Trial Synopsis

Re-treatment with intravitreal application of ranibizumab guided by morphological macular changes documented by optical coherence tomography (OCT) in patients with macular edema due to branch retinal vein occlusion

A randomized, controlled interventional phase 2b (proof of concept) study of the efficacy, safety, and tolerability of repeated intravitreal administration of ranibizumab guided by morphological changes documented by optical coherence tomography (OCT) in subjects with macular edema secondary to branch retinal vein occlusion (BRVO)

RabOCT

Investigational product: Ranibizumab (Lucentis®)

Indication: patients with macular edema secondary to branch retinal vein occlusion (BRVO)

Phase of the clinical trial: IIb

EudraCT-No: 2012-005439-10

Registry-No: NCT01968239

Date: 07.03.2017

Version: final 1.0

Coordinating Investigator
Prof. Dr. med. Peter Wiedemann
Department of Ophthalmology,
University of Leipzig
Liebigstr. 10-14
D-04103 Leipzig

Sponsor
University of Leipzig
Ritterstr. 26, 04109 Leipzig

Biometry/ Project Management
Dr. Annegret Franke/ Dr. Marizel Schwarzkopf
Clinical trial centre Leipzig (ZKS – KKS)
Haertelstr. 16-18
04107 Leipzig
Tel.: 0341 97 16 254

Start of clinical trial: 10-Oct-2013
End of clinical trial: 17-May-2016

Report Signatures

We hereby certify that we agree with the content of this final report: this clinical trial was performed according to the Declaration of Helsinki, the guidelines for Good Clinical Practice (GCP), as well as all pertinent national laws.

Representative of the sponsor and Coordinating investigator
Prof. Dr. med. Peter Wiedemann:

21.3.17
Date

Signature

Biometry
Dr. Annegret Franke:

20.3.17
Date

Signature

Project Management
Dr. Marizel Schwarzkopf:

20.03.2017
Date

Signature

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1 Sponsor and authorized representative of the sponsor

University of Leipzig
Authorized representative of the sponsor:
Prof. Dr. med. Peter Wiedemann
Department of Ophthalmology, Universtity of Leipzig
Liebigstr. 10-14, 04103 Leipzig
Phone: 0049-341-97 21 650; Fax: 0049-341-97 21 659
E-Mail: augen@medizin.uni-leipzig.de

2 Investigational product	3 Active substance
Lucentis®	Ranibizumab

4 Individual Study Table

Not applicable

5 Study Title

Re-treatment with intravitreal application of ranibizumab guided by morphological macular changes documented by optical coherence tomography (OCT) in patients with macular edema due to branch retinal vein occlusion
Study protocol (Final1.0/10.07.2013)
Amendment No. 01 final/18.12.2013and
Amendment No. 02 final 1.0/03.12.2015

6 Investigator	7 Trial site
Prof. Dr. med. Peter Wiedemann From 14.02.2014 to end of study PD Dr. habil. Matus Rehak from 10.09.2013 to 13.02.2014	Department of Ophthalmology, Universtity of Leipzig Liebigstr. 10-14, 04103 Leipzig

8 Publications

The draft of scientific paper is currently under preparation; the results of the trial have not been presented or published yet.

9 Trial duration

The RabOCT study started on 10.10.2013 which was equal to the „First Patient In“(FPI) date. The last patient was included on 04.05.2015 and completed the study on 17.05.2016.

10 Development phase

RabOCT is a phase IIb clinical trial.
Ranibizumab (Lucentis®) is approved by European authorities for treatment of patients with macular oedema secondary to branch- and central-retinal vein occlusion.

11 Objectives of the trial

The primary objective was to evaluate whether a further improvement of the final BCVA could be achieved if the re-treatment with ranibizumab is guided by morphological changes detected by OCT.
Secondary objectives were:

- Change score in central retinal thickness (CRT), assessed by OCT between Week 1 and week 52 (EoS).
- Number of Ranibizumab injections applied per patients in total; maximally 11 injections may be applied based on standardized arm-specific retreatment criteria.
- Rate of patients per group progressing to neovascularization of the retina or anterior segment which require pan-retinal photocoagulation.
- Number of serious adverse events (SAEs)/ reactions (SARs – causally related to treatments) per group and
- Number of adverse events (AEs)/ reactions (ARs) per group observed during the entire course of study.

