Synopsis of the Clinical Trial Report

Ranibizumab combined with selective peripheral laser photocoagulation for treatment of central retinal vein occlusion

A randomized, controlled interventional phase 2b (proof of concept) study of the efficacy, safety, and tolerability of repeated intravitreal administration of ranibizumab combined with selective laser photocoagulation of non-perfused retinal areas in subjects with macular edema secondary to non-ischemic central retinal vein occlusion (CRVO)

CoRaLa-Study

(Combination of Ranibizumab and Laser)

investigational product: Ranibizumab

Indication: macular edema secondary to non-ischemic central retinal vein occlusion (CRVO)

Phase of the clinical trial: IIb

EudraCT-Nr: 2010-020441-27

Register-Nr: DRKS00000711

Date: 15.01.2014
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Start of clinical trial: 25.02.2011
End of clinical trial: 18.09.2012

Report Signatures

Confirmation of the Final Report

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

Authorized representative of the sponsor and coordinating investigator: Prof. Dr. med. Peter Wiedemann	21. Jan 2014 Date	 Signature
Biometrician: Dr. Annegret Franke	16.01.2014 Date	 Signature

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1 Title of study

Ranibizumab combined with selective peripheral laser photocoagulation for treatment of central retinal vein occlusion

2 Study type

Prospective, randomized, interventional, controlled phase IIb (proof of concept) clinical trial with parallel assignment according to the German drug law (AMG)

3 Sponsor and authorized representative of the sponsor

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5 Trial sites and principal investigators

The CoRaLa study is a single-centre trial conducted in the department of ophthalmology of the University of Leipzig. Prof. Dr. med. Peter Wiedemann is principal investigator and Dr. med. Matus Rehak investigator.

6 Publication of the clinical trial

The trial was registered at the online-register of "Deutsches Register Klinischer Studien (https://drks-neu.uniklinik-freiburg.de/drks_web/)" and has the register-Nr: DRKS00000711.

7 Trial duration

The CoRaLa study started on 25-FEB-2011 which was equal to the „First Patient In" (FPI) date. The last patient was recruited on 25-Oct-2011 and completed the study intervention as planned (with visit 8) on 13-Apr-2012. „Last Patient Out" (LPO) was the 48-weeks follow-up on 18-Sept-2012.

8 Objectives of the trial

The primary objective is to evaluate the efficacy of the combined treatment with respect to visual acuity, assessed by Best Corrected Visual Acuity (BCVA) of the study eye using the ETDRS chart.

Secondary objectives are:

- To evaluate the effects of the combined treatment regimen on central retinal thickness (CRT) measured by optical coherence tomography (OCT)
- To evaluate the amount of required intravitreal applications of ranibizumab
- To evaluate the proportion of patients progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring panretinal photocoagulation during the entire period of trial including the follow-up phase
- To evaluate the safety of the combined treatment regimen with respect to the adverse and serious adverse events (AEs / SAEs)

9 End points of the clinical trial

Primary end point:

Based on the Best Corrected Visual Acuity (BCVA) assessment of the study eye - performed at all study visits and measured in ETDRS letters - the primary end point was derived.

For confirmatory analysis the change score in BCVA (number of ETDRS letters) from Week 1 to week 24, i.e. final study visit, was evaluated. This intra-individual change averaged within the treatment arms served as primary outcome to identify potentially different treatments effects of the groups.

The secondary and safety end points are:

- Change score in central retinal thickness (CRT), assessed by OCT between Week 1 and week 24 (resp. last FU).
- Number of Ranibizumab injections applied per patients until end of treatment (EoT) and in total (until last FU); as all patients received 3 intraocular injections a range from 3 to maximally 6 injections was expected guided by the visual acuity of patients and standardized retreatment criteria. Maximally 6 additional injections were possible between EoT and the last (of at the 4-weekly performed) FU visits within routine care applications).
- Change score in BCVA between Week 1 and last FU

- Proportion of patients per group progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation.
  Neovascularizations was assessed at every visit and analyzed cumulatively per patient until week 24.
- Number of serious adverse events (SAEs)/ reactions (SAR – causally retaled to treatments) per group and
- Number of adverse events (AEs)/ ARs per group observed during the entire course of study (including critical ocular events like abrupt, clinically significant decrease in BCVA, new onset of a clinically significant increase in intraocular pressure, corneal edema, intraocular inflammatory response etc).

10 Clinical trial design / methodology

Patients were randomized to the experimental intervention arm (RL group) which received Ranibizumab plus laser or the control arm (R group) which received Ranibizumab only.
Randomisation of patients into both treatment arms was performed centrally by the ZKS Leipzig-KKS and was computer-assisted, based on block-randomization lists. A randomization ratio of 1:1 was used. Randomization was stratified according to BCVA at baseline (<=48 letters vs > 48 letters) to ensure structural equality between arms despite the rather small number of patients included with regard to the primary outcome measure.

11 Total number of patients

It was planned to assess 35 patients for eligibility, to allocate 22 patients to the trial and to analyze the results of 20 patients.

For an overview see Consort Flow Chart presented at the end of this report.

Randomisation was done in stratified manner according to the prepared scheme of randomisation. No randomisation failure occurred.

