Clinical report

Version 1.0

Ranibizumab and Vitrectomy in the Therapy of Diabetic Macular Edema

The R A V I T - D M E - Trial

EUDRACT Number 2012-001006-24

In the following, the active substance used as the clinical trial product is ranibizumab.

The trade name of the registered product with the active substance ranibizumab is Lucentis.

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1. List of abbreviations

AE	Adverse Event
AMG	German Drug Legislation
AMD	Age-related macular degeneration
BCVA	Best-corrected visual acuity
CI	Coordinating Investigator
CNV	Choroidal neovascularization
CRF	Case Report/Record File
DR	Diabetic Retinopathy
DSMB	Data Safety and Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
ETDRS	Early Treatment Diabetic Retinopathy Study
EMA	European Medicines Agency
FA	Fluorescein angiography
FAS	Full Analysis Set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IDDM	Insulin Dependent Diabetes Mellitus
ILM	Internal Limiting Membrane
IOL	Intraocular Lens
IOP	Intraocular Pressure
IRC	Independent Reading Center
ITT	Intention-to-treat
NIDDM	Non Insulin Dependent Diabetes Mellitus
OCT	Optical coherence tomography
PI	Principal Investigator
PDT	Photodynamic therapy
PPS	Per Protocol Set
RCT	Randomized controlled trial
SAE	Serious Adverse Event
SAERF	Serious Adverse Event Report Form
SD OCT	Spectral Domain Optical Coherence Tomography
SNVM	Subretinal Neovascular Membrane
SOP	Standard Operating Procedure
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
Y/N	Yes/No (answer options in the CRF)

Background

Diabetic retinopathy (DR), a microvascular complication of diabetes, is a leading cause of vision loss and blindness in the working-age population worldwide. Diabetic macular oedema (DME), swelling of the central retina, is a frequent manifestation of diabetic retinopathy and an important cause of impaired vision in individuals with diabetes.

The primary treatment of DME and macular oedema secondary to branch retinal vein occlusion (BRVO), supported by the Branch Retinal Vein Occlusion Study has been laser photocoagulation, supported by the Early Treatment Diabetic Retinopathy Study (ETDRS) [1]. Scatter laser photocoagulation reduced the risk of severe visual loss. The 5-year rates of severe visual loss were low whether scatter treatment was given early (2.5%) or deferred until the development of high-risk proliferative retinopathy (4%). A careful follow-up provided this therapy proved to be safe to defer scatter treatment until retinopathy approaches or reaches the high-risk stage.

However, improvement in VA cannot be observed. In search for a therapy also improving VA the steroid triamcinolone was tested. Both retrospective and short prospective studies showed an initial beneficial effect on retinal thickening and VA after 4 months, which diminished thereafter. A prospective long-term study directly comparing laser photocoagulation with triamcinolone[2] however showed a vision gain of 5 letters in the laser group. After 3-years the triamcinolone and the laser group showed no significant differences which argues against a long-term benefit of intravitreal triamcinolone relative to laser photocoagulation (focal/grid). Due to the more favourable profile of side effects the Diabetic Retinopathy Clinical Research Network (DRCR.net) gave preference to the laser treatment.

DME caused by age-related macular degeneration (AMD) is successfully treated by VEGF inhibitors such as bevacizumab and ranibizumab. Ranibizumab was approved for the treatment of DME [3]. The respective ophthalmological societies recommend ranibizumab as the first line treatment for treating DME with the fovea affected[4].

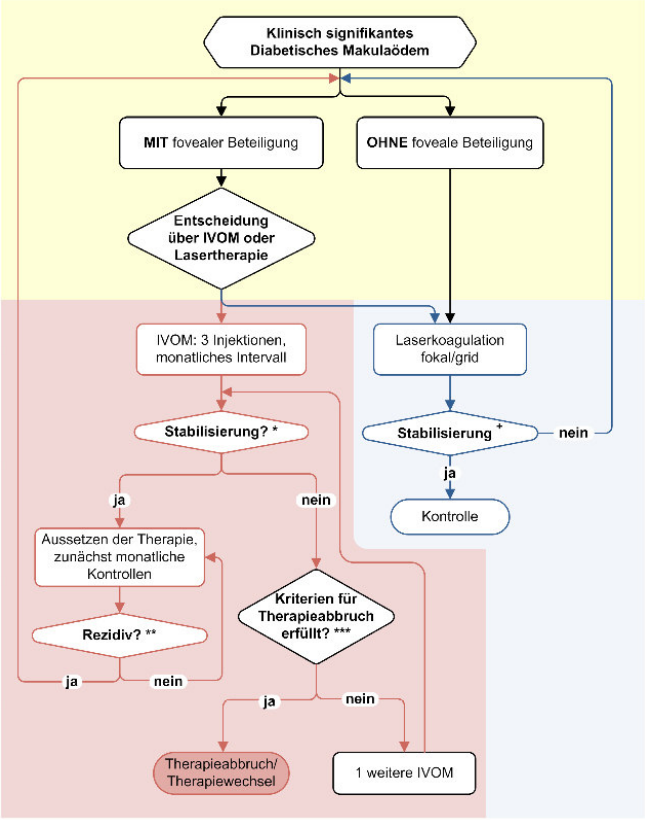

Fig. 1 Treatment algorithm, recommended by Deutsche Ophthalmologische Gesellschaft, Retinologische Gesellschaft, Berufsverband der Augenärzte, December 2010).

Ranibizumab is administered as a single injection intravitreally. The injection is given monthly three times and again, if the condition is found to be worsening. This therapeutic approach is based phase III study [5]. Since anti VEGF therapy does not cure DME but rather suppresses its symptoms, it is necessary that the patient's vision be monitored monthly to decide whether ranibizumab has to be continued. The study data suggest that during the first year 6 to 7 injections are necessary but no reliable data from clinical experience exist on this topic[5]. Many patients are unable to comply with such dense consultations.

Vitrectomy, i.e. surgical removal of some or all of the vitreous has been used for decades in the treatment of DME. Based on observation that DME is more common in eyes with attached and taut posterior hyaloid membrane retina surgeons used vitrectomy for visual improvement and resolution of DME by peeling off the posterior hyaloid membrane [6]; [7] The mechanism of action is not completely understood. Mechanical factors may support the development of DME [7] but the intraocular VEGF level seems to be important as well [8]. By vitrectomy the VEGF level may be reduced in the long term [9]. Thus, a preceding vitrectomy might reduce - due to a lower VEGF level- the number of intravitreal ranibizumab injections needed for the therapeutic effect. On the other hand, vitrectomy might reduce the half-life of ranibizumab in the eye resulting in a lower efficacy of the drug. For ethical reasons there will be no data for the half-life of ranibizumab in human vitrectomized eyes compared to non-vitrectomized eyes. In rabbit eyes half-life of antibiotics were significantly reduced by vitrectomy [10]. However it is unclear whether such data are predictive for other compounds and species.

At the time of the study protocol, several prospective and retrospective studies suggest a positive effect of vitrectomy on the VA in the course of DME. Currently, retina surgeons discuss the advantages and practical issues of additionally removing the inner limiting membrane of the retina, the lamina limitans interna (ILM). However other studies show inconsistent results [11-25]

Analysis of own observational data

In a retrospective case-control study 331 DME eyes undergoing vitrectomy (2001-2006) in the author`s unit were investigated, primarily differentiated between preoperative VA of above or below 0,3 (more data are given in the Study Procotcol). Eyes above this value showed a significantly worse VA outcome during the first weeks after surgery, which was not compensated completely up to one year after surgery. In contrast, eyes with a VA of 0,3 or less postoperatively showed a moderate increase in VA, which was stable up to one year

In addition development of VA after vitrectomy and ILM peeling for DME was followed up to one year. Eyes with preoperative VA of 0,3 or less showed a slight but statistically significant improvement of VA. In contrast eyes with a better preoperative VA showed a significant vision loss (P values compared to preoperative VA; internal process analysis, unpublished). Similarly, mean BCVA was analysed over 5 years for a smaller group of patients (51 eyes). It could be shown that vitrectomy had a stabilizing effect in eyes with a preoperative VA of 0,3 or less without any significant vision loss during five years

Another analysis of our own long-term data showed that in 47 % of vitrectomized eyes a further treatment of diabetic maculopathy was necessary: In 10 % of the cases a disseminated laser coagulation therapy was performed because of developing peripheral diabetic retinopathy. 22 % received additional focal laser treatment and 24 % were treated with triamcinolone over a period of 5 years after vitrectomy (Figure 2). Compared to the current therapeutic standard with Ranibizumab with a mean number of 7-8 injections in the first year of therapy [5], this number of follow-up therapies is extremely small.

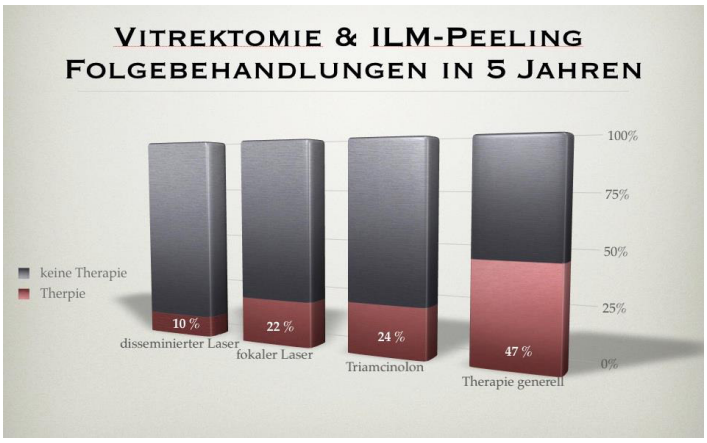

Figure 2. 5-year follow-up of diabetic retinopathy (and maculopathy) after vitrectomy and ILM peeling for diabetic macular oedema during 5 year follow-up. In the majority of cases no further therapy was necessary (n=53). (Author´s data, unpublished).

2. Study purpose

The study was designed to evaluate the efficacy of vitrectomy including ILM-peeling plus ranibizumab administered intravitreally in comparison to ranibizumab alone with respect to the number of doses of ranibizumab, to the change of visual acuity measured by the number of letters 12 months after first treatment compared with baseline (primary endpoints) and other secondary clinical outcome parameter. The hypothesis was that vitrectomy in combination with ranibizumab is superior to ranibizumab alone.

3. Sponsor of the study

Sponsor of this multicentre trial is Augenklinik Universitätsallee, Parkallee 301, 28213 Bremen.

4. Study design

The study was a randomized prospective controlled 1:1 two-arm, multicenter trial. The Coordinating Investigator is Private Lecturer MD Andreas Schüler. The trial center, directing and controlling study conduction, handling of study drug and treatment of patients, is located at the Augenklinik Universitätsallee, Parkallee 301, 28213 Bremen. According to the statistical assessment plan, 110 patients with visual impairment due to Diabetic macular oedema (DME) were to be enrolled. The trial duration was planned to be 12 months.

Study population

The study population was planned to consist of a consecutively recruited group of adult patients with visual impairment due to DME. Patients were to be treated in an outpatient setting.

Inclusion criteria

- Patients aged 18 years and older
- Diabetes mellitus type 2 (insulin-dependent diabetes mellitus (IDDM) and noninsulin-dependent diabetes mellitus (NIDDM))
- Clinical significant diabetic macular oedema (diffuse or focal)
- Visual acuity (decimal) reduced by diabetic macular oedema to ≤ 0,3 and ≥ 0,05 (LogMar ≤ 1,3 and ≥ 0,5) stated by EDTRS charts.
- The investigator has to be clinically convinced about vitrectomy might be beneficial and appropriate for the patient enrolled.
- Signed informed consent

Exclusion criteria

The list of exclusion criteria is given in the attached Study protocol.

5. Study treatment

Patients were assigned to one of the following two treatment arms in a ratio of 1:1.

Arm A

Initial Vitrectomy with internal limiting membrane (ILM) peeling - on an inpatient or outpatient basis with intraoperative administration of ranibizumab 0,5 mg intravitreally. After vitrectomy, 2 further injections of 0,5 mg Ranibizumab every 4 weeks will be performed, according to the label of Ranibizumab (Lucentis ®). After the first 3 obligatory treatments with Ranibizumab,

examination will be performed every 4 weeks. Further injections will be given, according to the label of Ranibizumab (Lucentis ®), if indicated.

Arm B
Three initial injections of 0,5 mg Ranibizumab every 4 weeks will be performed, according to the label of Ranibizumab (Lucentis ®). After the first 3 obligatory treatments with Ranibizumab, examination will be performed every 4 weeks. Further injections will be given, according to the label of Ranibizumab (Lucentis ®), if indicated

6. Study protocol

The complete protocol of the RAVIT-study is documented in the attached „Study protocol“

7. Statistical procedures

Descriptive statistics and treatment group comparisons

Every variable (item) documented in the CRF was analysed by descriptive methods. Number of observations, mean, standard deviation, maximum, minimum, median and interquartile range were tabulated for quantitative data. Counts and column percentages were presented for categorical data. These summaries are given for the total data set and separately for each treatment group, stratum and department.

Treatment groups were compared with respect to baseline efficacy variables, diagnoses, age and gender. The comparison was performed in a descriptive manner.

Analysis of Primary Endpoints

Superiority of vitrectomy in combination with ranibizumab over ranibizumab with respect to the number of intravitreal injections was tested by the Wilcoxon-Mann-Whitney-U-Test.

Non-inferiority of vitrectomy plus ranibizumab to ranibizumab in BCVA mean change from baseline at month 12 were claimed if the one-sided 97.5% confidence interval based on the large-sample normal approximation excludes the non-inferiority of -5 letters.

Analysis of Secondary Endpoints, Protocol Violations

Summaries and confidence intervals were to be calculated for all efficacy variables. Between-group comparisons were to use analogue methods but keep an exploratory character.

Safety analyses

Safety and vital signs analyses were performed on all treated patients. AEs were to be classified and analysed by organ system, severity and relation to treatment. Pre-post-differences were calculated for laboratory data.

Deviations from the protocol for the administration of ranibizumab were described on the appropriate Visit Form of the CRF.

Concomitant medications, reason for use, start date, and stop date (or ‘on-going’) of medications used within 30 days prior to visit 1 or during the study were collected on the Concomitant Medications Form of the CRF.

Monitoring and handling of safety data

To ensure patient's safety, every SAE occurring after the patient is randomized and until 4 weeks after the patient has stopped study participation, were reported to the Coordinating Investigator (Augenklinik Universitätsallee, Parkallee 301, 28213 Bremen) within 24 hours of noticing its occurrence.

SAEs experienced later than 4 weeks after the patient has stopped to participate had to be reported to the CI as well, independent of whether the investigator suspects a causal relationship to the study drug or not. In this case, in contrast, the time lag between observation and report to the CI, could be up to seven days.

Each recurrence, complications or further aggravation of the initial SAE was to report as follow-up to the original SAE within 24 hours after the investigator was informed.

All information about SAEs was recorded on the Serious Adverse Event Report Form (SAERF). The investigator had to assess the potential relationship to study drug application or to study procedures.

The original copy of the SAERF, together with the confirmation of successful fax transmission is kept with the CRF at the study site. The follow-up information was sent by using a new SAERF clearly defining this report as a follow-up information to an already reported SAE (including the date of the initial report).

Reports on recurrence, complications or further aggravation of the initial SAE had to be sent to the CI clearly marked as follow-up to the original SAE regardless of when it occurred.

Data review

A Site Initiation Visit was held, by the study team, at any study site before study initiation. At the occasion of a Study Initiation, all necessary information on protocol, CRFs, SAE reporting, were given and the respective forms were reviewed with all investigators and their staff. During the study, a member of the study team visited the study site at regular time intervals to ensure accordance to GCP.

Data collection

The CRFs were stored at the Department of Pharmacology in the Klinikum Bremen-Mitte, one copy being retained at the investigational site. When the CRFs arrived at the Department of Pharmacology, Klinikum Bremen-Mitte, their receipt was recorded according to GCP.

Database management and quality control

Data from the CRFs were entered into the study database by members of the Statistics Department following the internal standard operating procedures.

All errors or missing data were entered on Data Query Forms, which were sent to the investigator's site for correction or addition. Copies of the completed and signed Data Query Forms are stored together with the CRFs at the investigator's site and the originals were submitted to the Statistics Department where the corrections and additions were entered into the database. A quality control audit of 10% of all data in the database was made by the staff of the Statistics Department prior to locking the database. AEs were coded using the WHO dictionary. All protocol violations were determined. After locking no changes to the main database were allowed.

Amendments to the protocol

Protocol changes were documented by a written Protocol Amendment. Due to the problems with patient recruitment, one amendment to the study protocol was written and approved in June 2014.

The changes related to exclusion criteria. The time distance between previous treatment with intravitreal steroids of VEGF-inhibitors or a previous cataract surgery and the inclusion of patients in the study was reduced from 6 months to 3 months. YAG-laser capsulotomy was allowed, as far as this laser treatment was performed more than 3 months before the patient recruitment for the study.

8. Summary of RAVIT-DME Study results

Study course and reasons for early termination

The study protocol was written and finalized on 12.02.2013. After approval of the protocol by the Ethikkommission des Landes Bremen on 15.10.2013 and permission of the Paul Ehrlich Institut on 14.08.2013, eight study centres in Germany were initiated. The first patient was enrolled in the study on 07.04.2014. Based on power calculations, it was planed, to enrol 110 patients in the study with a scheduled inclusion of the last patient in August 2016.

After the onset of the study, it became obvious, that the recruiting of patients for the RAVIT-DME study was more difficult than expected. Between 07.04.2014 and 03.08.2015, only 5 of the eight study centres were able to include a total of 15 patients into the study. Keeping in mind that the scheduled timeline of the study should have reached a number of more than 60 patients, several attempts to improve the recruitment (study meetings, telephone conferences) showed no beneficial effect on the recruitment. Due to this lack of patients, that could be included in the study, the sponsor decided for an early termination of the study. It was obvious, that it was impossible to finalize the study, even within a further prolonged timeline. The last patient was enrolled in the study on 03.08.2015 and had his last visit on 01.08.2016. After the closing of all study centres, descriptive statistical analysis of the available data was performed and summarized in in a statistical report by the responsible Centre of Competence for Clinical Trials, Bremen (see supplement).

In fact, instead of the planed 110 patients, just 15 patients could be enrolled in the study. With this low number of patients, no conclusive results were available. Due to the small sample size, only the descriptive analyses planned in the SAP could be conducted. Significance tests planned in the SAP were also not done. No PPS evaluation was done because only two patients remain in the per-protocol-set that both belong to arm A.

Detailed data of the statistical analysis are listed in the statistical report in the supplement of this clinical report.

Patient characteristics

Before cessation of the study, a total 15 Patients were enrolled in 4 of the 8 study centres (8 female, 7 male). Mean age was 68,7 ± 7,4 years.
In the vitrectomy + Ranibizumab group, 6 patients, and in the Ranibizumab group 5 patients completed the study. Seven patients were randomized to the vitrectomy + Ranibizumab group, 6 patients were randomized to the Ranibizumab alone group.
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Basic demographic and ophthalmological data

Gender and ethnicity

Demographics		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
Gender	Female	3	42.9	5	62.5	8	53.3
	Male	4	57.1	3	37.5	7	46.7
Ethnicity	Caucasian	7	100.0	7	87.5	14	93.3

Demographics		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
	Arabic	0	0.0	1	12.5	1	6.7

Overall the number of males and females is similar. Only one patient in the study was not Caucasian.

Age

Age in years	N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	7	66.3	7.4	53.0	64.0	66.0	74.0	75.0
Ranibizumab	8	70.9	7.2	61.0	65.0	70.5	77.0	81.0
Overall	15	68.7	7.4	53.0	64.0	68.0	75.0	81.0

There was an age difference of about four years in the mean and median between the two treatment groups. The 25% and 75% quantiles were similar.

Laterality

Study eye	Vitrectomy + Ranibizumab		Ranibizumab		Overall	
	N	%	N	%	N	%
left	4	57.1	4	50.0	8	53.3
right	3	42.9	4	50.0	7	46.7
Total	7	100.0	8	100.0	15	100.0

The numbers of left and right study eyes were similar between the two treatment groups. Fundus photography was done at baseline for all 15 patients.
They were similar between the treatment groups except for the occurrence of retinal lesions, which were more frequent in the vitrectomy + Ranibizumab arm.
Baseline values from the optical coherence tomography are given below. The difference between the treatment groups is overall small compared to the standard deviation. Only for the superior quadrant of the macula a distinct difference in the mean (and median) is observed which, given the small sample size, is still explainable by chance.

Previous therapies of study eyes

DME treatment in study eye	Vitrectomy + Ranibizumab		Ranibizumab		Overall	
	N	%	N	%	N	%
0	2	28.6	4	50.0	6	40.0
1	1	14.3	3	37.5	4	26.7
2	4	57.1	0	0.0	4	26.7
4	0	0.0	1	12.5	1	6.7
Total	7	100.0	8	100.0	15	100.0

Numbers of previous DME treatments were equally distributed between the two groups.

Ophthalmological findings at baseline

Ophthalmological examinations (baseline)		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
Diagnosis	focal	1	14.3	2	25.0	3	20.0
	diffus	6	85.7	6	75.0	12	80.0
	both	0	0.0	0	0.0	0	0.0
Lens	clear	0	0.0	0	0.0	0	0.0
	cataract	5	71.4	4	50.0	9	60.0
	IOL	2	28.6	4	50.0	6	40.0
Retinal lesions	Yes	4	57.1	1	12.5	5	33.3
	No	3	42.9	7	87.5	10	66.7

Intraocular pressure was normal for all patients. The classification of diabetic macular oedema as focal or diffuse was equally distributed between the groups. Slitlamp examination had normal age related results for all 7 patients in the vitrectomy + Ranibizumab arm, and 6 patients in the Ranibizumab arm. In the Ranibizumab arm, there was one case of dermalaxia.

Concomitant diseases

Frequency of concomitant diseases by system organ class	Vitrectomy + Ranibizumab		Ranibizumab		Overall	
	N	%	N	%	N	%
Cardiac disorders	1	9.1	0	0.0	1	3.6
Endocrine disorders	4	36.4	7	41.2	11	39.3
Gastrointestinal disorders	0	0.0	1	5.9	1	3.6
Infections and infestations	0	0.0	1	5.9	1	3.6
Metabolism and nutrition disorders	2	18.2	2	11.8	4	14.3
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	1	9.1	0	0.0	1	3.6
Reproductive system and breast disorders	0	0.0	1	5.9	1	3.6
Vascular disorders	3	27.3	5	29.4	8	28.6
Total	11	100.0	17	100.0	28	100.0

Number of concomitant diseases per patient	Vitrectomy + Ranibizumab		Ranibizumab		Overall	
	N	%	N	%	N	%
0	0	0.0	3	37.5	3	20.0
1	3	42.9	0	0.0	3	20.0
2	4	57.1	0	0.0	4	26.7
3	0	0.0	3	37.5	3	20.0
4	0	0.0	1	12.5	1	6.7
6	0	0.0	1	12.5	1	6.7
Total	7	100.0	8	100.0	15	100.0

Concomitant diseases of patients were comparable between the groups.

In summary, basic characteristics and ophthalmological findings were similar when comparing the two treatment groups. Small differences between the groups can be explained by chance and the small sample size.

Visual acuity

Results of the descriptive statistical analysis of the RAVIT-DME study showed a lower improvement of mean visual acuity in the vitrectomy group at one year. Mean initial VA was slightly lower in the Vitrectomy + Ranibizumab group (46.4 ± 9,2 ETDRS letters) compared to the Ranibizumab group (52.3 ± 17 ETDRS letters). At one year (Visus 13), VA improved in both groups. Final VA was 52.7 ± 15.4 in the vitrectomy group and 67,0 ±5,8 in the Ranibizumab alone group.

Best corrected visual acuity at baseline

BCVA in ETDRS letters at baseline	N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	7	46.4	9.2	35.0	38.0	48.0	50.0	63.0
Ranibizumab	8	52.3	17.0	19.0	45.5	58.0	62.5	67.0
Overall	15	49.5	13.8	19.0	38.0	50.0	60.0	67.0

Change of visual acuity from baseline at month 12

Mean change from baseline in BCVA at month 12	N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	7	6.9	13.6	-12.0	-5.0	12.0	22.0	22.0
Ranibizumab	8	4.9	8.6	-10.0	-1.5	8.0	11.0	14.0
Overall	15	5.8	10.8	-12.0	-5.0	8.0	12.0	22.0

Overall the mean change from baseline at one year is somewhat larger in the vitrectomy + ranibizumab group than in the group, treated with ranibizumab alone with a mean difference of 2 letters. Due to the small number patients, no reliable lower confidence bound can be determined and hence non-inferiority at a margin of 5 letters cannot be verified.

Central macular thickness

Central macular thickness at baseline

Retinal thickness at baseline		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
central	**Vitrectomy + Ranibizumab**	7	455.1	200.9	150.0	311.0	447.0	631.0	683.0
	Ranibizumab	8	491.3	146.4	313.0	416.5	451.5	538.0	805.0
infra	**Vitrectomy + Ranibizumab**	7	444.4	100.4	342.0	362.0	410.0	543.0	601.0
	Ranibizumab	8	447.0	128.1	331.0	356.0	403.5	506.0	714.0
nasal	**Vitrectomy + Ranibizumab**	7	447.9	111.9	310.0	347.0	418.0	577.0	610.0
	Ranibizumab	8	431.3	109.5	337.0	351.0	394.0	494.0	635.0
supra	**Vitrectomy + Ranibizumab**	7	496.0	99.1	361.0	368.0	524.0	537.0	638.0
	Ranibizumab	8	442.6	158.2	287.0	336.0	396.5	514.0	761.0
temporal	**Vitrectomy + Ranibizumab**	7	465.4	144.9	286.0	319.0	489.0	586.0	649.0
	Ranibizumab	8	477.6	160.5	377.0	396.5	423.5	470.5	863.0

Change of central macular thickness compared to baseline
(Arm A: vitrectomy + Ranibizumab, Arm B: Ranibizumab)

Change from baseline for retinal thickness in µm		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
central	Arm A	6	-147.2	306.4	-445.0	-407.0	-171.5	-87.0	399.0
	Arm B	5	-200.8	148.0	-438.0	-232.0	-151.0	-136.0	-47.0
infra	Arm A	6	-96.2	166.1	-259.0	-251.0	-102.5	-56.0	194.0
	Arm B	5	-93.4	103.8	-263.0	-124.0	-30.0	-28.0	-22.0
nasal	Arm A	6	-74.5	205.5	-268.0	-265.0	-89.5	-27.0	292.0
	Arm B	5	-76.8	78.1	-186.0	-118.0	-73.0	-6.0	-1.0
supra	Arm A	6	-146.8	169.1	-322.0	-262.0	-176.5	-105.0	161.0
	Arm B	5	-89.2	117.6	-296.0	-73.0	-37.0	-23.0	-17.0
temporal	Arm A	6	-150.8	179.9	-272.0	-270.0	-231.5	-89.0	189.0
	Arm B	5	-108.4	50.7	-178.0	-136.0	-103.0	-77.0	-48.0

Change of macular thickness at month 12 (visit 13) compared to baseline

All patients had initially a high macular oedema due to their diabetic maculopathy, with a thickness in OCT of > 400 µm. Results of the descriptive statistical analysis of the RAVIT-DME study showed a faster reduction and initially more pronounced reduction of the central macular thickness in the vitrectomy group (details in Statistical Report). Due to the low number of patients per group, no further conclusions can be drawn from this data.

Number of Ranibizumab injections

Number of injections	N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	7	9.0	2.7	4.0	8.0	9.0	12.0	12.0
Ranibizumab	8	7.9	2.5	5.0	5.5	8.0	9.5	12.0
Overall	15	8.4	2.6	4.0	6.0	9.0	10.0	12.0

Number of Ranibizumab injections

All patients received Ranibizumab injections during the study period of one year. The mean number of injections was 9.0 in the vitrectomy group and 7.9 in the Ranibizumab alone group.

This might be a signal, that treatment of DME in vitrectomized eyes needs a higher number of injections of Ranibizumab. This can probably be explained by the known increased clearance of intravitreal drugs in eyes after vitrectomy.

Vitrectomy:

Vitrectomy has been conducted for all 7 patients in the surgical group, three with 20G, two with 23G, another two with 25G. All 7 patients received ILM-peeling, an intravitreal administration of 0.5 mg Ranibizumab. None of the patients met an intraoperative exclusion criterion and there were no intraoperative complications. Postoperative intraocular pressure was normal for all 7 patients. No surgical complications were recorded.

Details about vitrectomy procedures:

Lens	N	%
pseudophakic	2	28.6
remained phakic	2	28.6
phako with IOL	3	42.9
Total	7	100.0

Patient	Lens	Surgical removal of after cataract in case of pseudophakic lens
1	pseudophakic	No
37	pseudophakic	No

Intraoperative attachment of vitreous to macula

Vitreous body intraoperative	N	%
attached	5	71.4
detached	2	28.6
Total	7	100.0

Dyes used for intraoperative staining for ILM-Peeling

Stain used in vitrectomy	N	%
trypan blue	0	0.0
brilliant blue	2	28.6
both	5	71.4
none	0	0.0
Total	7	100.0

Diameter of ILM peeling zone

Patient	ILM peeling	Estimated papilla diameters
1	Yes	4
3	Yes	5
4	Yes	4
19	Yes	10
25	Yes	.
37	Yes	2
38	Yes	2

Focal laser treatment during vitrectomy

Focal or disseminated laser treatment	N	%
Yes	0	0.0
No	7	100.0
Total	7	100.0

Additional (disseminated) laser treatment during vitrectomy

Paracentral laser treatment	N	%
Yes	0	0.0
No	7	100.0
Total	7	100.0

Tamponades used during vitrectomy

Tamponade	N	%
none	7	100.0
SF6	0	0.0
C2F5	0	0.0
C3F8	0	0.0
silicone	0	0.0
Total	7	100.0

Vitrectomy was uneventful in all cases; no adverse intraoperative events were recorded.

Adverse events

There were 7 patients with adverse events, 4 in the vitrectomy + Ranibizumab group, and 3 in the Ranibizumab group. One patient in vitrectomy + Ranibizumab group had 9 AEs, whereas all other patients had at most two AEs. None of the documented AEs were considered to be related to the study treatment.

A patient-wise listing of all adverse events is in Listing 3 at the statistical report (supplement). Only two AEs were severe (both in the Ranibizumab alone group). None of the AEs caused a therapy stop, 5 AEs (four in the vitrectomy + Ranibizumab group and one in the Ranibizumab group) caused a drug administration delay. There were no drop-outs caused by an AE/SAE. 7 AEs (five in vitrectomy + Ranibizumab group, and two in Ranibizumab group) required a drug therapy. The recovery from two AEs (one in the vitrectomy + Ranibizumab group and one in the Ranibizumab group) was with sequelae and for 6 AEs (all in the Ranibizumab group) there was no recovery until study end.

Efficacy Results

In sample of 15 patients vitrectomy plus Ranibizumab lead to a larger number of injections as Ranibizumab alone. Due to the small and unbalanced sample size in the PPS, the primary non-inferiority analysis could not be done. In the FAS (sensitivity analysis) the change from baseline in the BCVA in EDTRS letters was similar between the treatment groups with a slightly higher improvement of the VA at on year in the vitrectomy + Ranibizumab group. Because of the small sample size no hypothesis tests and no confidence intervals were calculated.
The only noticeable difference in the secondary endpoints was a more pronounced decrease in retina thickness in the vitrectomy + Ranibizumab group in most quadrants, in particular at 4 months after treatment start.

Safety results
Vitrectomy plus Ranibizumab lead to a larger number of non-serious AEs. However, the number of patients with AEs was similar in the treatment groups. The number of SAEs was similar as well. No AEs and SAEs were reported as treatment related.

Complete statistical Results

The complete statistical report is listed in the attached statistical report.

9. Summary and Discussion

Due to the small sample size it is not possible to draw conclusive conclusions. In addition, study compliance with regard to the timing of the visits was rather poor. We therefore restrict the discussion to the descriptive findings without any intention for generalizations.

The efficacy data, in particular the number of injections, are not in line with the study hypothesis that vitrectomy with inner limiting membrane peeling reduces the number of doses of Ranibizumab: the number of injections for patients in the Ranibizumab + vitrectomy group was in average higher than for the patients in the control group. The same holds true for the number of patients with a treatment-free interval of 3 months which was slightly smaller in the Ranibizumab + vitrectomy group. The BCVA change from baseline at 12 months was similar for both treatment groups in FAS (sensitivity analysis) with a slightly higher improvement in the vitrectomy + ranibizumab group. Nevertheless, the mean difference of 2 letters in improvement of the visual acuity between the groups is clinically not relevant. In the PPS no comparison was possible since no patients remained in the control arm.

With regard to the secondary endpoints only the change in retinal thickness showed some noticeable treatment difference: Retinal thickness appeared to decrease more in the Ranibizumab + vitrectomy group in the majority of quadrants, in particular after 4 months. There was no clear treatment difference in health related quality of life (VFQ25) and there were no treatment related AE or SAE reported (details in Statistical Report).