12 Clinical trial design / methodology

The RabOCT trial, an open, placebo-controlled, randomised monocentre, two-armed therapy trial of phase 2b, was designed as proof- of-concept study to evaluate the therapeutic benefit of ranibizumab injections at the first sign of morphological changes compared to recent standard therapy acc. to guidelines.
Patients were randomised in a 1:1 ratio. Treatment effects were assessed using standard ophthalmological measures.

13 Total number of patients

27 screened for morphological changes via OCT over 6 months after the initial monthly treatment with 3 ranibizumab injections; 18 randomised to the study interventions.

14 Inclusion and exclusion criteria

Inclusion criteria:

- Completed up-load phase of ranibizumab treatment (at least 3 monthly intravitreal injections) due to macular edema secondary to branch retinal vein occlusion with presence of recurrence of macular edema detected by optical coherence tomography (OCT) without decrease of BCVA score more than 3 ETDRS letters when compared with BCVA on day of 3rd ranibizumab application
- BCVA score in the study eye between 20 letters (20/400) and 78 letters (20/32) measured in ETDRS chart and foveal thickness ≥ 250 µm (measured by OCT) and prior to the first ranibizumab injection
- Age ≥ 18 years
- Written informed consent of the patient
- The history of BRVO no longer than 8 months prior to the first ranibizumab injection
- Ability and willingness to attend all scheduled visits and assessments

Exclusion criteria:

- Macular edema due to another etiology than retinal vein occlusion (e.g. diabetic maculopathy, uveitis, age related macular degeneration, Irvine-Gass syndrome)
- Evidence upon examination of vitreoretinal interface disease (e.g., vitreomacular traction, epiretinal membrane), either on clinical examination or OCT, thought to be contributing to macular edema
- An eye that, in the investigator's opinion, would not benefit from resolution of macular edema, such as eyes with foveal atrophy, dense pigmentary changes, or dense subfoveal hard exudates

- Aphakia
- Macular laser photocoagulation in the study eye prior to study entry
- Use of intraocular or periocular injection of steroids in the study eye prior to study entry
- Cataract surgery or Yttrium-Aluminum-Garnet (YAG) laser capsulotomy or any other intraocular surgery in the study eye within 3 months prior to study entry
- History of cerebral vascular accident, myocardial infarction, transient ischemic attacks in last 6 months prior to randomization
- The presence of active malignancy
- Pregnancy (positive pregnancy test) or lactation
- History of allergy to humanized antibodies or any component of the ranibizumab formulation
- Participation in another simultaneous medical investigation or trial
- Women with child bearing potency without effective contraception (i. e. implants, injectables, combined oral contraceptives, some IUDs or vasectomised partner) during the conduct of the trial.

15 Investigational product

Ranibizumab inhibits the already existing VEGF (Vascular Endothelial Growth Factor) molecules in the vitreous. The adverse reactions are described in the SmPC (Summary of medicinal Product Characteristics).

16 Duration/dosage of treatment and trial procedures

Experimental intervention (OCT guided group): Patients randomized to this group got the intravitreal injection of 0.5 mg ranibizumab if the morphological macular changes for recurrence of macular edema (microcystic changes with or without increase of central retinal thickness) was detected by OCT.

Control intervention (Standard treatment): Patients randomized to this group got the intravitreal injection of 0.5 mg ranibizumab according to the in SmPC defined re-treatment criteria (re-injection if decrease of BCVA was detected).

The treatment period was 12 months after randomisation.

AEs and SAEs were documented from randomization up to 30 days after the last study intervention or the termination visit, whichever is later.

17 Reference therapy

See chapter 15 and 16

18 Evaluation criteria

18.1 Efficacy

Based on the BCVA assessment of the study eye - performed at all study visits and measured in ETDRS letters - the primary end was the change score in BCVA from randomization (week 1) to week 52, i.e. end of study (EoS
Secondary end points are:

- Change score in central retinal thickness (CRT), assessed by OCT between Week 1 and week 52 (EoS);
- Number of Ranibizumab injections applied per patients in total; maximally 11 injections may be applied based on standardized arm-specific retreatment criteria.

- Rate of patients per group progressing to neovascularization of the retina or anterior segment which require pan-retinal photocoagulation. Occurrence of a neovascularization was assessed at every visit and analyzed cumulatively per patient until EoS.