Table 11.1: Frequency of group allocation

	Frequency	Percent
RL group	10	45,5
R group	12	54,5
Total	22	100,0

There were two patients who prematurely terminated the trial one (P10 - R group) underwent progression into ischemic CRVO which was the reason for the early termination according to protocol definition. In another patients (P24 RL - group) only weak and short-term effects of Lucentis were observed which required the change of treatment to Ozurdex after V9 but not during the regular period of intervention.

No relevant arm differences were observed regarding sociodemographic data although the heterogeinity in age is apparantly larger in the RL group.

12 Inclusion criteria

1. Diagnosis of macular edema due to central retinal vein occlusion foveal thickness ≥ 250 µm (measured by OCT)
2. Age ≥ 18 years
3. Written informed consent of the patient
4. BCVA score in the study eye between 24 letters (20/320) and 73 letters (20/40) measured in ETDRS chart
5. The history of CRVO no longer than 8 months
6. Presence of capillary non-perfusion in peripheral retina larger than 1 and smaller than 10 disc areas documented in fluorescein angiography
7. Ability and willingness to attend all scheduled visits and assessments

13 Exclusion criteria

1. Ischemic CRVO defined as presence of capillary non-perfusion larger than 10 optic disc areas in fluorescein angiography
2. Macular edema due to another etiology than retinal vein occlusion (e.g. diabetic maculopathy, uveitis, age related macular degeneration, Irvine-Gass syndrome)
3. Diagnosis of CRVO in both eyes with macular edema requiring any kind of treatment
4. History of rhegmatogenous retinal detachment
5. History of idiopathic central serous chorioretinopathy
6. Presence of vitreoretinal interface disease (e.g., vitreomacular traction, epiretinal membrane), either on clinical examination or in OCT
7. An eye that, in the investigator's opinion, would not benefit from resolution of macular edema, such as eyes with foveal atrophy, dense pigmentary changes, or dense subfoveal hard exudates
8. Patients in which at time of screening the anti-VEGF treatment is planned for the fellow eye for any reason
9. Aphakia
10. Improvement of > 10 letters on BCVA between screening and Day 1
11. Scatter laser photocoagulation or macular photocoagulation in the study eye prior to study entry
12. Use of intraocular or periocular injection of steroids in the study eye prior to study entry
13. Previous use of an anti-VEGF drug in the study eye

14. Cataract surgery or Yttrium-Aluminum-Garnet (YAG) laser capsulotomy or any other intraocular surgery in the study eye within 3 months prior to study entry
15. History or presence of AMD (dry or wet form)
16. Uncontrolled glaucoma (defined as intraocular pressure ≥ 30 mm Hg despite treatment with anti-glaucoma medications)
17. Uncontrolled blood pressure defined as pressure ≥ 160/90 mmHg in at least 3 consecutive measurements
18. History of cerebral vascular accident
19. Pregnancy (positive pregnancy test) or lactation
20. The presence of active malignancy, including lymphoproliferative disorders.
21. History of allergy to humanized antibodies or any component of the ranibizumab formulation
22. Inability to comply with study procedures
23. Participation in another simultaneous medical investigation or trial
24. Ongoing drug abuse
25. HIV positive
26. Women with child bearing potency without effective contraception (i. e. implants, injectables, combined oral contraceptives, some IUDs or vasectomised partner) during the conduct of the trial.
27. Expected low compliance (e.g. by travel distance to trial site)

14 Investigational Product

Ranibizumab (Lucentis®) is formulated as a sterile solution aseptically filled in a sterile glass vial. Each vial contains 0.23 mg Ranibizumab in an aqueous solution (pH 5.5) as active ingredient and was administered after withdrawn to a syringe as intravitreal injection.
The study drug was supplied by Novartis. It represents a commercially available and approved medication and was applied according to the prescribing information. Ranibizumab was approved during the course of this clinical trial by European authorities on 06.06.2011 for treatment of macular oedema secondary to branch- and central-retinal vein occlusion.
Laser photocoagulation is an established therapy and was applied in accordance with its specific medical purpose.

14.1 Experimental intervention

RL group (Ranibizumab plus laser): Patients randomized to this group received an intravitreal injection of 0.5 mg ranibizumab with additional selective laser photocoagulation for capillary non-perfusion in the retinal periphery. All patients received in the first 3 months (loading phase) 3 intravitreal injections of ranibizumab (every 4 weeks). Thereafter up to

three further injections were administered as needed (pro re nata) if the re-treatment criteria were met, which were as follows:

1. Increase of CRT of more than 50 µm compared to the lowest CRT value measured in any of all previous visits

   and

2. Decrease of BCVA ≥ 5 ETDRS letters compared to the best BCVA reached in any of all previous visits.

or

independent on the other two criteria: Macular oedema with a central retinal thickness > 250 µm

During the first three months laser photocoagulation was performed up to three time along with ranibizumab injections and was restricted to peripheral retinal areas of capillary non-perfusion (detected by fluorescein angiography at the screening visit) outside the macula. A control fluorescein angiography was scheduled three months after randomization (week 12). If new areas of capillary non-perfusion were detected, further selective laser photocoagulation was performed on a monthly basis.

14.2 Control intervention

R group (Ranibizumab only): Patients randomized to this group received intravitreal injections of 0.5 mg ranibizumab without additional laser photocoagulation. The intravitreal application of ranibizumab was performed per protocol as in the RL group.