Vitrectomy plus Ranibizumab lead to a larger number of AEs as vitrectomy alone. However, the number of patients with AEs was similar between the treatment groups. The number of SAEs was similar as well. No AE or SAE was reported as treatment related.

In conclusion, there is no indication that vitrectomy plus Ranibizumab is more efficient than Ranibizumab alone. With regard to safety, vitrectomy plus Ranibizumab may lead to more non-severe AEs. However, the observation is based on a single patient and all AEs were reported as unrelated to treatment. For the 15 patients in the study there was no significant safety signal observed.

Our limited results are consistent with recently published data about the effect of vitrectomy alone on central macular thickness.

Kumagai et al. analysed the outcome of 168 eyes with diabetic macular edema after vitrectomy with and without peeling of the internal limiting membrane. In the ILM-peeling group, visual acuity improved significantly from 0,55±0,31 to 0,35 ± 0,35 ($p<0,0001$) after one year, and in the group without ILM-peeling during vitrectomy from 0,55±0,41 to 0,43±0,38 ($p=0,01$) after one year. There was no significant difference between the two groups regarding visual acuity [26].

Ulrich analysed the outcome of 31 eyes with diabetic macula edema after vitrectomy with ILM-peeling and showed a significant reduction of the retinal thickness form 427 to 357 µm ($p=0,03$) and an improvement of visual acuity from 20(82 to 20/49 ($p=0,03$) after vitrectomy [27].

Bonnin et al retrospectively analysed the long-term outcome of vitrectomy for DME in 73 eyes. With a mean follow-up of 5,3±2.4 years, After 3 years, VA had improved from 0,78 to 0,58 ($p<0,0001$) in a group with tractional DME and from 0,75 to 0,45 ($p<0,0001$) in the group with nontractional DME. At the time of last visit, there was no difference in regard to VA and macular thickness between the two groups [28].

Ghassemi found in a retrospective analysis of 11 eyes a significant reduction of central macular thickness after vitrectomy for DME with a non-significant change of visual acuity [29]. These latest publications about vitrectomy for DME showed, similar to more recent publications, a more pronounced reduction of the central macular thickness. The effect on visual acuity was inconsistent. Beside studies that showed a significant improvement on VA, there are studies that could not find a significant improvement [27] [28] [29]

There is an ongoing discussion about the effect of ILM-peeling during vitrectomy for non-tractional diabetic macular edema. In a review and meta-analysis about this topic, Rinaldi and coworkers summarised 4 studies with 672 patients. They conclude, that VA outcomes after vitrectomy for DME showed no significant differences in the vitrectomy-groups with and without ILM-Peeling for DME [30]. Another meta-analysis of the so far published data from Nakajima analysed 741 patients treated with vitrectomy with and without ILM-peeling. Superiority in postoperative VA was 0,04 logMAR for the ILM-peeing group, compared to the non-peeling group. There was no significant difference on postoperative central macular thickness of reduction of macular thickness between the groups [31]. Both authors recommend further controlled studies regarding role of vitrectomy and ILM-peeling for DME.

Based on our limited results, we can confirm these conclusions. In our study, vitrectomy in combination with intravitreal ranibizumab injections achieved an improvement of the visual acuity after one year. Nevertheless, due to the small sample size, we are not able to confirm or reject the initial hypothesis of the study, that vitrectomy in combination with ranibizumab is superior to ranibizumab alone.
Further controlled studies will be necessary to come to a conclusive result, regarding the role of vitrectomy in the treatment of diabetic macular oedema. Currrently it is a valid treatment option, reserved for selected cases with a proven tractive component of the macular edema, either by epiretinal membranes or traction of the vitreous on the macula. In the majority of the non-tractional cases of diabetic macular edema, standard therapy with either focal laser therapy or intravitreal injection of VEGF-inhibitors is still recommended as standard care.
One interesting observation of our prospective case series was, that a higher number of intravitreal injections in the group of eyes, treated with the combination of vitrectomy and intravitreal ranibizumab was needed in the first year of treatment to achieve a similar improvement of visual acuity after one year. If this result can be interpreted as a signal that the increased drug clearance after vitrectomy outweighs the effect of vitrectomy with ILM peeling itself on the clinical course of diabetic macular edema, remains unclear.

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Synopsis

<table>
<tr><td colspan="2">Sponsor: Augenklinik Universitätsallee Bremen GmbH
Sponsor representative: Dr. Andreas Schüler, MD, PD
Coordinating Investigator: Dr. Andreas Schüler, MD, PD</td></tr>
<tr><td colspan="2">Investigators:
Andreas Schüler, MD, PD (Bremen); Andreas Mohr, MD (Bremen), Klaus-Martin Kreusel, MD, PD (Berlin); Joachim Wachtlin, MD, PD (Berlin); Lothar Krause, MD, PD (Dessau-Roßlau); Albrecht Lommatzsch, MD, PD (Münster); Gerasimos Anastassiou, MD, PD (Gelsenkirchen); Josep Callizo, MD (Göttingen) – details see page 5 Appendix</td></tr>
<tr><td colspan="2">Study title:
Ranibizumab and vitrectomy in the therapy of diabetic macular edema - the RAVIT - DME - Trial</td></tr>
<tr><td colspan="2">Design:
The trial is a randomized controlled multicentre trial.</td></tr>
<tr><td>Study period:
First patient in: April 7th, 2014
Last patient out: August 1st, 2016
Follow up period: 1 year</td><td>Study phase: III</td></tr>
<tr><td colspan="2">Patients:
Main inclusion criteria:
• Patients aged 18 years and older
• Patients with diabetes mellitus type 2 (insulin-dependent diabetes mellitus (IDDM) and noninsulin-dependent diabetes mellitus (NIDDM)) and clinical significant diabetic macular edema (diffuse or focal)
• Visual acuity (decimal) reduced by diabetic macular edema to ≤ 0,3 and ≥ 0,05 (LogMar ≤ 1,3 and ≥ 0,5) stated by EDTRS charts
• Signed informed consent
Main exclusion criteria:
• The investigator is clinically not convinced about vitrectomy being indicated or the possible side effects outweigh the possible positive effects of vitrectomy
• Diabetes mellitus type 1</td></tr>
</table>

- Criteria (6.-16.) concerning study eye (see page 6/21 of Statistical Report = Appendix A2)
- Criteria (17.-19.) concerning either eye (see page 7 of Statistical Report) = Appendix A2
- General criteria (20.-28), see page 7 of Statistical Report) = Appendix A2

Number of patients:

Planning: 110 (55 in each treatment); Actually recruited: 15 (Arm A: 7, Arm B: 8)

Intervention:

According to randomization the patients received either

Arm A: Vitrectomy plus ranibizumab administered intravitreally

or

Arm B: Ranibizumab (Appendix_3) administered intravitreally

Duration of treatment:

12 months

Objectives:

To evaluate the efficacy of vitrectomy including inner limiting membrane (ILM) peeling plus ranibizumab administered intravitreally in comparison to ranibizumab administered intravitreally in respect to the number of doses of ranibizumab, to the change of visual acuity measured by the number of letters 12 months after first treatment compared with baseline (primary endpoints) and other secondary clinical outcome parameters.

Criteria for evaluation:

Primary endpoints:

- Number of injections of study drug during the first year of treatment
- Mean change from baseline in BCVA at month 12 (visit 13)

Secondary Endpoints:

- Proportion of patients with a vision acuity loss of fewer than 15 letters at month 12 (visit 13) compared with baseline
- Proportion of patients with a vision acuity loss of more than 15 letters at month 12 (visit 13) compared with baseline
- Proportion of patients with a treatment-free interval of at least 3 months duration at any time point following visit 3
- Dropout rates
- Rate of non-responders
- Retinal Lesions
- Changes in retinal thickness from baseline at month 4 and 12 (visit 13)
- AEs
- Quality of Life at visit 1 (before treatment) and visit 13 (month 12)

Statistical methods:

Due to the small sample size, only the descriptive analyses planned in the SAP are presented. All significance tests planned in the SAP are omitted.
All results of statistical analyses – whether explicitly discussed in the following sections or not – are presented by statistical tables. All data collected is presented in the individual subject data listings.

Summary - Conclusions:

Efficacy Results:

In sample of 15 patients vitrectomy plus ranibizumab lead to a larger number of injections as ranibizumab alone. Due to the small and unbalanced sample size in the PPS, the primary non-inferiority analysis could not be done. In the FAS (sensitivity analysis) the change from baseline in the BCVA in EDTRS letters was similar between the treatment groups. Because of the small sample size no hypothesis tests and no confidence intervals were calculated. The only noticeable difference in the secondary endpoints was the decrease in retina thickness which was more pronounced in the vitrectomy plus ranibizumab group in most quadrants, in particular at 4 months after treatment start.

Safety results

Vitrectomy plus ranibizumab lead to a larger number of non-serious AEs. However, the number of patients with AEs was similar in the treatment groups. The number of SAEs was similar as well. No AEs and SAEs were reported as treatment related.

Conclusion:

The efficacy data for the first primary endpoint were not in line with efficacy hypothesis of the study. The treatment groups were similar with regard to the second primary endpoint. A noticeable difference was only found for the decrease in the retina thickness. For the 15 patents in the study no significant safety signals were observed.

Due to the small sample size, results are purely descriptive and are not generalizable.

Appendix A1

Study Sites/Investigators	
Augenklinik Universitätsallee GmbH Parkallee/Universitätsallee 301 28213 Bremen	Andreas Schüler, MD, PD
Krankenhaus St. Joseph-Stift, Augenkllnik Schwachhauser Heerstr.54, 28209 Bremen	Andreas Mohr, MD
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Augenärzte am St. Franziskus-Hospital Hohenzollernring 74, 48145 Münster	Albrecht Lommatzsch, MD, PD
Augenzentrum Gelsenkirchen Munckelstr.27. 45879 Gelsenkirchen	Gerasimos Anastassiou, MD, PD
Universitätsmedizin Göttingen Augen- und Poliklinik Georg-August-Universität Robert-Koch-Str.40, 37075 Göttingen	Josep Callizo, MD

Appendix A2

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9.3 Selection of Study Population

The study population consists of a consecutively recruited group of adult patients with visual impairment due to diabetic macular edema. Approximately 110 patients with diabetes mellitus type 2 (about 55 in each treatment arm) were planned to be enrolled in 8 to 10 study sites in Germany. Patients were treated in an outpatient setting.

The recruitment of appropriate subjects for the study started after approval by the Legal Authority and the Ethics Committee. For the individual patient, the study consisted of two periods: a Recruitment Period and a Treatment Period.

With patient's screening, the Recruitment Period began. It required up to 28 days and ended when the patient signed the Informed Consent Form. During the Recruitment Period the eligibility of the patients was verified. The examination for evaluating the eligibility of the patients for the study followed the clinically typical diagnostic pathway for such diagnosis and included BCVA, a standard ophthalmic examination, optical coherence tomography (OCT), Fluorescein Angiography (FA) and color fundus photography. The investigator assessed the results of the examinations and approved eligibility.

9.3.1. Inclusion criteria

Subjects had to meet the following criteria:

1. Patients aged 18 years and older
2. Diabetes mellitus type 2 (insulin-dependent diabetes mellitus (IDDM) and noninsulin-dependent diabetes mellitus (NIDDM))
3. Clinical significant diabetic macular edema (diffuse or focal)
4. Visual acuity (decimal) reduced by diabetic macular edema to ≤ 0,3 and ≥ 0,05 (LogMar ≤ 1,3 and ≥ 0,5) stated by EDTRS charts
5. Signed informed consent

9.3.2. Exclusion criteria

According to the study protocol any of the following should have led to an exclusion from study participation:

6. The investigator is clinically not convinced about vitrectomy being indicated or the possible side effects outweigh the possible positive effects of vitrectomy
7. Diabetes mellitus type 1

Study Eye:

8. Visual acuity of the study eye (decimal) > 0,3 (LogMar < 0,5)

Appendix A2

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9. Visual acuity of the study eye (decimal) < 0,05 (LogMar > 1,3)
10. Central retinal thickness of the study eye stated by SD-OCT < 250 µm
11. Any clouding of optical media influencing the evaluation of the retina in the study eye
12. Previous focal laser coagulation of the macula in the study eye within 3 months prior to baseline
13. Previous treatment of diabetic macular edema in the study eye involving intravitreal steroids or VEGF blockers within 6 months prior to baseline
14. Previous vitrectomy in the study eye
15. Previous cataract surgery in the study eye within 6 months prior to baseline
16. Pseudophakia with opening of the posterior capsule by surgery or YAG laser capsulotomy in the study eye prior to baseline
17. Pseudoexfoliative syndrome
18. Known ocular ischemia syndrome in either eye (occlusion of extraocular arteries, influencing the vascularisation of the study eye)
19. Retinal venous occlusion in the study eye
20. Tractive retinal detachment due to diabetic epiretinal proliferation in the study eye
21. Intravitreal hemorrhage interfering with the assessment of the posterior pole in the study eye prior to baseline

Either Eye:

22. History of glaucoma (including or excluding local or systemic therapy) in either eye
23. Uveitis or extraocular inflammation in either eye
24. History of retinal detachment (including or excluding any therapy) in either eye

General:

25. Active malignancies (history of successful treated malignancies is not an exclusion criterion)
26. History of cerebral vascular accident or myocardial infarction within 12 months prior to baseline
27. Diabetes mellitus with HbA1c > 10 % or if it can be expected that the patient's diabetes cannot be controlled adequately during the trial
28. Uncontrolled arterial Hypertension defined as a systolic value of > 180 mmHg and/or a diastolic value of > 110 mmHg
29. Systemic therapy with steroids or anticoagulative therapy with coumarin derivatives or heparin (Aspirin or Clopidogrel is allowed)
30. History of allergy to fluorescein or ranibizumab
31. Women who are pregnant or planning a pregnancy

Appendix A3

The active substance used as the clinical trial product is ranibizumab.

The trade name of the registered product with the active substance ranibizumab is Lucentis.

- Confidential - Confidential - Confidential - Confidential -

Clinical Study Protocol

Version 4.0 including Amendment No.1

Ranibizumab and Vitrectomy in the Therapy of Diabetic Macular Edema

The R A V I T - D M E - Trial

EUDRACT Number 2012-001006-24

Table of contents

1. List of abbreviations

AE	Adverse Event
AMG	German Drug Legislation
AMD	Age-related macular degeneration
BCVA	Best-corrected visual acuity
CI	Coordinating Investigator
CNV	Choroidal neovascularization
CRF	Case Report/Record File
DR	Diabetic Retinopathy
DSMB	Data Safety and Monitoring Board
EC	Ethics Committee
ECG	Electrocardiogram
ETDRS	Early Treatment Diabetic Retinopathy Study
EMA	European Medicines Agency
FA	Fluorescein angiography
FDA	Food and Drug Administration
GCP	Good Clinical Practice
IDDM	Insulin Dependent Diabetes Mellitus
ILM	Internal Limiting Membrane
IOL	Intraocular Lens
IOP	Intraocular Pressure
IRC	Independent Reading Center
ITT	Intention-to-treat
NIDDM	Non Insulin Dependent Diabetes Mellitus
OCT	Optical coherence tomography
PI	Principal Investigator
PDT	Photodynamic therapy
RCT	Randomized controlled trial
SAE	Serious Adverse Event
SAERF	Serious Adverse Event Report Form
SD OCT	Spectral Domain Optical Coherence Tomography
SNVM	Subretinal Neovascular Membrane
SOP	Standard Operating Procedure
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
Y/N	Yes/No (answer options in the CRF)

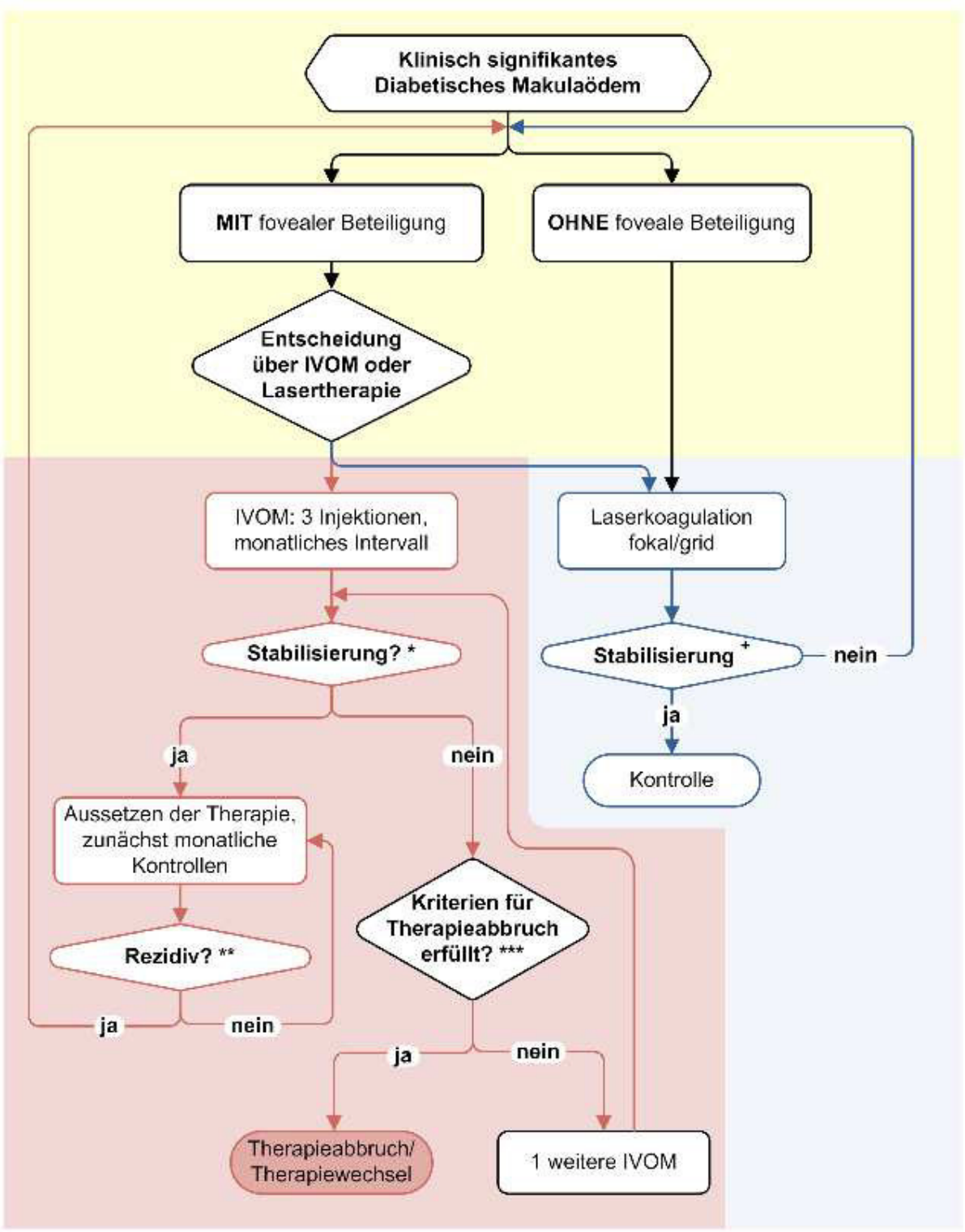
1. Background

Diabetic retinopathy (DR), a microvascular complication of diabetes, is a leading cause of vision loss and blindness in the working-age population worldwide. Diabetic macular edema (DME), swelling of the central retina, is a frequent manifestation of diabetic retinopathy and an important cause of impaired vision in individuals with diabetes.

The primary treatment of DME and macular edema secondary to branch retinal vein occlusion (BRVO), supported by the Branch Retinal Vein Occlusion Study has been laser photocoagulation, supported by the Early Treatment Diabetic Retinopathy Study (ETDRS) [1]. In this study (1979-1984), focal laser photocoagulation reduced the risk of moderate visual loss from diabetic macular edema from 24% to 12% 3 years after initiation of treatment. Scatter laser photocoagulation reduced the risk of severe visual loss. The 5-year rates of severe visual loss were low whether scatter treatment was given early (2.5%) or deferred until the development of high-risk proliferative retinopathy (4%). A careful follow-up provided this therapy proved to be safe to defer scatter treatment until retinopathy approaches or reaches the high-risk stage.

These data set the guidelines for DME treatment by laser photocoagulation. However, since vision loss is stopped, improvement in VA cannot be observed. In search for a therapy also improving VA the steroid triamcinolone was tested. Both retrospective and short prospective studies showed an initial beneficial effect on retinal thickening and VA after 4 months which diminished thereafter. A prospective long-term study directly comparing laser photocoagulation with triamcinolone[2] however showed a vision gain of 5 letters in the laser group. After 3-years the triamcinolone and the laser group showed no significant differences which argues against a long-term benefit of intravitreal triamcinolone relative to laser photocoagulation (focal/grid). Due to the more favourable profile of side effects the Diabetic Retinopathy Clinical Research Network (DRCR.net) gave preference to the laser treatment.

DME caused by age-related macular degeneration (AMD) is successfully treated by VEGF inhibitors such as bevacizumab and ranibizumab both binding to and inhibiting VEGF receptors. The VEGF inhibitor ranibizumab effectively improves BCVA also in DME and was approved for the treatment of DME in this indication [3]. The Deutsche Retinologische Gesellschaft (German Retina Society), the Deutsche Opthalmologische Gesellschaft , DOG (German Opthalmologic Society) and the Berufsverband der Augenärzte, BVA (Association of German Ophthalmologists) recommend ranibizumab as the first line treatment for treating DME with the fovea affected[4].



(Original treatment algorithm, recommended by Deutsche Ophthalmologische Gesellschaft, Retinologische Gesellschaft, Berufsverband der Augeärzte, December 2010).

The thereby arising treatment algorithm is summarized above. Ranibizumab is administered as a single injection intravitreally. The injection is given once a month in the first 3 months. Afterwards BCVA is monitored monthly. If the condition is found to be worsening, ranibizumab is administered again. If the patient's vision remains the same during three following visits, the therapeutic procedure is interrupted. This therapeutic approach is based on a randomized, double-masked, multicenter, laser-controlled phase III study[5]. Ranibizumab alone and combined with laser were superior to laser alone in improving mean average

change in BCVA. At month 12, a significantly greater proportion of patients had a BCVA letter score ≥15 and BCVA letter score level >73 (20/40 Snellen equivalent) with ranibizumab (22.6% and 53%, respectively) and ranibizumab + laser (22.9% and 44.9%) versus laser alone (8.2% and 23.6%). Based on these data it is now accepted that the treatment of DME by intravitreal ranibizumab, after one year, shows the best visual results[5].

Since anti VEGF therapy does not cure the cause of DME but only suppresses its imposing clinical symptoms, it is necessary that the patient's vision is monitored on a monthly basis to decide whether ranibizumab has to be continued. For the patient this means monthly contacts with his doctor. The study data suggest that during the first year 6 to 7 injections are necessary but no reliable data from clinical experience exist on this topic[5]. Many patients are unable to comply with such dense consultations. Therefore, therapeutic alternatives are still needed.

Vitrectomy, i.e. surgical removal of some or all of the vitreous has been used for twenty years in the treatment of DME. Based on observation that DME is more common in eyes with attached and taut posterior hyaloid membrane retina surgeons used vitrectomy for visual improvement and resolution of DME by peeling off the posterior hyaloid membrane[6, 7]. The mechanism of action is not completely understood. Mechanical factors (traction of the vitreous humor) may support the development of DME [7] but the intraocular VEGF level seems to be important as well [8]. By vitrectomy the VEGF level may be reduced in the long term [9]. Thus, a preceeding vitrectomy might reduce - due to a lower VEGF level- the following intravitreal ranibizumab injections to maintain the therapeutic effect. However, vitrectomy might reduce the half-life of ranibizumab in the eye resulting in a lower efficacy of the drug requesting more injections to achieve the same clinical effect. For ethical reasons there will be no data for the half-life of ranibizumab in human vitrectomized eyes compared to non-vitrectomized eyes. In rabbit eyes half-life of antibiotics were significantly reduced by vitrectomy [10]. However it is unclear whether such data are predictive for other compounds and species.

Several prospective and retrospective studies suggest a positive effect of vitrectomy on the clinical course (visual acuity) of DME. The largest of them investigating 241 eyes showed higher benefits of vitrectomy in eyes with initially poor VA and eyes with an operative epiretinal removal of a membrane across the macula[11]. Currently, retina surgeons discuss the advantages and practical issues of additionally removing the inner limiting membrane of the retina, the lamina limitans interna (ILM). Several retrospective studies show inconsistent results [11-25] [5] [11] [12] [13] [14] [15] [16] [17] [18] [19]

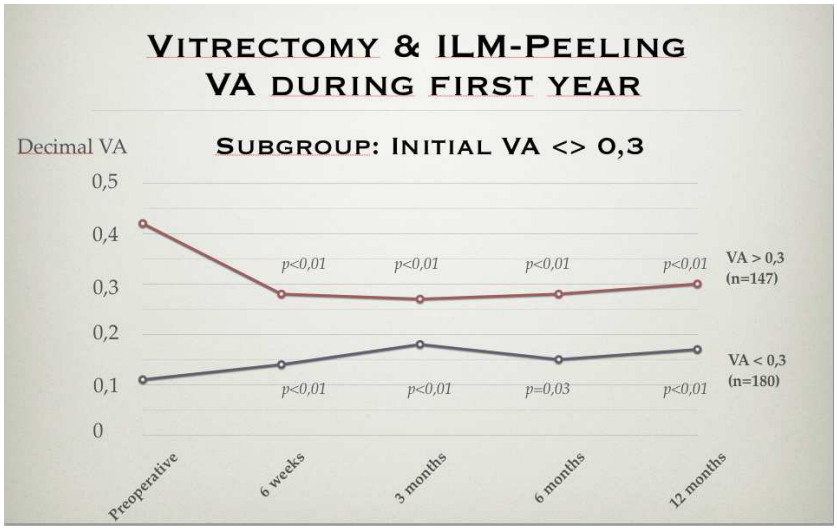
A recent prospective study[12] compared vitrectomy combined with the removal of only the epiretinal membranes and the vitreous limiting membrane after ILM removal additionally to the epiretinal membranes. However, the preoperative clinical evaluation of the vitreous status did not correlate with the intraoperative anatomic situation so that this evaluation of the detached or attached vitreous cannot give decisive guidance for or against surgery. No significant difference in the development of visual acuity was observed between the two comparison groups, even if the macular edema in the group with ILM peeling was reduced. Long-term follow-up showed that the functional and anatomic effect persisted up to 54 months after surgery. In addition, the intraoperative dying of the ILM adversely influenced the visual acuity although dying eased the complete removal the ILM[12].

Internal data analysis

In a retrospective case-control study 331 DME eyes undergoing vitrectomy (2001-2006) were retrospectively investigated, primarily differentiated between preoperative VA of above or below 0,3 (generally considered the minimum enabling to read). Eyes above this value

showed a significantly worse VA outcome during the first weeks after surgery which was not compensated completely up to one year after surgery. In contrast, eyes with a VA of 0,3 or less postoperatively showed a moderate increase in VA which was stable up to one year (see Figure 1)

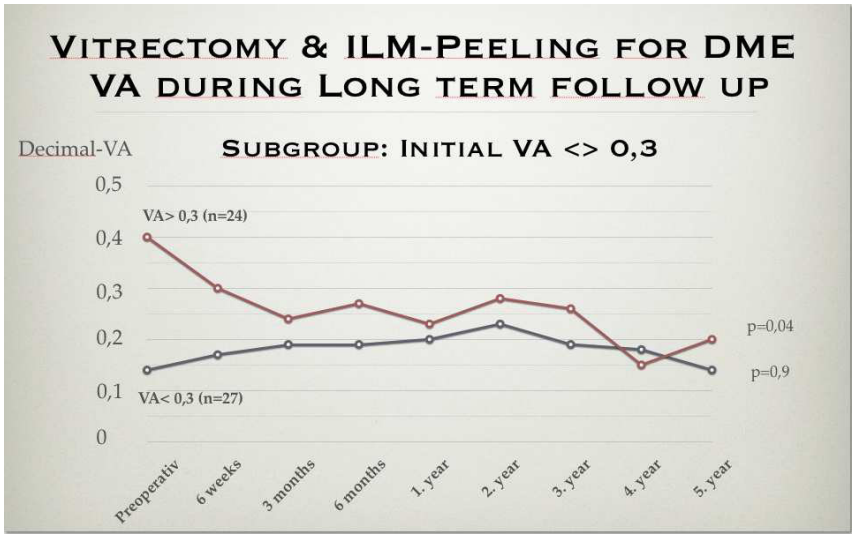
Figure 1



In addition development of VA after vitrectomy and ILM peeling for DME was followed up to one year. Eyes with preoperative VA of 0,3 or less showed a slight but statistically significant improvement of VA. In contrast eyes with a better preoperative VA showed a significant vision loss (P values compared to preoperative VA; internal process analysis, unpublished).

In an observation over 5 years mean BCVA was analysed for a smaller group of patients (51 eyes). It could be shown that vitrectomy had a stabilizing effect in eyes with a preoperative VA of 0,3 or less without any significant vision loss during five years (see Figure 2).

Figure 2



VA development of DME eyes after vitrectomy and ILM peeling was followed over 5 years. No change occurred in eyes with preoperative VA of 0,3 or less. In contrast eyes with a preoperative VA greater than 0.3 lost VA during the first postoperative year and improved moderately thereafter. At 5 years no significant difference in VA between the two groups was observed which might reflect the natural course of diabetic retinopathy. In the absence of control groups it cannot be answered whether vitrectomy accelerates or slows down VA loss in eyes with an initial value of 0.3 or more (Figure 1/2, internal process analysis, unpublished).

Another analysis of own long-term data showed that in 47 % of vitrectomized eyes a further treatment of diabetic maculopathy was necessary: In 10 % of the cases a disseminated laser coagulation therapy was performed because of developing peripheral diabetic retinopathy. 22 % received additional focal laser treatment and 24 % were treated with triamcinolone over 5 years. Compared to the current therapeutic standard with ranibizumab this number of follow-up therapies is extremely small (Figure 4).

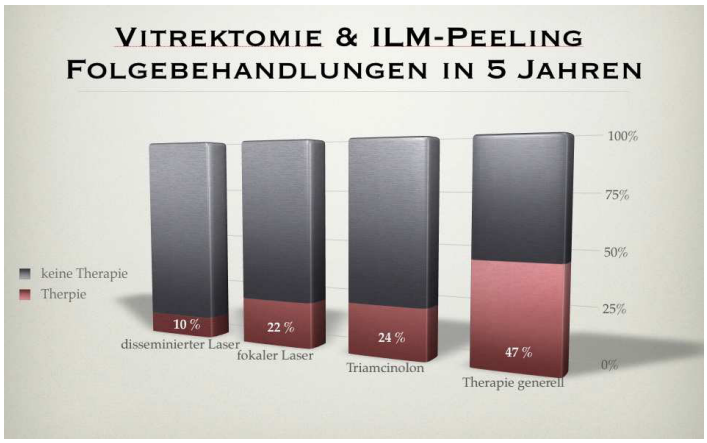


Figure 3. Documented follow-up therapy of diabetic retinopathy (and maculopathy) after vitrectomy and ILM peeling for diabetic macular edema during 5 year follow-up. In the majority of cases no further therapy was necessary (n=53). (internal process analysis,unpublished).

Summary on vitrectomy

All in all the study data on few patients and own uncontrolled long-term observations on large number of patients with DME suggest that vitrectomy is able to stabilize the edema. Eyes with poor preoperative VA (0,3 or less) appear to benefit more while eyes with better VA a significantly worsen immediately after surgery might occur, which is not compensated over years.

2. Study purpose

The study is designed to evaluate the efficacy of vitrectomy including ILM-peeling plus ranibizumab administered intravitreally in comparison to ranibizumab administered intravitreally in respect to the number of doses of ranibizumab, to the change of visual acuity measured by the number of letters 12 months after first treatment compared with baseline (primary endpoints) and other secondary clinical outcome parameter.

Based on clinical experience showing that vitrectomy is able to stabilize diabetic macular edema, vitrectomy in combination with ranibizumab might be of a better therapeutic efficacy, characterized by fewer injections necessary to maintain the therapeutic effect. Therefore we hypothesize that vitrectomy in combination with ranibizumab is superior to ranibizumab with regard to the number of injections and is non-inferior with regard to the mean change from baseline in best corrected visual acuity (BCVA) at month 12 since first treatment.

3. Sponsor of the study

Sponsor of this multicenter trial is the Augenklinik Universitätsallee, Parkallee 301, 28213 Bremen.

4. Study design

The study is designed as a randomized prospective controlled two-arm, multicenter trial. The main objective is to demonstrate superiority of vitrectomy in combination with ranibizumab over ranibizumab with regard to the number of ranibizumab injections and non-inferiority with regard to the mean change from baseline in BCVA at month 12 after treatment start.

The Coordinating Investigator is Private Lecturer MD Andreas Schüler. The trial center, directing and controlling study conduction, handling of study drug and treatment of patients, is located at the Augenklinik Universitätsallee, Parkallee 301, 28213 Bremen.