18.2 Safety

Number of serious adverse events (SAEs)/ reactions (SARs – causally related to treatments) per group and number of adverse events (AEs)/ reactions (ARs) per group observed during the entire course of study (including critical ocular events like abrupt, clinically significant decrease in BCVA, new onset of a clinically significant increase in intraocular pressure, corneal edema, intraocular inflammatory response) were analysed.

19 Statistical methods / criteria for evaluation

Confirmatory analysis was done by means of estimation of the between-group mean and median difference with the corresponding 95% confidence interval for the primary endpoint - the change in BCVA from randomization to the EoS visit. CRT change was analysed in the manner.
The number of indicated Ranibizumab injections in the two groups until last FU visit was compared by Mann-Whitney-U-Test.
For safety analyses, all (S)AEs will be reported. Rates of (S)ARs were estimated. Due to the small number of AR and SAE the were analysed only descriptively.

20 Summary

20.1 Primary Endpoint

The between-groups differences of BCVA resulted in (OCT minus control group):

- a mean difference of -2,44 [95% CI: -11.06; 6.17] letters; p=0.556
- a median difference of -2 [-8 ;6] letters; p=0,796.

without significance.
A difference of about 2 letters with the corresponding 95%-confidence intervals did not reveal a descriptive tendency toward a higher gain in BCVA for the OCT group.

20.2 Secondary endpoints

The between-groups central retinal thickness (CRT) differences assessed by OCT between Week 1 and week 52 resulted in (OCT minus control group):

- a mean difference of 38,33 [95% CI: -94.35; 171.01] letters; p=0.539,
- a median difference of 11 [-86; 156] letters; p=0,796,

without significance. The mean/median group differences at EoS indicate no descriptive benefit regarding either or the other group.

Until EoS median numbers of 9 [IQR: 7 to 12.5] ranibizumab injections in the OCT arm and 8 [IQR: 4.5 to 9] injections in the control arm were observed. The respective group difference (by Hodges-Lehmann statistic) resulted in a value of 2 [95% CI: -1; 5] and a nonsignificant p=0.258.

No neovascularizations occurred during the course of trial within the total sample.

20.3 Adverse Events

In total, 102 AEs in 18 (all treated) patients were reported. One AE was assessed to be possibly related to ranibizumab, eight AEs in six patients were reported to be possibly related to the intravitreal injections. With 5 AR in the OCT and 4 AR in the Control arm, no relevant arm differences occurred – neither in number of AR nor in number of patients involved.

20.4 Serious adverse events (SAE)

No deaths occured during the course of the trial. Three SAEs in two patients were reported in the RabOCT trial. For none of the SAE observed a causality was regarded possible with respect to the IMPs of the trial - Ranibizumab or injection procedure.

21 Conclusions

The between-group differences observed in the primary and secondary outcomes of the RabOCT study were quite small in the descriptive measures and not significant regarding the confidence intervals and test results. Therefore, it had to be concluded from results and the rather small sample sizes in this proof-of-concept trial that an early intervention might not influence the mid-term course of visual acuity in BRVO.
From the clinical point of view, the trial did not show that an immediate re-application of ranibizumab at the time, when intraretinal microcystic changes become present, would improve the functional treatment results at month 12. However, during the course of the trial the general treatment strategy changed. The indication for retreatment is now grounded on OCT results and not on visual acuity in routine care. Therefore, the treatment strategy as applied in the control arm (i.e. to wait until the visual acuity decreased due to recurrence of macular edema, according to protocol) did not reflect the currently recommended therapy any longer. We may conclude that the results of the RabOCT study are in line with the recent re-treatment recommendations and give additional evidence on the importance of the morphological criteria (based on OCT scans) in decisions of re-application. Up to now, the period within re-application needs to be performed remains still unclear. The results of the RabOCT study suggest that the re-treatment does not need to be done immediately at the first presence of the intraretinal fluid.