14.3 Follow-up

As Ranibizumab was approved for treatment of macular oedema secondary to branch- and central-retinal vein occlusion, all patients were asked to continue the follow-up phase of additional 24 weeks. They were informed by the investigator about the assessment and processing of additional data on the patients' health during three additional (8-weekly) study documentations at every 2nd of the performed (4-weekly) clinical visits and the possibility of further ranibizumab injections within the context of usual daily care and not belonging to study intervention.

15 Duration of treatment and trial procedures

The study was composed of a screening phase, a 12 week loading treatment phase with visits every 4 weeks followed by a 12 week PRN (pro re nata) treatment phase with visits every 4 weeks up to week 24, which was the end of study intervention. During the 24-weeks follow-up phase patients were treated within the context of usual daily care within every 4 weeks, but only every 8 weeks additional data on the patients' health were assessed.

16 Statistical methods / criteria for evaluation

16.1 Primary endpoint

The aim of the study was to investigate whether there is a significant and relevant difference in BCVA Change score between the two treatment groups at the end of the study period (after 24 weeks of supervision and/ or treatment). For this purpose, the mean of the between-group difference with the corresponding 95% confidence interval was estimated according to protocol.

Furthermore, to deal with the small number of patients and potential events which may occur and lead to extreme BCVA changes (like neovascularizations) the Hodges-Lehmann statistics is presented with 95% confidence intervals which estimates median location differences in otherwise similar distributed data.

We expect superiority of the RL treatment over Ranibizimab alone. This means that the confidence interval estimated should not contain the zero difference between groups for significant group differences. Definitely, it should indicate an advantage/ remarkably larger gain in number of ETDRS letters legible in favour of the RL group after the end of intervention.

Due to the predefined primary end point and the estimation of potentially different treatment effects between groups no adjustment on multiplicity is necessary.

The Safety Analysis Population (SAP) was defined by all patients randomised who received at least once the study treatment. Since all patients were allocated and treated according to intention-to treat the SAP is identical to the FAS here.

16.2 Primary endpoint / Secondary analysis

In secondary analyses, BCVA changes (from baseline values) at every study visit were analysed by repeated-measures ANCOVA with treatment as factor and baseline BCVA values as covariate as well as with or without number of Ranibizumab injections (indicated). Complementary, the rate of patients with an improvement of >= 15 letters at the end of intervention (after 24 weeks) and study (last FU) wascompared between groups using Fisher's exact test (results not presented here).Descriptive methods were applied to quantify and visualize the time course of the BCVA.

16.3 Secondary endpoints

The secondary - endpoint central retinal thickness (CRT) - was analysed with the same methods as the primary endpoint.

The number of indicated Ranibizumab injections until EoT and until last FU visit was described and compared between groups by Mann-Whitney-U-Test.

This secondary endpoint was the reason for the prolongation of observation time and the resulting protocol amendment.

Furthermore, the rate of neovascularisation was estimated and compared between groups using Fisher's exact test.

16.4 Safety analyses

For safety analyses, all AEs and SAEs are reported. No SAR was observed.

Vitreous opacities/degeneration observed in 1 patient each was related to the procedure of intravitreal drug application but not directly to the drug itself.

Essential safety endpoints were:

- Number of serious adverse events (SAEs) per group and
- Number of adverse events (Aes) per group observed during the entire course of study (including critical ocular events like abrupt, clinically significant decrease in BCVA, new onset of a clinically significant increase in intraocular pressure, corneal edema, intraocular inflammatory response etc).