In this trial 110 patients with visual impairment due to Diabetic macular edema (DME) will be enrolled. The design uses equal patient numbers (1:1) for the therapy groups, group A vitrectomy including ILM-peeling plus Ranibizumab versus group B Ranibizumab alone.

The trial duration will be 12 months.

Sample size calculation

A total of 110 patients will be enrolled in this trial, in order to have data from about 98 individuals assuming a drop-out rate of 10%. The patients will be recruited in several ophthalmologic outpatient departments in Germany. The enrolment is competitive among the recruiting institutions.

The sample size of 98 was calculated to detect a significant difference in the number of intravitreal injections (within 12 months) between the two study arms with a power of 90 % using the Wilcoxon-Mann-Whitney-U-Test at the two-sided significance level of 5%. It was assumed that the number of injections is larger in group B than in group A with a probability of at least 69%. Assuming an approximately normal distribution, this corresponds to a mean difference of 2 injections with a common standard deviation of 2.85. In the RESTORE study [5] the mean number of injections were 7 with a standard deviation of 2.81. Given these numbers, a mean reduction of 2 injections per year appears realistic and relevant. The Mann-Whitney-U-Test is a non-parametric test which does not require a normally distributed

endpoint. With the sample size of 98, non-inferiority with respect to the mean change from baseline in BCVA at month 12 (at the margin of -5 letters and the one-sided significance level of 2.5%) can be verified with a power of 90%, if the standard deviation is 7.5 letters (which is in accordance to the RESTORE-study data) and the treatments are equivalent with respect to this endpoint.

Since we aim on the verification of both, superiority with regard to the number of injections and non-inferiority with regard to mean change of BCVA, no multiplicity adjustment is required, Under the assumption of the above power calculations, the probability to verify both, superiority and non-inferiority, will be at least 80%.

Randomization

To assure an unbiased treatment, patients will be randomized to the study arms. Subjects will be randomized at a ratio of 1:1 (A:B). Randomization will be stratified by center. Treatments will be assigned in sequentially numbered, sealed envelopes.

Trial duration

Recruitment is planned to be from autumn 2013 to autumn 2014. The estimated date of last patient out will be at the end of 2015.

Study population

The study population will consist of a consecutively recruited group of adult patients with visual impairment due to diabetic macular edema. Approximately 110 patients with diabetes mellitus type 2 (about 55 in each treatment arm) will be enrolled in 8 to 10 study sites in Germany. Patients will be treated in an outpatient setting.

Inclusion criteria

- Patients aged 18 years and older
- Diabetes mellitus type 2 (insulin-dependent diabetes mellitus (IDDM) and noninsulin-dependent diabetes mellitus (NIDDM))
- Clinical significant diabetic macular edema (diffuse or focal)
- Visual acuity (decimal) reduced by diabetic macular edema to ≤ 0,3 and ≥ 0,05 (LogMar ≤ 1,3 and ≥ 0,5) stated by EDTRS charts.
- Signed informed consent

Exclusion criteria

- The investigator is clinically not convinced about vitrectomy being indicated or the possible side effects outweigh the possible positive effects of vitrectomy
- Diabetes mellitus type 1
- Visual acuity of the study eye (decimal) > 0,3 (LogMar < 0,5)
- Visual acuity of the study eye (decimal) < 0,05 (LogMar > 1,3)
- Central retinal thickness stated by SD-OCT < 250 µm
- Any clouding of optical media influencing the evaluation of the retina
- Previous focal laser coagulation of the macula in the study eye within 3 months prior to baseline
- Previous treatment of diabetic macular edema involving intravitreal steroids or VEGF blockers within 3 months prior to baseline
- Previous vitrectomy in the study eye
- Previous cataract surgery in the study eye within 3 months prior to baseline
- Pseudophakia with opening of the posterior capsule by surgery or YAG laser capsulotomy within 3 months prior to baseline
- History of glaucoma (including or excluding local or systemic therapy) in either eye
- Uveitis or extraocular inflammation in either eye
- Pseudoexfoliative syndrome
- Known ocular ischemia syndrome in either eye (occlusion of extraocular arteries, influencing the vascularisation of the study eye)
- Retinal venous occlusion in the study eye
- History of retinal detachment (including or excluding any therapy) in either eye

- Tractive retinal detachment due to diabetic epiretinal proliferation in the study eye
- Intravitreal hemorrhage interfering with the assessment of the posterior pole in the study eye prior to baseline
- Active malignancies (history of successful treated malignancies is not an exclusion criterion)
- History of cerebral vascular accident or myocardial infarction within 12 months prior to baseline
- Diabetes mellitus with HbA1c > 10 % or if it can be expected that the patient's diabetes cannot be controlled adequately during the trial
- Uncontrolled arterial Hypertension defined as a systolic value of > 180 mmHg and/or a diastolic value of > 110 mmHg
- Systemic therapy with steroids or anticoagulative therapy with coumarin derivatives or heparin (Aspirin or Clopidogrel is allowed)
- History of allergy to fluorescein or ranibizumab
- Women who are pregnant or planning a pregnancy
- Women who are breast feeding
- Inability to comply with study or follow-up procedures

Recruitment

The recruitment of appropriate subjects for the study will start after approval by the Legal Authority and the Ethics Committee. For the individual patient, the study consists of two periods: a Recruitment Period and a Treatment Period.

With patient's screening, the Recruitment Period begins. It requires up to 28 days and will end, when the patient signs the Informed Consent Form. During the Recruitment Period the eligibility of the patients will be verified. The examination for evaluating the eligibility of the patients for the study follows the clinically typical diagnostic pathway for such diagnosis and includes BCVA, a standard ophthalmic examination, optical coherence tomography (OCT), Fluorescein Angiography (FA) and color fundus photography. The investigator will assess the results of the examinations and approve eligibility.

The SOPs 'Visual Acuity', 'Optical Coherence Tomography' and 'Color Fundus Photography and Fluorescein Angiography' will be available in each study site. The investigator has to comply with these SOPs when verifying the patients's eligibility.

After signing the Informed Consent Form, the patient will be randomized to a treatment arm.

5. Study treatment

Patients will be assigned to one of the following two treatment arms in a ratio of 1:1. The treatment arms will be as follows:

Arm A:
Initial Vitrectomy with internal limiting membrane (ILM) peeling - on an inpatient or outpatient basis with intraoperative administration of ranibizumab 0,5 mg intravitreally. After vitrectomy, 2 further injections of 0,5 mg Ranibizumab every 4 weeks will be performed, according to the label of Ranibizumab (Lucentis ®). After the first 3 obligatory treatments with Ranibizumab, examination will be performed every 4 weeks. Further injections will be given, according to the label of Ranibizumab (Lucentis ®), if indicated.

Arm B:
Three initial injections of 0,5 mg Ranibizumab every 4 weeks will be performed, according to the label of Ranibizumab (Lucentis ®). After the first 3 obligatory treatments with Ranibizumab, examination will be performed every 4 weeks. Further injections will be given, according to the label of Ranibizumab (Lucentis ®), if indicated

Study drug supply, storage and transport

The supply of the study sites with study drugs will be performed according to the German Drug Legislation (AMG). To warrant pharmaceutical quality of the study drug, the cold chain must be maintained and documented.

For patients of Arm A all study sites receive the study drug for baseline visit (for the first intraoperative injection of Ranibizumab) from the Augenklinik Universitätsallee, Parkallee 301, 28213 Bremen.

For all subsequent visits the patients will bring the study drug. For this purpose, they are supplied with individual cold boxes. Before application of the study drug, the maintenance of the cold chain has to be verified and documented by the patients' signature in the CRF. The drug accountability will be monitored by the study team during its regular monitoring visits.

Treatment frequency and duration

The Treatment Period will last up to 12 months. It will begin when the patient has signed the Informed Consent Form and end at month 12.The efficacy analysis of the Primary Endpoint will refer to 12 months after the day of the first injection.

After randomization the study drug is administered at least three times in each patient: on day 0 (visit 1), on day 28 ± 3 (visit 2), and on day 56 ± 3 (visit 3). If an investigator decides to prescribe prophylactic topical ocular antibiotics prior to administration of the intravitreal injection, the first injection has to be delayed at least 3 days.

Thereafter, patients are examined every 28 days (28 ± 3). The study medication is applied until at three consecutive visits no increase of VA is encountered.
If topical ocular antibiotics are required the following injection has to be delayed at least 3 days.

The criterion to stop the treatment is:

- If during 3 consecutive visits no further increase of VA is encountered

The criteria to continue or restart the treatment are:

- the loss of VA by more than 4 letters compared to VA score from the previous scheduled study visit
- loss of more than 9 letters compared to achieved BCVA at visit 4

Medication and study drug administration

The study drug will be the commercially available ranibizumab. Ranibizumab vials contain 2.3 mg ranibizumab in 0.23 ml solution (administered dosage for RAVIT-DME: 0,5 mg in 0,05 ml solution) consisting of α,α-trehalose-dihydrate, histidine-hydrochloride-monohydrate, histidin, polysorbate 20, and water ad injectabile. The solution will be used unchanged for injection purposes. Ranibizumab is the fragment of a humanized monoclonal antibody produced with recombinant DNA-technologies in E. coli.

According to the study protocol the patients will bring the study drug for intravitreal application.
See Study drug supply, storage and transport (p.15) for transport conditions.

Registration of application of study drugs

All study drugs administered to the patient during the study must be reported in the CRF.

Hygienic conditions prior to study drug administration

The intravitreal injection should be performed under aseptic conditions in a surgical environment, including the use of surgical hand disinfection, sterile gloves, sterile drapes and a sterile eyelid speculum. A sterile paracentesis equipment must be available if needed. Prior to intravitreal injection an adequate local anesthesia and the broad-spectrum topical microbicide PVP iodine (poly[1-vinyl2-pyrrolidone]-iodine-complex (5% PVP) is applied In case of an e.g. allergic reaction to PVP iodine, all other established and / or certified alternative procedures instead of PVP iodine disinfection prior to the intravitreal injection of the study drug are allowed (e.g. local administration of Polihexanid 0,04% eye drops). The injection needle should be fully inserted 3.5 - 4.0 mm posterior to the limbus into the vitreous cavity towards the center of the globe. The injection volume is to be injected slowly. The scleral site should be rotated for subsequent injections (corresponding to the SOP ‘Hygienics ICOM’ available at each study site).

Vitrectomy

Preamble

The main goal of vitrectomy, performed during this study, is to achieve a detachment of the posterior vitreous (if attached) and to remove the ILM in an area of at least about one disc diameter around the fovea. The SOP ‘Vitrectomy” will be available at each study site. The investigator has to comply with this SOP when performing a vitrectomy.

Cataract and pseudophakia

Phakic and pseudophakic eyes are accepted.

Phakic eyes: It is at the surgeon's discretion if a combined surgery with phacoemulsification and IOL-implantation is performed or if the eye remains phakic. If during the study duration of one year a sight threatening cataract is likely to occur, an additional phako and IOL-implantation should be performed during the vitrectomy.

Pseudophakic eyes: opacifications of the posterior capsule (secondary cataract) should be documented. Neither a YAG-Laser capsulotomy nor a surgical removal of the posterior capsule during vitrectomy should be performed during the study period. In case of a massive deterioration of the VA induced by the opacification of the posterior capsule a YAG-capsulotomy can be performed and an AE-report has to be filled in.

Allowed intraoperative dyes

To guarantee the successful removal of the ILM a dye-assisted ILM-peeling **must** be performed

Allowed dyes are

Brilliant blue

Trypan blue

A mixture of Brilliant blue and Trypan blue (e.g. Dualblue®)

It is recommended to use certified dyes (Brilliant-blue and Trypan blue). Intraoperative staining with indocyanine-green (ICG) is not allowed due to the unclear toxicity and the not standardized concentration and preparation of this dye.

Vitrectomy technique

Vitrectomy can be performed as an outpatient procedure or as an inpatient treatment.

Vitrectomy can be performed under local anaesthesia or under general anaesthesia.

Size of instruments

Vitrectomy can be performed with 20G-technique, transconjunctival 23G-technique or 25G-technique at the surgeon's discretion.

Intraoperative procedures necessarily to be executed (in any case**)**

- Core-vitrectomy
- Detachment of the posterior vitreous (if still attached)
- Staining of the ILM at the posterior pole
- Membrane / ILM-Peeling in an area of at least 1 disc diameter around the fovea
- Extend of the removal of the vitreous base at the surgeon's discretion
- Focal or disseminated laser coagulation outside the temporal vessel arcade is allowed
- No laser coagulation in an area of 2 disc diameter around the foveola
- Partial air or gas tamponade is allowed

Intraoperative exclusion criteria

- no ILM peeling possible
- Silicon oil tamponade necessary

- Development of intraoperative retinal detachment
- Complete gas tamponade necessary
- No intraoperative ranibizumab administration possible
- Intraoperative administration of intraocular steroids (temporary staining of the vitreous with triamconolone is allowed, the triamcinolone should be removed completely before the end of surgery

Postoperative care

Regular postoperative treatment after vitrectomy should be performed with topical steroid and antibiotic eye drops (e.g. a fixed combination of dexamethasone and gentamicin, alternatively other combinations of steroids and antibiotic eye drops are accepted).

Temporary postoperative mydriasis for diagnostic or therapeutic reasons is accepted.

Postoperative increased eye pressure can be treated with local antiglaucomatous eye drops and/or systemic acetazolamide at the surgeon's / ophthalmologist's discretion.

Temporary postoperative decompensation of the eye pressure up to 39 mmHg after the surgery should be documented, eye pressure of 40 mmHg or more should be reported as an AE.

Post-treatment care

Intravitreal injection procedures imply specific ocular risks jeopardizing patient's vision. Therefore patients are scheduled for a second standard ophthalmic examination (using the slit lamp) within three days after the injection. For the patient's convenience this examination will be conducted by their ophthalmologists. In case of inflammation or abnormal results, the investigators have to conduct subsequent treatment, if required**.**

Besides, patients will be instructed how antimicrobial eye drops can be self-administered into the study eye following intravitreal injection. Since the necessity of such a procedure depends on the individual patient's conditions, the choice whether such an antibiotic prophylaxis is indicated and which drugs are applied is at the investigator's discretion.

Concomitant ocular and non-ocular treatment

The investigator should instruct the patient to inform the investigator's staff about any new medication taken during the study. All medications beside the study drugs, ocular or non-ocular and all non-drug therapies (including blood transfusions) applied after the patient's participation in the study must be reported on the CRF.

Study drug discontinuation, definition of non-responder

The investigator will terminate the study attendance of an individual patient if a treatment failure is suspected in sense of a non-responder. This regulation is intended to ensure the possibility that the patient will receive an open therapeutic strategy regarding the standard treatment at that time. Treatment failure is suspected,

- if at visit 4, i.e. the first visit following the third scheduled injection of study drug, a VA loss of more than 14 letters (ETDRS charts) compared with the baseline value, is encountered, which is not caused by vitreous or epiretinal hemorrhage in

the macula or by the development of a secondary cataract, induced by vitrectomy of an injury of the lens by the injection needle (In case of a secondary cataract, a SAE must be reported. The patient should be treated with a cataract surgery and remain in the study afterwards).

or

- if a VA loss of more than 15 letters (ETDRS charts) in comparison with the value at visit 4, is encountered at two consecutive visits in spite of study drug administration at the last study visit, which is not caused by a probably transient bleeding.

In such a case, the patient is regarded a non-responder.

If the investigator defines that further application of the study drug would result in a safety risk for the patient the intravitreal injections within the study must be terminated. Occurrence of any of the following AEs requires a discontinuation of the study drug:

- rhegmatogenous retinal break or detachment
- macular hole

If the investigator is convinced that, for any other reason, continuation of study drug application would be unfavourable for the patient's health, the study drug has to be discontinued.

This decision must be well-founded on best clinical judgment and must estimate the benefit of therapeutic effect or the risk of the treatment for each patient.

Study completion

Patients who successfully complete the Treatment Period of the trial have completed the study.

Patients in whom administration of study drug is discontinued for any reason earlier than completing the study, and patients who prematurely withdraw consent and study participation for any reason, are to be visited at the earliest possible date (Early Termination Visit).

6. Endpoints

Primary Endpoint

- Number of injections of study drug during the first year of treatment
- Mean change from baseline in BCVA at month 12 (visit 13)

Secondary Endpoints

- Proportion of patients with a vision acuity loss of fewer than 15 letters at month 12 (visit 13) compared with baseline
- Proportion of patients with a vision acuity loss of more than 15 letters at month 12 (visit 13) compared with baseline
- Proportion of patients with a treatment-free interval of at least 3 months duration at any time point following visit 3
- Drop out rates
- Rate of non-responders
- Retinal lesions
- Changes in retinal thickness from baseline at month 4 and 12 (visit 13)

- AEs
- Quality of Life at visit 1 (before treatment) and visit 13 (month 12).

Methods to evaluate efficacy

Visual Acuity

Measurement of the BCVA and ophthalmoscopy of the ocular fundus will be performed at every visit.

The SOP “Visual Acuity” for performing VA examinations will be available at each study department. An assessment of BCVA will be conducted at every visit in a sitting position with a distance of 4 meters by means of ETDRS charts after measurement of the best correction. The investigator has to comply with this SOP when assessing visual acuity.

Visual Acuity: Technical recommendations:

1. Charts to use

The visual acuity testing for the RAVIT-DME-Study will be carried out with retro-illuminated EDTRS-Charts. Only chart “R” will be used to measure visual acuity of both right and left eye.

2. Conditions for testing

The charts will be inserted in a retro-illuminator cabinet, which has to provide a uniform illumination of 80 - 320 (luminance). Each cabinet is set up with two fluorescent lamps. The lamps have to be replaced after one year or after 2000 hours of operating time, respectively. It is recommended to change both lamps at the same time.

Prior to first use the lamps need four days of burn-in time. Then the charts can be used for measurement immediately after illumination. Measurement of visual acuity will be performed under standardized lighting conditions. The examination room has to be shaded, the illuminance must not be more than 150 lux measured with cabinet switched off.

3. Testing procedures

Only the visual acuity of the study eye is required to be measured in the course of the trial. The testing distance is 4 meters between the patient and the chart. Refraction will be determined first. Subjective refraction will be measured. After refraction measurement visual acuity will be determined by Chart R for the right eye as well as for the left eye. While testing one eye, the other has to be covered. If the patient is unable to read correctly at least three letters of the first line at a distance of 4 meters, the testing will be repeated at 1 meter distance. Considering the closer distance, a+ 0.75 sphere lens has to be added. At the 1 meter distance only the first six lines will be read by the patient, with 30 letters maximum obtainable at that distance.

4. Patient information before and during examinations

The patient will be informed that only letters are found on the chart, five letters in each line. The patient reads down the chart slowly, beginning to read the first letter in the top line (from the left to the right) and continues with the second line, the third line etc.. Reading of each letter is allowed only once, so slow and careful reading has to be emphasized to the patient. When a patient has difficulties in reading a letter, the patient is encouraged to guess. Once a patient has identified a letter with a definite single-letter response and has read or begun to

read the next letter, a correction of the previous letter cannot be accepted. Examiners should never point to the chart or to specific letters on the chart or read any of the letters during the test.

5. Recording results

Report the total number of letters the patient read correctly as ETDRS letters. Report the last line with at least 3 letters read correctly as Snellen equivalent. Letters will be documented in the CRF in the appropriate Visit Form (Unit "Visual acuity, ETDRS letters read, reading distance") and corresponding Snellen values next to it.

Visual acuity is specified as ETDRS letters read and Snellen acuity (20/20 or 4/4, and 1/1 in patients with poor vision). ETDRS charts used carry a Snellen and decimal visual acuity scale for a distance of 4 meters on the left side of the chart.

Ophthalmoscopy

For standard ophthalmic examination a slit lamp and an indirect stereo ophthalmoscope is to be utilized. If needed, the pupils have to be dilated with eye drops (e.g. tropicamide and/or phenylephrine).

IOP measurement

An examination of IOP has to be conducted at all study visits. After every intravitreal injection the functional integrity of the central artery has to be ensured and recorded in the CRF. Patients who develop an increase of IOP (>30 mmHG) during the study will need to be reexamined at the investigator's discretion. To assure comparable results, a standard procedure for assessing IOP should be used for each patient during the study.

If there are, after an intravitreal injection, any concerns regarding the effective injection or the patient's safety, the patient has to be monitored and treated according to the results of the examinations.

Optical Coherence Tomography

Further ophthalmic evaluations including OCT (a SD OCT is needed), Color fundus and FA are performed at baseline. Thereafter, OCT is performed at every visit (according to scheduled visits). FA and Color fundus will be conducted at baseline, month 6 and month 12.

OCT of study eyes and the analysis of the images must be performed prior to any study drug administration. The SOP 'Optical Coherence Tomography" will be available at each study side. The investigator has to comply with this SOP when performing OCT.

OCT is a noninvasive method that provides visualization of retinal structures. Light waves of 850 nanometers, emitted by a superluminescent diode, are used to determine images. The light is reflected and presents cross sectional images. A false color scheme configurates the images (bright colors such as red and white correspond to highly reflective areas and darker colors such as blue and black correspond to areas of lower reflectivity). For this examination the pupil has to be dilated.

The following OCT (a SD OCT is needed) scan pattern can be assessed to evaluate the treatment effect:

Macular cube showing a representative area around the fovea

Macular thickness is estimated by the medium retinal thickness in the fovea region

Optical Coherence Tomography: Technical recommendations:

OCT is required at all visits.
Technical recommendations: OCT should be performed with a spectral domain OCT, using a macular volume scan (no singe line scans).

Approved OCT machines are e.g.

- Cirrus OCT (Zeiss MediTec)
- Spectralis OCT (Heidelberg Engineering)
- 3D OCT (Topcon)
- Stratus OCT is an exception

Other SD-OCT from different manufacturers can be allowed as long as a representative scan area of the macula can be assessed and measured with a macular volume scan, comparable to the volume scan of the above listed SD-OCT machines.

If no SD-OCT is available a Stratus-OCT (Zeiss MediTec) with a software version 4.0 or higher might be used.

OCT examination Cirrus OCT (Zeiss MediTec)
Examination should be performed with a macular cube 512 x 128.
Choose Capture.
Choose macular cube 512 x 128.
Signal strength should be at least 6/10.
If the quality of the scan is not sufficient (artefacts e.g. by eye movements): repeat scan.

OCT-examination with Spectralis OCT (Heidelberg Engineering):
Perform examination in “high speed mode” (resolution 768x768 pixels)
Choose volume scan mode in IR+OCT mode
Choose ART-scan (ART 9 frames)
Start examination
If the quality of the scan is not sufficient (artefacts e.g. by eye movements) repeat scan

OCT-examination 3D OCT (Topcon)
Choose the macular mode.
Choose 3D scan with 6.0 mm x 6.0 mm, Scan resolution: 512 x 128.
Signal strength should be ≥ 50 if possible.
If the quality of the scan is not sufficient (artefacts e.g. by eye movements): repeat scan.

OCT examination with 3D OCT (Topcon)
Choose macular mode.
Choose 3D-Scan with 6.0 x 6.0 mm (512 x 128).
(make sure the correct parameters are chosen in „change settings“ (6.0 x 6.0 mm and 512 x 128).
If the quality of the scan is not sufficient (artefacts e.g. by eye movements): repeat scan.

OCT examination with Stratus OCT
(Straus OCT should only be used as an exception, if no spectral domain OCT is available.)
Two scans are required

- Fast macula thickness map
- Radial lines scan

Before scan: set parameters height and width to 6.0 mm.

Before scan: optimize Parameters z-offset AND polarisation.

After scan: check quality: signal strength should be at least „5“ and standard deviation should be equal or less than 10%.

Analysing and measurement of retinal thickness

Central retinal thickness should be measured by the analysis of the macular volume scan (512 x 128). The graphical visualisation of the retinal thickness in the macula is normally presented in a pie-chart with a central area and 4 quadrants (upper temporal, upper nasal, lower temporal, lower nasal). Choose the thickness in the central part of the “pie-chart” and document this central macular thickness as the representative thickness for the analysis of the clinical course.

Color Fundus Photography and Fluorescein Angiography

For FA fluorescein will be injected intravenously. A camera with special filters illuminates the retina with light of 490 nanometers wavelength. Photographs will be taken before, 40 seconds after and 2, 5, and 8 minutes after fluorescence media administration. The digital angiography presents the fluorescence and determines abnormal circulation and increased vascular permeability and the presence or absence of CNV.

The SOP ‘Color Fundus Photography and Fluorescein Angiography’ will be available at each study side. The investigator has to comply with this SOP when performing OCT.

Color Fundus Photography and Fluorescein Angiography Technical recommendations

Time table for imaging procedure

Procedure	Fundus Photo	FA
Initiation visit	Study eye	Study eye
Visit 7 (month 6)	Study eye	Study eye
Visit 13 (month 12)	Study eye	Study eye

During this study, 3 different imaging procedures will be used. SD-OCT is the main examination to determine and measure the amount of the macular edema.

Additionally, color fundus photography and fluorescein angiography will be performed at the initiation visit and after month 6 and 12 according to the table (s. above).

Fundus cameras

Color fundus photograpy: All digital cameras with an angle of view of 45° or more

are accepted

Fluorescein angiography: All digital cameras and scanners are accepted. For

digital cameras, using a flash, the angle of view should be 45° or more. If a scanner

system is used (e.g. Heidelberg HRA), a field of view of 30° is accepted, but an automated composite of the fundus should be performed, if possible

All photographs of the fundus must be performed after pupil dilation!

Fundus photography

At the initiation visit and at visit 13 (last visit), fundus color photography should be performed with 7 fields (according to ETDRS standard) with a color fundus camera with 45° of 50° angle of view.

During visit 7 a standard photo of the central field, showing the optic disc and a representative region of the central macula should be performed (45° or 50°).

The digital pictures should be saved on DVD and sent to the principal investigator after Termination Visit (visit13) or, in case of a patient's early termination immediately after the patient's last visit.

Fluorescein angiography

Pictures for FA should show the optic disc and a representative region of the macula, comparable to field 1 of the ETDRS-standard photography.

Before fluorescein dye injection a red free image should be performed. Following fluorescein dye injection pictures of the early, mid- and late phase of the macula region should be performed. The latest picture should be taken at least after 5 minutes.

The digital pictures should be saved on DVD and sent to the principal investigator after Visit 13 (last visit) or in case of a patient's early termination immediately after the patient's last visit.

Quality of life

To assess modification in patient's Quality of Life the patients asked to answer a self-administered questionnaire (VFQ-25) before administration of study drug at Visit 1 and at month 12.

Adverse events

An AE is the occurrence or worsening of any unwanted symptom or medical condition observed after the commencement of the study even if the event is not related to the study drug itself.

A disease which has started before the study drug was applied is only defined to be an AE if it worsened after the first dose of the study drug was given. Results of laboratory examinations or tests are defined as AEs if they result in significant clinical signs or symptoms or a therapy has to be conducted.

Thus, AEs can be revealed by the patient him/herself, mentioning a change in health condition, by physical examination or abnormal laboratory results. A non-directive questioning of the patient at every study visit should try to determine the existence of AEs.

Each AE should be evaluated to determine:

- the severity grade (mild, moderate, severe)
- its relationship to the study drugs and the injection site (related/not related)
- its duration (start and end dates, continuation until last visit)
- following consequences (no consequences; study drug interrupted; study drug discontinued as a result of the AE; administration of concomitant medication; non-drug therapy; hospitalization as a result of AE)

A Serious Adverse Event (SAE) is defined as:

- fatal or life-threatening
- resulting in persistent or significant disability/incapacity

- causing hospitalization or its prolongation for reasons other than:
  - observation or routine treatment of the studied indication, if not associated with any worsening in condition
  - a treatment (elective or pre-planned) for a pre-existing disease not referred to the study examination disease and not worsened since start of study drug
  - treatment on an emergency outpatient department for an event other than SAE and not resulting in hospital admission
  - social reasons
- invalidity, congenital anomaly

An event is medically significant, if it can harm the patient or may require medical therapy (including surgical intervention) to prevent one of the findings given above.

SAEs require ongoing control and have special reporting requirements.

As an analogue to the non-responder definition, a SAE is defined as a vision loss of more than 14 letters in the study eye, either at the first visit after the first three scheduled study drug administrations in comparison to the baseline value, or, at any time of the study, at two consecutive visits (in comparison to the value at visit 4) in spite of regular application of the study drug. Such an event has to be reported within 24 hours and the patient must be excluded from study, to provide further treatment with a therapy that seems to be necessary to the ophthalmologist's discretion.

Reduced VA caused by a transient bleeding in the vitreous of the eye is not defined as an SAE but an AE.

All AEs should be treated adequately. If required the administration of a study drug has to be interrupted or stopped. Treatment with concomitant medication according to the symptoms, accommodation of monitoring and assessments, hospitalization, or any other therapy, including surgical intervention has to be ascertained. An AE should be monitored until patient's recovery and appropriate assessment has to be made as often as necessary.

Changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome must be recorded.

If clinical monitoring is required, the patient will be asked to return to the outpatient department.

7. Statistical procedures

Descriptive statistics and treatment group comparisons

Every variable (item) documented in the CRF will be analyzed by descriptive methods. Number of observations, mean, standard deviation, maximum, minimum, median and interquartile range will be tabulated for quantitative data. Counts and column percentages will be presented for categorical data. These summaries will be given for the total data set and separately for each treatment group, stratum and department.

Treatment groups will be compared with respect to baseline efficacy variables, diagnoses, age and gender. The comparison will be done in a descriptive manner. Tests for homogeneity may be conducted for descriptive purposes.

Analysis of Primary Endpoints

Superiority of vitrectomy in combination with ranibizumab over ranibizumab with respect to the number of intravitreal injections will be tested by the Wilcoxon-Mann-Whitney-U-Test.

Non-inferiority of vitrectomy plus ranibizumab to ranibizumab in BCVA mean change from baseline at month 12 will be claimed if the one-sided 97.5% confidence interval based on the large-sample normal approximation excludes the non-inferiority of -5 letters.

The superiority analysis will be based on the full analysis following the ITT principle as close as possible. The non-inferiority analysis is performed on a per-protocol basis excluding patients with major protocol violations in order to avoid misleading conservative results. In a sensitivity analysis, superiority will also be tested in the per-protocol and non-inferiority in full analysis set. The full analysis set and the per-protocol population will be specified in the statistical analysis plan. Superiority will be claimed only if superiority with regard to the number of intravitreal injections and non-inferiority with regard to the BCVA mean change from baseline have both been established.

The Statistic Analysis Plan including the specification of the full analysis set and the per-protocol population will be available before recruiting the first patient.

Analysis of Secondary Endpoints

Summaries and confidence intervals will be calculated for all efficacy variables. Between-group comparisons will use analogue methods but keep an exploratory character. Additionally, exploratory analysis of variance methods will be used.

Safety analyses

Safety and vital signs analyses will be performed on all treated patients. AEs will be classified and analyzed by organ system, severity and relation to treatment. Pre-post-differences will be calculated for laboratory data

Patients data collected in the CRF

The following demographic and baseline characteristics will be collected for each patient, recorded in the CRF:

- General items:
  Random number, department, documentation of patients inclusion/exclusion criteria and Informed Consent
- Demographic data:
  year of birth, gender, ethnicity, age
  height and weight (baseline, 13, final visit)
- Relevant medical history and past ocular history
- Specific diagnostics (baseline):
  study eye, recruitment VA, OCT, FA, retinal thickness, IOP, standard ophthalmic examination
- Therapeutical schedule:
  Number and date of therapy, derivation from treatment procedures a defined in SOPs
  decision for discontinuation of therapy: date, reasons (Study Conclusion Form)
- Observation with respects to efficacy (data for each visit after month 2):
  retinal thickness and its increase/decrease,
  development of new retinal edema,
  VA and its increase/decrease ,
  control of IOP before and after injection, additional measurements for pressure above 30mmHg,
  OCT at baseline and at each visit (see page 14, efficacy evaluation)
  FA at baseline and month 3 and 12

- Quality of life assessment:
  VFQ-25 Questionnaire

- Concomitant therapies:
  concomitant and ongoing medications (date, drug, dose, application, indication)
- significant non-drug therapies:
  any ongoing therapies
- For each visit:
  safety concerns (Y/N treatment necessary, details)
  AEs documented in a standard form
- Completion of study:
  date, final examination and specific eye diagnostics (see baseline), drop out: reason, last study drug administration, last observation, comments of investigators

Deviations from the protocol for the administration of ranibizumab must be described on the appropriate Visit Form of the CRF.

Concomitant medications, reason for use, start date, and stop date (or 'ongoing') of medications used within 30 days prior to visit 1 or during the study will be collected on the Concomitant Medications Form of the CRF.

Information about patients who withdraw from the study, including patient's number, last administration of study drug, date of early termination and the primary reason for not continuing will be obtained and recorded on the Study Conclusion Form.

Monitoring and handling of safety data

To ensure patient's safety, every SAE occurring after the patient is randomized and until 4 weeks after the patient has stopped study participation, will be reported to the Coordinating Investigator (Augenklinik Universitätsallee, Parkallee 301, 28213 Bremen) within 24 hours of noticing its occurrence. This applies without regard to suspicion of causality or not.

