Protocol

Long-term need of Ranibizumab injections with or without early targeted peripheral laser photocoagulation for treatment of macular edema due to central retinal vein occlusion

CoRaLa II trial

*(**Co**mbination of **Ra**nibizumab and targeted **La**ser)*

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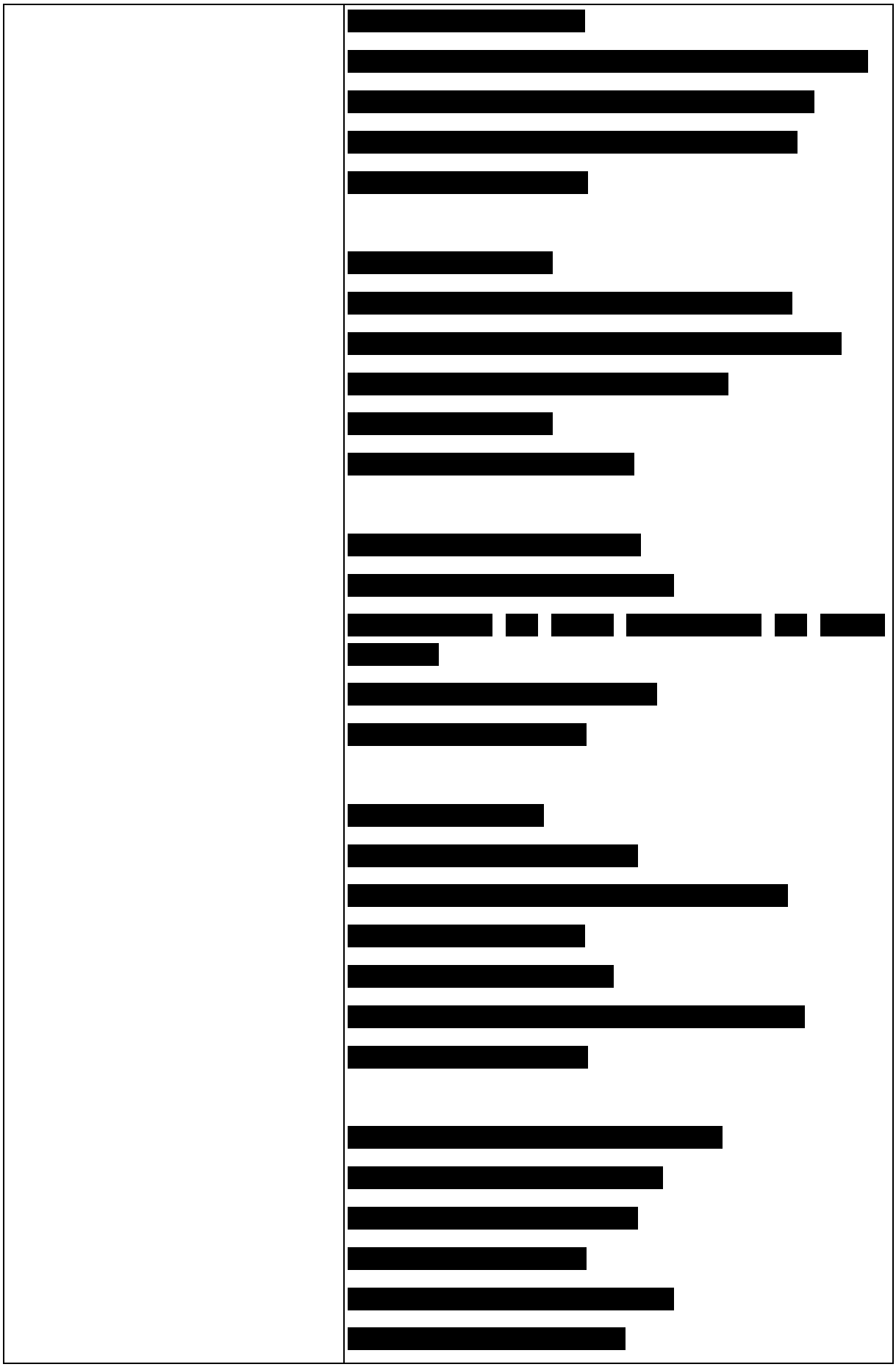