17 Summary

17.1 Efficacy results

17.1.1 BCVA assessments

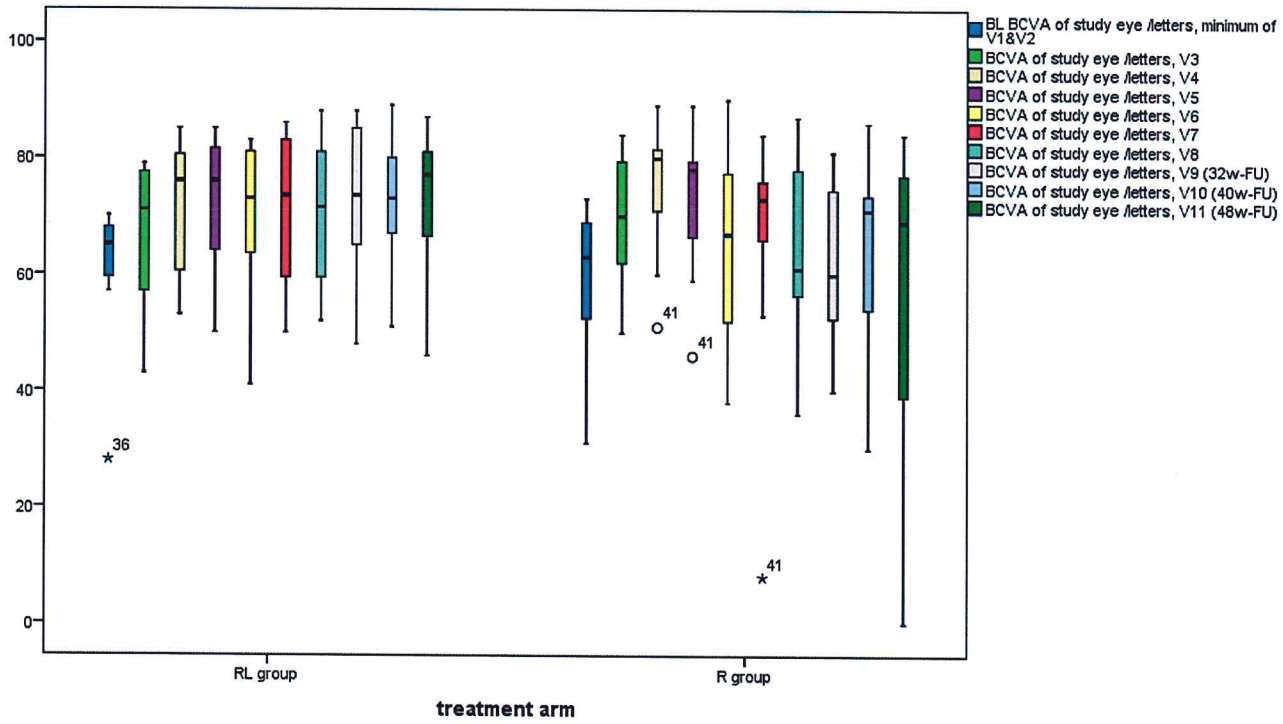
Table 17.1 shows the baseline values and change scores at end of trial (EoT) and all 3 FU visits per group. Like to be seen at EoT and all FU visits BCVA could be measured in 11 patients of the R group (instead of 12) only since one (P10- R group) developed an ischemic CRVO before visit 7 and terminated the trial prematurely according to protocol. Another premature termination of FU period occurred in one patient (P24 RL - group) at V10 since only weak and short-term effects of Lucentis were observed and a change to Orzudex was decided. Due to poor compliance no change score could be obtained in one (P16 RL - group) at V10 since she missed the respective visit but could be convinced to complete the final visit.

Table 17.1: Baseline (BL) levels and Change scores of BCVA

		treatment arm		Total
		RL group	R group	
BL BCVA of study eye /letters, minimum of V1&V2	N	N=10	N=12	N=22
	MW	61,6	58,6	60,0
	SD	12,7	12,4	12,4
	Min	28,0	31,0	28,0
	25%	59,3	50,5	52,8
	50%	65,0	61,0	63,5
	75%	69,3	70,0	69,3
	Max	73,0	73,0	73,0
Change of BCVA score at v8 (EoT), pEP	N	N=10	N=11	N=21
	MW	7,30	4,82	6,00
	SD	15,02	17,28	15,89
	Min	-24,00	-25,00	-25,00
	25%	-5,25	-10,00	-8,00
	50%	14,00	7,00	12,00
	75%	18,25	16,00	17,00
	Max	24,00	28,00	28,00
Change of BCVA score at v9 (FU1, after 32 weeks)	N	N=10	N=11	N=21
	MW	9,30	2,82	5,90
	SD	11,33	16,12	14,10
	Min	-10,00	-19,00	-19,00
	25%	,25	-10,00	-8,50
	50%	13,50	-1,00	6,00
	75%	19,00	18,00	18,50
	Max	20,00	29,00	29,00
Change of BCVA score at v10 (FU2, after 40 weeks)	N	N=8	N=11	N=19
	MW	12,13	4,82	7,89
	SD	8,11	17,47	14,46
	Min	1,00	-21,00	-21,00
	25%	3,00	-12,00	1,00
	50%	13,50	9,00	12,00
	75%	19,00	13,00	16,00
	Max	23,00	35,00	35,00
Change of BCVA score at v11 (FU3, after 48 weeks, EoS)	N	N=9	N=11	N=20
	MW	11,78	-2,27	4,05
	SD	6,44	25,57	20,32
	Min	-2,00	-53,00	-53,00
	25%	7,50	-25,00	,00
	50%	14,00	8,00	12,00
	75%	16,50	13,00	15,00
	Max	18,00	26,00	26,00

EoT: End of treatment
pEP: primary endpoint
EoS: End of study

Fig. 17.1: BCVA assessments during the total course of trial



17.1.2 Primary Endpoint / Confirmatory analysis

To ensure confirmatory analysis within the Full-analysis-set (FAS) of all randomised patients mean value (MV) imputation for the dropout P10 was performed in two ways: a) last-observation-carried-forward (LOCF) and b) by imputation of worst group value observed at V8. The respective impact on the data observed was presented in the following table.