22 Appendix

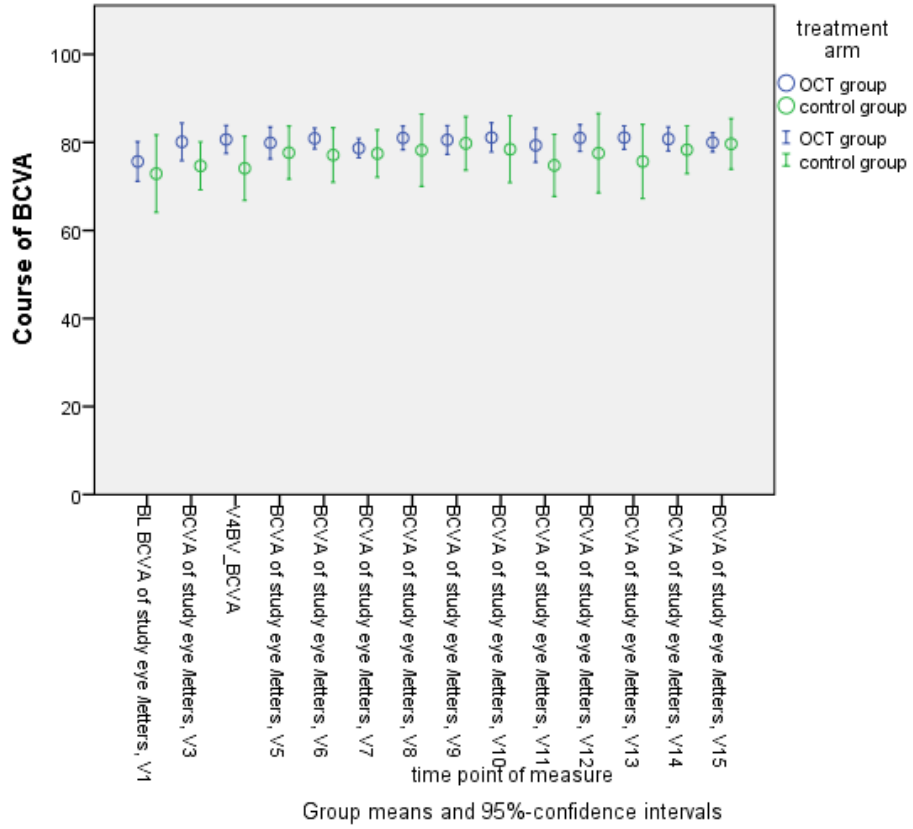
Primary and secondary endpoints

		arm allocation		
		OCT group	control group	total
Change of BCVA score at v15 (EoT & EoS, post minus BL value)	Mean	4,3	6,8	5,6
	SD	6,1	10,6	8,5
	Min	-3	-6	-6
	Med	2,0	6,0	5,0
	Max	14	32	32
	Valid N	9	9	18
Change of CRT (from OCT) at v15 (EoT & EoS; post minus BL value)	Mean	-42,4	-80,8	-61,6
	SD	76,9	164,4	126,1
	Min	-169	-437	-437
	Med	2,0	-9,0	-8,5
	Max	49	88	88
	Valid N	9	9	18
No. of ranibizumab injections during the trial	Mean	9,2	6,8	8,0
	SD	2,9	3,2	3,2
	Min	5	1	1
	Med	9,0	8,0	8,0
	Max	13	10	13