SAEs experienced later than 4 weeks after the patient has stopped to participate must be reported to the CI as well, independent of whether the investigator suspects a causal relationship to the study drug or not. In this case, in contrast, the time lag between observation and report to the CI, maybe up to seven days.

Each recurrence, complications or further aggravation of the initial SAE must be reported as follow-up to the original SAE within 24 hours after the investigator was informed.

All SAEs which occur at another time interval or which are considered completely unrelated to a previously reported SAE will be reported separately as a new event.

All information about SAEs are recorded on the Serious Adverse Event Report Form (SAERF). The investigator must assess the suspected relationship to study drug application or to study procedures. Thereafter, he will send the signed SAERF by fax within 24 hours to the CI.

The original copy of the SAERF, together with the confirmation of successful fax transmission must be kept with the CRF at the study site. The follow-up information is sent by using a new SAERF clearly defining this report as a follow-up information to an already reported SAE (including the date of the initial report).

Reports on recurrence, complications or further aggravation of the initial SAE must be sent to the CI clearly marked as follow-up to the original SAE regardless of when it occurs. The follow-up report is expected to contain information on resolving or continuation of the AE, if there was any medical treatment and, in this case, which therapeutic measures were applied. In addition the follow-up report has to contain the information if the patient continues or has withdrawn from the study participation.

If SAEs are noticed which are not documented in the actual version of the Summary of Product Characteristics and which are suspected to be related to the study drug (SUSARS). a physician at the study site or the CI will immediately report this SAE to the German Health Authorities, responsible ethics committees and to the manufacturer. In addition, the CI will inform, by an Investigator Notification, all investigators about this SAE.

Data Safety and Monitoring Board

A Data Safety Monitoring Board will not be installed since this study will be performed in a short time frame and vitrectomy and the drug under investigation are well characterised and known for not harming patients.

Data review

A Site Initiation Visit will be held, by the study team, at any study site before study initiation. At the occasion of a Study Initiation meeting, all necessary information on protocol, CRFs, SAE reporting, will be given and the respective forms will be reviewed with all investigators and their staff.

During the study, a member of the study team will visit the study site at regular time intervals. At these visits the completeness of patient records, the accuracy of entries on the CRFs are checked and potential violations documented. In addition, the adherence to the protocol and to GCP are monitored. The investigator must give the CI’s study team member access to all relevant source documents. It is expected that members of the study site personnel will be present at these occasions to assist the CI's study team.

According to GCP all investigators will store the source documents for each patient in the study. These source documents will contain all information such as case and visit notes (including all medical records, laboratory data, ECGs), and also the demographics. All information noted in the CRFs must by traceable to the respective source data. Other data which can be recorded directly on the CRFs and have not necessarily to be documented in the patients medical file will be accepted as the source data.

In addition, at all study sites the original of the Informed Consent Form signed by the patient has to be maintained while a signed copy must be handed out to the patient.

The CI's study team will monitor and document the presence of all relevant documents, and check the adherence to the criteria for inclusion and exclusion of patients, handling of SAE, and, in sense of source data verification, the record of data used for primary and secondary and safety variables.

Data collection

All personnel of the investigator's site integrated in the study have to be designated in the Study Site Personnel Form and only personnel designated as such is allowed to enter the study information into the CRFs. CI's study team members will review the CRFs for completeness and accuracy. In the case of missing data, obviously false or implausible data entries the site personnel will be instructed to enter all necessary corrections or additions.

The CRFs are stored at the Department of Pharmacology in the Klinikum Bremen-Mitte, one copy being retained at the investigational site. When the CRFs arrive at the Department of Pharmacology, Klinikum Bremen-Mitte, their receipt is recorded and stored according to GCP.

Database management and quality control

Data from the CRFs are entered into the study database by members of the Statistics Department following the internal standard operating procedures. Subsequently, the entered data are systematically checked by Data Management staff at the Statistics Department, using error messages printed from validation programs and database listings.

All errors or missing data are entered on Data Query Forms, which are sent to the investigator's site for correction or addition. Copies of the completed and signed Data Query Forms are stored together with the CRFs at the investigator's site and the originals are submitted to the Statistics Department where the corrections and additions will be entered into the database. A quality control audit of 10% of all data in the database is made by the staff of the Statistics Department prior to locking the database. AEs will be coded using the WHO dictionary. All protocol violations will be determined. Thereafter, the database will be declared to be accurate and will be locked. Changes to the main database are not allowed after that time, unless it is agreed upon in written form, between the Head of the Statistics Department and the CI.

Baseline data

For statistical purposes, baseline will be considered the last assessment collected just prior to start of treatment.

Populations for analysis

The randomized patient population will consist of all patients, who received a randomization number.

All safety data will be analyzed using the safety population. The safety population will consist of all patients who received at least one application of study treatment (including vitrectomy) and have had at least one post-baseline safety assessment. The statement that a patient had no AEs also constitutes a safety assessment. Patients will be analyzed according to treatment received.

The superiority analysis will base on the full analysis set following the ITT principles. The non-inferiority analysis will be performed on the per-protocol population (observed data). The per-protocol population will consist of all patients in the ITT population who have no major protocol violations.

For sensitivity purposes the analyses of all efficacy variables will be repeated on the per-protocol and full analysis set, both with and without imputation of missing values. The full analysis set will consist of all patients randomized that received at least one application of study treatment and have at least one post-baseline assessment for BCVA. Following the ITT principle, patients will be analyzed according to the treatment they were assigned to at randomization.

If any significant protocol deviations are noticed, data from specific patient visits or evaluations may be excluded from the per-protocol analysis. The criteria and the determination of the clinically relevant protocol deviations together with the corresponding patient specific identification of data to be excluded from the per-protocol analysis will be finalized prior to locking the database.

Amendments to the protocol

Protocol changes have to be documented by a written Protocol Amendment. No changes or additions to the protocol may be made unless it is approved by the ethics committees and by the Legal Authority. Exceptions from this regulation can only be made in case patient's safety

appears to be threatened. The amendment has to be sent to all investigators. Irrespective of the need for approval of a formal protocol amendment each investigator is committed to take immediately any action that she / he considers necessary in the interest of any patient's safety, even if such action would be a protocol deviation. In such cases, the CI has to be informed instantly about this action.

Discontinuation of the study

The CI reserves the right to discontinue the study at any time, if he comes to the conclusion that, in the case of continuation, the risk of harm for the patients might prevail over their potential individual benefit or over the scientific interest within this group of patients.

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Centre of Competence for Clinical Trials Bremen

Biometry

Authors:

Prof. Dr. Werner Brannath

Dr. Sylvia Schmidt

Acronym:

RAVIT - DME

EudraCT-Number: 2012-001006-24

1 Title Page

Study title:

RANIBIZUMAB AND VITRECTOMY IN THE THERAPY OF DIABETIC MACULAR EDEMA

Acronym:

RAVIT - DME

Therapy:

Vitrectomy plus ranibizumab administered intravitreally (in comparison to ranibizumab administered intravitreally)

Indication:

Patients with diabetes mellitus type 2 and clinical significant diabetic macular edema

Study design:

Randomized prospective controlled two-arm, multicenter trial

Study Sponsor:	Augenklinik Universitätsallee Bremen GmbH
EudraCT Number:	2012-001006-24
Study Phase:	Phase III
Date of first patient in:	April 7th, 2014
Date of last patient out:	August 1st, 2016
Coordinating Investigator:	Andreas Schüler, MD, PD
Date of the report:	16th August 2017

1.1 Signatures

Study title: RANIBIZUMAB AND VITRECTOMY IN THE THERAPY OF DIABETIC MACULAR EDEMA

Acronym: RAVIT - DME

This statistical report has been produced in concordance with the principles of good clinical praxis with special respect to guidelines ICH E3, E6 and E9. The statistical analysis presented here is based on the study protocol and the statistical analysis plan.

Bremen, …… ……

Prof. Dr. Werner Brannath

Competence Centre for Clinical Trials (KKSB) – Biometry

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2 Synopsis

Sponsor: Augenklinik Universitätsallee Bremen GmbH
Sponsor representative: Dr. Andreas Schüler, MD, PD
Coordinating Investigator: Dr. Andreas Schüler, MD, PD

Investigators:
Andreas Schüler, MD, PD (Bremen); Andreas Mohr, MD (Bremen), Klaus-Martin Kreusel, MD, PD (Berlin); Joachim Wachtlin, MD, PD (Berlin); Lothar Krause, MD, PD (Dessau-Roßlau); Albrecht Lommatzsch, MD, PD (Münster); Gerasimos Anastassiou, MD, PD (Gelsenkirchen); Josep Callizo, MD (Göttingen)

Study title:
Ranibizumab and vitrectomy in the therapy of diabetic macular edema - the RAVIT - DME - Trial

Design:
The trial is a randomized controlled multicenter trial.

Study period:	**Study phase: III**
First patient in: April 7th, 2014	
Last patient out: August 1st, 2016	
Follow up period: 1 year	

Patients:

Main inclusion criteria:

- Patients aged 18 years and older
- Patients with diabetes mellitus type 2 (insulin-dependent diabetes mellitus (IDDM) and noninsulin-dependent diabetes mellitus (NIDDM)) and clinical significant diabetic macular edema (diffuse or focal)
- Visual acuity (decimal) reduced by diabetic macular edema to $\leq 0{,}3$ and $\geq 0{,}05$ (LogMar $\leq 1{,}3$ and $\geq 0{,}5$) stated by EDTRS charts
- Signed informed consent

Main exclusion criteria:

- The investigator is clinically not convinced about vitrectomy being indicated or the possible side effects outweigh the possible positive effects of vitrectomy
- Diabetes mellitus type 1
- Criteria (3.-16.) concerning study eye (see page 20 of this report)

- Criteria (17.-19.) concerning either eye (see page 21of this report)
- General criteria (20.-28., see page 21 of this report)

Number of patients:

Planning: 110 (55 in each treatment); Actually recruited: 15 (Arm A: 7, Arm B: 8)

Intervention:

According to randomization the patients received either

Arm A: Vitrectomy plus ranibizumab administered intravitreally

or

Arm B: Ranibizumab administered intravitreally

Duration of treatment:

12 months

Objectives:

To evaluate the efficacy of vitrectomy including inner limiting membrane (ILM) peeling plus ranibizumab administered intravitreally in comparison to ranibizumab administered intravitreally in respect to the number of doses of ranibizumab, to the change of visual acuity measured by the number of letters 12 months after first treatment compared with baseline (primary endpoints) and other secondary clinical outcome parameters.

Criteria for evaluation:

Primary endpoints:

- Number of injections of study drug during the first year of treatment
- Mean change from baseline in BCVA at month 12 (visit 13)

Secondary Endpoints:

- Proportion of patients with a vision acuity loss of fewer than 15 letters at month 12 (visit 13) compared with baseline
- Proportion of patients with a vision acuity loss of more than 15 letters at month 12 (visit 13) compared with baseline
- Proportion of patients with a treatment-free interval of at least 3 months duration at any time point following visit 3
- Dropout rates
- Rate of non-responders
- Retinal Lesions
- Changes in retinal thickness from baseline at month 4 and 12 (visit 13)
- AEs
- Quality of Life at visit 1 (before treatment) and visit 13 (month 12)

Statistical methods:

Due to the small sample size, only the descriptive analyses planned in the SAP are presented. All significance tests planned in the SAP are omitted.
All results of statistical analyses – whether explicitly discussed in the following sections or not – are presented by statistical tables. All data collected is presented in the individual subject data listings.

Summary - Conclusions:

Efficacy Results:

In sample of 15 patients vitrectomy plus ranibizumab lead to a larger number of injections as ranibizumab alone. Due to the small and unbalanced sample size in the PPS, the primary non-inferiority analysis could not be done. In the FAS (sensitivity analysis) the change from baseline in the BCVA in EDTRS letters was similar between the treatment groups. Because of the small sample size no hypothesis tests and no confidence intervals were calculated. The only noticeable difference in the secondary endpoints was the decrease in retina thickness which was more pronounced in the vitrectomy plus ranibizumab group in most quadrants, in particular at 4 months after treatment start.

Safety results

Vitrectomy plus ranibizumab lead to a larger number of non-serious AEs. However, the number of patients with AEs was similar in the treatment groups. The number of SAEs was similar as well. No AEs and SAEs were reported as treatment related.

Conclusion:

The efficacy data for the first primary endpoint were not in line with efficacy hypothesis of the study. The treatment groups were similar with regard to the second primary endpoint. A noticeable difference was only found for the decrease in the retina thickness. For the 15 patents in the study no significant safety signals were observed.

Due to the small sample size, results are purely descriptive and are not generalizable.

Date of the report:

16th of August 2017

3 Table of Contents

List of Tables

4 List of Abbreviations and Definitions of Terms

AE	Adverse event
AMD	Age-related macular edema
BCVA	Best-corrected visual acuity
BRVO	Branch retinal vein occlusion
CDC	Clinical data care
CI	Coordinating Investigator
CPMP	Committee for Proprietary Medicinal Products
CRF	Case Report Form
DIMDI	Deutsches Institut für Medizinische Dokumentation und Information
DME	Diabetic macular edema
DR	Diabetic retinopathy
EMA	European Medicines Agency
FAS	Full analysis set
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GIF	Graphics Interchange Format
ICH	International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use
ILM	Inner limiting membrane
ITT	Intention-to-treat
KKSB	Competence Center for Clinical Trials Bremen
LOCF	Last observation carried forward
MD	Doctor of Medicine
PPS	Per protocol set

PhD	Doctor of Philosophy
PD	Private lecturer
RTF	Rich Text Format
SAE	Serious adverse event
SAP	Statistical analysis plan
SOP	Standard Operation Procedure
VA	Visual acuity
VEGF	Vascular endothelial growth factor

5 Ethics

5.1 Statements of IEC

To be presented in the clinical report

5.2 Ethical Conduct of the Study

The clinical trial has been conducted in compliance with the protocol and according to the European Medicines Agency (EMA) Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95 – in operation 17.01.97) and the Food and Drug Administration (FDA) Good Clinical Practice: Consolidated Guideline (FDA Docket Number 95D-0219 in operation 09.05.97) base on the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use (ICH) guidelines for Good Clinical Practice (GCP) and according to national regulations.

5.3 Patient Information and Consent

The Informed Consent Form documents the study-specific information the investigator provides to the patients. It was the investigator's responsibility to obtain written informed consent after adequate explanation in layman's terms of the aims, methods, anticipated benefits, potential risks and discomforts, and any monetary compensation participation might entail.

It was required to obtain the assent of the patient to participate in the study. The Informed Consent Form has been signed and dated by each patient and witnessed by the person providing the explanation before entering the study.

A copy of the signed Informed Consent Form was given to the patient. The original is placed in the patient's medical record, and the Investigator keeps a second copy.

6 Investigators and Study Administrative Structure

See study protocol (to be filled out in clinical report)

7 Introduction

7.1 Background

Kommentiert [WB1]: Aus unserem SAP übernommen; eine Überarbeitung könnte nötig sein.

Diabetic retinopathy (DR), a microvascular complication of diabetes, is a leading cause of vision loss and blindness in the working-age population worldwide. Diabetic macular edema (DME), swelling of the central retina, is a frequent manifestation of diabetic retinopathy and an important cause of impaired vision in individuals with diabetes.

The primary treatment of DME and macular edema secondary to branch retinal vein occlusion (BRVO), has been laser photocoagulation. However, improvement in visual acuity (VA) cannot be observed. In search for a therapy also improving VA the steroid triamcinolone was tested. Both retrospective and short prospective studies showed an initial beneficial effect on retinal thickening and VA after 4 months which diminished thereafter. However, a long-term benefit of intravitreal triamcinolone relative to laser photocoagulation (focal/grid) could not be demonstrated. Due to the more favourable profile of side effects the Diabetic Retinopathy Clinical Research Network (DRCR.net) gave preference to the laser treatment.

DME caused by age-related macular degeneration (AMD) is successfully treated by vascular endothelial growth factor (VEGF) inhibitors such as bevacizumab and ranibizumab both binding to and inhibiting VEGF receptors. The VEGF inhibitor ranibizumab effectively improves best-corrected visual acuity (BCVA) also in DME and was approved for the treatment of DME in this indication. The Deutsche Retinologische Gesellschaft (German Retina Society), the Deutsche Opthalmologische Gesellschaft (German Opthalmologic Society) and the Berufsverband der Augenärzte (Association of German Ophthalmologists) recommend ranibizumab as the first line treatment for treating DME with the fovea affected.

Ranibizumab is administered as a single injection intravitreally. The injection is given once a month in the first 3 months. Afterwards BCVA is monitored monthly. If the condition is found to be worsening, ranibizumab is administered again. If the patient's vision remains the same during three following visits, the therapeutic procedure is interrupted.

Since anti VEGF therapy does not cure the cause of DME but only suppresses its imposing clinical symptoms, it is necessary that the patient's vision is monitored on a monthly basis to decide whether ranibizumab has to be continued. For the patient this means monthly contacts with his doctor. Many patients are unable to comply with such dense consultations. Therefore, therapeutic alternatives are still needed.

Vitrectomy, i.e. surgical removal of some or all of the vitreous has been used for twenty years in the treatment of DME. Based on observation that DME is more common in eyes with attached and taut posterior hyaloid membrane retina, surgeons used vitrectomy for visual improvement and resolution of DME by peeling off the posterior hyaloid membrane. The mechanism of action is not completely understood. Mechanical factors (traction of the vitreous humor) may support the development of DME but the intraocular VEGF level seems to be important as well. By vitrectomy the VEGF level may be reduced in the long term. Thus, a preceeding vitrectomy might reduce - due to a lower VEGF level- the following intravitreal ranibizumab injections to maintain the therapeutic effect. However,

vitrectomy might reduce the half-life of ranibizumab in the eye resulting in a lower efficacy of the drug requesting more injections to achieve the same clinical effect.

All in all the study data on few patients and own uncontrolled long-term observations on a large number of patients with DME suggest that vitrectomy is able to stabilize the edema. Eyes with poor preoperative VA (0,3 or less) appear to benefit more while eyes with better VA a significantly worsen immediately after surgery might occur, which is not compensated over years.

7.2 Rationale

The guiding principles of this protocol's therapeutic rationale are based on clinical experience and actual treatment recommendations for diabetic macula edema. Treatment with ranibizumab is based on the actual label of ranibizumab during the study.

8 Study objectives

The study is designed to evaluate the efficacy of vitrectomy including inner limiting membrane (ILM) peeling plus ranibizumab administered intravitreally in comparison to ranibizumab administered intravitreally in respect to the number of doses of ranibizumab, to the change of visual acuity measured by the number of letters 12 months after first treatment compared with baseline (primary endpoints) and other secondary clinical outcome parameter.

Based on clinical experience showing that vitrectomy is able to stabilize diabetic macular edema, vitrectomy in combination with ranibizumab might be of a better therapeutic efficacy, characterized by fewer injections necessary to maintain the therapeutic effect. Therefore we hypothesize that vitrectomy in combination with ranibizumab is superior to ranibizumab with regard to the number of injections and is non-inferior with regard to the mean change from baseline in BCVA at month 12 since first treatment.

9 Investigational Plan

9.1 Overall Study Design and Plan-Description

The study is designed as a randomized prospective controlled two-arm, multicenter trial.

9.1.1 Study Treatment

Patients were assigned to one of the following two treatment arms in a ratio of 1:1. The treatment arms are as follows:

Arm A: Initial Vitrectomy with ILM-peeling - on an inpatient or outpatient basis with intraoperative administration of ranibizumab 0,5 mg intravitreally. After vitrectomy, 2 further injections of 0,5 mg

Ranibizumab every 4 weeks will be performed, according to the label of Ranibizumab (Lucentis ®). After the first 3 obligatory treatments with Ranibizumab, examination will be performed every 4 weeks. Further injections will be given, according to the label of Ranibizumab (Lucentis ®), if indicated.

Arm B: Three initial injections of 0,5 mg Ranibizumab every 4 weeks will be performed, according to the label of Ranibizumab (Lucentis ®). After the first 3 obligatory treatments with Ranibizumab, examination will be performed every 4 weeks. Further injections will be given, according to the label of Ranibizumab (Lucentis ®), if indicated.

To assure an unbiased treatment, patients were randomized to the study arms. Subjects were randomized at a ratio of 1:1 (A:B). Randomization was stratified by center. Treatments were assigned in sequentially numbered, sealed envelopes.

9.2 Discussion of Study Design

This is a randomized two arm trial. Due to the surgical procedure blinding is impossible. The control group (arm B) represents the current treatment standard for significant diabetic macular edema. The experimental arm meets similar treatment standards. The primary goals of the study are to show superiority of arm B with regard to the number of injections and also non-inferiority with regard to the mean change from baseline in the BCVA at month 12. The non-inferiority margin of 5 letter meets the non-inferiority margins of other studies. Due to the non-inferiority goal there may an issue of assay sensitivity which however can be investigated based e.g. on the mean change from baseline in BCVA and the number of responder.

9.3 Selection of Study Population

The study population consists of a consecutively recruited group of adult patients with visual impairment due to diabetic macular edema. Approximately 110 patients with diabetes mellitus type 2 (about 55 in each treatment arm) were planned to be enrolled in 8 to 10 study sites in Germany. Patients were treated in an outpatient setting.

The recruitment of appropriate subjects for the study started after approval by the Legal Authority and the Ethics Committee. For the individual patient, the study consisted of two periods: a Recruitment Period and a Treatment Period.

With patient's screening, the Recruitment Period began. It required up to 28 days and ended when the patient signed the Informed Consent Form. During the Recruitment Period the eligibility of the patients was verified. The examination for evaluating the eligibility of the patients for the study fol-

lowed the clinically typical diagnostic pathway for such diagnosis and included BCVA, a standard ophthalmic examination, optical coherence tomography (OCT), Fluorescein Angiography (FA) and color fundus photography. The investigator assessed the results of the examinations and approved eligibility.

9.3.1 Inclusion criteria

Subjects had to meet the following criteria:

1. Patients aged 18 years and older
2. Diabetes mellitus type 2 (insulin-dependent diabetes mellitus (IDDM) and noninsulin-dependent diabetes mellitus (NIDDM))
3. Clinical significant diabetic macular edema (diffuse or focal)
4. Visual acuity (decimal) reduced by diabetic macular edema to ≤ 0,3 and ≥ 0,05 (LogMar ≤ 1,3 and ≥ 0,5) stated by EDTRS charts
5. Signed informed consent

9.3.2 Exclusion criteria

According to the study protocol any of the following should have led to an exclusion from study participation:

6. The investigator is clinically not convinced about vitrectomy being indicated or the possible side effects outweigh the possible positive effects of vitrectomy
7. Diabetes mellitus type 1

Study Eye:

8. Visual acuity of the study eye (decimal) > 0,3 (LogMar < 0,5)
9. Visual acuity of the study eye (decimal) < 0,05 (LogMar > 1,3)
10. Central retinal thickness of the study eye stated by SD-OCT < 250 µm
11. Any clouding of optical media influencing the evaluation of the retina in the study eye
12. Previous focal laser coagulation of the macula in the study eye within 3 months prior to baseline
13. Previous treatment of diabetic macular edema in the study eye involving intravitreal steroids or VEGF blockers within 6 months prior to baseline
14. Previous vitrectomy in the study eye
15. Previous cataract surgery in the study eye within 6 months prior to baseline
16. Pseudophakia with opening of the posterior capsule by surgery or YAG laser capsulotomy in the study eye prior to baseline

17. Pseudoexfoliative syndrome
18. Known ocular ischemia syndrome in either eye (occlusion of extraocular arteries, influencing the vascularisation of the study eye)
19. Retinal venous occlusion in the study eye
20. Tractive retinal detachment due to diabetic epiretinal proliferation in the study eye
21. Intravitreal hemorrhage interfering with the assessment of the posterior pole in the study eye prior to baseline

Either Eye:

22. History of glaucoma (including or excluding local or systemic therapy) in either eye
23. Uveitis or extraocular inflammation in either eye
24. History of retinal detachment (including or excluding any therapy) in either eye

General:

25. Active malignancies (history of successful treated malignancies is not an exclusion criterion)
26. History of cerebral vascular accident or myocardial infarction within 12 months prior to baseline
27. Diabetes mellitus with HbA1c > 10 % or if it can be expected that the patient's diabetes cannot be controlled adequately during the trial
28. Uncontrolled arterial Hypertension defined as a systolic value of > 180 mmHg and/or a diastolic value of > 110 mmHg
29. Systemic therapy with steroids or anticoagulative therapy with coumarin derivatives or heparin (Aspirin or Clopidogrel is allowed)
30. History of allergy to fluorescein or ranibizumab
31. Women who are pregnant or planning a pregnancy
32. Women who are breast feeding
33. Inability to comply with study or follow-up procedures

9.3.3 Patient Withdrawal

Patients were free to withdraw from the trial at any time without providing reason(s) for withdrawal and without prejudice for further treatment. The reason for withdrawal may include, but is not restricted to, withdrawal of consent, adverse event(s) or loss to follow-up. The reason(s) were to be recorded in the CRF.

Patients in whom administration of study drug is discontinued for any reason earlier than completing the study, and patients who prematurely withdraw consent and study participation for any reason, are to be visited at the earliest possible date (Early Termination Visit).

9.4 Treatments

9.4.1 Intended Dosage and Duration of Treatment

The Treatment Period lasted up to 12 months. It began when the patient had signed the Informed Consent Form and ended at month 12. The efficacy analysis of the primary endpoint refers to 12 months after the day of the first injection.

After randomization the study drug was administered at least three times in each patient: on day 0 (visit 1), on day 28 ± 3 (visit 2), and on day 56 ± 3 (visit 3).

Thereafter, patients were examined every 28 days (28 ± 3). The study medication was applied until at three consecutive visits no increase of VA was encountered.

The criteria to continue or restart the treatment were:

- The loss of VA by more than 4 letters compared to VA score from the previous scheduled study visit
- loss of more than 9 letters compared to achieved BCVA at visit 4

9.4.2 Study Discontinuation

The investigator will terminate the study attendance of an individual patient if a treatment failure is suspected in sense of a non-responder. This regulation is intended to ensure the possibility that the patient will receive an open therapeutic strategy regarding the standard treatment at that time. Treatment failure is suspected,

- if at visit 4, i.e. the first visit following the third scheduled injection of study drug, a VA loss of more than 14 letters (ETDRS charts) compared with the baseline value, is encountered, which is not caused by vitreous or epiretinal hemorrhage in the macula or by the development of a secondary cataract, induced by vitrectomy of an injury of the lens by the injection needle (In case of a secondary cataract, a SAE must be reported. The patient should be treated with a cataract surgery and remain in the study afterwards).

or

- if a VA loss of more than 15 letters (ETDRS charts) in comparison with the value at visit 4, is encountered at two consecutive visits in spite of study drug administration at the last study visit, which is not caused by a probably transient bleeding.

In such a case, the patient is regarded a non-responder.

If the investigator defines that further application of the study drug would result in a safety risk for the patient the intravitreal injections within the study must be terminated. Occurrence of any of the following AEs requires a discontinuation of the study drug:

- rhegmatogenous retinal break or detachment
- macular hole

If the investigator is convinced that, for any other reason, continuation of study drug application would be unfavourable for the patient's health, the study drug has to be discontinued. This decision must be well-founded on best clinical judgment and must estimate the benefit of therapeutic effect or the risk of the treatment for each patient.

9.4.3 Concomitant Medication

Concomitant medication required for the well being of the patient is permitted. No systemic drug interaction is expected. However, caution is advised, especially if medication is introduced shortly after treatment.

The investigator should instruct the patient to inform the investigator's staff about any new medication taken during the study. All medications beside the study drugs, ocular or nonocular and all non-drug therapies (including blood transfusions) applied after the patient's participation in the study must be reported on the CRF.

9.5 Efficacy and Safety Variables

9.5.1 Primary Endpoints

- Number of injections of study drug during the first year of treatment
- Mean change from baseline in BCVA at month 12 (visit 13)

9.5.2 Secondary Endpoints

- Proportion of patients with a vision acuity loss of fewer than 15 letters at month 12 (visit 13) compared with baseline
- Proportion of patients with a vision acuity loss of more than 15 letters at month 12 (visit 13) compared with baseline
- Proportion of patients with a treatment-free interval of at least 3 months duration at any time point following visit 3
- Dropout rates
- Rate of non-responders
- Retinal Lesions

- Changes in retinal thickness from baseline at month 4 and 12 (visit 13)
- AEs
- Quality of Life at visit 1 (before treatment) and visit 13 (month 12)

9.6 Data Quality Assurance

9.6.1 Data Safety and Monitoring Board

A Data Safety Monitoring Board was not installed since this study was be performed in a short time frame and vitrectomy and the drug under investigation are well characterised and known for not harming patients.

9.6.2 Data review

A Site Initiation Visit was held, by the study team, at any study site before study initiation. At the occasion of a Study Initiation meeting, all necessary information on protocol, CRFs, SAE reporting, were given and the respective forms will be reviewed with all investigators and their staff.

During the study, a member of the study team visited the study site at regular time intervals. At these visits the completeness of patient records, the accuracy of entries on the CRFs were checked and potential violations documented. In addition, the adherence to the protocol and to GCP were monitored. The investigator must give the CI's study team member access to all relevant source documents. It is expected that members of the study site personnel are present at these occasions to assist the CI's study team.

According to GCP all investigators stored the source documents for each patient in the study. These source documents contain all information such as case and visit notes (including all medical records, laboratory data, ECGs), and also the demographics. All information noted in the CRFs must be traceable to the respective source data. Other data which can be recorded directly on the CRFs and have not necessarily to be documented in the patients' medical file are accepted as the source data.

In addition, at all study sites the original of the Informed Consent Form signed by the patient has to be maintained while a signed copy must be handed out to the patient. The CI's study team monitored and documented the presence of all relevant documents, and checked the adherence to the criteria for inclusion and exclusion of patients, handling of SAE, and, in sense of source data verification, the record of data used for primary and secondary and safety variables.

9.6.3 Database management and quality control

Data from the CRFs were entered into the study database by members of the Statistics Department following the internal standard operating procedures. Subsequently, the entered data were systemati-

cally checked by Data Management staff at the Statistics Department, using error messages printed from validation programs and database listings.

All errors or missing data were entered on Data Query Forms, which were sent to the investigator's site for correction or addition. Copies of the completed and signed Data Query Forms are stored together with the CRFs at the investigator's site and the originals are submitted to the Statistics Department where the corrections and additions were entered into the database. A quality control audit of 10% of all data in the database was made by the staff of the Statistics Department prior to locking the database.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Populations Analysed

Sample Size

A total of 110 patients were planned to be enrolled in this trial, in order to have data from about 98 individuals assuming a drop-out rate of 10%. The patients will be recruited in several ophthalmologic outpatient departments in Germany. The enrolment is competitive among the recruiting institutions.

The sample size of 98 was calculated to detect a significant difference in the number of intravitreal injections (within 12 months) between the two study arms with a power of 90 % using the Wilcoxon-Mann-Whitney-U-Test at the two-sided significance level of 5%. It was assumed that the number of injections is larger in group B than in group A with a probability of at least 69%. Assuming an approximately normal distribution, this corresponds to a mean difference of 2 injections with a common standard deviation of 2.85. In the RESTORE study [5] the mean number of injections was 7 with a standard deviation of 2.81. Given these numbers, a mean reduction of 2 injections per year appears realistic and relevant. The Mann-Whitney-U-Test is a non-parametric test which does not require a normally distributed endpoint. With the sample size of 98, non-inferiority with respect to the mean change from baseline in BCVA at month 12 (at the margin of -5 letters and the one-sided significance level of 2.5%) can be verified with a power of 90%, if the standard deviation is 7.5 letters (which is in accordance to the RESTORE-study data) and the treatments are equivalent with respect to this endpoint.

Since we aim on the verification of both, superiority with regard to the number of injections and non-inferiority with regard to mean change of BCVA, no multiplicity adjustment is required. Under the assumption of the above power calculations, the probability to verify both, superiority and non-inferiority, will be at least 80%.

Safety Set

The safety set consists of all randomized patients. The statement that a patient had no AEs also constitutes a safety assessment. Patients are analyzed according to treatment received.

Full Analysis Set

The full analysis set consists of all patients randomized. Following the intention-to-treat (ITT) principle, patients are analyzed according to the treatment they were assigned to at randomization.

Per Protocol Set

All patients within the full analysis set who have no major protocol violations, are included in the per protocol set. The major protocol violations are:

- Failure to fulfill the eligibility criteria but still entered the study
- Missing BCVA scores of the study eye at baseline or month 12
- Visit date deviation of more than 20%
- Loss to follow-up
- Wrong study medication or dose of medication
- Not sufficiently compliant with the protocol

Patients are analyzed according to treatment received.

9.7.2 Plausibility Checks

Appropriate plausibility checks will be performed before analyzing the data. Special emphasis will be placed on plausibility checks for all variables related to the primary and secondary endpoints. A list of all important variables for each endpoint that are checked for inconsistencies is given in the following two sections.

The full list of variables to be checked is given in the SAP.