Table 17.2: Change scores of BCVA (with or without MV-imputation)

		treatment arm		insg.
		RL group	R group	
Change of BCVA score at v8 (EoT), pEP	N	N=10	N=11	N=21
	MW	7,30	4,82	6,00
	SD	15,02	17,28	15,89
	Min	-24,00	-25,00	-25,00
	25%	-5,25	-10,00	-8,00
	50%	14,00	7,00	12,00
	75%	18,25	16,00	17,00
	Max	24,00	28,00	28,00
Change of BCVA score at v8 (EoT) with LOCF-imputation, for FAS analysis	N	N=10	N=12	N=22
	MW	7,30	1,17	3,95
	SD	15,02	20,78	18,24
	Min	-24,00	-39,00	-39,00
	25%	-5,25	-13,00	-10,00
	50%	14,00	6,50	9,50
	75%	18,25	15,75	16,50
	Max	24,00	28,00	28,00
Change of BCVA score at v8 (EoT) with Minimum-imputation per group, pEP in FAS	**N**	**N=10**	**N=12**	**N=22**
	MW	**7,30**	**2,33**	**4,59**
	SD	**15,02**	**18,59**	**16,86**
	Min	**-24,00**	**-25,00**	**-25,00**
	25%	**-5,25**	**-13,00**	**-10,00**
	50%	**14,00**	**6,50**	**9,50**
	75%	**18,25**	**15,75**	**16,50**
	Max	**24,00**	**28,00**	**28,00**

EoT: End of treatment
pEP: primary end point
LOCF: last-observation-carried-forward

According to protocol the 95%-confidence intervals of the mean difference between both treatment arms were calculated and presented.

Table 17.3: Group mean difference and 95% confidence interval of BCVA change at V8 (EoT)

	Group Mean Difference	Std. Error of Difference	95% Confidence Interval of the Difference (lower to higher limit)	
Change of BCVA score at v8 (EoT) with LOCF-imputation, pEP in FAS	6,13333	7,65009	-9,84172	22,10839
Change of BCVA score at v8 (EoT) with Minimum-change-per-group imputation, pEP in FAS	**4,96667**	**7,16692**	**-9,98372**	**19,91706**
Change of BCVA score at v8 (EoT, pre minus post value)	2,48182	7,10052	-12,37975	17,34339

Since the minimum-change-per-group imputation [method b)] is less conservative regarding the results within the reference group, it was chosen for confirmatory analysis. With positive BCVA change scores indicating an improvement (value in the course of trial minus baseline value) and a positive group difference indicating descriptive superiority of the RL group, a mean difference of 5.0 letters and a 95%-confidence interval of [-10.0; 19.9] a descriptive tendency toward a higher gain in BCVA was observed for the RL group although no significant group difference was found since the confidence interval contains zero.

However, because of the rather small samples, their asymmetric distribution (including potential extreme values due to clinical events), and the differences between group means and medians (see table 17.2) the median was additionally presented to describe the difference between both groups. The respective **Hodges-Lehmann** estimator showed an observed group difference of 4 [95%-KI: -11; 22] which is similar to the parametrically estimated confidence interval.

For power estimations the median group difference of 7.5 letters (i.e. 14 in RL- minus 6.5 in R-group) was used while from the respective interquartile ranges of the groups suitable SD estimates were performed and resulted in SD_{RL} group=17.0 resp. SD_R group=21.5. One may pay attention to the fact that both SD estimations refer to more heterogeneous situations than the SDs of means presented in the really measured change scores without MV imputations indicate. This relativizes the somewhat larger group difference of medians compared to the observed group mean differences.

17.1.3 Primary endpoint / Secondary analyses

- Change score in BCVA between Baseline and all FU measures.

Table 17.4: Group Mean Difference and 95% Confidence Interval of BCVA changes during FU

	Group Mean Difference	Std. Error of Difference	95% Confidence Interval of the Difference (lower to higher limit)	
Change of BCVA score at v9 (FU1, after 32 weeks; n=21)	6,48182	6,03975	-6,21042	19,17406
Change of BCVA score at v10 (FU2, after 40 weeks; n=19)	7,30682	5,99919	-5,48513	20,09877
Change of BCVA score at v11 (FU3, after 48 weeks, EoS; n=20)	14,05051	8,00382	-3,46879	31,56980

A Tendency toward more pronounced improvements were observed during the course of FU with most pronounced mean difference between groups but also more heterogeneous situation at End of Study. However, similarly to the EoT observations the medians showed deviations from the group means (s. table 17.1) during the FU period and the SD estimated from the quartiles per group at EoS and used for power calculations showed a larger heterogeinity and resulted in $SD_{RL\ group}$=7.4 resp. $SD_{R\ group}$=28.2.

The respective **Hodges-Lehmann** estimators for medians plus confidence intervals were:

- At FU1 (32 weeks): 9,5 [-8; 21],
- At FU2 (40 weeks): 6 [-7; 22], and
- At FU3 (48 weeks): 5 [-6; 33].

17.1.4 Analyses of secondary endpoints

- Change score in central retinal thickness (CRT), assessed by OCT between Week 1 and week 24 resp. all FU time points.