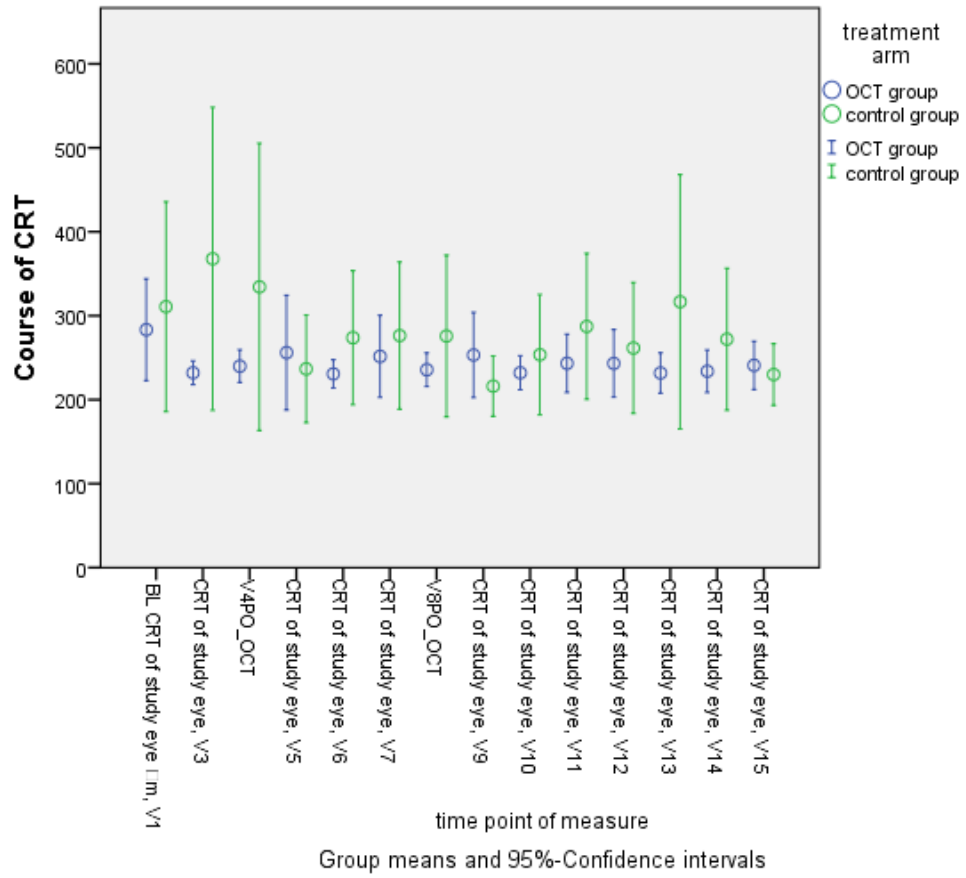
			arm allocation		
			OCT group	control group	total
	Valid N		9	9	18
Neovascularization observed (inbetween V3 and V15)	no	No	9	9	18
		%	100,0%	100,0%	100,0%
	yes	No	0	0	0
		%	0,0%	0,0%	0,0%
	data pending/ missing	No	0	0	0
		%	0,0%	0,0%	0,0%
Number of AE per patient	no AE reported	No	0	0	0
		%	0,0%	0,0%	0,0%
	1	No	1	0	1
		%	11,1%	0,0%	5,6%
	2	No	2	0	2
		%	22,2%	0,0%	11,1%
	3	No	0	2	2
		%	0,0%	22,2%	11,1%
	4	No	1	2	3
		%	11,1%	22,2%	16,7%
	5	No	2	0	2
		%	22,2%	0,0%	11,1%
	6	No	1	1	2
		%	11,1%	11,1%	11,1%
	7	No	1	0	1
		%	11,1%	0,0%	5,6%
	8	No	0	1	1
		%	0,0%	11,1%	5,6%
	9	No	1	0	1
		%	11,1%	0,0%	5,6%
	10	No	0	2	2
		%	0,0%	22,2%	11,1%
	13	No	0	1	1
		%	0,0%	11,1%	5,6%
Number of AE with causality to study IMPs p.pt.	no AE reported	No	0	0	0
		%	0,0%	0,0%	0,0%
	0	No	6	6	12
		%	66,7%	66,7%	66,7%
	1	No	3	3	6
		%	33,3%	33,3%	33,3%
Number of SAE per patient	no SAE reported	No	8	8	16

			arm allocation		
			OCT group	control group	total
		%	88,9%	88,9%	88,9%
	1	No	1	0	1
		%	11,1%	0,0%	5,6%
	2	No	0	1	1
		%	0,0%	11,1%	5,6%
(at least) one SAE with causality to study IMPs p.pt.	no	No	1	1	2
		%	100,0%	100,0%	100,0%
	yes	No	0	0	0
		%	0,0%	0,0%	0,0%