	[redacted]

Synopsis

Title of the trial	Long-term need of ranibizumab injections with or without early targeted peripheral laser photocoagulation for treatment of macular edema due to central retinal vein occlusion
Acronym	CoRaLa II trial (Combination of Ranibizumab and Laser)
Indication	Macular edema due to central retinal vein occlusion
Primary goal of the trial / primary end point	The primary objective is to evaluate whether or not the duration of guideline-conform [1] periodic ranibizumab injections may be shortened or even be successfully terminated in patient with macular edema due to central retinal vein occlusion if early targeted peripheral laser photocoagulation is applied in parallel. Primary efficacy endpoint is the time to treatment success, defined as time from randomisation until the date of last criteria-based intravitreal injection in case that thereafter a treatment-free period for (at least) 6 months was observed.
Secondary goals of the trial / secondary end points	Secondary objectives are to evaluate the visual acuity during and after the course of intervention, quality of life associated aspects and possible problems which might possibly be associated with the trial's intervention. *Secondary endpoints (sEP) are:* • the best corrected visual acuity (BCVA) • central subfield thickness (CST) • the number of ranibizumab injections required until treatment success and up to the end of observation. *Complementary outcomes of interest are:* • the proportion of subjects developing neovascularization(s) over total observation period. • health-related quality of life (HrQoL) • the area of non-perfusion • vessel density & areal of fovelar avascular zone • potential visual field loss • development of collaterals • the number of laser treatments and the laser spots given in the experimental group (RL-arm)
Trial design	Multi-centric, prospective, randomized, interventional, clinical trial with two parallel groups, phase IIIb
Trial population	**Inclusion Criteria** Patients must meet ALL of the following criteria: 1. Diagnosis of macular edema due to central retinal vein occlusion foveal thickness >250 µm (measured by optical coherence tomography (OCT)) 2. Age ≥ 18 years 3. Written informed consent of the patient 4. Best corrected visual acuity (BCVA) score in the study eye between 24 letters (20/320) and 78 letters (20/25) measured in

	ETDRS chart 5. History of central retinal vein occlusion (CRVO) no longer than 6 months 6. Presence of capillary non-perfusion in peripheral retina larger than 5 disc areas documented in ultra wide-field fluorescein angiography 7. Ability and willingness to attend all scheduled visits and assessments **Exclusion Criteria** Patients will be excluded for ANY ONE of the following reasons: 1. CRVO with ischemic maculopathy defined as diameter of the foveolar avascular zone larger than 2 optic disc diameters 2. Macular edema due to another etiology than retinal vein occlusion (e.g. diabetic maculopathy, uveitis, age related macular degeneration, Irvine-Gass syndrome) 3. History of idiopathic central serous chorioretinopathy 4. Presence of vitreoretinal interface disease (e.g., vitreomacular traction, epiretinal membrane), either on clinical examination or in OCT 5. 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 6. Aphakia in the study eye 7. Scatter laser photocoagulation or macular photocoagulation in the study eye prior to study entry 8. Intraocular or periocular injection of steroids in the study eye prior to study entry 9. Previous use of an anti-VEGF drug in the study eye 10. Cataract surgery or any other intraocular surgery in the study eye within 3 months prior to study entry 11. Uncontrolled glaucoma (defined as intraocular pressure ≥ 30 mmHg despite treatment with maximal anti-glaucoma medications) 12. History of stroke, myocardial infarction, transient ischemic attacks within 3 months prior to the study 13. Pregnancy (positive urine pregnancy test) or lactation 14. The presence of active malignancy, including lymphoproliferative disorders. 15. History of allergy to fluorescein or any component of the ranibizumab formulation 16. Active intraocular infection 17. Participation in another simultaneous interventional medical investigation or trial 18. 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.
Sample size	• to be assessed for eligibility: 130 • to be allocated to trial: 110 • to be analysed: 110