9.7.3 Handling of Incomplete Data

If the Clinical Data Care (CDC) detects CRFs with missing or inconsistent data, queries will be sent to the monitor for correction by the investigator. The reasons for any missing data must be noted on the CRFs.

Entries that do not apply to a certain item for a specific patient will be marked N.A.: not applicable. Entries that were missed or where the information is lost will be marked N.D.: not done.

Imputations will be applied to both analysis sets (FAS and PPS).

Number of injections: The number of injections is derived from the respective CRF entries regarding injection at visits 1 to 12. Imputation will be performed on the injection indicators at each visit (ADM_None).

As the three injections at visits 1 to 3 are mandatory according to the study protocol, missing values at these visits will be regarded as if an injection has been performed, i.e. ADM_None=false.

At the subsequent visits 4 to 12 the treating physician will decide mainly according to the label of ranibizumab whether an injection is performed or not. For this reason, there is additional CRF information concerning the administration of ranibizumab. On the one hand, this is the CRF section on therapy decision and on the other hand these are the BCVA values (ETDRS and Snellen) at the respective (and previous) visits. If the injection identifier (ADM_None) is missing, the additional information will be used in order to impute the missing values. First, the physician's CRF entries regarding therapy decision will be used. If these entries are also missing, the BCVA course will be evaluated to see if an injection should have been carried out or not (according to the label of ranibizumab). In case that the injection indicator cannot be reconstructed, it will be assumed that an injection has been performed. However, as there is wide range of extra information, we expect these cases to be rare for patients with complete follow-up. For non-responders and patients that are lost to follow-up, the imputation method implies that for all missing visits an injection is assumed.

Imputation method for the BCVA: Impute the mean of all available baseline BCVA values. Intermediate missing values will be imputed by means of linear interpolation. For all drop outs last observation carried forward (LOCF) will be performed.

Additionally, a sensitivity analysis was planned in the SAP, which is not carried out because of the low sample size.

9.7.4 Handling of Withdrawals and Dropouts

All deviations related to the study inclusion or exclusion criteria, conduct of trial, patient management or patient assessment and respecting reasons will be described. Special investigation will be applied for:

- those who entered the study even though they violated the entry criteria
- those who developed withdrawal criteria during the study but were not withdrawn
- those who received the wrong treatment or incorrect dose

Regarding to ICH-E3 individual patients with these protocol deviations will be listed by treatment group in appendices of the statistical report.

9.7.5 Data Transformation

According to the Clinical Data Management Plan all concomitant diseases and adverse events are coded with MedDRA, Version 12.0. Coding will be done manually by experienced data management staff, using MedDRA Browser Version 3.0. Moreover, concomitant medication will be coded using ATC/DDD version 2013 list, available from Deutsches Institut für Medizinische Dokumentation und Information (DIMDI).

Data transformation and derivation of primary and secondary endpoints from the respective CRF variables (see Edit Check Specifications) is described in the following sections.

Primary Endpoints

1. Number of injections of study drug during the first year of treatment

- Derived as 12 minus the number of visits with ADM_None = true, i.e. no study drug administration.

2. Mean change from baseline in BCVA at month 12 (visit 13)

- Determined as the difference in BCVA score (measured in ETDRS letters) between visit 13 and visit 1 (variable OEX_ETDRS).

Secondary Endpoints

1. Proportion of patients with a vision acuity loss of fewer than 15 letters at month 12 (visit 13) compared with baseline

- If a patient has a visual acuity loss of fewer than 15 letters at visit 13 compared with baseline or not, is calculated by means of the second primary endpoint (change from baseline in BCVA at month 12).

2. Proportion of patients with a vision acuity loss of more than 15 letters at month 12 (visit 13) compared with baseline

- Determined analogously to the first secondary endpoint (vision acuity loss of fewer than 15 letters at visit 13 compared with baseline).

3. Proportion of patients with a treatment-free interval of at least 3 months duration at any time point following visit 3

- Calculated by means of variable ADM_None indicating if the study drug has been administered or not. If ADM_None = true for at least 3 visits (visit 4 – 13) in a row, a patient is regarded to have a treatment-free interval of at least 3 months duration following visit 3.

4. Dropout rates

- Early study termination is determined by means of the variable TER_Part (True = regular study participation, False = early termination).

5. Rate of non-responders

- On the one hand, drug non-response is determined according to judgment of the treating physician, i.e. variable TER_Fail (suspected treatment failure, Yes / No) on the study conclusion form.
- On the other hand, drug non-response will be determined irrespective of the physicians' judgment by means of the non-responder definition given in Section 9.4.2. This includes the BCVA scores measure in ETDRS letters at visits 4 to 12 (OEX_ETDRS) and the evaluation of AEs (AE_Desc).

6. Retinal Lesions

- Determined with the variable regarding retinal lesions at baseline, visit 7 and 13 (OEX_LesNone).

7. Changes in retinal thickness from baseline at month 4 and 12 (visit 13)

- Derived as the difference of the retinal thickness at visit 5 respectively 13 to the retinal thickness at baseline. As the retinal thickness in the study eye is measured at different areas (Central, Supra, Infra, Nasal, Temporal; OCT_Central, OCT_Supra, OCT_Infra, OCT_Nasal, OCT_Temporal), five differences for each patient will be calculated and evaluated.

8. AEs

- Number of AEs, time to AE and other relevant variables will be derived from the entries of the AE and SAE forms. For more information see also Section 0.

9. Quality of Life at visit 1 (before treatment) and visit 13 (month 12)

- All items on the VFQ-25 questionnaire will be recoded into individual item scores according to the respective VFQ-25 manual, Version 2000. These will be used to determine the 12 different subscales scores and an overall composite score. All derived scores range from 0 to 100, where high scores represent better functioning. In this format scores represent the achieved percentage of the total possible score, e.g. a score of 50 represents 50% of the highest possible score. For each score individual differences between visit 13 and visit 1 will be calculated.

9.7.6 Multicentre Trials

As the study is a multicentre trial, heterogeneity of baseline values, treatment success and safety between the different ophthalmologic outpatient departments were planned in the SAP to be analyzed. *Due to the small sample size, these analyses are omitted.*

9.7.7 Statistical Analysis

Descriptive Statistics and Treatment Group Comparisons

Every variable (item) documented in the CRF will be analyzed by descriptive methods. Number of observations, mean, standard deviation, maximum, minimum, median, lower and upper quartile will be tabulated for quantitative data. Counts and percentages will be presented for categorical data. These summaries were planned to be given for the total data set and separately for each treatment group, study center, analysis set (FAS, PPS) and with/without imputation. *Because of the small sample size, tabulations by study center were omitted.*

Treatment groups will be compared with respect to baseline efficacy variables, diagnoses, age and gender. The comparison will be done in a descriptive manner.

Further analyses and significance tests are described in the SAP. Because of the small sample size, these analyses are omitted.

Safety Variables

Safety analyses will be performed on all patients in the safety set. AEs will be classified and analyzed by organ system, severity and relation to treatment. Pre-post-differences will be calculated for laboratory data.

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA, Version 12.0), which replaced the Coding Symbols for a Thesaurus of Adverse Reaction Terms (COSTART).

Safety and tolerability issues will be addressed by recording the:

- Case-wise listing of AEs and SAEs (death and others)
- Occurrence and classification of AE and SAEs using frequency tables
- Kaplan-Meier estimation for occurrence of AE and SAEs (overall and for each system organ class)
- Rate of premature withdrawal due to AE/SAE
- Kaplan-Meier estimation for occurrence of withdrawal due to AE/SAE
- Changes in Safety Laboratory parameters with:
    - Comparison of pre-/post values of blood test results using Wilcoxon signed-rank test

- Summary statistic per visit (baseline, month 12, (early) termination visit) for every variable of vital signs

Due to the small sample size, the Wilcoxon signed-test and Kaplan-Meier estimates were omitted.

9.8 Changes in the conduct of the study or planned analyses

Due to the small sample size, only the descriptive analyses planned in the SAP could be conducted. Significance tests planned in the SAP were also not done. No PPS evaluation was done because only two patients remain in the per-protocol-set that both belong to arm A.

Furthermore, the results for the primary endpoints are presented only for the imputed data, for the following reasons: For the number of injections (primary endpoint 1), the imputation consisted rather of a plausibility correction assuring conservative estimates (see chapter 11.4.1.1 for details). For the mean change of BCVA (primary endpoint 2), no PPS-analysis were possible.

10 Study Patients

10.1 Disposition of patients

Recruitment took place from April 2014 to August 2015. Fifteen patients have been recruited in four study centers, see Table 10-1. Four further centers participated in the study, but did not recruit patients.

Table 10-1: Participating patients by center

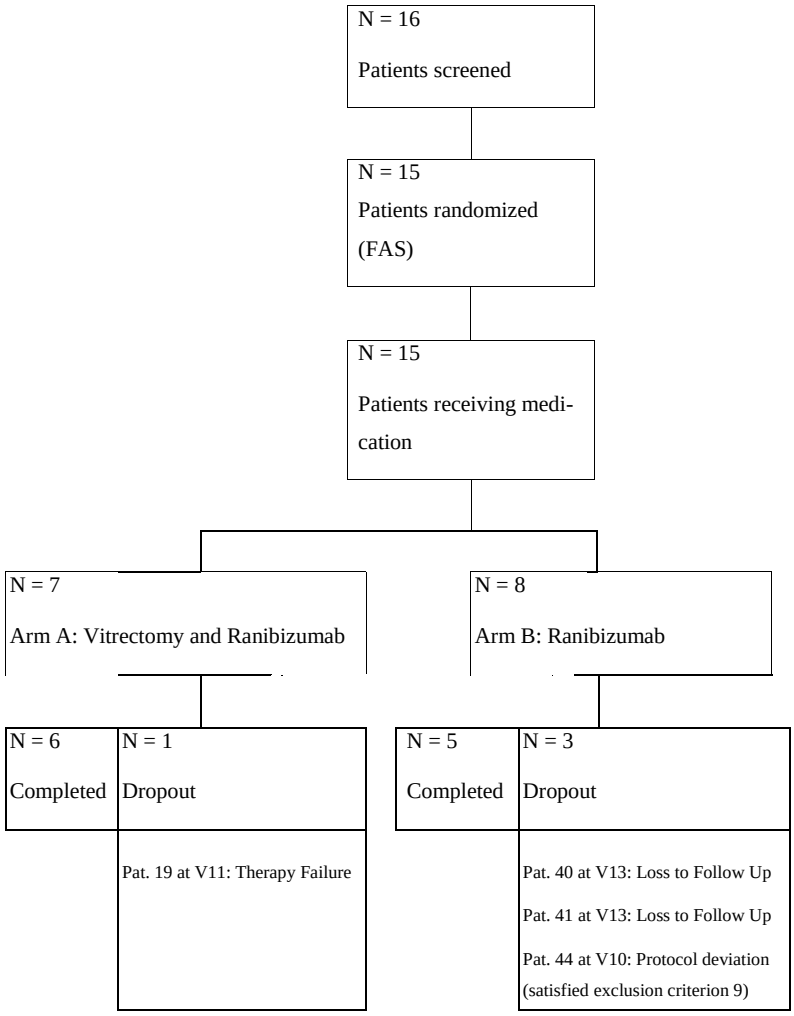
Participating Patients	Vitrectomy + Ranibizumab		Ranibizumab		Overall	
	N	%	N	%	N	%
Augenklinik Universitätsallee Bremen	3	42.9	3	37.5	6	40.0
St. Joseph-Stift Bremen	0	0.0	0	0.0	0	0.0
Westend Berlin	0	0.0	0	0.0	0	0.0
St. Gertrauden Berlin	1	14.3	0	0.0	1	6.7
Städtisches Klinikum Dessau	1	14.3	0	0.0	1	6.7
Franziskus-Hospital Münster	0	0.0	0	0.0	0	0.0
Augenzentrum Gelsenkirchen	2	28.6	3	37.5	5	33.3
Augen- und Poliklinik Georg-August-Universität Göttingen	0	0.0	2	25.0	2	13.3
Total	7	100.0	8	100.0	15	100.0

Because of the small number of patients in the study centers the anticipated analyses by center where all omitted.

10.1.1 Full-analysis-set

Out of 16 screened patients, 15 have been randomized. These patients form the full analysis set (FAS). The following figure 10.1 provides the study flow for the patients in the FAS. Here and in the remainder of the report, “arm A” refers to Vitrectomy + Ranibizumab and “arm B” to Ranibizumab arms.

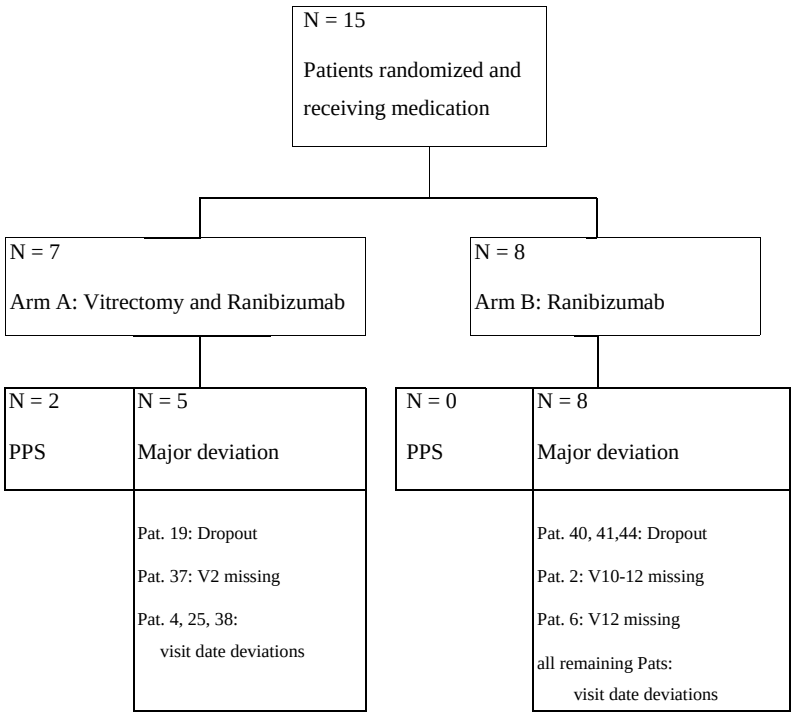
Figure 10.1: Arms of Full-Analysis-Set and Dropouts



10.1.2 Per-protocol-set

There have been 13 patients with major protocol deviations, for details see the following section 10.2. The remaining 2 patients represent the per-protocol-set (PPS). Figure 10.2 describes the composition of the PPS.

Figure 10.2: Per-protocol set and major deviations



10.2 Protocol deviations

According to the SAP, the following major protocol violations were determined.

1. Failure to fulfill the eligibility criteria but still entering the study

   - Pat. 2 satisfies exclusion criterion 24 (systemic therapy with steroids or anticoagulative therapy with coumarin derivatives or heparin). A query was sent and concluded that in this case, no influence on the therapy or progress of the disease is expected.

- Pat. 44 satisfies exclusion criterion 9 (previous vitrectomy in the study eye). This was noticed only at visit 10 and the patient terminated the study at this time point.

2. Missing BCVA scores of the study eye at baseline or month 12
   - Pat. 40 did not appear at the termination visit at month 12
   - Pat. 41 decided not to go to visit 13 at the study site
3. Visit date deviation of more than 20%

   Visits 1, 2 and 3 were scheduled at day 0, 28 and 56, respectively. A deviation of more than 20% occurred if the difference between visit 1 and 2 or the difference between visit 2 and 3 was not between 23 and 33 days.

   Visits 4-13 were scheduled at month 3-12, respectively. A deviation of more than 20% occurred if the difference of one of these visits to the previous visit was not between 24 and 36 days.

   Table 10-2 shows the differences between visits for all patients. Except for Pat.1 and Pat. 3, all patients have visit date differences that do not fall in the required interval, or even missing visits.
4. Loss to follow-up and dropout
   - Pat. 40 was lost to follow-up at the termination visit V13
   - Pat. 41 was lost to follow-up at the termination visit V13
   - Pat. 19 terminated at visit 11 (month 10) because of suspected therapy failure
   - Pat. 44 terminated at visit 10 (month 9) because he satisfied an exclusion criterion.
5. Wrong study medication or dose of medication
   - All patients were treated according to the arm they were randomized to.
   - Pat. 37 missed visit 2 and therefore also the second obligatory injection.
6. Not sufficient compliant with the protocol

   Besides missing or delayed visits, there were no apparent additional signs of non-compliance.

To summarize, 13 out of 15 patients exhibit major protocol deviations. For details see Table 10-3.

Table 10-2: Difference to previous visit in days for visit 2 (V2) to visit 13 (V13).

All protocol deviations are highlighted. n.v. = no visit documented. Note that missing values also appear for visits following non-documented visits because no difference can be calculated.

Pat.	Diff V2	Diff V3	Diff V4	Diff V5	Diff V6	Diff V7	Diff V8	Diff V9	Diff V10	Diff V11	Diff V12	Diff V13
1	29	28	28	28	28	28	28	28	28	28	28	36
2	28	28	**43**	34	**64**	29	33	**56**	**n.v.**	**n.v.**	**n.v.**	
3	29	28	28	28	35	28	35	28	28	28	28	29
4	29	**35**	35	28	28	28	35	28	28	28	35	28
5	28	28	28	28	28	28	28	28	28	28	28	**56**
6	**35**	28	28	28	35	28	**42**	29	**44**	33	**n.v.**	
19	31	29	32	38	28	28	28	28	32	**41**	**n.v.**	**n.v.**
25	**36**	28	28	**n.v.**		27	29	**n.v.**		28	28	**84**
37	**n.v.**		28	28	28	28	**37**	26	30	33	35	30
38	28	28	28	23	36	**46**	35	**57**	**49**	**49**	**51**	**61**
39	**37**	**35**	34	28	29	28	34	28	30	**54**	30	35
40	**55**	**35**	29	**n.v.**	**n.v.**	**n.v.**		**49**	34	31	**40**	**n.v.**
41	**41**	**35**	35	**43**	35	**42**	35	35	**42**	**42**	33	**n.v.**
43	28	28	28	28	29	28	35	**23**	28	28	26	27
44	28	28	29	28	30	28	28	28	26	**n.v.**	**n.v.**	**n.v.**

Table 10-3: Patients with major protocol deviations

Patient.	Arm	Deviations
2	B	Missing visits, visit data deviations
4	A	Visit date deviation
5	B	Visit date deviation
6	B	Missing visit, visit date deviations
19	A	Dropout, visit date deviation
25	A	Missing visits, visit date deviations
37	A	Missing visit (obligatory injection), visit date deviation
38	A	Visit date deviations
39	B	Visit date deviations
40	B	Dropout, Missing visits (including termination visit), visit date deviations
41	B	Dropout, visit date deviations
43	B	Visit date deviation
44	B	Dropout, exclusion criterion satisfied

11 Efficacy Evaluation

11.1 Data Sets Analyzed

According to the SAP, the results presented for the first primary endpoints are based on the Full Analysis Set (FAS) including all 15 randomized subjects with imputations. Because of the low sample size, no hypothesis tests are performed. The results for the second primary endpoints were planned to be carried out with the per-protocol set (PPS). Since only two patients (both in Arm A) have no major protocol violations, no analyses of the PPS can be done. A sensitivity analysis is carried out for the second primary endpoint for the FAS (with imputation). All other results are based on the available original data without imputations.

Only the most important results are discussed in the following sections, more information is contained in the Chapter 14 and the Listings at the end of the report.

11.2 Demographic and Other Baseline Characteristics

The following sections provide information about the baseline variables. More detailed data are provided by the tables in Section 14.1 and Listing 1 at the end of the report.

Due to the small number, none of the results have confirmative character. Differences between treatment arms may therefore be caused by chance.

11.2.1 Demographics

Table 11-1: Categorical demographics at baseline

Demographics		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
Gender	**Female**	3	42.9	5	62.5	8	53.3
	Male	4	57.1	3	37.5	7	46.7
Ethnicity	**Caucasian**	7	100.0	7	87.5	14	93.3
	Arabic	0	0.0	1	12.5	1	6.7

Overall the number of males and females is similar. Only one patient in the study was not Caucasian.

Table 11-2: Age at baseline

Age in years	N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	7	66.3	7.4	53.0	64.0	66.0	74.0	75.0
Ranibizumab	8	70.9	7.2	61.0	65.0	70.5	77.0	81.0
Overall	15	68.7	7.4	53.0	64.0	68.0	75.0	81.0

There was a age difference of about four years in the mean and median between the two treatment groups. The 25% and 75% quantiles were similar.

11.2.2 Diagnosis and ophtalmological examinations of study eye

Table 11-3: Study eye

Study eye	Vitrectomy + Ranibi-zumab		Ranibizumab		Overall	
	N	%	N	%	N	%
left	4	57.1	4	50.0	8	53.3
right	3	42.9	4	50.0	7	46.7
Total	7	100.0	8	100.0	15	100.0

The numbers of left and right study eyes were similar between the two treatment groups (see Table Table 11-3). Fundus photography was done at baseline for all 15 patients. The results of the ophtalmological examinations at baseline are given in Table 11-4. They were similar between the treatment groups except for the occurrence of retinal lesions which were more frequent in arm A.

Baseline values from the optical coherence tomography are given in Table 11-5. The difference between the treatment groups is overall small compared to the standard deviation. Only for the supra quadrant a distinct difference in the mean (and median) is observed which, given the small sample size, is still explainable by chance.

Table 11-4: Ophtalmological examinations at baseline

Ophtalmological examinations (baseline)		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
Diagnosis	**focal**	1	14.3	2	25.0	3	20.0
	diffus	6	85.7	6	75.0	12	80.0
	both	0	0.0	0	0.0	0	0.0
Lens	**clear**	0	0.0	0	0.0	0	0.0
	cataract	5	71.4	4	50.0	9	60.0
	IOL	2	28.6	4	50.0	6	40.0
Retinal lesions	**Yes**	4	57.1	1	12.5	5	33.3
	No	3	42.9	7	87.5	10	66.7

Table 11-5: Retinal thickness at baseline

Retinal thickness at baseline		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
central	**Vitrectomy + Ranibizumab**	7	455.1	200.9	150.0	311.0	447.0	631.0	683.0
	Ranibizumab	8	491.3	146.4	313.0	416.5	451.5	538.0	805.0
infra	**Vitrectomy + Ranibizumab**	7	444.4	100.4	342.0	362.0	410.0	543.0	601.0
	Ranibizumab	8	447.0	128.1	331.0	356.0	403.5	506.0	714.0
nasal	**Vitrectomy + Ranibizumab**	7	447.9	111.9	310.0	347.0	418.0	577.0	610.0
	Ranibizumab	8	431.3	109.5	337.0	351.0	394.0	494.0	635.0
supra	**Vitrectomy + Ranibizumab**	7	496.0	99.1	361.0	368.0	524.0	537.0	638.0
	Ranibizumab	8	442.6	158.2	287.0	336.0	396.5	514.0	761.0
tempora	**Vitrectomy + Ranibizumab**	7	465.4	144.9	286.0	319.0	489.0	586.0	649.0
	Ranibizumab	8	477.6	160.5	377.0	396.5	423.5	470.5	863.0

Intraocular pressure was normal for all patients. Slitlamp examination had normal results for all 7 patients in arm A and 6 patients in arm B. In arm B there was one case of dermalaxia and one case of cataract. Results from fluorescein angiography can be found in Section 14.1.4.

11.2.3 Baseline of efficacy parameters

Baseline of primary endpoint 1 (Number of injections)

All patients received their first injection at the baseline visit or – in arm A – during vitrectomy.

Baseline of primary endpoint 2 (BCVA in ETDRS letters)

For all 7 patients in the Vitrectomy + Ranibizumab arm and 7 patients in the Ranibizumab arm, visual acuity measurement was done at a distance of 4 meters. One patient in the Ranibizumab arm read the letters at a distance of 1 meter. Table 11-6 summarizes the baseline BCVA values in ETDRS letters. The mean difference between the treatment groups is moderate compared to the standard deviations.

Table 11-6: BCVA at baseline

BCVA in ETDRS letters at baseline	N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	7	46.4	9.2	35.0	38.0	48.0	50.0	63.0
Ranibizumab	8	52.3	17.0	19.0	45.5	58.0	62.5	67.0
Overall	15	49.5	13.8	19.0	38.0	50.0	60.0	67.0

11.2.4 Concomitant diseases and preceding diseases of study eye

Table 11-7 gives the number of concomitant diseases per patient. All 7 patients in arm A and 5 of 8 patients in arm B had at least one concomitant disease. Treatment arm B contains 4 patients with more than 2 diseases whereas all patients in arm A had at most 2 diseases. In summary, there is no striking difference in the concomitant diseases between the two treatment arms. The number of concomitant diseases by system organ class can be found in

Table 11-8. In both treatment arms the most frequent concomitant diseases were endocrine, vascular and metabolism and nutrition disorders.

Two patients (28.6%) in arm A and five patients (62.5%) in arm B had preceding diseases of the study eye other than DME (no table shown). According to Table 11-9, 5 patients (71.4%) in arm A and 4 patients (50.0%) in arm B had previous DME treatments of the study eye. All previous diseases of the study eye and previous DME treatments of the study eye are listed patient-wise in Listing 1.

Table 11-7: Number of concomitant diseases per patient

Number of concomitant diseases per patient	Vitrectomy + Ranibizumab		Ranibizumab		Overall	
	N	%	N	%	N	%
0	0	0.0	3	37.5	3	20.0
1	3	42.9	0	0.0	3	20.0
2	4	57.1	0	0.0	4	26.7
3	0	0.0	3	37.5	3	20.0
4	0	0.0	1	12.5	1	6.7
6	0	0.0	1	12.5	1	6.7
Total	7	100.0	8	100.0	15	100.0

Table 11-8: Concomitant diseases by system organ class

Frequency of concomitant diseases by system organ class	Vitrectomy + Ranibizumab		Ranibizumab		Overall	
	N	%	N	%	N	%
Cardiac disorders	1	9.1	0	0.0	1	3.6
Endocrine disorders	4	36.4	7	41.2	11	39.3
Gastrointestinal disorders	0	0.0	1	5.9	1	3.6
Infections and infestations	0	0.0	1	5.9	1	3.6
Metabolism and nutrition disorders	2	18.2	2	11.8	4	14.3
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	1	9.1	0	0.0	1	3.6
Reproductive system and breast disorders	0	0.0	1	5.9	1	3.6

Frequency of concomitant diseases by system organ class	Vitrectomy + Ranibizumab		Ranibizumab		Overall	
	N	%	N	%	N	%
Vascular disorders	3	27.3	5	29.4	8	28.6
Total	11	100.0	17	100.0	28	100.0

Table 11-9: Number of previous DME treatment in study eye

DME treatment in study eye	Vitrectomy + Ranibizumab		Ranibizumab		Overall	
	N	%	N	%	N	%
0	2	28.6	4	50.0	6	40.0
1	1	14.3	3	37.5	4	26.7
2	4	57.1	0	0.0	4	26.7
4	0	0.0	1	12.5	1	6.7
Total	7	100.0	8	100.0	15	100.0

11.3 Measurements of Compliance

As has been seen in chapter 10.2, several protocol violations in terms of visit date differences occurred in both study arms. Some patients even missed one or more visits. Table 11-10 summarizes the number of patients per arm who occurred at each visit.

In arm B, more visits are missing (altogether 10) compared to arm A (altogether 5). Especially, more patients of arm B missed some of the later visits. Two patients (from arm B) were lost to follow-up. For two patients the study was terminated early according to the protocol (arm A: therapy failure; arm B: late discovery of an exclusion criterion). Only one patient (in arm A) missed one of the obligatory first three visits, namely visit 2.

Table 11-10: Compliance measured by participation at visit.

MV: missing visits altogether (e.g. arm A: 7 patients à 13 visits = 91 visits, of which 86 occurred)

Number of patients at Visits	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Vitrectomy + Ranibizumab (7 patients)	7	6	7	7	6	7	7
Ranibizumab (8 patients)	8	8	8	8	7	7	7
	8	**9**	**10**	**11**	**12**	**13**	**MV**
Vitrectomy + Ranibizumab (7 patients)	7	6	7	7	6	6	5
Ranibizumab (8 patients)	8	8	7	6	5	5	10

Concerning visit dates, two patients in arm A are the only patients where all visits followed the foreseen schedule (see Table 10-2).

To summarize, overall compliance in the study was not perfect. There was a tendency of better compliance in the Vitrectomy + Ranibizumab arm. Due to the small sample size, the result cannot be generalized.

11.4 Efficacy Results and Tabulations of Individual Patient Data

11.4.1 Analysis of efficacy

11.4.1.1 FAS analysis of primary endpoint 1: Number of injections

The number of injections of the study drug during the first year of treatment is calculated as 12 minus the number of omitted injections (ADM_None) over visits 1 to 12. At the termination visit 13, no injection was foreseen.

First, plausibility checks and imputations for the variable ADM_None were performed, as indicated in the SAP. The variable ADM_None was e.g. cross checked with a missing date of injection and batch number or a missing visit. In concordance with the SAP, for the 13 cases of missing visits, it was assumed that an injection took place. Table 11-11 and Table 11-12 show the results for the number of injections per treatment group (with the imputations). A listing of all injections for all patients can be found in chapter 11.4.2 (Table 11-19). A list of the visits were the investigator has deviated from the suggested decision criterion for an injection (as indicated in the protocol and CRF) can be found in

Listing 6. There have been 4 cases where decision of the investigator as marked in the CRF was actually not implemented. These cases are listed in Listing 6 as well.

Table 11-11: Primary endpoint 1 for FAS: Number of injections (frequencies)

Number of injections	Vitrectomy + Ranibizumab		Ranibizumab		Overall	
	N	%	N	%	N	%
4	1	14.3	0	0.0	1	6.7
5	0	0.0	2	25.0	2	13.3
6	0	0.0	1	12.5	1	6.7
7	0	0.0	1	12.5	1	6.7
8	1	14.3	0	0.0	1	6.7
9	3	42.9	2	25.0	5	33.3
10	0	0.0	1	12.5	1	6.7
12	2	28.6	1	12.5	3	20.0
Total	7	100.0	8	100.0	15	100.0

Table 11-12: Primary endpoint 1 for FAS: Number of injections (summary statistics)

Number of injections	N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	7	9.0	2.7	4.0	8.0	9.0	12.0	12.0
Ranibizumab	8	7.9	2.5	5.0	5.5	8.0	9.5	12.0
Overall	15	8.4	2.6	4.0	6.0	9.0	10.0	12.0

The number of injection was slightly higher in arm A with a difference of about one injection. Due to the small number of patients the difference may be due to chance.

11.4.1.2 PPS analysis of primary endpoint 2: Mean change from baseline in BCVA at month 12

Due to the small and unbalanced sample size of the PPS, no analysis can be done. A sensitivity analysis with the FAS was carried out and is presented in chapter 11.4.1.4.

11.4.1.3 FAS analysis of secondary endpoints

Secondary endpoint 1: Vision acuity loss of fewer than 15 letters at month 12 (visit 13)

This endpoint is calculated with the corrected and imputed ETDRS as described in chapter 11.4.1.4. All patients had a vision acuity loss of less than 15 letters.

Secondary endpoint 2: Vision acuity loss of more than 15 letters at month 12 (visit 13)

No patient hat a vision acuity loss of more than or equal to 15 letters.

Secondary endpoint 3: Treatment-free interval of at least 3 months duration

This endpoint is calculated with the corrected variable ADM_None as described in chapter 11.4.1.1.

Table 11-13: Secondary endpoint 3 – treatment-free interval of at least 3 months

Patients with a treatment-free interval of	Vitrectomy + Ranibizumab		Ranibizumab		Overall	
	N	%	N	%	N	%
< 3 months	5	71.4	4	50.0	9	60.0
≥ 3 months	2	28.6	4	50.0	6	40.0
Total	7	100.0	8	100.0	15	100.0

Two patients from arm A and four patients from arm B had a treatment-free interval of at least 3 months. In arm A one of these patients stopped all treatments at visit 5 and in arm B one patient at visit 7 and one patient at visit 9. The other patients restarted treatment later.

A listing of all injections for all patients can be found in chapter 11.4.2 (Table 11-19).

Secondary endpoint 4: Dropout rates

As discussed in section 10.1, there were four dropouts: Patient 19 (arm A) because of therapy failure, patients 40 and 41 (arm B) were lost to follow-up and patient 44 (arm B) left the study because he satisfied an exclusion criterion.

Secondary endpoint 5: Rate of non-responder

The criterion for non-response is calculated with the corrected, but not imputed ETDRS values, see chapter 11.4.1.4. According to the criterion in the SAP (see chapter 9.4.2 of this report), no patient was regarded a non-responder. However, patient 19 from the Vitrectomy + Ranibizumab arm left the study because of therapy failure, which is considered as non-response. Hence, the rate of non-responders is 14.3% in arm A and 0% in arm B.

Secondary endpoint 6: New retinal lesions at visit 7 or 13

Only one of the 15 patients, belonging to arm A, had a new retinal lesion, namely at visit 7. There were no new lesions at visits 7 or 13 in arm B. In chapter 11.4.2 (

Table **11-22**), a patient-wise listing for the retinal lesions is given.