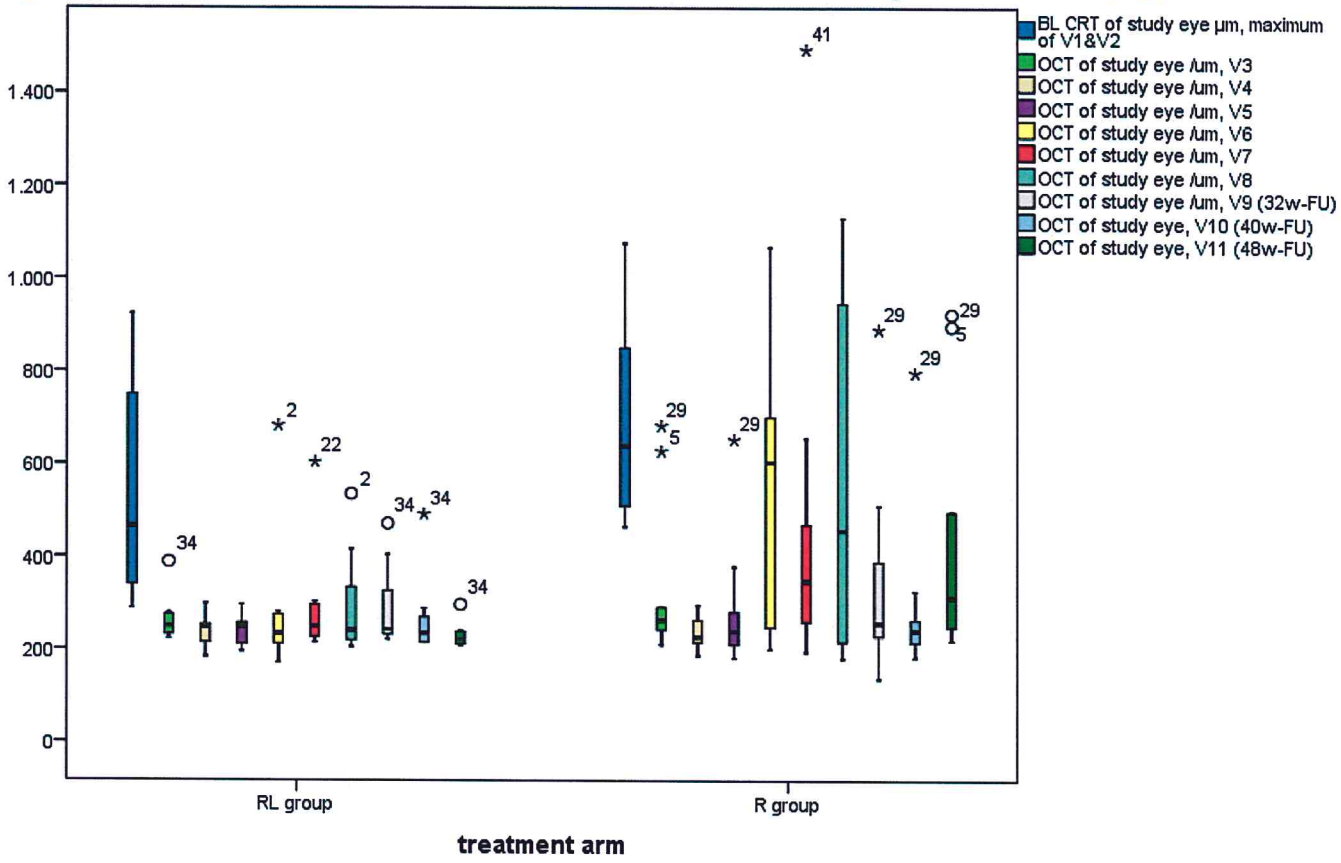
A tendency toward higher CRT values was registered (see below) although the mean/ median discrepancy between groups is rather small compared to the standard deviations within both groups.

Table 17.9: Baseline and change scores of central retinal thickness (CRT)

		treatment arm		Total
		RL group	R group	
BL CRT of study eye in [µm], maximum of V1&V2	N	N=10	N=12	N=22
	MW	572,5	696,0	639,9
	SD	248,4	212,9	232,7
	Min	288,0	464,0	288,0
	25%	339,0	507,5	473,8
	50%	547,0	637,5	617,5
	75%	863,3	851,5	852,0
	Max	923,0	1075,0	1075,0
Change of CRT (from OCT) in [µm], at v8 (EoT; pre minus post value)	N	N=10	N=11	N=21
	MW	-178,50	-159,91	-168,76
	SD	301,18	336,75	312,43
	Min	-328,75	-394,00	-339,50
	25%	-374,00	-394,00	-373,00
	50%	-176,00	-291,00	-223,00
	75%	-16,00	54,00	3,50
	Max	425,00	481,00	481,00
Change of CRT (from OCT) in [µm], at v9 (FU1, after 32 weeks)	N	N=10	N=11	N=21
	MW	-163,30	-333,36	-252,38
	SD	346,52	315,72	333,84
	Min	-695,00	-895,00	-895,00
	25%	-459,25	-582,00	-564,50
	50%	-76,00	-283,00	-254,00
	75%	81,75	-121,00	-6,50
	Max	407,00	232,00	407,00
Change of CRT (from OCT) in [µm], at v10 (FU2, after 40 weeks)	N	N=8	N=11	N=19
	MW	-271,88	-382,00	-335,63
	SD	301,93	259,64	275,72
	Min	-709,00	-893,00	-893,00
	25%	-564,25	-525,00	-525,00
	50%	-245,00	-355,00	-355,00
	75%	-44,25	-272,00	-124,00
	Max	152,00	139,00	152,00
Change of CRT (from OCT) at v11 (FU3, after 48 weeks, EoS)	N	N=9	N=10	N=19
	MW	-308,33	-260,00	-282,89
	SD	241,65	250,23	240,57
	Min	-709,00	-634,00	-709,00
	25%	-516,00	-416,50	-419,00
	50%	-301,00	-269,00	-301,00
	75%	-91,50	-118,00	-130,00
	Max	-43,00	239,00	239,00

OCT: optical coherence tomography
EoT: end of treatment;
EoS: end of Study

Fig. 17.4: Central retinal thickness (CRT) values measured during the course of trial



With negative CRT change scores indicating an improvement (value in the course of trial minus baseline value → decline in CRT) and a negative group difference indicating descriptive superiority of the RL group, the mean differences at EoT and EoS indicate a small descriptive tendency in favour of the RL group while the FUs at 32 and 40 weeks do not.

