 hours of being made aware of the SAE. Herewith the investigators fulfill their obligation of reporting SAEs to the PCI.

All cases of suspected SAEs are assessed by the PCI with regard to seriousness (see Section 7.1.3), causality (see Section 7.2.3) and expectedness (see Section 7.1.4), regardless of the investigator's assessments.

7.3.2. Unblinding when treatment is blinded

Not applicable: not a blinded study

7.3.3. Notification of ethics committee

SUSARs that become known in this clinical trial will be reported by the PCI to the ethics committee.

The principle investigator of each study Centre is responsible for reporting SUSARs to the local ethics committee if required.

Over and above this, reporting responsibilities and deadlines for Great Britain have to be respected for the trial site in Great Britain. All reporting requirements will be cleared and regulated by the responsible PI before the trial site starts recruitment to ensure that appropriate organisational measures can be taken.

Fatal and life-threatening SUSARs

The ethics committee responsible must be informed by the PCI of all fatal or life-threatening SUSARs. This must be done without delay, at the latest 7 calendar days after becoming aware of the minimum criteria for reporting. In all cases, attempts must be made to obtain further relevant information which must be supplied to the ethics committee within a further 8 days. Furthermore, if a trial subject dies, this information must be passed on to the ethics committee responsible for the region in which the death occurred.

SUSARs that are not fatal or life-threatening

The ethics committee responsible will be informed without delay by the PCI of all SUSARs, at the latest within 15 calendar days of becoming aware of the minimum criteria for reporting. Further relevant details will be passed on as soon as possible.

If the information at the time of reporting is incomplete, further information to enable adequate assessment of the case will be requested from the reporter or other available sources.

7.3.4. Review and reporting of changes in the risk-benefit ratio

Without delay, and at the latest within 15 days of the decision for the need to do so, the PCI will inform the ethics committee responsible of any events or factors that mean that the risk-benefit ratio of the study has to be reviewed. These consist of especially:

- Individual reports of expected serious ARs with an unexpected outcome
- A clinically relevant increase in the rate of occurrence of expected SARs
- Factors emerging in connection with trial conduct that may affect the safety of persons concerned.

7.3.5. Informing the Data Monitoring Committee

No DMC is installed for this study

7.3.6. Informing the investigators

The PCI will inform investigators of all SUSARs including all relevant further information.

If new information becomes known that is different from the scientific information given to the investigator, all investigators will be informed of this by the PCI.

7.3.7. Informing the marketing authorisation holder

not applicable

7.4. Annual safety report of trial subjects

not applicable

8. Use of trial findings and publication

8.1. Reports

8.1.1. Interim reports

No interim analysis is planned, so interim reports will only be provided in case of premature termination of the study.

8.1.2. Final report

The ethics committee will be informed within 90 days that the trial has officially ended.

Within one year of the completion of the trial, the ethics committee will be supplied with a summary of the final report or an adequate publication on the clinical trial containing the principle results.

8.2. Publication

It is planned to publish the trial results, in mutual agreement with the PCI, in a scientific journal and at German or international congresses. Publication of the results of the trial as a whole is intended. Any publication will take account of the 'Uniform requirements for manuscripts submitted to biomedical journals (International Committee of Medical Journal Editors' (ICMJE) [JAMA 1997;277:927-34]).

The trial will also be registered in a public register in accordance with the recommendations of the ICMJE (see also Section 5.3).

Any published data will observe data protection legislation covering the trial subject and investigators. Success rates or individual findings at individual trial sites are known only to the sponsor.

Publications or lectures on the findings of the present clinical trial either as a whole or at individual investigation sites must be approved by the PCI in advance, and the PCI reserves the right to review and comment on such documentation before publication.

By signing the contract to participate in this trial, the investigator declares that he or she agrees to submission of the results of this trial to national and international authorities for approval and surveillance purposes, and to the Federal Physicians Association, the Association of Statutory Health Fund Physicians and to statutory health fund organisations, if required. At the same time, the investigator agrees that his or her name, address, qualifications and details of his or her involvement in the clinical trial may be made known to these bodies.

The support by the ZKS is to be mentioned in any publication. ZKS staff will be included as coauthors as applicable and the Grant number oft the ZKS (01KN0706) is mentioned in an acknowledgement. A copy of all publications will be sent to the ZKS.

9. Amendments to the trial protocol

To ensure that comparable conditions are achieved as far as possible at individual trial sites and in the interests of a consistent and valid data analysis, changes to the provisions of this trial protocol are not planned. In exceptional cases, however, changes may be made to the trial protocol. Such changes can only be made if agreed by the PCI, the ZKS project manager and the biometrician, and all Authors of this trial protocol. Any changes to the trial procedures must be made in writing and must be documented with reasons and signed by all Authors of the original trial protocol.

Amendments made in accordance with § 10 Secs. 1 and 4 GCP Regulations that require approval are submitted to the ethics committee and will not be implemented until approved. Exceptions to this are amendments made to avoid immediate dangers.

10. References

1. The European Agency for the Evaluation of Medicinal Product. Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).
2. The European Agency for the Evaluation of Medicinal Product. Note for Guidance Structure and Content of Clinical Study Reports (CPMP/ICH/137/95).
3. National Cancer Institute. Protocol Templates, Applications and Guidelines http://ctep.cancer.gov/guidelines/templates.html.
4. EMEA-Guideline On Data Monitoring Committees: EMEA/CHMP/EWP/5872/03 Corr
5. The DAMOCLES Study Group. A proposed charter for clinical trial 2005 data monitoring committees: helping them do their job well. Lancet 2005; 365: 711-22
6. Clinical trial registration: a statement from the International Committee of Medical Journal Editors. Accessed at http://www.icmje.org/clin_trial.pdf on 22 May 2007.
7. WHO. Causality Assessment of Suspected Adverse Reactions. http://www.who-umc.org/DynPage.aspx?id=22682
8. *Heimann et al: Ophthalmology 114; 2142-54, 2007.*. „Scleral buckling versus primary vitrectomy in rhegmatogenous retinal detachment: a prospective randomized multicenter clinical study.“ Heimann H, Bartz-Schmidt KU, Bornfeld N, Weiss C, Hilgers RD, Foerster MH; Scleral Buckling versus Primary Vitrectomy in Rhegmatogenous Retinal Detachment Study Group.
9.

11. Appendices

11.1. Trial sites and principle investigators

11.2. Protocol Agreement Form

11.3. Patient information sheet and informed consent form

11.4. Confirmation of insurance

11.5. Conditions of insurance