Secondary endpoint 7: Changes in retinal thickness from baseline at month 4 and 12

Table 11-14 and Table 11-15 give summaries for the change from baseline in retinal thickness at months 4 (visit 5) and 12 (visit 13). The patient-wise listing of the differences can be found in the chapter 11.4.2 and (Table 11-24). The changes from baseline were negative throughout. In most quadrants the retina thickness decreased more in arm A than in arm B after 4 and 12 months with a small to moderate treatment difference (in comparison to the standard deviation). An exception is the central quadrant where at month 12 the decrease was higher in arm B in the mean, however, smaller in the median. Due to the small number of patients it is difficult to draw a clear conclusion from these results.

Table 11-14: Change from basline in retinal thickness at month 4 (visit 5)

Change from baseline for retinal thickness in µm		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
central	**Arm A**	5	-143.8	360.5	-472.0	-431.0	-139.0	-106.0	429.0
	Arm B	7	-49.9	112.8	-236.0	-160.0	-12.0	20.0	98.0
infra	**Arm A**	5	-76.0	167.7	-245.0	-231.0	-89.0	54.0	131.0
	Arm B	7	-20.3	159.8	-199.0	-120.0	-24.0	-11.0	308.0

Change from baseline for retinal thickness in µm		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
nasal	**Arm A**	5	-68.0	194.6	-325.0	-199.0	2.0	11.0	171.0
	Arm B	7	-14.0	50.9	-113.0	-33.0	-11.0	25.0	45.0
supra	**Arm A**	5	-160.0	154.4	-353.0	-219.0	-199.0	-88.0	59.0
	Arm B	7	-30.3	97.9	-214.0	-77.0	-17.0	45.0	93.0
temporal	**Arm A**	5	-135.4	203.8	-301.0	-281.0	-246.0	-15.0	166.0
	Arm B	7	-18.1	180.4	-269.0	-100.0	-45.0	34.0	330.0

Table 11-15: Change from basline in retinal thickness at month 12 (visit 5)

Change from baseline for retinal thickness in µm		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
central	**Arm A**	6	-147.2	306.4	-445.0	-407.0	-171.5	-87.0	399.0
	Arm B	5	-200.8	148.0	-438.0	-232.0	-151.0	-136.0	-47.0
infra	**Arm A**	6	-96.2	166.1	-259.0	-251.0	-102.5	-56.0	194.0
	Arm B	5	-93.4	103.8	-263.0	-124.0	-30.0	-28.0	-22.0
nasal	**Arm A**	6	-74.5	205.5	-268.0	-265.0	-89.5	-27.0	292.0
	Arm B	5	-76.8	78.1	-186.0	-118.0	-73.0	-6.0	-1.0
supra	**Arm A**	6	-146.8	169.1	-322.0	-262.0	-176.5	-105.0	161.0
	Arm B	5	-89.2	117.6	-296.0	-73.0	-37.0	-23.0	-17.0
temporal	**Arm A**	6	-150.8	179.9	-272.0	-270.0	-231.5	-89.0	189.0
	Arm B	5	-108.4	50.7	-178.0	-136.0	-103.0	-77.0	-48.0

Secondary endpoint 8: Adverse events

The discussion of the number of AEs/SAs and other relevant summaries can be found in chapter 12.2.

Secondary endpoint 9: Quality of life at visit 1 and visit 13

In Table 11-16, the two arms are compared with regard to the subscales and the overall composite score of the VFQ25 questionnaire. The endpoint is the difference between visit 1 and visit 13. Separate summary statistics of visit 1 and visit 13 for all scores can be found in the Section 14.2.6.

The treatment differences were generally small or only moderate compared to the standard deviations. The difference is particular small for the overall composite score. With regard to the sub-items no clear trend is visible: e.g. for arm A there is a higher value for the driving score but a smaller value for dependency score when compared to arm B.

Table 11-16: Secondary endpoint 9 - Difference between visit 13 and visit 1 of subscales and overall composite score of quality of life questionnaire

Quality of Life (VFQ25) Difference V13 - V1		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
General health score	**Vitrectomy + Ranibizumab**	5	5.0	20.9	-25.0	0.0	0.0	25.0	25.0
	Ranibizumab	5	10.0	28.5	-25.0	0.0	0.0	25.0	50.0
General vision score	**Vitrectomy + Ranibizumab**	5	8.0	17.9	-20.0	0.0	20.0	20.0	20.0
	Ranibizumab	5	8.0	33.5	-20.0	-20.0	0.0	20.0	60.0
Ocular pain score	**Vitrectomy + Ranibizumab**	5	-12.5	17.7	-37.5	-25.0	0.0	0.0	0.0
	Ranibizumab	5	2.5	10.5	-12.5	0.0	0.0	12.5	12.5
Near activities score	**Vitrectomy + Ranibizumab**	5	18.3	21.6	-8.3	8.3	16.7	25.0	50.0
	Ranibizumab	5	0.0	39.5	-50.0	-16.7	0.0	8.3	58.3
Distance activities score	**Vitrectomy + Ranibizumab**	5	2.5	15.5	-16.7	-4.2	0.0	8.3	25.0
	Ranibizumab	5	6.7	19.0	-16.7	0.0	0.0	16.7	33.3

Quality of Life (VFQ25) Difference V13 - V1		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Social functioning score	**Vitrectomy + Ranibizumab**	5	7.5	28.8	-37.5	0.0	12.5	25.0	37.5
	Ranibizumab	5	-2.5	18.5	-25.0	-12.5	0.0	0.0	25.0
Mental health score	**Vitrectomy + Ranibizumab**	5	-3.8	15.7	-31.3	0.0	0.0	6.3	6.3
	Ranibizumab	5	0.0	15.3	-12.5	-12.5	0.0	0.0	25.0
Role difficulties score	**Vitrectomy + Ranibizumab**	5	5.0	14.3	-12.5	0.0	0.0	12.5	25.0
	Ranibizumab	5	2.5	5.6	0.0	0.0	0.0	0.0	12.5
Dependency score	**Vitrectomy + Ranibizumab**	5	-13.3	37.5	-75.0	-16.7	0.0	0.0	25.0
	Ranibizumab	5	8.3	11.8	0.0	0.0	0.0	16.7	25.0
Driving score	**Vitrectomy + Ranibizumab**	4	25.0	39.7	0.0	0.0	8.3	50.0	83.3
	Ranibizumab	4	-20.8	41.7	-83.3	-41.7	0.0	0.0	0.0
Color vision score	**Vitrectomy + Ranibizumab**	5	5.0	11.2	0.0	0.0	0.0	0.0	25.0
	Ranibizumab	4	6.3	23.9	-25.0	-12.5	12.5	25.0	25.0
Peripheral vision score	**Vitrectomy + Ranibizumab**	5	5.0	11.2	0.0	0.0	0.0	0.0	25.0
	Ranibizumab	5	20.0	32.6	0.0	0.0	0.0	25.0	75.0
Overall composite score	**Vitrectomy + Ranibizumab**	4	4.1	18.3	-20.6	-8.8	7.3	17.0	22.5
	Ranibizumab	3	7.7	14.0	-4.5	-4.5	4.6	22.9	22.9

11.4.1.4 Sensitivity analysis: FAS analysis of primary endpoint 2

As a plausibility check, the ETDRS values indicated in the CRF were compared to the quotient of the Snellen values, which were also indicated in the CRF. Listing 2 at the end of the report shows the plausible ranges for ETDRS given all possible Snellen quotients. It was found out that the indicated ETDRS values follow different documentation norms when measured at 4 meters distance: some investigators had added 30 letters to the gathered number of letters and others did not. Altogether, there were 11 observations from one patient who read from 1 meter distance, and 170 observations read from 4 meters distance. Of the latter, 145 were identified to use the documentation without adding 30 letters. For the statistical analyses, 30 letters were added to these measurements. After this transformation, there remained 15 observations where the ETDRS and the Snellen quotient were not compatible. Comparing the ETDRS values of the respective patients with their other visits and considering the rather unusual Snellen results in some cases, the ETDRS values were treated as the more plausible data and therefore retained for the analyses.

All missing values of the (corrected) ETDRS at the 17 missing visits were imputed by linear interpolation or LOCF. Table 11-17 gives a summary of the corrected/imputed ETDRS values by visit and treatment arm. In Section 14.2.1 tables with complete statistics for the imputed and non-imputed, as well as baseline-adjusted ETDRS values can be found.

Table 11-17: ETDRS letters by visits (FAS with imputation)

BCVA in ETDRS letters	Vitrectomy + Ranibizumab			Ranibizumab		
	N	Mean	Std	N	Mean	Std
Visit 1	7	46.4	9.2	8	52.3	17.0
Visit 2	7	47.4	8.7	8	54.3	17.6
Visit 3	7	52.7	13.6	8	52.6	16.1
Visit 4	7	54.7	12.9	8	56.6	17.7
Visit 5	7	50.2	13.7	8	59.3	22.0
Visit 6	7	52.4	11.1	8	59.4	16.6
Visit 7	7	53.3	12.5	8	60.8	17.6
Visit 8	7	53.7	14.9	8	61.3	24.5
Visit 9	7	53.9	12.7	8	59.9	17.1

BCVA in ETDRS letters	Vitrectomy + Ranibizumab			Ranibizumab		
	N	Mean	Std	N	Mean	Std
Visit 10	7	53.9	15.9	8	54.1	19.8
Visit 11	7	56.0	15.9	8	56.6	20.1
Visit 12	7	51.1	13.3	8	58.0	20.7
Visit 13	7	53.3	14.2	8	57.1	20.5

Table 11-18: Sensitivity analysis - primary endpoint 2 for FAS

Mean change from baseline in BCVA at month 12	N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	7	6.9	13.6	-12.0	-5.0	12.0	22.0	22.0
Ranibizumab	8	4.9	8.6	-10.0	-1.5	8.0	11.0	14.0
Overall	15	5.8	10.8	-12.0	-5.0	8.0	12.0	22.0

Overall the mean change from baseline is somewhat larger in arm A than in arm B with a mean difference of 2 letters. Due to the small number patients, no reliable lower confidence bound can be determined and hence non-inferiority at a margin of 5 letters cannot be verified.

11.4.2 Tabulation of individual response data

Table 11-19: Injections and number of injections by patient and visit.

1 = injection, 0 = no injection. Values are plausibility corrected and imputed. Injections that were changed from no to yes (see 11.4.1.4) are highlighted.

Patient	V1	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	Total
Vitrectomy + Ranibizumab:													
1	1	1	1	1	1	1	1	1	1	1	1	1	12
3	1	1	1	1	1	1	0	0	0	1	1	1	9
4	1	1	1	1	1	0	1	1	0	1	0	1	9
19	1	1	1	1	1	1	1	1	1	1	1	1	12
25	1	1	1	1	1	0	1	1	1	1	0	0	9
37	1	1	1	1	0	0	0	0	0	0	0	0	4
38	1	1	1	0	0	1	0	1	1	1	1	0	8
Ranibizumab:													
2	1	1	1	1	1	1	1	1	1	1	1	1	12
5	1	1	1	0	0	0	1	0	0	1	0	0	5
6	1	1	1	1	1	1	1	1	0	0	0	1	9
39	1	1	1	0	1	0	1	0	0	1	0	0	6
40	1	1	1	0	1	1	1	1	0	0	0	0	7
41	1	1	1	1	0	1	0	0	0	0	0	0	5
43	1	1	1	0	1	1	1	1	1	0	1	1	10
44	1	1	1	1	1	1	0	1	0	0	1	1	9

Table 11-20: Summary of primary endpoints and of secondary endpoints 1-5 for patients of arm A (Vitrectomy + Ranibizumab).

PE = primary endpoint, SE = secondary endpoint.

	PE 1	PE 2	SE 1	SE 2	SE 3	SE 4	SE 5
Patient	No. of injections	Change in BVCA	VA loss < 15 letters	VA loss > 15 letters	3 months treatment-free	Dropout	Non-respond-er
1	12	12	yes	no	no	no	no
3	9	22	yes	no	yes	no	no
4	9	12	yes	no	no	no	no
19	12	22	yes	no	no	yes	yes
25	9	-3	yes	no	no	no	no
37	4	-12	yes	no	yes	no	no
38	8	-5	yes	no	no	no	no

Table 11-21: Summary of primary endpoints and of secondary endpoints 1-5 for patients of arm B (Ranibi-zumab).

PE = primary endpoint, SE = secondary endpoint.

	PE 1	PE 2	SE 1	SE 2	SE 3	SE 4	SE 5
Patient	No. of injections	Change in BCVA0	VA loss < 15 letters	VA loss > 15 letters	3 months treatment-free	Dropout	Non-respond-er
2	12	8	yes	no	no	no	no
5	5	-10	yes	no	yes	no	no
6	9	12	yes	no	yes	no	no
39	6	10	yes	no	no	no	no
40	7	8	yes	no	yes	yes	no

41	5	3	yes	no	yes	yes	no
43	10	14	yes	no	no	no	no
44	9	-6	yes	no	no	yes	no

Table 11-22: Patient-wise listing of retinal lesions at visits 1, 7 and 13 (secondary endpoint 6).

Secondary endpoint 6	Patient	Lesion at visit 1	New lesion at visit 7	New lesion at visit 13
Vitrectomy + Ranibizumab	1	no	no	no
	3	no	no	no
	4	no	no	no
	19	yes	yes	(missing)
	25	yes	no	no
	37	yes	no	no
	38	yes	no	no
Ranibizumab	2	no	no	no
	5	no	no	no
	6	no	no	no
	39	no	no	no
	40	no	(missing)	(missing)
	41	no	no	(missing)
	43	no	no	no
	44	yes	no	(missing)

Table 11-23: Patient-wise listing of change from baseline in retinal thickness at month 4 (visit 5)

"n.d.": measurement at visit 5 not done

Secondary endpoint 7 – change from baseline in retinal thickness at visit 5 in µm						
Treatment	**Patient**	**central**	**supra**	**infra**	**nasal**	**temporal**
Vitrectomy + Ranibizumab	1	429	59	131	171	166
	3	-139	-199	-89	2	-301
	4	-472	-219	-231	-199	-246
	19	-106	-88	54	11	-15
	25	n.d.	n.d.	n.d.	n.d.	n.d.
	37	-431	-353	-245	-325	-281
	38	n.d.	n.d.	n.d.	n.d.	n.d.
Ranibizumab	2	-236	-77	-199	-113	-100
	5	20	93	-120	5	34
	6	98	45	308	45	330
	39	-12	-17	-17	-16	-29
	40	n.d.	n.d.	n.d.	n.d.	n.d.
	41	-12	-7	-11	25	-45
	43	-47	-35	-24	-11	-48
	44	-160	-214	-79	-33	-269

Table 11-24: Patient-wise listing of change from baseline in retinal thickness at month 12 (visit 13)

"n.d.": measurement at visit 13 not done

Secondary endpoint 7 - change from baseline in retinal thickness at visit 13 in µm						
Treatment	**Patient**	**central**	**supra**	**infra**	**nasal**	**temporal**
Vitrectomy + Ranibizumab	**1**	**399**	**161**	**194**	**292**	**189**
	3	-101	-195	-74	-27	-272
	4	-407	-262	-259	-265	-214
	19	n.d.	n.d.	n.d.	n.d.	n.d.
	25	-87	-105	-56	-103	-89
	37	-445	-322	-251	-268	-249
	38	-242	-158	-131	-76	-270
Ranibizumab	2	-232	-73	-263	-118	-178
	5	-151	-23	-124	-73	-103
	6	-438	-296	-28	-186	-136
	39	-136	-17	-30	-6	-77
	40	n.d.	n.d.	n.d.	n.d.	n.d.
	41	n.d.	n.d.	n.d.	n.d.	n.d.
	43	-47	-37	-22	-1	-48
	44	n.d.	n.d.	n.d.	n.d.	n.d.

A patient-wise listing of adverse events (secondary endpoint 8) and of the VFQ25 (secondary endpoint 9) can be found in Listings L3 and L2 at the end of the report.

12 Safety Evaluation

12.1 Extent of Exposure

The study drug injections given to the patients can be found in Table 11-19 of chapter 11.4.2.

12.2 Adverse Events (AEs)

12.2.1 Brief summary of adverse events

There were 7 patients with adverse events, 4 in arm A and 3 in arm B. As can be seen in Table 12-1, one patient in arm A had 9 AEs, whereas all other patients had at most two AEs. None of the documented AEs were considered to be related to the study treatment.

From the total of 17 adverse events, 13 were not serious (11 in arm A, 2 in arm B), see

Table 12-2. The four serious adverse events are described in detail in chapter 12.3.

Table 12-1: Number of adverse events by patient

Number of AEs	Vitrectomy + Ranibizumab		Ranibizumab		Overall	
	N	%	N	%	N	%
1	2	50.0	2	66.7	4	57.1
2	1	25.0	1	33.3	2	28.6
9	1	25.0	0	0.0	1	14.3

Table 12-2: Serious adverse events

AEs	Vitrectomy + Ranibizumab		Ranibizumab		Overall	
	N	%	N	%	N	%
not serious	11	84.6	2	50.0	13	76.5
fatal	0	0.0	0	0.0	0	0.0
life threatening	0	0.0	1	25.0	1	5.9
(prolonged) hospitalization	2	15.4	1	25.0	3	17.6

AEs	Vitrectomy + Ranibizumab		Ranibizumab		Overall	
	N	%	N	%	N	%
permanently disabling	0	0.0	0	0.0	0	0.0
other	0	0.0	0	0.0	0	0.0
Total	13	100.0	4	100.0	17	100.0

12.2.2 Details of adverse events

A patient-wise listing of all adverse events is in Listing 3 at the end of the report. Table 12-3 shows the number of AEs by organ class. Table 12-4 gives summaries of the severity, the related therapy decisions and Table 12-4the outcome of the AEs. Only two AEs were severe (both in arm B). None of the AEs caused a therapy stop, 5 AEs (four in arm A and one in arm B) caused a drug administration delay. There were no drop-outs caused by an AE/SAE. 7 AEs (five in arm A and two in arm B) required a drug therapy. The recovery from two AEs (one in arm A and one in arm B) were with sequelae and for 6 AEs (all in arm B) there was no recovery till study end.

Table 12-3: Frequency of AEs by system organ class

Frequency of AEs by system organ class	Vitrectomy + Ranibizumab		Ranibi-zumab		Overall	
	N	%	N	%	N	%
Cardiac Disorders	1	7.7	1	25.0	2	11.8
Eye disorders	3	23.1	0	0.0	3	17.6
General disorders and administration site conditions	3	23.1	0	0.0	3	17.6
Infections and infestations	1	7.7	0	0.0	1	5.9
Musculoskeletal and connective tissue disorders	1	7.7	0	0.0	1	5.9
Reproductive system and breast disorders	0	0.0	1	25.0	1	5.9
Respiratory, thoracic and mediastinal disorders	1	7.7	1	25.0	2	11.8
Skin and subcutaneous tissue disorders	0	0.0	1	25.0	1	5.9
Surgical and medical procedures	2	15.4	0	0.0	2	11.8

Frequency of AEs by system organ class	Vitrectomy + Ranibizumab		Ranibi-zumab		Overall	
	N	%	N	%	N	%
Vascular disorders	1	7.7	0	0.0	1	5.9
Total	13	100.0	4	100.0	17	100.0

Table 12-4: Details of AE

Details of AEs		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
Severity of AEs	**mild**	5	38.5	2	50.0	7	41.2
	moderate	8	61.5	0	0.0	8	47.1
	severe	0	0.0	2	50.0	2	11.8
Study drug administration in case of AEs	**continued**	9	69.2	3	75.0	12	70.6
	delayed	4	30.8	1	25.0	5	29.4
	stopped	0	0.0	0	0.0	0	0.0
Therapy of AEs	**none**	4	30.8	1	25.0	5	29.4
	non drug therapy	5	38.5	2	50.0	7	41.2
	drug therapy	4	30.8	1	25.0	5	29.4
Outcome of AEs	**recovered**	5	38.5	3	75.0	8	47.1
	recovered with sequelae	1	7.7	1	25.0	2	11.8
	not yet recovered	6	46.2	0	0.0	6	35.3
	patient died	0	0.0	0	0.0	0	0.0
	unknown	1	7.7	0	0.0	1	5.9

12.3 Deaths and other Serious Adverse Events

No deaths occurred.

Two patients from arm A and two patients from arm B had one serious adverse event. They are listed in Table 12-5 and Table 12-6. No SAE was considered to be related to the study drug.

Table 12-5: Listing of serious adverse events (1)

Patient	Description	Grade	SAE	Therapy	Outcome
Vitrectomy + Ranibizumab:					
4	stationäre Herzkatheter-untersuchung mit Stenteinset-zung	mild	(prolonged) hos-pitalization	non drug therapy	recovered with sequelae
37	Pneumonie mit Pleuritis und Myokarditis	moderate	(prolonged) hos-pitalization	drug therapy	recovered
Ranibizumab:					
5	Koronare Dreigefäßerkran-kung mit hochprozentigen Stenosen -> OP	severe	life threatening	drug therapy	recovered with sequelae
44	cystocele	severe	(prolonged) hos-pitalization	non drug therapy	recovered

Table 12-6: Listing of serious adverse events (2)

Patient	System organ class	Study drug	Time to AE in days	AE duration in days
Vitrectomy + Ranibizumab:				
4	Cardiac Disorders	continued	92	1
37	Respiratory, thoracic and me-diastinal disorders	delayed	7	15
Ranibizumab:				
5	Cardiac disorders	delayed	310	8
44	Reproductive system and breast disorders	continued	31	6

12.4 Clinical Laboratory Evaluation

Table 12-7: Results of blood test

HbA1c in %		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	V1	7	7.6	1.2	5.4	7.1	8.1	8.5	8.8
	V13	5	7.0	1.2	5.2	6.6	7.0	7.7	8.4
	V13 - V1	5	-0.4	0.3	-0.7	-0.6	-0.4	-0.2	-0.1
Ranibizumab	V1	8	7.1	0.6	6.2	6.6	7.2	7.7	7.9
	V13	4	7.6	1.2	6.0	6.7	7.9	8.5	8.5
	V13 - V1	4	0.6	1.2	-0.6	-0.3	0.3	1.4	2.2

There was a small mean decrease in HbA1c for arm A and a small increase for arm B with a treatment difference of about 1% which may be due to chance.

12.5 Vital Signs, Physical Findings, and Other Observations Related to Safety

12.5.1 Height and Weight

The baseline average height was about 170 cm in both treatment arms (see Table 12-8). As expected, height remained rather constant over time. Table 12-9 gives a summary for the weight. In average (and median) the weight change from baseline was rather small with a small treatment difference only.

Table 12-8: Height

Height in cm		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	V1	7	169.0	5.9	160.0	166.0	168.0	175.0	178.0
	V13	6	169.7	6.6	160.0	168.0	168.0	175.0	179.0
	V13 - V1	6	0.5	0.8	0.0	0.0	0.0	1.0	2.0

Height in cm		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Ranibizumab	**V1**	7	170.0	10.7	156.0	165.0	167.0	176.0	190.0
	V13	4	171.5	14.5	158.0	160.0	169.0	183.0	190.0
	V13 - V1	4	-0.5	2.5	-4.0	-2.0	0.0	1.0	2.0

Table 12-9: Weight

Weight in kg		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	7	94.1	14.3	82.0	85.0	88.0	110.0	118.8
	V13	6	94.7	15.1	80.0	80.0	91.0	111.0	115.0
	V13 - V1	6	-0.5	4.0	-5.0	-3.8	-0.5	1.0	6.0
Ranibizumab	**V1**	7	87.1	26.7	54.0	72.0	80.0	94.0	140.0
	V13	4	101.0	33.3	80.0	80.0	87.0	122.0	150.0
	V13 - V1	4	2.5	5.0	0.0	0.0	0.0	5.0	10.0

12.5.2 Heart rate

Table 12-10: Heart rate

Heart rate in bpm		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	5	79.8	8.0	72.0	74.0	78.0	83.0	92.0
	V13	5	82.2	5.2	74.0	80.0	85.0	86.0	86.0
	V13 - V1	3	-1.3	4.2	-6.0	-6.0	0.0	2.0	2.0
Ranibizumab	**V1**	6	69.8	13.9	52.0	56.0	71.0	81.0	88.0
	V13	4	72.8	8.9	62.0	66.0	73.0	79.5	83.0
	V13 - V1	4	4.0	14.0	-8.0	-5.0	0.0	13.0	24.0

The change from baseline in the heart rate was in the mean (and median) small in both treatment groups with only a small mean difference between the treatment groups.

12.5.3 Blood pressure

Table 12-11: Systolic blood pressure

Blood pressure systolic in mmhg		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	V1	7	149.7	19.8	130.0	130.0	155.0	168.0	177.0
	V13	6	148.0	12.5	130.0	140.0	147.5	158.0	165.0
	V13 - V1	6	-0.8	21.6	-30.0	-18.0	-1.5	18.0	28.0
Ranibizumab	V1	7	134.7	17.3	107.0	120.0	135.0	150.0	158.0
	V13	4	146.0	26.0	120.0	130.0	141.0	162.0	182.0
	V13 - V1	4	11.5	21.9	-13.0	-6.5	12.0	29.5	35.0

In treatment arm A there was almost no change from baseline in the systolic blood pressure whereas in arm B the mean blood pressure increased by about 11 mmhg (see Table 12-11). Due to the small sample size, this change from baseline and the treatment difference may be a chance finding. The mean diastolic blood pressure decreased in in both treatment groups by about 10 mmhg and the median decrease was similar between the treatment groups as well (see Table 12-12).

Table 12-12: Diastolic blood pressure

Blood pressure diastolic in mmhg		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	V1	7	82.1	12.3	65.0	66.0	88.0	90.0	96.0
	V13	6	70.3	7.1	59.0	68.0	70.0	75.0	80.0
	V13 - V1	6	-10.5	14.1	-28.0	-20.0	-12.5	0.0	10.0
Ranibizumab	V1	7	81.0	8.9	64.0	80.0	80.0	86.0	93.0
	V13	4	75.8	19.5	58.0	59.0	75.0	92.5	95.0
	V13 - V1	4	-10.0	23.0	-35.0	-29.5	-7.5	9.5	10.0

12.5.4 Vitrectomy

Vitrectomy has been conducted for all 7 patients in arm A; three with 20G, two with 23G another two with 25G. All 7 patients received ILM-peeling and intravitreuous administration of 0.5 mg ranbizumab. None of the patients met an intraoperative exclusion criterion and there were no intraoperative complications. Postoperative intraocular pressure was normal for all 7 patients. Further information on the intraoperative procedures and findings can be found in Section 14.2.2.

12.5.5 Concomitant medication

Table 12-13 summarizes the number concomitant medications by anatomical main group. The total number of concomitant medication was higher in arm B. This difference is mainly due to medications concerning the alimentary tract and metabolism and cardiovascular systems. The number of concomitant medication for sensory organs was higher in arm A. A patient-wise listing of the concomitant medications can be found in Listing 4 at the end of the report.

Table 12-13: Concomitant medication by anatomical main group

Frequency of concomitant medication by anatomical main group		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
Code	**Contents**						
A	**Alimentary tract and metabolism**	8	29.6	23	39.7	31	36,5
B	**Blood and blood forming organs**	5	18.5	7	12.1	12	14,1
C	**Cardiovascular system**	6	22.2	18	31.0	24	28,2
G	**Genito-urinary system and sex hormones**	0	0.0	3	5.2	3	3,5
H	**Systemic hormonal preparations, excluding sex hormones and insulins**	0	0.0	1	1.7	1	1,2
L	**Antineoplastic and immunomodulating agents**	0	0.0	1	1.7	1	1,2
M	**Musculo-skeletal system**	1	3.7	0	0.0	1	1,2
N	**Nervous system**	0	0.0	4	6.9	4	4,7

Frequency of concomitant medication by anatomical main group		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
S	Sensory organs	7	25.9	1	1.7	8	9,4
Total		27	100.0	58	100.0	85	100.0

13 Discussion and Conclusion

Kommentiert [b2]: Medizinische Aspekte müssten ergänzt werden.

Due to the small sample size it is difficult to draw particular conclusions and impossible to make any general claims. In addition, study compliance with regard to the timing of the visits was rather poor. We therefore restrict the discussion to the descriptive findings without any intention for generalizations.

The efficacy data, in particular the number of injections, are not in line with the study hypothesis that vitrectomy with inner limiting membrane peeling reduces the number of doses of ranibizumab: the number of injections for patients in the ranbizumab + vitrectomy group was in average higher than for the patients in the control group. The same holds for the number of patients with a treatment-free interval of 3 months which was slightly smaller in the ranbizumab + vitrectomy group. The BCVA change from baseline at 12 months was similar for both treatment groups in FAS (sensitivity analysis). In the PPS no comparison was possible since no patients remained in the control arm. With regard to the secondary endpoints only the change in retinal thickness showed some noticeable treatment difference: Retinal thickness appeared to decrease more in the ranbizumab + vitrectomy group in the majority of quadrants, in particular after 4 months. There was no clear treatment difference in health related quality of life (VFQ25) and there were no treatment related AE or SAE reported.

Vitrectomy plus ranibizumab lead to a larger number of AEs as vitrectomy alone. However, the number of patients with AEs was similar between the treatment groups. The number of SAEs was similar as well. No AE or SAE was reported as treatment related.

In conclusion, there is no indication that vitrectomy plus ranibizumab is more efficient than ranibizumab alone. With regard to safety, vitrectomy plus ranibizumab may lead to more non-severe AEs. However, the observation is based on a single patient and all AEs were reported as unrelated to treatment. For the 15 patients in the study there was no significant safety signal observed.