Table 17.10: Group Mean Difference and 95% Confidence Interval of CRT changes at EoT and EoS

	Group Mean Difference	Std. Error of Difference	95% Confidence Interval of the Difference (lower to higher limit)	
Change of CRT (from OCT) at v8 (EoT)	-18,59091	139,99184	-311,59721	274,41539
Change of CRT (from OCT) at v9 (FU1, after 32 weeks)	170,06364	144,47860	-132,33356	472,46083
Change of CRT (from OCT) at v10 (FU2, after 40 weeks)	110,12500	129,09758	-162,24709	382,49709
Change of CRT (from OCT) at v11 (FU3, after 48weeks, EoS)	-48,33333	113,13451	-287,02629	190,35963

The respective Hodges-Lehmann estimators for medians and 95%-confidence intervals were:

- At EoT: -2.5 [95%KI: -297; 272],
- At FU1 (32 weeks): 192 [95%KI: -128; 507],
- At FU2 (40 weeks): 160.5[95%KI: -184; 401], and
- At FU3 (48 weeks): -35 [95%KI: -292; 215].

In summary, no clear tendency from the EoT and FU values could be found toward a more pronounced improvement for the RL group regarding CRT values although different courses during the treatment phase might be possible.

- Number of Ranibizumab injections applied per patients in total;

As all patients at least received 3 intraocular injections in the up-load phase of treatment 3 additional injections were possible based on standardized retreatment criteria until EoT (V8). Further 6 injections could have been applied on the regular 4-weekly visits during the FU phase if medically indicated. Of course, unscheduled visits were possible, too, in case of acute decline of visual acuity. All injections performed were registered and counted for analysis. The median group difference of injections estimated by Hodges-Lehmann statistic was

- until EoT: -1 [95% CI: -1; 0]; p_{EoT}=0.107 (by Mann-Whitney-U-Test),
- until EoS: -2 [95% CI: -4; 0]; p_{EoS}=0,152.

Table 17.11: Nb. of injections until EoT and EoS

		treatment arm		insg.
		RL group	R group	
Nb. of Ranibizumab injections applied until EoT (max.6)	N	N=10	N=12	N=22
	MW	3,60	4,17	3,91
	StdAbw	,70	,72	,75
	Min	3,00	3,00	3,00
	25%	3,00	4,00	3,00
	50%	3,50	4,00	4,00
	75%	4,00	4,00	4,00
	Max	5,00	6,00	6,00
Nb. of Ranibizumab injections applied in total (until EoS) (max.9)	N	N=9	N=11	N=20[1]
	MW	5,0	6,7	6,0
	StdAbw	2,2	2,5	2,5
	Min	3,00	3,00	3,00
	25%	3,0	5,0	3,3
	50%	4,0	7,0	6,0
	75%	7,5	8,0	8,0
	Max	8,0	12,0	12,0

[1] w/o Pat-ID no. 10 (developed ischemic CRVO during the trial) and no. 24 (treatment change during FU from lucentis to orzudex because of non-response)

- Proportion of patients per group progressing to anterior segment neovascularization, neovascularization of the optic disc (NVD), or neovascularization of the retina elsewhere (NVE) requiring pan-retinal photocoagulation during the course of trial

Table 17.12: Neovascularisation developed during the course of trial

		treatment arm		Total
		RL group	R group	
Neovascularization observed (inbetween V3 and V11)	no	10	10	20
	yes	0	2	2
Total		9	10	12

Although only 2 neovascularizations were observed (both in the R-group) the sample sizes and rates were too small to show significance (exact Fisher test: p=0,481).

17.2 Safety results

17.2.1 Adverse Events

In total, 96 AEs in 21 patients have been reported in the CoRaLa study. Four of these AEs were reported after the Cutoff date of the ASR (21 February 2012).

In table 17.13, all AEs were classified by the respective preferred terms (PT) and system organ classes (SOC) of MedDRA and presented with causality assessments and outcomes. From the ophthalmic AEs which were the events of the special interest in the safety analysis one patient (P10) underwent the progression into to the ischemic CRVO which was the reason for his early termination.

Vitreous opacities/degeneration observed in 1 patient each was related to the procedure of intravitreal drug application but not directly to the drug itself.

None of the AEs was related to ranibizumab nor to laser photocoagulation (see table 17.13). Therefore, no specific risk in safety can be derived from detailed results of AE analyses.