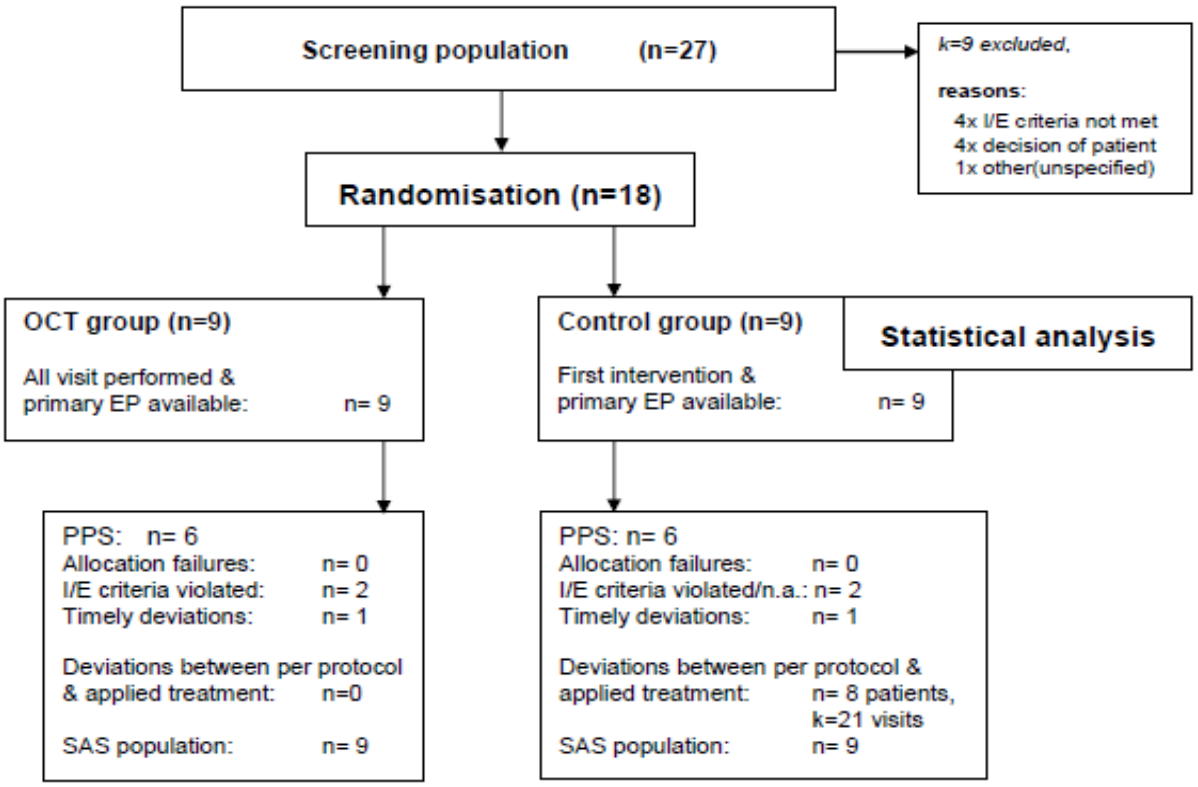
Course of BCVA during the trial



course of CRT during the trial



Consort flow chart of the RabOCT trial



Attachment to trial synopsis

Information about Amendments during the trial

Re-treatment with intravitreal application of ranibizumab guided by morphological macular changes documented by optical coherence tomography (OCT) in patients with macular edema due to branch retinal vein occlusion

Study Code: RabOCT

Investigational product: Ranibizumab (Lucentis®)

Indication: patients with macular edema secondary to branch retinal vein occlusion (BRVO)

Phase of the clinical tria: IIb

EudraCT-No: 2012-005439-10

Sponsor of the clinical trial:

University of Leipzig
Ritterstr. 26, 04109 Leipzig

Coordinating Investigator:

Prof. Dr. med. Peter Wiedemann

Authors of the trial synopsis:

Prof. Dr. med. Peter Wiedemann /
Dr. Annegret Franke / Dr. Marizel Schwarzkopf

Start and End of clinical trial:
Start of clinical trial: 10-Oct-2013
End of clinical trial: 17-May-2016

Amendment 1 (18.12.2013)

Change of Coordinating Investigator and Authorised Representative of the Sponsor. PD Dr. habil. Matus Rehak left the Department of Ophthalmology of the University of Leipzig on January 2014. Therefore Prof. Dr. med. Peter Wiedemann took over the responsibilities of the coordinating investigator as well as of the authorised representative of the sponsor. Furthermore, some corrections and clarifications were described.

Amendment 2 (03.12.2015)

Change in number of recruited patients and prolongation of trial duration and stop of recruitment phase. The recruitment of patients was low and although the recruitment phase was prolonged, 18 instead of 24 patients were allocated to the study up to May 2015. Therefore, it was decided to stop the recruitment of further patients. All patients enrolled up to this time point completed the trial according to the protocol. The statistical analyses were performed with these 18 patients.