14 Tables, Figures and Graphs referred to but not included in the Text

14.1 Demographics and other baseline characteristic

14.1.1 BCVA in ETDRS and Snellen quotient

BCVA in ETDRS letters at baseline	N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	7	46.4	9.2	35.0	38.0	48.0	50.0	63.0
Ranibizumab	8	52.3	17.0	19.0	45.5	58.0	62.5	67.0
Overall	15	49.5	13.8	19.0	38.0	50.0	60.0	67.0

BCVA in Snellen at baseline	N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	7	0.2	0.1	0.1	0.1	0.2	0.3	0.4
Ranibizumab	8	0.3	0.1	0.1	0.2	0.3	0.4	0.4
Overall	15	0.2	0.1	0.1	0.1	0.3	0.3	0.4

14.1.2 Ophtomological examination (lens, retinal lesions, diagnosis, slitlamp)

Lens at baseline	Vitrectomy + Ranibizumab		Ranibizumab		Overall	
	N	%	N	%	N	%
clear	0	0.0	0	0.0	0	0.0
cataract	5	71.4	4	50.0	9	60.0
IOL	2	28.6	4	50.0	6	40.0
Total	7	100.0	8	100.0	15	100.0

Retinal lesion at baseline	Vitrectomy + Ranibizumab		Ranibizumab		Overall	
	N	%	N	%	N	%
yes	4	57.1	1	12.5	5	33.3
no	3	42.9	7	87.5	10	66.7
Total	7	100.0	8	100.0	15	100.0

Diagnosis at baseline	Vitrectomy + Ranibizumab		Ranibizumab		Overall	
	N	%	N	%	N	%
focal	1	14.3	2	25.0	3	20.0
diffus	6	85.7	6	75.0	12	80.0
both	0	0.0	0	0.0	0	0.0
Total	7	100.0	8	100.0	15	100.0

Slitlamp examination at baseline	Vitrectomy + Ranibizumab		Ranibizumab		Overall	
	N	%	N	%	N	%
Dermatochalasis	0	0.0	1	12.5	1	6.7
Katarakt	0	0.0	1	12.5	1	6.7
normal	7	100.0	6	75.0	13	86.7
Total	7	100.0	8	100.0	15	100.0

14.1.3 Retinal thickness at baseline

Retinal thickness at baseline		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
central	**Vitrectomy + Ranibizumab**	7	455.1	200.9	150.0	311.0	447.0	631.0	683.0
	Ranibizumab	8	491.3	146.4	313.0	416.5	451.5	538.0	805.0
infra	**Vitrectomy + Ranibizumab**	7	444.4	100.4	342.0	362.0	410.0	543.0	601.0
	Ranibizumab	8	447.0	128.1	331.0	356.0	403.5	506.0	714.0
nasal	**Vitrectomy + Ranibizumab**	7	447.9	111.9	310.0	347.0	418.0	577.0	610.0
	Ranibizumab	8	431.3	109.5	337.0	351.0	394.0	494.0	635.0
supra	**Vitrectomy + Ranibizumab**	7	496.0	99.1	361.0	368.0	524.0	537.0	638.0
	Ranibizumab	8	442.6	158.2	287.0	336.0	396.5	514.0	761.0
temporal	**Vitrectomy + Ranibizumab**	7	465.4	144.9	286.0	319.0	489.0	586.0	649.0
	Ranibizumab	8	477.6	160.5	377.0	396.5	423.5	470.5	863.0

14.1.4 Fluorescein angiography

Microaneurysms		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
central	yes	6	85.7	5	62.5	11	73.3
	no	1	14.3	3	37.5	4	26.7
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
infra	yes	5	71.4	7	87.5	12	80.0
	no	2	28.6	1	12.5	3	20.0
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
nasal	yes	6	85.7	6	75.0	12	80.0
	no	1	14.3	2	25.0	3	20.0
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
supra	yes	6	85.7	6	75.0	12	80.0
	no	1	14.3	2	25.0	3	20.0
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
tempo-ral	yes	5	71.4	7	87.5	12	80.0
	no	2	28.6	1	12.5	3	20.0
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0

Edema		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
central	yes	7	100.0	8	100.0	15	100.0
	no	0	0.0	0	0.0	0	0.0
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0

Edema		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
infra	yes	5	71.4	8	100.0	13	86.7
	no	2	28.6	0	0.0	2	13.3
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
nasal	yes	6	85.7	6	75.0	12	80.0
	no	1	14.3	2	25.0	3	20.0
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
supra	yes	5	71.4	7	87.5	12	80.0
	no	2	28.6	1	12.5	3	20.0
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
tempo-ral	yes	5	71.4	8	100.0	13	86.7
	no	2	28.6	0	0.0	2	13.3
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0

Lipids		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
central	yes	5	71.4	3	37.5	8	53.3
	no	2	28.6	5	62.5	7	46.7
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
infra	yes	4	57.1	2	25.0	6	40.0
	no	3	42.9	6	75.0	9	60.0
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
nasal	yes	4	57.1	3	37.5	7	46.7
	no	3	42.9	5	62.5	8	53.3
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0

Lipids		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
supra	yes	5	71.4	3	37.5	8	53.3
	no	2	28.6	5	62.5	7	46.7
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
tempo-ral	yes	4	57.1	4	50.0	8	53.3
	no	3	42.9	4	50.0	7	46.7
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0

14.1.5 Vitrectomy

Lens	N	%
pseudophakic	2	28.6
remained phakic	2	28.6
phako with IOL	3	42.9
Total	7	100.0

Patient	Lens	Surgical removal of after cataract in case of pseudophakic lens
1	pseudophakic	No
37	pseudophakic	No

Vitreous body intraoperative	N	%
attached	5	71.4
detached	2	28.6
Total	7	100.0

Stain used in vitrectomy	N	%
trypan blue	0	0.0
brilliant blue	2	28.6
both	5	71.4

Stain used in vitrectomy	N	%
none	0	0.0
Total	7	100.0

Details on ILM peeling

Patient	ILM peeling	Estimated papilla diameters
1	Yes	4
3	Yes	5
4	Yes	4
19	Yes	10
25	Yes	.
37	Yes	2
38	Yes	2

Focal or disseminated laser treatment	N	%
Yes	0	0.0
No	7	100.0
Total	7	100.0

Paracentral laser treatment	N	%
Yes	0	0.0
No	7	100.0
Total	7	100.0

Tamponade	N	%
none	7	100.0
SF6	0	0.0
C2F5	0	0.0
C3F8	0	0.0
silicone	0	0.0
Total	7	100.0

14.2 Efficacy and Opthtomological Data for all visits

14.2.1 BCVA in ETDRS (with/without imputation) and Snellen quotient

BCVA in ETDRS letters (no imputation)		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	7	46.4	9.2	35.0	38.0	48.0	50.0	63.0
	V2	6	47.3	9.5	35.0	43.0	46.5	50.0	63.0
	V3	7	52.7	13.6	41.0	44.0	50.0	53.0	82.0
	V4	7	54.7	12.9	40.0	43.0	56.0	68.0	74.0
	V5	6	50.7	14.9	30.0	40.0	52.0	57.0	73.0
	V6	7	52.4	11.1	39.0	41.0	53.0	58.0	72.0
	V7	7	53.3	12.5	37.0	41.0	57.0	65.0	70.0
	V8	7	53.7	14.9	36.0	40.0	54.0	65.0	77.0
	V9	6	55.5	13.1	35.0	48.0	56.5	64.0	73.0
	V10	7	53.9	15.9	35.0	38.0	54.0	60.0	83.0
	V11	7	56.0	15.9	38.0	39.0	57.0	64.0	84.0
	V12	6	50.2	14.3	32.0	42.0	48.0	57.0	74.0
	V13	6	52.7	15.4	36.0	38.0	52.5	62.0	75.0
Ranibizumab	**V1**	8	52.3	17.0	19.0	45.5	58.0	62.5	67.0
	V2	8	54.3	17.6	26.0	41.5	56.5	69.0	74.0
	V3	8	52.6	16.1	22.0	44.5	54.0	65.5	71.0
	V4	8	56.6	17.7	24.0	44.5	62.5	68.0	79.0
	V5	7	61.7	22.6	23.0	40.0	69.0	74.0	90.0
	V6	7	61.9	16.3	27.0	62.0	65.0	68.0	79.0
	V7	7	63.6	17.1	26.0	63.0	70.0	74.0	75.0
	V8	8	61.3	24.5	11.0	51.5	66.0	80.0	84.0
	V9	8	59.9	17.1	26.0	53.5	67.5	69.5	72.0
	V10	7	52.0	20.5	13.0	40.0	58.0	68.0	72.0
	V11	6	61.8	11.1	41.0	60.0	64.5	68.0	73.0
	V12	5	63.2	13.0	41.0	65.0	67.0	68.0	75.0
	V13	5	67.0	5.8	57.0	68.0	68.0	70.0	72.0

Baseline-adjusted BCVA in ETDRS letters (no imputation)		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V2 - V1**	6	1.2	6.1	-7.0	0.0	0.0	2.0	12.0
	V3 - V1	7	6.3	7.1	0.0	1.0	3.0	13.0	19.0
	V4 - V1	7	8.3	11.8	-8.0	-3.0	11.0	19.0	21.0
	V5 - V1	6	4.5	17.8	-13.0	-8.0	0.0	13.0	35.0
	V6 - V1	7	6.0	10.5	-9.0	-2.0	4.0	18.0	20.0
	V7 - V1	7	6.9	13.7	-11.0	-3.0	7.0	22.0	27.0
	V8 - V1	7	7.3	14.4	-12.0	-8.0	11.0	19.0	27.0
	V9 - V1	6	9.3	13.7	-13.0	5.0	8.5	21.0	26.0
	V10 - V1	7	7.4	12.9	-10.0	-8.0	10.0	19.0	20.0
	V11 - V1	7	9.6	13.4	-10.0	-4.0	14.0	22.0	22.0
	V12 - V1	6	1.8	9.7	-16.0	-1.0	4.5	8.0	11.0
	V13 - V1	6	4.3	12.9	-12.0	-5.0	4.5	12.0	22.0
Ranibizumab	**V2 - V1**	8	2.0	8.7	-8.0	-5.0	-0.5	10.5	14.0
	V3 - V1	8	0.4	9.5	-12.0	-7.5	-0.5	9.0	13.0
	V4 - V1	8	4.4	10.4	-12.0	-3.5	6.5	10.0	21.0
	V5 - V1	7	6.7	15.0	-18.0	-2.0	6.0	16.0	30.0
	V6 - V1	7	6.9	7.2	0.0	1.0	7.0	9.0	21.0
	V7 - V1	7	8.6	6.8	-4.0	6.0	8.0	15.0	16.0
	V8 - V1	8	9.0	12.6	-8.0	-2.0	8.0	22.0	24.0
	V9 - V1	8	7.6	4.5	0.0	5.0	8.0	10.5	14.0
	V10 - V1	7	0.9	9.0	-9.0	-9.0	3.0	7.0	14.0
	V11 - V1	6	5.3	6.3	-7.0	5.0	8.0	8.0	10.0
	V12 - V1	5	7.0	7.1	-2.0	3.0	8.0	9.0	17.0
	V13 - V1	5	6.8	9.7	-10.0	8.0	10.0	12.0	14.0

BCVA in ETDRS letters (imputed)		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	7	46.4	9.2	35.0	38.0	48.0	50.0	63.0
	V2	7	47.4	8.7	35.0	43.0	48.0	50.0	63.0
	V3	7	52.7	13.6	41.0	44.0	50.0	53.0	82.0
	V4	7	54.7	12.9	40.0	43.0	56.0	68.0	74.0
	V5	7	50.2	13.7	30.0	40.0	48.0	57.0	73.0
	V6	7	52.4	11.1	39.0	41.0	53.0	58.0	72.0
	V7	7	53.3	12.5	37.0	41.0	57.0	65.0	70.0
	V8	7	53.7	14.9	36.0	40.0	54.0	65.0	77.0
	V9	7	53.9	12.7	35.0	44.4	56.0	64.0	73.0
	V10	7	53.9	15.9	35.0	38.0	54.0	60.0	83.0
	V11	7	56.0	15.9	38.0	39.0	57.0	64.0	84.0
	V12	7	51.1	13.3	32.0	42.0	50.0	57.0	74.0
	V13	7	53.3	14.2	36.0	38.0	57.0	62.0	75.0
Ranibizumab	**V1**	8	52.3	17.0	19.0	45.5	58.0	62.5	67.0
	V2	8	54.3	17.6	26.0	41.5	56.5	69.0	74.0
	V3	8	52.6	16.1	22.0	44.5	54.0	65.5	71.0
	V4	8	56.6	17.7	24.0	44.5	62.5	68.0	79.0
	V5	8	59.3	22.0	23.0	41.2	67.0	72.5	90.0
	V6	8	59.4	16.6	27.0	52.0	65.0	67.5	79.0
	V7	8	60.8	17.6	26.0	52.3	68.0	72.5	75.0
	V8	8	61.3	24.5	11.0	51.5	66.0	80.0	84.0
	V9	8	59.9	17.1	26.0	53.5	67.5	69.5	72.0
	V10	8	54.1	19.8	13.0	44.5	61.0	68.4	72.0
	V11	8	56.6	20.1	13.0	50.5	64.5	68.2	73.0
	V12	8	58.0	20.7	13.0	53.0	66.8	68.1	75.0
	V13	8	57.1	20.5	13.0	49.0	68.0	69.0	72.0

Baseline-adjusted BCVA in ETDRS letters (imputed)		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V2 - V1**	7	1.0	5.6	-7.0	0.0	0.0	2.0	12.0
	V3 - V1	7	6.3	7.1	0.0	1.0	3.0	13.0	19.0
	V4 - V1	7	8.3	11.8	-8.0	-3.0	11.0	19.0	21.0
	V5 - V1	7	3.8	16.3	-13.0	-8.0	-0.5	13.0	35.0
	V6 - V1	7	6.0	10.5	-9.0	-2.0	4.0	18.0	20.0
	V7 - V1	7	6.9	13.7	-11.0	-3.0	7.0	22.0	27.0
	V8 - V1	7	7.3	14.4	-12.0	-8.0	11.0	19.0	27.0
	V9 - V1	7	7.5	13.4	-13.0	-3.6	7.0	21.0	26.0
	V10 - V1	7	7.4	12.9	-10.0	-8.0	10.0	19.0	20.0
	V11 - V1	7	9.6	13.4	-10.0	-4.0	14.0	22.0	22.0
	V12 - V1	7	4.7	11.7	-16.0	-1.0	7.0	11.0	22.0
	V13 - V1	7	6.9	13.6	-12.0	-5.0	12.0	22.0	22.0
Ranibizumab	**V2 - V1**	8	2.0	8.7	-8.0	-5.0	-0.5	10.5	14.0
	V3 - V1	8	0.4	9.5	-12.0	-7.5	-0.5	9.0	13.0
	V4 - V1	8	4.4	10.4	-12.0	-3.5	6.5	10.0	21.0
	V5 - V1	8	7.1	13.9	-18.0	1.0	7.7	13.5	30.0
	V6 - V1	8	7.1	6.7	0.0	1.5	7.5	9.0	21.0
	V7 - V1	8	8.6	6.3	-4.0	6.5	8.3	13.5	16.0
	V8 - V1	8	9.0	12.6	-8.0	-2.0	8.0	22.0	24.0
	V9 - V1	8	7.6	4.5	0.0	5.0	8.0	10.5	14.0
	V10 - V1	8	1.8	8.8	-9.0	-7.5	4.5	7.9	14.0
	V11 - V1	8	4.3	6.8	-7.0	-0.5	8.0	8.2	10.0
	V12 - V1	8	5.7	7.2	-6.0	0.5	8.1	8.8	17.0
	V13 - V1	8	4.9	8.6	-10.0	-1.5	8.0	11.0	14.0

BCVA in Snellen		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	7	0.20	0.10	0.10	0.13	0.16	0.25	0.40
	V2	7	0.32	0.31	0.10	0.16	0.20	0.40	1.00
	V3	7	0.31	0.31	0.13	0.16	0.20	0.25	1.00
	V4	7	0.30	0.19	0.10	0.16	0.25	0.50	0.63
	V5	7	0.37	0.34	0.01	0.10	0.32	0.63	1.00
	V6	7	0.29	0.24	0.10	0.10	0.25	0.32	0.80
	V7	7	0.30	0.21	0.06	0.10	0.31	0.50	0.63
	V8	7	0.31	0.25	0.05	0.13	0.25	0.40	0.80
	V9	7	0.41	0.32	0.05	0.20	0.32	0.63	1.00
	V10	7	0.29	0.25	0.06	0.10	0.25	0.32	0.80
	V11	7	0.36	0.32	0.05	0.13	0.31	0.50	1.00
	V12	7	0.37	0.34	0.02	0.20	0.20	0.63	1.00
	V13	6	0.28	0.21	0.04	0.16	0.24	0.40	0.63
Ranibizumab	**V1**	8	0.27	0.14	0.05	0.18	0.32	0.36	0.40
	V2	8	0.33	0.23	0.05	0.14	0.29	0.56	0.63
	V3	8	0.29	0.19	0.06	0.16	0.25	0.41	0.63
	V4	8	0.35	0.23	0.06	0.16	0.36	0.45	0.80
	V5	8	0.57	0.40	0.06	0.26	0.55	0.81	1.25
	V6	8	0.52	0.28	0.08	0.40	0.50	0.65	1.00
	V7	8	0.58	0.31	0.08	0.40	0.55	0.81	1.00
	V8	8	0.57	0.42	0.04	0.28	0.45	0.90	1.25
	V9	8	0.41	0.20	0.06	0.28	0.45	0.56	0.63
	V10	8	0.39	0.30	0.04	0.18	0.36	0.51	1.00
	V11	7	0.48	0.27	0.16	0.32	0.40	0.60	1.00
	V12	7	0.70	0.32	0.16	0.50	0.63	1.00	1.00
	V13	5	0.48	0.15	0.32	0.33	0.50	0.63	0.63

BCVA in Snellen		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Overall	**V1**	15	0.24	0.12	0.05	0.13	0.25	0.32	0.40
	V2	15	0.33	0.26	0.05	0.16	0.25	0.50	1.00
	V3	15	0.30	0.24	0.06	0.16	0.25	0.32	1.00
	V4	15	0.33	0.21	0.06	0.16	0.32	0.50	0.80
	V5	15	0.48	0.38	0.01	0.13	0.40	0.63	1.25
	V6	15	0.41	0.28	0.08	0.20	0.40	0.50	1.00
	V7	15	0.45	0.30	0.06	0.16	0.40	0.63	1.00
	V8	15	0.45	0.36	0.04	0.16	0.40	0.80	1.25
	V9	15	0.41	0.25	0.05	0.20	0.40	0.63	1.00
	V10	15	0.35	0.27	0.04	0.16	0.32	0.40	1.00
	V11	14	0.42	0.29	0.05	0.20	0.36	0.50	1.00
	V12	14	0.53	0.36	0.02	0.20	0.55	1.00	1.00
	V13	11	0.37	0.20	0.04	0.16	0.33	0.63	0.63

Baseline-adjusted BCVA in Snellen		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V2 - V1**	7	0.1	0.3	-0.1	0.0	0.0	0.1	0.8
	V3 - V1	7	0.1	0.2	0.0	0.0	0.0	0.1	0.6
	V4 - V1	7	0.1	0.1	-0.1	0.0	0.2	0.2	0.3
	V5 - V1	7	0.2	0.4	-0.2	-0.1	0.1	0.5	0.8
	V6 - V1	7	0.1	0.2	-0.1	-0.1	0.0	0.2	0.4
	V7 - V1	7	0.1	0.2	-0.1	-0.1	0.1	0.2	0.4
	V8 - V1	7	0.1	0.2	-0.2	-0.0	0.2	0.3	0.4
	V9 - V1	7	0.2	0.3	-0.2	0.0	0.2	0.3	0.8
	V10 - V1	7	0.1	0.2	-0.1	-0.1	0.1	0.2	0.4
	V11 - V1	7	0.2	0.2	-0.2	-0.0	0.2	0.3	0.6
	V12 - V1	7	0.2	0.3	-0.2	0.0	0.1	0.2	0.9
	V13 - V1	6	0.1	0.1	-0.2	0.0	0.1	0.2	0.2

Baseline-adjusted BCVA in Snellen		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Ranibizumab	**V2 - V1**	8	0.1	0.2	-0.1	-0.1	0.0	0.2	0.3
	V3 - V1	8	0.0	0.2	-0.2	-0.1	-0.0	0.1	0.3
	V4 - V1	8	0.1	0.2	-0.2	-0.0	0.1	0.1	0.5
	V5 - V1	8	0.3	0.4	-0.2	0.0	0.2	0.6	1.0
	V6 - V1	8	0.3	0.3	0.0	0.1	0.1	0.3	1.0
	V7 - V1	8	0.3	0.3	0.0	0.1	0.2	0.5	1.0
	V8 - V1	8	0.3	0.4	-0.0	0.1	0.1	0.6	0.9
	V9 - V1	8	0.1	0.1	0.0	0.1	0.1	0.2	0.3
	V10 - V1	8	0.1	0.3	-0.1	-0.0	0.1	0.2	0.7
	V11 - V1	7	0.2	0.2	-0.1	0.1	0.1	0.2	0.7
	V12 - V1	7	0.4	0.2	0.1	0.2	0.3	0.7	0.7
	V13 - V1	5	0.1	0.2	-0.1	0.0	0.2	0.3	0.3

14.2.2 Ophtomological examination

Lens		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	**clear**	0	0.0	0	0.0	0	0.0
	cataract	5	71.4	4	50.0	9	60.0
	IOL	2	28.6	4	50.0	6	40.0
	Total	7	100.0	8	100.0	15	100.0
V4	**clear**	0	0.0	2	25.0	2	13.3
	cataract	2	28.6	3	37.5	5	33.3
	IOL	5	71.4	3	37.5	8	53.3
	Total	7	100.0	8	100.0	15	100.0

Retinal lesions		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	**Yes**	4	57.1	1	12.5	5	33.3
	No	3	42.9	7	87.5	10	66.7
	Total	7	100.0	8	100.0	15	100.0

Retinal lesions		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V2	Yes	0	0.0	0	0.0	0	0.0
	No	6	100.0	8	100.0	14	100.0
	Total	6	100.0	8	100.0	14	100.0
V3	Yes	0	0.0	0	0.0	0	0.0
	No	7	100.0	8	100.0	15	100.0
	Total	7	100.0	8	100.0	15	100.0
V4	Yes	0	0.0	0	0.0	0	0.0
	No	7	100.0	8	100.0	15	100.0
	Total	7	100.0	8	100.0	15	100.0
V5	Yes	0	0.0	0	0.0	0	0.0
	No	6	100.0	7	100.0	13	100.0
	Total	6	100.0	7	100.0	13	100.0
V6	Yes	0	0.0	0	0.0	0	0.0
	No	7	100.0	7	100.0	14	100.0
	Total	7	100.0	7	100.0	14	100.0
V7	Yes	1	14.3	0	0.0	1	7.1
	No	6	85.7	7	100.0	13	92.9
	Total	7	100.0	7	100.0	14	100.0
V8	Yes	0	0.0	0	0.0	0	0.0
	No	7	100.0	8	100.0	15	100.0
	Total	7	100.0	8	100.0	15	100.0
V9	Yes	0	0.0	0	0.0	0	0.0
	No	6	100.0	8	100.0	14	100.0
	Total	6	100.0	8	100.0	14	100.0
V10	Yes	0	0.0	0	0.0	0	0.0
	No	7	100.0	7	100.0	14	100.0
	Total	7	100.0	7	100.0	14	100.0
V11	Yes	0	0.0	0	0.0	0	0.0
	No	7	100.0	6	100.0	13	100.0
	Total	7	100.0	6	100.0	13	100.0

Retinal lesions		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V12	Yes	0	0.0	0	0.0	0	0.0
	No	6	100.0	5	100.0	11	100.0
	Total	6	100.0	5	100.0	11	100.0
V13	Yes	0	0.0	0	0.0	0	0.0
	No	6	100.0	5	100.0	11	100.0
	Total	6	100.0	5	100.0	11	100.0

Distance visual acuity test in m		Vitrectomy + Ranibi-zumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	1 m	0	0.0	1	12.5	1	6.7
	4 m	7	100.0	7	87.5	14	93.3
	Total	7	100.0	8	100.0	15	100.0
V2	1 m	0	0.0	1	12.5	1	7.1
	4 m	6	100.0	7	87.5	13	92.9
	Total	6	100.0	8	100.0	14	100.0
V3	1 m	0	0.0	1	12.5	1	6.7
	4 m	7	100.0	7	87.5	14	93.3
	Total	7	100.0	8	100.0	15	100.0
V4	1 m	0	0.0	1	12.5	1	6.7
	4 m	7	100.0	7	87.5	14	93.3
	Total	7	100.0	8	100.0	15	100.0
V5	1 m	0	0.0	1	14.3	1	7.7
	4 m	6	100.0	6	85.7	12	92.3
	Total	6	100.0	7	100.0	13	100.0
V6	1 m	0	0.0	1	14.3	1	7.1
	4 m	7	100.0	6	85.7	13	92.9
	Total	7	100.0	7	100.0	14	100.0
V7	1 m	0	0.0	1	14.3	1	7.1
	4 m	7	100.0	6	85.7	13	92.9
	Total	7	100.0	7	100.0	14	100.0

Distance visual acuity test in m		Vitrectomy + Ranibi-zumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V8	1 m	0	0.0	1	12.5	1	6.7
	4 m	7	100.0	7	87.5	14	93.3
	Total	7	100.0	8	100.0	15	100.0
V9	1 m	0	0.0	1	12.5	1	7.1
	4 m	6	100.0	7	87.5	13	92.9
	Total	6	100.0	8	100.0	14	100.0
V10	1 m	0	0.0	1	14.3	1	7.1
	4 m	7	100.0	6	85.7	13	92.9
	Total	7	100.0	7	100.0	14	100.0
V11	1 m	0	0.0	0	0.0	0	0.0
	4 m	7	100.0	6	100.0	13	100.0
	Total	7	100.0	6	100.0	13	100.0
V12	1 m	0	0.0	0	0.0	0	0.0
	4 m	6	100.0	5	100.0	11	100.0
	Total	6	100.0	5	100.0	11	100.0
V13	1 m	0	0.0	0	0.0	0	0.0
	4 m	6	100.0	5	100.0	11	100.0
	Total	6	100.0	5	100.0	11	100.0

Result of examination with slit lamp		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	normal	7	100.0	6	75.0	13	86.7
	other	0	0.0	2	25.0	2	13.3
	Total	7	100.0	8	100.0	15	100.0
V2	normal	6	100.0	7	87.5	13	92.9
	other	0	0.0	1	12.5	1	7.1
	Total	6	100.0	8	100.0	14	100.0
V3	normal	7	100.0	7	87.5	14	93.3
	other	0	0.0	1	12.5	1	6.7
	Total	7	100.0	8	100.0	15	100.0

Result of examination with slit lamp		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V4	**normal**	7	100.0	7	87.5	14	93.3
	other	0	0.0	1	12.5	1	6.7
	Total	7	100.0	8	100.0	15	100.0
V5	**normal**	5	83.3	6	85.7	11	84.6
	other	1	16.7	1	14.3	2	15.4
	Total	6	100.0	7	100.0	13	100.0
V6	**normal**	7	100.0	7	100.0	14	100.0
	other	0	0.0	0	0.0	0	0.0
	Total	7	100.0	7	100.0	14	100.0
V7	**normal**	7	100.0	7	100.0	14	100.0
	other	0	0.0	0	0.0	0	0.0
	Total	7	100.0	7	100.0	14	100.0
V8	**normal**	7	100.0	8	100.0	15	100.0
	other	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
V9	**normal**	6	100.0	8	100.0	14	100.0
	other	0	0.0	0	0.0	0	0.0
	Total	6	100.0	8	100.0	14	100.0
V10	**normal**	7	100.0	7	100.0	14	100.0
	other	0	0.0	0	0.0	0	0.0
	Total	7	100.0	7	100.0	14	100.0
V11	**normal**	7	100.0	6	100.0	13	100.0
	other	0	0.0	0	0.0	0	0.0
	Total	7	100.0	6	100.0	13	100.0
V12	**normal**	6	100.0	5	100.0	11	100.0
	other	0	0.0	0	0.0	0	0.0
	Total	6	100.0	5	100.0	11	100.0
V13	**normal**	5	100.0	5	100.0	10	100.0
	other	0	0.0	0	0.0	0	0.0
	Total	5	100.0	5	100.0	10	100.0

Details of non-normal results of examination with slit lamp

Patient	Treatment	Visit number	Specification
38	Vitrectomy + Ranibizumab	5	Cat Matura - Quellende Linse
39	Ranibizumab	3	Kapselfibrose
43	Ranibizumab	1	Katarakt
43	Ranibizumab	4	Cataracta corticalis provecta
43	Ranibizumab	5	Cataracta corticalis
44	Ranibizumab	1	Dermatochalasis
44	Ranibizumab	2	Dermatochalasis

Funduscopy		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	done	7	100.0	8	100.0	15	100.0
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
V4	done	5	71.4	6	75.0	11	73.3
	not done	2	28.6	2	25.0	4	26.7
	Total	7	100.0	8	100.0	15	100.0
V7	done	7	100.0	7	100.0	14	100.0
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	7	100.0	14	100.0
V13	done	6	100.0	5	100.0	11	100.0
	not done	0	0.0	0	0.0	0	0.0
	Total	6	100.0	5	100.0	11	100.0

Intraocular pressure in mmHG		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	normal	7	100.0	8	100.0	15	100.0
	increased >= 30 mmHg	0	0.0	0	0.0	0	0.0
	increased < 30 mmHg	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0

Intraocular pressure in mmHG		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V2	normal	5	83.3	8	100.0	13	92.9
	increased >= 30 mmHg	1	16.7	0	0.0	1	7.1
	increased < 30 mmHg	0	0.0	0	0.0	0	0.0
	Total	6	100.0	8	100.0	14	100.0
V3	normal	7	100.0	8	100.0	15	100.0
	increased >= 30 mmHg	0	0.0	0	0.0	0	0.0
	increased < 30 mmHg	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
V4	normal	6	85.7	8	100.0	14	93.3
	increased >= 30 mmHg	0	0.0	0	0.0	0	0.0
	increased < 30 mmHg	1	14.3	0	0.0	1	6.7
	Total	7	100.0	8	100.0	15	100.0
V5	normal	6	100.0	7	100.0	13	100.0
	increased >= 30 mmHg	0	0.0	0	0.0	0	0.0
	increased < 30 mmHg	0	0.0	0	0.0	0	0.0
	Total	6	100.0	7	100.0	13	100.0
V6	normal	7	100.0	6	85.7	13	92.9
	increased >= 30 mmHg	0	0.0	0	0.0	0	0.0
	increased < 30 mmHg	0	0.0	1	14.3	1	7.1
	Total	7	100.0	7	100.0	14	100.0
V7	normal	7	100.0	7	100.0	14	100.0
	increased >= 30 mmHg	0	0.0	0	0.0	0	0.0
	increased < 30 mmHg	0	0.0	0	0.0	0	0.0
	Total	7	100.0	7	100.0	14	100.0
V8	normal	7	100.0	8	100.0	15	100.0
	increased >= 30 mmHg	0	0.0	0	0.0	0	0.0
	increased < 30 mmHg	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
V9	normal	6	100.0	8	100.0	14	100.0
	increased >= 30 mmHg	0	0.0	0	0.0	0	0.0
	increased < 30 mmHg	0	0.0	0	0.0	0	0.0
	Total	6	100.0	8	100.0	14	100.0

Intraocular pressure in mmHG		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V10	**normal**	7	100.0	7	100.0	14	100.0
	increased >= 30 mmHg	0	0.0	0	0.0	0	0.0
	increased < 30 mmHg	0	0.0	0	0.0	0	0.0
	Total	7	100.0	7	100.0	14	100.0
V11	**normal**	7	100.0	6	100.0	13	100.0
	increased >= 30 mmHg	0	0.0	0	0.0	0	0.0
	increased < 30 mmHg	0	0.0	0	0.0	0	0.0
	Total	7	100.0	6	100.0	13	100.0
V12	**normal**	6	100.0	5	100.0	11	100.0
	increased >= 30 mmHg	0	0.0	0	0.0	0	0.0
	increased < 30 mmHg	0	0.0	0	0.0	0	0.0
	Total	6	100.0	5	100.0	11	100.0
V13	**normal**	5	100.0	5	100.0	10	100.0
	increased >= 30 mmHg	0	0.0	0	0.0	0	0.0
	increased < 30 mmHg	0	0.0	0	0.0	0	0.0
	Total	5	100.0	5	100.0	10	100.0

Non-normal intraocular pressure values

Patient	Treatment	Visit number	Intraocular pressure in mmHg
2	Ranibizumab	6	29
25	Vitrectomy + Ranibizumab	2	38
25	Vitrectomy + Ranibizumab	4	27

14.2.3 OCT results

OCT results for central and supra		Central						Supra					
		artefacts		not done		value		artefacts		not done		value	
		N	%	N	%	N	%	N	%	N	%	N	%
V1	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	0	0.00	8	100.00	0	0.00	0	0.00	8	100.00
	Overall	0	0.00	0	0.00	15	100.00	0	0.00	0	0.00	15	100.00
V2	Vitrectomy + Ranibizumab	0	0.00	1	14.29	6	85.71	0	0.00	1	14.29	6	85.71
	Ranibizumab	0	0.00	2	25.00	6	75.00	0	0.00	2	25.00	6	75.00
	Overall	0	0.00	3	20.00	12	80.00	0	0.00	3	20.00	12	80.00
V3	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Ranibizumab	1	12.50	0	0.00	7	87.50	1	12.50	0	0.00	7	87.50
	Overall	1	6.67	0	0.00	14	93.33	1	6.67	0	0.00	14	93.33
V4	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	1	12.50	7	87.50	0	0.00	1	12.50	7	87.50
	Overall	0	0.00	1	6.67	14	93.33	0	0.00	1	6.67	14	93.33
V5	Vitrectomy + Ranibizumab	1	14.29	1	14.29	5	71.43	1	14.29	1	14.29	5	71.43
	Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Overall	1	7.14	1	7.14	12	85.71	1	7.14	1	7.14	12	85.71
V6	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Overall	0	0.00	0	0.00	14	100.00	0	0.00	0	0.00	14	100.00
V7	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Overall	0	0.00	0	0.00	14	100.00	0	0.00	0	0.00	14	100.00
V8	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Ranibizumab	1	12.50	0	0.00	7	87.50	0	0.00	0	0.00	8	100.00
	Overall	1	6.67	0	0.00	14	93.33	0	0.00	0	0.00	15	100.00

OCT results for central and supra		Central						Supra					
		artefacts		not done		value		artefacts		not done		value	
		N	%	N	%	N	%	N	%	N	%	N	%
V9	Vitrectomy + Ranibizumab	0	0.00	1	14.29	6	85.71	0	0.00	1	14.29	6	85.71
	Ranibizumab	0	0.00	0	0.00	8	100.00	0	0.00	0	0.00	8	100.00
	Overall	0	0.00	1	6.67	14	93.33	0	0.00	1	6.67	14	93.33
V10	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	1	12.50	7	87.50	0	0.00	1	12.50	7	87.50
	Overall	0	0.00	1	6.67	14	93.33	0	0.00	1	6.67	14	93.33
V11	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	1	14.29	6	85.71	0	0.00	1	14.29	6	85.71
	Overall	0	0.00	1	7.14	13	92.86	0	0.00	1	7.14	13	92.86
V12	Vitrectomy + Ranibizumab	0	0.00	1	14.29	6	85.71	0	0.00	1	14.29	6	85.71
	Ranibizumab	0	0.00	2	28.57	5	71.43	0	0.00	2	28.57	5	71.43
	Overall	0	0.00	3	21.43	11	78.57	0	0.00	3	21.43	11	78.57
V13	Vitrectomy + Ranibizumab	0	0.00	0	0.00	6	100.00	0	0.00	0	0.00	6	100.00
	Ranibizumab	0	0.00	0	0.00	5	100.00	0	0.00	0	0.00	5	100.00
	Overall	0	0.00	0	0.00	11	100.00	0	0.00	0	0.00	11	100.00