Therapy	Intravitreal injections of Ranibizumab will be applied in all patients according to treatment guidelines [1]. The experimental group will receive additional targeted laser photocoagulation of the peripheral areas of capillary non-perfusion (up to 4 laser treatments within 1st year of the study). No further additional treatments of the study eye will be given in any of the arms of the trial.
Biometry	Analysis of the primary endpoint (within the FAS) will follow the intent-to treat principle and will be based on COX regression with the stratification factor baseline BCVA (≤ 55 letters vs > 55 letters) as fixed covariate as confirmatory analysis. Further models will include potentially prognostic factors and compliance for sensitivity reasons. The assumption of proportional hazard may be justified although no similar data are available by now. It will be checked and otherwise adequately dealt with. Kaplan-Meier curves provide time without treatment success per arm. The number of ranibizumab injections required after the initial three injections will be analysed by linear regression model including treatment as factor with the stratification factor baseline BCVA as covariate; for sensitivity reasons, further models may include the same prognostic factors of potential relevance as selected for analyses of the primary endpoint.
Trial Duration	First patient in to last patient out (months): 59 Duration of the entire trial (months): 72 Recruitment period (months): 30 Treatment period (months per patient): 23 and 6 months follow-up

Synopse (German version)

Titel der Studie	Langzeitbedarf von Ranibizumab-Injektionen mit oder ohne frühzeitige gezielte periphere Laser-Photokoagulation zur Behandlung des Makulaödems infolge eines Zentralvenenverschlusses
Kurzbezeichnung der Studie	CoRaLa II (Combination of Ranibizumab and Laser)
Indikation	Makulaödem infolge eines Zentralvenenverschlusses
Primäres Ziel der Studie/ primärer Endpunkt	Das primäre Ziel ist die Beurteilung, ob die Dauer der Leitlinien-konformen periodischen Ranibizumab-Injektionen bei Patienten mit Makulaödem aufgrund eines Zentralvenenverschlusses verkürzt oder sogar erfolgreich beendet werden kann, wenn parallel dazu eine frühzeitige, gezielte periphere Laser-Photokoagulation durchgeführt wird. Der primäre Endpunkt ist die Zeit bis zum Behandlungserfolg, definiert als die Zeit ab Randomisation bis zur letzten kriterienbasiert

	vorgenommenen Injektion, vorausgesetzt, der Patient wies anschließend mindestens 6 Monate lang keinen erneuten Re-Injektionsbedarf (gemäß den Behandlungsrichtlinien) auf.
Sekundäre Ziele der Studie/ sekundäre Endpunkte	Sekundäre Ziele sind die Untersuchung der Sehschärfe während und nach der Behandlungszeit, Auswirkungen auf die Lebensqualität und die Erfassung von möglichen Problemen, die möglicherweise in Zusammenhang mit der Studientherapie stehen. Sekundäre Ziele sind: • die bestkorrigierte Sehschärfe • die zentralen Netzhautdicke, gemessen mit optischer Kohärenztomografie • die Anzahl an benötigten Ranibizumab-Injektionen bis zum Therapieerfolg, sowie bis Studienende Ergänzende Messgrößen von Interesse sind: • Anteil der Patienten mit Entwicklung von neovaskulären Komplikationen über die gesamte Beobachtungszeit hinweg • Gesundheitsbezogene Lebensqualität (HrQoL) • ischämische Netzhautareale • Kapilarendichte und Größe der zentralen avaskulären Zone • Möglicher Verlust des Gesichtsfeldes • Entwicklung von Kollateralen • Anzahl Laserbehandlungen und verabreichte Laserstrahlung im experimentellen Arm (RL-Arm)
Studiendesign	Multizentrische, prospektive, randomisiert, interventionelle, klinische Studie mit zwei parallelen Gruppen, Phase IIIb
Studienpopulation	**Einschlusskriterien** Alle folgenden Einschlusskriterien müssen erfüllt werden: 1. Gesichertes Makulaödem als Folge eines Zentralvenenverschlusses. Zentrale Netzhautdicke > 250 µm (mittels OCT bestimmt). 2. Alter ≥ 18 Jahre 3. Schriftliche Zustimmung der Teilnahme an der Studie 4. Sehschärfe am Studienauge zwischen 24 Buchstaben (20/320) und 78 Buchstaben (20/25) – gemessen mittels ETDRS Prüftafel 5. Zentralvenenverschluss nicht älter als 6 Monate 6. Angiographisch gesicherte periphere ischämische Netzhautareale mit einer Größe von > 5 Papillenflächen (mittels Weitwinkel-FAG) 7. Bereitschaft und Fähigkeit die vorgeschriebenen Studienvisiten einzuhalten **Ausschlusskriterien** Es erfolgt kein Studieneinschluss, wenn eines der folgenden Ausschlusskriterien erfüllt ist: 1. Ischämischer Zentralvenenverschluss definiert durch Vorhandensein von ischämischen Netzhautareale in der