Table 17.13: All 96 AEs classified by System Organ Class (SOC) and Preferred Term (PT; by MedDRA) and presented with causal relationship with study procedures and reported outcome

		Code causal relationship AE <-> IMP		Outcome (Code)			
SOC	PT	Not Possible	Total	Recovered/ Resolved	Recovering/ Resolving	Not Recovered/ Not Resolved	Total
Eye disorders	Blepharitis	1	1	0	0	1	1
	Conjunctivitis	1	1	1	0	0	1
	Corneal erosion	1	1	1	0	0	1
	Eye pain	2	2	2	0	0	2
	Eye pruritus	1	1	1	0	0	1
	Eye swelling	1	1	1	0	0	1
	Keratitis	1	1	1	0	0	1
	Lacrimation increased	1	1	1	0	0	1
	Macular oedema	18	18	16	0	2	18
	Macular pigmentation	1	1	0	0	1	1
	Ocular hyperaemia	2	2	2	0	0	2
	Retinal exudates	3	3	3	0	0	3
	Retinal fibrosis	1	1	0	0	1	1
	Visual acuity reduced	17	17	14	0	3	17
	Vitreous degeneration	1	1	0	0	1	1
	Vitreous opacities	1	1	0	0	1	1
	Total	53	53	43	0	10	53
General disorders and administration site conditions	Chest pain	1	1	1	0	0	1
	Injection site pain	1	1	1	0	0	1
	Pain	2	2	2	0	0	2
	Sensation of foreign body	1	1	1	0	0	1
	Total	5	5	5	0	0	5
Infections and infestations	Appendicitis	1	1	1	0	0	1
	Cystitis	3	3	3	0	0	3
	Herpes simplex	1	1	1	0	0	1
	Herpes zoster	1	1	1	0	0	1
	Infection	2	2	2	0	0	2
	Nasopharyngitis	1	1	1	0	0	1
	Peritoneal abscess	1	1	1	0	0	1
	Total	10	10	10	0	0	10
Investigations	Blood pressure increased	1	1	1	0	0	1

		Code causal relationship AE <-> IMP		Outcome (Code)			
SOC	PT	Not Possible	Total	Recovered/ Resolved	Recovering/ Resolving	Not Recovered/ Not Resolved	Total
	Intraocular pressure increased	1	1	1	0	0	1
	Total	2	2	2	0	0	2
Metabolism and nutrition disorders	Diabetes mellitus	1	1	0	0	1	1
	Total	1	1	0	0	1	1
Musculoskeletal and connective tissue disorders	Musculoskeletal pain	1	1	1	0	0	1
	Sjogren`s syndrome	2	2	0	1	1	2
	Total	3	3	1	1	1	3
Neoplasms benign, malignant and unspecified (incl. cysts and polyps)	Renal cancer	1	1	1	0	0	1
	Total	1	1	1	0	0	1
Nervous system disorders	Headache	6	6	6	0	0	6
	Sciatica	1	1	1	0	0	1
	Total	7	7	7	0	0	7
Respiratory, thoracic and mediastinal disorders	Cough	1	1	1	0	0	1
	Dyspnoea	1	1	1	0	0	1
	Total	2	2	2	0	0	2
Skin and subcutaneous tissue disorders	Hypertrophic scar	1	1	0	0	1	1
	Pigmentation disorder	1	1	0	0	1	1
	Rash	1	1	1	0	0	1
	Total	3	3	1	0	2	3
Surgical and medical procedures	Cardioversion	2	2	1	0	1	2
	Cataract operation	1	1	1	0	0	1
	Tooth extraction	2	2	2	0	0	2
	Total	5	5	4	0	1	5
Vascular disorders	Hypertension	2	2	1	0	1	2
	Hypertensive crisis	2	2	2	0	0	2
	Total	4	4	3	0	1	4

17.2.2 Serious advers events (SAE)

No deaths occured during the course of the trial.

Nine SAEs in 6 patients were reported in the CoRaLa trial. For none of the SAEs observed a causality was regarded possible with respect to the IMPs of the trial - Ranibizumab or laser photocoagulation.

Table 17.14: SAEs with causality assessment and outcome reported within System organ classes and Preferred terms

		Causality Event <-> IMP		SAE: outcome		
SOC	PT	Not possible	Total	Recovered/ Resolved	Not Reco-vered/ Not Resolved	Total
Eye disorders	Macular oedema	1	1	1	0	1
	Visual acuity reduced	3	3	2	1	3
	Total	4	4	3	1	4
Infections and infestations	Appendicitis	1	1	1	0	1
	Peritoneal abscess	1	1	1	0	1
	Total	2	2	2	0	2
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	Renal neoplasm	1	1	1	0	1
	Total	1	1	1	0	1
Surgical and medical procedures	Cardio-version	2	2	2	0	2
	Total	2	2	2	0	2

18 Conclusions

The evaluation of efficacy of the combined treatment with respect to visual acuity, assessed by Best Corrected Visual Acuity (BCVA) of the study eye using the ETDRS chart up to end of treatment showed no significant group difference. The reason is the rather small samples of this proof-of-concept study.

- Regarding the median differences and estimated group standard deviations of 21.5 and 17 letters in the R resp. RL-Group (from the 1st and 3rd quartiles) at EoT the observed power was about 14%. Assuming similar effects like the observed a power of 80% would have required group sample sizes of 106 patients per arm (instead of 12 resp. 10).
- With regard to the EoS results giving a difference between group medians of 6 letters and estimated group SD of 28.2 resp. 7.4 the observed power was 10% which would have required group sample sizes of 186 patients per arm to achieve 80% power.

CONSORT Flow Diagramm