OCT results for infra and nasal		Infra						Nasal					
		artefacts		not done		value		artefacts		not done		value	
		N	%	N	%	N	%	N	%	N	%	N	%
V1	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	0	0.00	8	100.00	0	0.00	0	0.00	8	100.00
	Overall	0	0.00	0	0.00	15	100.00	0	0.00	0	0.00	15	100.00
V2	Vitrectomy + Ranibizumab	0	0.00	1	14.29	6	85.71	0	0.00	1	14.29	6	85.71
	Ranibizumab	0	0.00	2	25.00	6	75.00	0	0.00	2	25.00	6	75.00
	Overall	0	0.00	3	20.00	12	80.00	0	0.00	3	20.00	12	80.00

OCT results for infra and nasal		Infra						Nasal					
		artefacts		not done		value		artefacts		not done		value	
		N	%	N	%	N	%	N	%	N	%	N	%
V3	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Ranibizumab	1	12.50	0	0.00	7	87.50	1	12.50	0	0.00	7	87.50
	Overall	1	6.67	0	0.00	14	93.33	1	6.67	0	0.00	14	93.33
V4	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	1	12.50	7	87.50	0	0.00	1	12.50	7	87.50
	Overall	0	0.00	1	6.67	14	93.33	0	0.00	1	6.67	14	93.33
V5	Vitrectomy + Ranibizumab	1	14.29	1	14.29	5	71.43	1	14.29	1	14.29	5	71.43
	Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Overall	1	7.14	1	7.14	12	85.71	1	7.14	1	7.14	12	85.71
V6	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Overall	0	0.00	0	0.00	14	100.00	0	0.00	0	0.00	14	100.00
V7	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Overall	0	0.00	0	0.00	14	100.00	0	0.00	0	0.00	14	100.00
V8	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	0	0.00	8	100.00	0	0.00	0	0.00	8	100.00
	Overall	0	0.00	0	0.00	15	100.00	0	0.00	0	0.00	15	100.00
V9	Vitrectomy + Ranibizumab	0	0.00	1	14.29	6	85.71	0	0.00	1	14.29	6	85.71
	Ranibizumab	0	0.00	0	0.00	8	100.00	0	0.00	0	0.00	8	100.00
	Overall	0	0.00	1	6.67	14	93.33	0	0.00	1	6.67	14	93.33
V10	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	1	12.50	7	87.50	0	0.00	1	12.50	7	87.50
	Overall	0	0.00	1	6.67	14	93.33	0	0.00	1	6.67	14	93.33

OCT results for infra and nasal		Infra						Nasal					
		artefacts		not done		value		artefacts		not done		value	
		N	%	N	%	N	%	N	%	N	%	N	%
V11	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	1	14.29	6	85.71	0	0.00	1	14.29	6	85.71
	Overall	0	0.00	1	7.14	13	92.86	0	0.00	1	7.14	13	92.86
V12	Vitrectomy + Ranibizumab	0	0.00	1	14.29	6	85.71	0	0.00	1	14.29	6	85.71
	Ranibizumab	0	0.00	2	28.57	5	71.43	0	0.00	2	28.57	5	71.43
	Overall	0	0.00	3	21.43	11	78.57	0	0.00	3	21.43	11	78.57
V13	Vitrectomy + Ranibizumab	0	0.00	0	0.00	6	100.00	0	0.00	0	0.00	6	100.00
	Ranibizumab	0	0.00	0	0.00	5	100.00	0	0.00	0	0.00	5	100.00
	Overall	0	0.00	0	0.00	11	100.00	0	0.00	0	0.00	11	100.00

OCT results temporal		Temporal					
		artefacts		not done		value	
		N	%	N	%	N	%
V1	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	0	0.00	8	100.00
	Overall	0	0.00	0	0.00	15	100.00
V2	Vitrectomy + Ranibizumab	0	0.00	1	14.29	6	85.71
	Ranibizumab	0	0.00	2	25.00	6	75.00
	Overall	0	0.00	3	20.00	12	80.00
V3	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00
	Ranibizumab	1	12.50	0	0.00	7	87.50
	Overall	1	6.67	0	0.00	14	93.33
V4	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	1	12.50	7	87.50
	Overall	0	0.00	1	6.67	14	93.33
V5	Vitrectomy + Ranibizumab	1	14.29	1	14.29	5	71.43
	Ranibizumab	0	0.00	0	0.00	7	100.00
	Overall	1	7.14	1	7.14	12	85.71

OCT results temporal		Temporal					
		artefacts		not done		value	
		N	%	N	%	N	%
V6	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	0	0.00	7	100.00
	Overall	0	0.00	0	0.00	14	100.00
V7	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	0	0.00	7	100.00
	Overall	0	0.00	0	0.00	14	100.00
V8	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	0	0.00	8	100.00
	Overall	0	0.00	0	0.00	15	100.00
V9	Vitrectomy + Ranibizumab	0	0.00	1	14.29	6	85.71
	Ranibizumab	0	0.00	0	0.00	8	100.00
	Overall	0	0.00	1	6.67	14	93.33
V10	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	1	12.50	7	87.50
	Overall	0	0.00	1	6.67	14	93.33
V11	Vitrectomy + Ranibizumab	0	0.00	0	0.00	7	100.00
	Ranibizumab	0	0.00	1	14.29	6	85.71
	Overall	0	0.00	1	7.14	13	92.86
V12	Vitrectomy + Ranibizumab	0	0.00	1	14.29	6	85.71
	Ranibizumab	0	0.00	2	28.57	5	71.43
	Overall	0	0.00	3	21.43	11	78.57
V13	Vitrectomy + Ranibizumab	0	0.00	0	0.00	6	100.00
	Ranibizumab	0	0.00	0	0.00	5	100.00
	Overall	0	0.00	0	0.00	11	100.00

14.2.4 Retinal thickness

Retinal thickness (central)		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	7	455.1	200.9	150.0	311.0	447.0	631.0	683.0
	V2	6	321.0	50.9	265.0	271.0	318.0	365.0	389.0
	V3	7	281.4	87.8	187.0	236.0	247.0	322.0	457.0
	V4	7	274.9	92.4	217.0	218.0	235.0	319.0	468.0
	V5	5	300.4	162.1	199.0	205.0	211.0	308.0	579.0
	V6	7	313.9	141.0	192.0	215.0	280.0	336.0	612.0
	V7	7	291.1	120.0	186.0	209.0	235.0	371.0	526.0
	V8	7	288.3	91.3	183.0	213.0	239.0	389.0	404.0
	V9	6	291.7	109.9	198.0	212.0	251.5	353.0	484.0
	V10	7	303.9	109.5	205.0	209.0	245.0	412.0	475.0
	V11	7	306.1	105.5	210.0	217.0	243.0	414.0	467.0
	V12	6	305.7	63.2	231.0	259.0	299.5	365.0	380.0
	V13	6	332.0	128.5	185.0	247.0	311.0	389.0	549.0
Ranibizumab	**V1**	8	491.3	146.4	313.0	416.5	451.5	538.0	805.0
	V2	6	480.8	130.7	315.0	411.0	457.5	553.0	691.0
	V3	7	445.7	164.0	281.0	352.0	409.0	493.0	787.0
	V4	7	441.1	116.7	311.0	318.0	413.0	593.0	598.0
	V5	7	451.0	147.2	288.0	301.0	423.0	645.0	650.0
	V6	7	403.1	143.1	230.0	278.0	370.0	527.0	646.0
	V7	7	382.0	187.3	114.0	290.0	347.0	482.0	717.0
	V8	7	416.1	244.7	248.0	270.0	293.0	462.0	942.0
	V9	8	342.9	156.6	159.0	255.0	311.5	384.5	682.0
	V10	7	413.3	235.0	171.0	243.0	409.0	459.0	892.0
	V11	6	293.5	130.0	105.0	244.0	274.5	377.0	486.0
	V12	5	283.4	61.8	185.0	262.0	313.0	319.0	338.0
	V13	5	276.8	109.7	114.0	273.0	282.0	292.0	423.0

Retinal thickness (supra)		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	7	496.0	99.1	361.0	368.0	524.0	537.0	638.0
	V2	6	334.2	59.2	278.0	307.0	311.5	352.0	445.0
	V3	7	333.6	59.7	270.0	272.0	323.0	380.0	438.0
	V4	7	331.0	61.2	259.0	289.0	314.0	395.0	432.0
	V5	5	355.4	70.6	285.0	311.0	318.0	427.0	436.0
	V6	7	347.4	66.4	255.0	313.0	328.0	436.0	436.0
	V7	7	343.7	85.6	236.0	253.0	334.0	445.0	458.0
	V8	7	348.6	65.9	253.0	297.0	338.0	398.0	454.0
	V9	6	360.2	74.5	279.0	315.0	336.0	411.0	484.0
	V10	7	359.3	81.5	258.0	310.0	331.0	426.0	501.0
	V11	7	351.1	83.1	252.0	285.0	322.0	412.0	496.0
	V12	6	342.3	50.9	257.0	317.0	351.0	373.0	405.0
	V13	6	344.5	99.4	256.0	275.0	315.5	376.0	529.0
Ranibizumab	**V1**	8	442.6	158.2	287.0	336.0	396.5	514.0	761.0
	V2	6	453.2	121.5	305.0	366.0	425.5	596.0	601.0
	V3	7	419.7	108.7	334.0	362.0	373.0	441.0	653.0
	V4	7	423.4	98.7	333.0	352.0	382.0	520.0	600.0
	V5	7	426.3	116.9	310.0	354.0	380.0	547.0	629.0
	V6	7	388.7	96.2	278.0	298.0	390.0	417.0	571.0
	V7	7	374.0	127.2	238.0	309.0	346.0	406.0	636.0
	V8	8	412.6	212.1	290.0	300.5	343.0	398.5	927.0
	V9	8	356.9	108.8	259.0	286.5	335.0	375.5	602.0
	V10	7	413.1	195.1	259.0	324.0	353.0	401.0	844.0
	V11	6	346.0	48.5	294.0	303.0	345.5	358.0	430.0
	V12	5	343.4	22.8	308.0	342.0	345.0	351.0	371.0
	V13	5	325.6	57.4	264.0	288.0	310.0	359.0	407.0

Retinal thickness (infra)		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	7	444.4	100.4	342.0	362.0	410.0	543.0	601.0
	V2	6	362.8	38.5	312.0	322.0	374.0	388.0	407.0
	V3	7	346.0	52.2	278.0	308.0	329.0	396.0	417.0
	V4	7	347.9	47.7	304.0	309.0	317.0	393.0	421.0
	V5	5	376.6	68.8	312.0	321.0	356.0	421.0	473.0
	V6	7	386.9	79.2	308.0	327.0	392.0	407.0	541.0
	V7	7	348.4	92.0	210.0	305.0	334.0	381.0	514.0
	V8	7	364.6	51.5	305.0	324.0	356.0	407.0	451.0
	V9	6	372.0	73.5	298.0	321.0	362.5	380.0	508.0
	V10	7	370.0	60.0	306.0	321.0	351.0	430.0	473.0
	V11	7	362.3	62.5	303.0	320.0	348.0	379.0	490.0
	V12	6	364.8	55.6	308.0	331.0	345.0	400.0	460.0
	V13	6	361.2	89.8	284.0	306.0	343.0	355.0	536.0
Ranibizumab	**V1**	8	447.0	128.1	331.0	356.0	403.5	506.0	714.0
	V2	6	423.8	139.6	319.0	327.0	375.0	457.0	690.0
	V3	7	411.4	161.5	293.0	350.0	361.0	387.0	772.0
	V4	7	426.7	139.0	313.0	325.0	356.0	613.0	641.0
	V5	7	435.4	139.3	329.0	339.0	355.0	635.0	639.0
	V6	7	425.3	94.2	307.0	362.0	396.0	482.0	597.0
	V7	7	378.0	117.0	294.0	300.0	343.0	390.0	630.0
	V8	8	389.4	181.8	277.0	301.0	334.0	368.5	831.0
	V9	8	374.1	119.9	272.0	299.0	328.0	415.0	637.0
	V10	7	396.6	155.2	304.0	305.0	345.0	389.0	742.0
	V11	6	334.3	54.6	272.0	305.0	326.0	348.0	429.0
	V12	5	329.0	24.2	300.0	307.0	340.0	342.0	356.0
	V13	5	328.6	47.7	275.0	303.0	316.0	350.0	399.0

Retinal thickness (nasal)		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	7	447.9	111.9	310.0	347.0	418.0	577.0	610.0
	V2	6	364.0	35.9	316.0	340.0	359.0	396.0	414.0
	V3	7	362.9	31.1	327.0	335.0	370.0	377.0	416.0
	V4	7	364.7	32.5	322.0	337.0	359.0	406.0	408.0
	V5	5	382.0	73.4	285.0	349.0	378.0	417.0	481.0
	V6	7	405.7	106.4	285.0	317.0	377.0	497.0	589.0
	V7	7	383.9	88.6	266.0	310.0	402.0	410.0	543.0
	V8	7	393.1	74.5	310.0	310.0	393.0	482.0	493.0
	V9	6	398.8	69.0	321.0	347.0	389.0	431.0	516.0
	V10	7	385.4	74.0	310.0	312.0	381.0	462.0	505.0
	V11	7	384.9	75.9	307.0	308.0	363.0	433.0	513.0
	V12	6	368.5	72.8	278.0	313.0	365.5	441.0	448.0
	V13	6	380.3	112.5	312.0	315.0	331.0	391.0	602.0
Ranibizumab	**V1**	8	431.3	109.5	337.0	351.0	394.0	494.0	635.0
	V2	6	464.7	121.7	345.0	386.0	411.5	590.0	644.0
	V3	7	415.0	130.7	325.0	329.0	386.0	415.0	699.0
	V4	7	425.0	111.9	317.0	339.0	375.0	575.0	591.0
	V5	7	428.4	123.4	315.0	321.0	374.0	601.0	602.0
	V6	7	402.7	98.0	308.0	328.0	383.0	432.0	605.0
	V7	7	378.1	121.3	261.0	314.0	330.0	419.0	628.0
	V8	8	391.0	156.1	305.0	310.5	335.0	382.5	767.0
	V9	8	348.8	112.1	196.0	299.5	327.5	380.5	579.0
	V10	7	395.9	166.4	230.0	332.0	345.0	421.0	751.0
	V11	6	343.8	68.4	267.0	315.0	333.5	342.0	472.0
	V12	5	336.4	16.7	323.0	328.0	330.0	336.0	365.0
	V13	5	345.8	56.6	287.0	310.0	331.0	370.0	431.0

14.2.5 Fluorescein angiography

Microaneurysms central		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	yes	6	85.7	5	62.5	11	73.3
	no	1	14.3	3	37.5	4	26.7
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
V7	yes	4	57.1	4	57.1	8	57.1
	no	1	14.3	1	14.3	2	14.3
	not done	2	28.6	2	28.6	4	28.6
	Total	7	100.0	7	100.0	14	100.0
V13	yes	1	16.7	1	20.0	2	18.2
	no	3	50.0	4	80.0	7	63.6
	not done	2	33.3	0	0.0	2	18.2
	Total	6	100.0	5	100.0	11	100.0

Microaneurysms supra		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	yes	6	85.7	6	75.0	12	80.0
	no	1	14.3	2	25.0	3	20.0
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
V7	yes	4	57.1	5	71.4	9	64.3
	no	1	14.3	0	0.0	1	7.1
	not done	2	28.6	2	28.6	4	28.6
	Total	7	100.0	7	100.0	14	100.0
V13	yes	2	33.3	4	80.0	6	54.5
	no	2	33.3	1	20.0	3	27.3
	not done	2	33.3	0	0.0	2	18.2
	Total	6	100.0	5	100.0	11	100.0

Microaneurysms infra		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	yes	5	71.4	7	87.5	12	80.0
	no	2	28.6	1	12.5	3	20.0
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
V7	yes	4	57.1	4	57.1	8	57.1
	no	1	14.3	1	14.3	2	14.3
	not done	2	28.6	2	28.6	4	28.6
	Total	7	100.0	7	100.0	14	100.0
V13	yes	2	33.3	4	80.0	6	54.5
	no	2	33.3	1	20.0	3	27.3
	not done	2	33.3	0	0.0	2	18.2
	Total	6	100.0	5	100.0	11	100.0

Microaneurysms nasal		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	yes	6	85.7	6	75.0	12	80.0
	no	1	14.3	2	25.0	3	20.0
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
V7	yes	4	57.1	4	57.1	8	57.1
	no	1	14.3	1	14.3	2	14.3
	not done	2	28.6	2	28.6	4	28.6
	Total	7	100.0	7	100.0	14	100.0
V13	yes	3	50.0	2	40.0	5	45.5
	no	1	16.7	3	60.0	4	36.4
	not done	2	33.3	0	0.0	2	18.2
	Total	6	100.0	5	100.0	11	100.0

Microaneurysms temporal		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	yes	5	71.4	7	87.5	12	80.0
	no	2	28.6	1	12.5	3	20.0
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
V7	yes	4	57.1	4	57.1	8	57.1
	no	1	14.3	1	14.3	2	14.3
	not done	2	28.6	2	28.6	4	28.6
	Total	7	100.0	7	100.0	14	100.0
V13	yes	3	50.0	5	100.0	8	72.7
	no	1	16.7	0	0.0	1	9.1
	not done	2	33.3	0	0.0	2	18.2
	Total	6	100.0	5	100.0	11	100.0

Edema central		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	yes	7	100.0	8	100.0	15	100.0
	no	0	0.0	0	0.0	0	0.0
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
V7	yes	4	57.1	3	42.9	7	50.0
	no	1	14.3	2	28.6	3	21.4
	not done	2	28.6	2	28.6	4	28.6
	Total	7	100.0	7	100.0	14	100.0
V13	yes	1	16.7	1	20.0	2	18.2
	no	3	50.0	4	80.0	7	63.6
	not done	2	33.3	0	0.0	2	18.2
	Total	6	100.0	5	100.0	11	100.0

Edema supra		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	yes	5	71.4	7	87.5	12	80.0
	no	2	28.6	1	12.5	3	20.0
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
V7	yes	4	57.1	4	57.1	8	57.1
	no	1	14.3	1	14.3	2	14.3
	not done	2	28.6	2	28.6	4	28.6
	Total	7	100.0	7	100.0	14	100.0
V13	yes	2	33.3	3	60.0	5	45.5
	no	2	33.3	2	40.0	4	36.4
	not done	2	33.3	0	0.0	2	18.2
	Total	6	100.0	5	100.0	11	100.0

Edema infra		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	yes	5	71.4	8	100.0	13	86.7
	no	2	28.6	0	0.0	2	13.3
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
V7	yes	4	57.1	4	57.1	8	57.1
	no	1	14.3	1	14.3	2	14.3
	not done	2	28.6	2	28.6	4	28.6
	Total	7	100.0	7	100.0	14	100.0
V13	yes	2	33.3	1	20.0	3	27.3
	no	2	33.3	4	80.0	6	54.5
	not done	2	33.3	0	0.0	2	18.2
	Total	6	100.0	5	100.0	11	100.0

Edema nasal		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	yes	6	85.7	6	75.0	12	80.0
	no	1	14.3	2	25.0	3	20.0
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
V7	yes	4	57.1	4	57.1	8	57.1
	no	1	14.3	1	14.3	2	14.3
	not done	2	28.6	2	28.6	4	28.6
	Total	7	100.0	7	100.0	14	100.0
V13	yes	3	50.0	0	0.0	3	27.3
	no	1	16.7	5	100.0	6	54.5
	not done	2	33.3	0	0.0	2	18.2
	Total	6	100.0	5	100.0	11	100.0

Edema temporal		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	yes	5	71.4	8	100.0	13	86.7
	no	2	28.6	0	0.0	2	13.3
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
V7	yes	3	42.9	5	71.4	8	57.1
	no	2	28.6	0	0.0	2	14.3
	not done	2	28.6	2	28.6	4	28.6
	Total	7	100.0	7	100.0	14	100.0
V13	yes	1	16.7	4	80.0	5	45.5
	no	3	50.0	1	20.0	4	36.4
	not done	2	33.3	0	0.0	2	18.2
	Total	6	100.0	5	100.0	11	100.0

Lipids central		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	yes	5	71.4	3	37.5	8	53.3
	no	2	28.6	5	62.5	7	46.7
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
V7	yes	1	14.3	0	0.0	1	7.1
	no	4	57.1	5	71.4	9	64.3
	not done	2	28.6	2	28.6	4	28.6
	Total	7	100.0	7	100.0	14	100.0
V13	yes	0	0.0	0	0.0	0	0.0
	no	4	66.7	5	100.0	9	81.8
	not done	2	33.3	0	0.0	2	18.2
	Total	6	100.0	5	100.0	11	100.0

Lipids supra		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	yes	5	71.4	3	37.5	8	53.3
	no	2	28.6	5	62.5	7	46.7
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
V7	yes	3	42.9	1	14.3	4	28.6
	no	2	28.6	4	57.1	6	42.9
	not done	2	28.6	2	28.6	4	28.6
	Total	7	100.0	7	100.0	14	100.0
V13	yes	1	16.7	0	0.0	1	9.1
	no	3	50.0	5	100.0	8	72.7
	not done	2	33.3	0	0.0	2	18.2
	Total	6	100.0	5	100.0	11	100.0

Lipids infra		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	yes	4	57.1	2	25.0	6	40.0
	no	3	42.9	6	75.0	9	60.0
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
V7	yes	1	14.3	0	0.0	1	7.1
	no	4	57.1	5	71.4	9	64.3
	not done	2	28.6	2	28.6	4	28.6
	Total	7	100.0	7	100.0	14	100.0
V13	yes	2	33.3	2	40.0	4	36.4
	no	2	33.3	3	60.0	5	45.5
	not done	2	33.3	0	0.0	2	18.2
	Total	6	100.0	5	100.0	11	100.0

Lipids nasal		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	yes	4	57.1	3	37.5	7	46.7
	no	3	42.9	5	62.5	8	53.3
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
V7	yes	1	14.3	0	0.0	1	7.1
	no	4	57.1	5	71.4	9	64.3
	not done	2	28.6	2	28.6	4	28.6
	Total	7	100.0	7	100.0	14	100.0
V13	yes	2	33.3	0	0.0	2	18.2
	no	2	33.3	5	100.0	7	63.6
	not done	2	33.3	0	0.0	2	18.2
	Total	6	100.0	5	100.0	11	100.0

Lipids temporal		Vitrectomy + Ranibizumab		Ranibizumab		Overall	
		N	%	N	%	N	%
V1	yes	4	57.1	4	50.0	8	53.3
	no	3	42.9	4	50.0	7	46.7
	not done	0	0.0	0	0.0	0	0.0
	Total	7	100.0	8	100.0	15	100.0
V7	yes	2	28.6	3	42.9	5	35.7
	no	3	42.9	2	28.6	5	35.7
	not done	2	28.6	2	28.6	4	28.6
	Total	7	100.0	7	100.0	14	100.0
V13	yes	1	16.7	3	60.0	4	36.4
	no	3	50.0	2	40.0	5	45.5
	not done	2	33.3	0	0.0	2	18.2
	Total	6	100.0	5	100.0	11	100.0

14.2.6 VFQ25

VFQ25 - general health score		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	V1	7	32.1	12.2	25.0	25.0	25.0	50.0	50.0
	V13	5	35.0	28.5	0.0	25.0	25.0	50.0	75.0
	V13 - V1	5	5.0	20.9	-25.0	0.0	0.0	25.0	25.0
Ranibizumab	V1	8	40.6	26.5	25.0	25.0	25.0	50.0	100.0
	V13	5	60.0	37.9	25.0	25.0	50.0	100.0	100.0
	V13 - V1	5	10.0	28.5	-25.0	0.0	0.0	25.0	50.0

VFQ25 - general vision score		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	V1	7	51.4	15.7	40.0	40.0	40.0	60.0	80.0
	V13	5	64.0	16.7	40.0	60.0	60.0	80.0	80.0
	V13 - V1	5	8.0	17.9	-20.0	0.0	20.0	20.0	20.0
Ranibizumab	V1	8	55.0	23.3	20.0	40.0	50.0	80.0	80.0
	V13	5	64.0	16.7	40.0	60.0	60.0	80.0	80.0
	V13 - V1	5	8.0	33.5	-20.0	-20.0	0.0	20.0	60.0

VFQ25 - ocular pain score		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	7	85.7	13.4	62.5	75.0	87.5	100.0	100.0
	V13	5	77.5	22.4	50.0	62.5	75.0	100.0	100.0
	V13 - V1	5	-12.5	17.7	-37.5	-25.0	0.0	0.0	0.0
Ranibizumab	**V1**	8	78.1	23.9	37.5	62.5	81.3	100.0	100.0
	V13	5	95.0	6.8	87.5	87.5	100.0	100.0	100.0
	V13 - V1	5	2.5	10.5	-12.5	0.0	0.0	12.5	12.5

VFQ25 - near activities score		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	7	57.1	13.1	41.7	50.0	58.3	58.3	83.3
	V13	5	78.3	17.3	50.0	75.0	83.3	91.7	91.7
	V13 - V1	5	18.3	21.6	-8.3	8.3	16.7	25.0	50.0
Ranibizumab	**V1**	8	72.9	27.0	25.0	54.2	83.3	91.7	100.0
	V13	5	76.7	28.5	41.7	50.0	91.7	100.0	100.0
	V13 - V1	5	-0.0	39.5	-50.0	-16.7	0.0	8.3	58.3

VFQ25 - distance activities score		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	7	65.5	23.3	41.7	41.7	66.7	91.7	100.0
	V13	5	72.5	28.2	33.3	62.5	66.7	100.0	100.0
	V13 - V1	5	2.5	15.5	-16.7	-4.2	0.0	8.3	25.0
Ranibizumab	**V1**	8	61.5	23.0	33.3	37.5	66.7	79.2	91.7
	V13	5	75.0	32.8	16.7	83.3	91.7	91.7	91.7
	V13 - V1	5	6.7	19.0	-16.7	0.0	0.0	16.7	33.3

VFQ25 - social functioning score		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	7	78.6	21.3	37.5	75.0	75.0	100.0	100.0
	V13	5	82.5	27.4	37.5	75.0	100.0	100.0	100.0
	V13 - V1	5	7.5	28.8	-37.5	0.0	12.5	25.0	37.5
Ranibizumab	**V1**	8	76.6	28.7	25.0	56.3	87.5	100.0	100.0
	V13	5	82.5	27.4	37.5	75.0	100.0	100.0	100.0
	V13 - V1	5	-2.5	18.5	-25.0	-12.5	0.0	0.0	25.0

VFQ25 - mental health score		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	7	64.3	12.9	50.0	50.0	62.5	75.0	81.3
	V13	5	61.3	22.3	25.0	56.3	68.8	75.0	81.3
	V13 - V1	5	-3.8	15.7	-31.3	0.0	0.0	6.3	6.3
Ranibizumab	**V1**	8	63.3	27.2	18.8	43.8	68.8	81.3	100.0
	V13	5	73.8	16.2	56.3	68.8	68.8	75.0	100.0
	V13 - V1	5	0.0	15.3	-12.5	-12.5	0.0	0.0	25.0

VFQ25 - role difficulties score		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	7	67.9	26.9	25.0	50.0	62.5	100.0	100.0
	V13	5	75.0	25.0	50.0	50.0	75.0	100.0	100.0
	V13 - V1	5	5.0	14.3	-12.5	0.0	0.0	12.5	25.0
Ranibizumab	**V1**	8	73.4	30.9	25.0	43.8	87.5	100.0	100.0
	V13	5	85.0	27.1	37.5	87.5	100.0	100.0	100.0
	V13 - V1	5	2.5	5.6	0.0	0.0	0.0	0.0	12.5

VFQ25 - dependency score		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	7	81.0	28.3	25.0	66.7	100.0	100.0	100.0
	V13	5	75.0	32.8	25.0	58.3	91.7	100.0	100.0
	V13 - V1	5	-13.3	37.5	-75.0	-16.7	0.0	0.0	25.0
Ranibizumab	**V1**	8	72.9	33.3	8.3	54.2	83.3	100.0	100.0
	V13	5	95.0	7.5	83.3	91.7	100.0	100.0	100.0
	V13 - V1	5	8.3	11.8	0.0	0.0	0.0	16.7	25.0

VFQ25 - driving score		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	5	46.7	46.2	0.0	0.0	50.0	83.3	100.0
	V13	4	62.5	43.8	0.0	33.3	75.0	91.7	100.0
	V13 - V1	4	25.0	39.7	0.0	0.0	8.3	50.0	83.3
Ranibizumab	**V1**	6	37.5	42.1	0.0	0.0	29.2	83.3	83.3
	V13	4	20.8	41.7	0.0	0.0	0.0	41.7	83.3
	V13 - V1	4	-20.8	41.7	-83.3	-41.7	0.0	0.0	0.0

VFQ25 - color vision score		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	7	92.9	12.2	75.0	75.0	100.0	100.0	100.0
	V13	5	95.0	11.2	75.0	100.0	100.0	100.0	100.0
	V13 - V1	5	5.0	11.2	0.0	0.0	0.0	0.0	25.0
Ranibizumab	**V1**	8	84.4	18.6	50.0	75.0	87.5	100.0	100.0
	V13	4	93.8	12.5	75.0	87.5	100.0	100.0	100.0
	V13 - V1	4	6.3	23.9	-25.0	-12.5	12.5	25.0	25.0

VFQ25 - peripheral vision score		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	7	89.3	13.4	75.0	75.0	100.0	100.0	100.0
	V13	5	95.0	11.2	75.0	100.0	100.0	100.0	100.0
	V13 - V1	5	5.0	11.2	0.0	0.0	0.0	0.0	25.0
Ranibizumab	**V1**	8	75.0	26.7	25.0	62.5	75.0	100.0	100.0
	V13	5	100.0	0.0	100.0	100.0	100.0	100.0	100.0
	V13 - V1	5	20.0	32.6	0.0	0.0	0.0	25.0	75.0

VFQ25 - overall composite score		N	Mean	Std	Min	Q_0.25	Median	Q_0.75	Max
Vitrectomy + Ranibizumab	**V1**	5	71.0	12.9	58.2	63.6	63.9	82.0	87.4
	V13	4	72.4	20.5	43.0	59.2	78.0	85.5	90.4
	V13 - V1	4	4.1	18.3	-20.6	-8.8	7.3	17.0	22.5
Ranibizumab	**V1**	6	68.3	23.6	31.9	51.9	73.0	87.7	92.3
	V13	3	76.8	17.6	56.5	56.5	86.1	87.8	87.8
	V13 - V1	3	7.7	14.0	-4.5	-4.5	4.6	22.9	22.9

14.3 Safety Data

14.3.1 Displays of adverse events and vital signs

See the tables in Chapter 12.

14.3.2 Listings of deaths, other serious and significant adverse events

See Section 12.3.

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16 Appendices

16.1 Study information

16.1.1 Protocol and protocol amendments

See Appendix A1

16.1.2 Sample CRF

See Appendix A2

16.1.3 List of IECs, patient information and consent form

To be appended to clinical report

16.1.4 List and description of investigators and other important participants

To be appended to clinical report

16.1.5 Signatures

To be appended to clinical report

16.1.6 List of patients receiving specific batches

Not applicable

16.1.7 Randomisation scheme and codes

Patient	Treatment	Patient	Treatment
1	Vitrectomy + Ranibizumab	37	Vitrectomy + Ranibizumab
2	Ranibizumab	38	Vitrectomy + Ranibizumab
3	Vitrectomy + Ranibizumab	39	Ranibizumab
4	Vitrectomy + Ranibizumab	40	Ranibizumab
5	Ranibizumab	41	Ranibizumab
6	Ranibizumab	43	Ranibizumab
19	Vitrectomy + Ranibizumab	44	Ranibizumab
25	Vitrectomy + Ranibizumab		

The randomisation code can be found in Appendix A3

16.1.8 Audit certificates

If existing to be appended to clinical report

16.1.9 Documentation of statistical methods – Statistical Analysis Plan

See Appendix A4

16.1.10 Documentation of inter-laboratory standardization

Not applicable

16.1.11 Publication based on the study

Not applicable

16.1.12 Important publications referenced in the report

To be appended to clinical report

16.2 Patient Data Listings

16.2.1 Discontinued patients

See Figure 10.1 in Section 10.1

16.2.2 Protocol deviations

See Table 10-3

16.2.3 Patients excluded from analysis

Not applicable

16.2.4 Demographic and other baseline data

See Listing L1

16.2.5 Compliance data

See Table 11-10

16.2.6 Individual efficacy response data

See also Table 11-19 to Table 11-23 and Listing L2

16.2.7 Adverse events listing (by patient)

See Listing L3

16.2.8 Listing of concomitant medication

See Listing L4

16.2.9 Listing of individual laboratory measurements

See Listing L5

16.2.10 Individual Patient Data Listings

See Listing L7

APPENDICES A

and

LISTINGS L

Appendix A1:

Study Protocol

Appendix A2:

Sample CRF

Appendix A3:

Randomization Code

Appendix A4:

Statistical Analysis Plan

LISTINGS L1:

Demographic and other baseline data

LISTINGS L2:

Individual efficacy response data

LISTINGS L3:

Patient-wise adverse events listing

LISTINGS L4:

Listing of concomitant medication

LISTINGS L5:

Listing of individual laboratory measurements

LISTINGS L6:

Deviations from suggested injection decision criterion

LISTINGS L7:

Individual Patient Data Listings