	Makula größer als 2 Papillenflächen 2. Makulaödem als Folge anderer Ursache als Zentralvenenverschluss (z.B. diabetische Retinopathie, Uveitis, altersabhängige Makuladegeneration, Irvine-Gass-Syndrom usw.) 3. Vorangegangene idiopathische zentrale seröse Netzhautschädigung 4. Bestehende Erkrankung der vitreoretinalen Grenzschicht (z.B. vitreomakuläre Traktionssyndrom, epiretinale Membran) festgestellt in klinischen Untersuchungen oder OCT 5. Ein Auge, für das in der Beurteilung des Prüfers kein Vorteil durch die Behandlung des Makulaödems zu erwarten ist, z.B. foveale Atrophie, dichte Pigmentveränderungen oder dichte subfoveale harte Exsudate 6. Aphakie im Studienauge 7. Laserphotokoagulation der Netzhautperipherie oder fokale zentrale Laserphotokoagulation im Studienauge vor Studieneinschluss 8. Intra- oder periokuläre Steroidapplikation am Studienauge vor Studieneinschluss 9. Vorherige Anwendung von VEGF-Hemmer am Studienauge 10. Kataraktoperation oder andere intraokulare Operationen am Studienauge innerhalb von 3 Monaten vor Studieneinschluss 11. Unkontrolliertes Glaukom (definiert als Augendruck ≥ 30 mmHg) trotz maximaler Glaukom-Behandlung 12. Vorausgegangener Schlaganfall, Herzinfarkt, transitorische ischämische Attacken innerhalb von 3 Monaten vor Studieneinschluss 13. Schwangere (mit positivem Urin-Schwangerschaftstest) oder stillende Frauen 14. Bekannte aktive maligne Erkrankung, einschließlich lymphoproliferative Erkrankungen. 15. Bekannte Allergie auf Fluoreszein oder Komponenten der Ranibizumab-Formulierung 16. Aktive intraokuläre Infektion 17. Aktuelle Teilnahme an anderen interventionellen klinischen Prüfungen 18. Frauen im gebärfähigen Alter ohne hochwirksame Empfängnisverhütung (z.B. Implantate, Spritzen, kombinierte orale Kontrazeptiva, intrauterine devices – Spiralen etc., vasektomierter Partner) während der Studienteilnahme
Patientenzahl	• Anzahl gescreente Patienten: 130 • Anzahl eingeschlossener Patienten: 110 • Anzahl Patienten, von denen die Daten analysiert werden: 110
Therapie	Intravitreale Ranibizumab-Injektionen werden allen Studienpatienten gemäß den Leitlinien verabreicht. Die Patienten des experimentellen Armes erhalten zusätzlich gezielte Laserphotokoagulation der peripheren ischämischen

	Netzhautareale (bis zu 4 Laserbehandlungen innerhalb des ersten Studienjahres). Keine weiteren zusätzlichen Behandlungen werden den Patienten in beiden Studienarmen verabreicht.
Biometrie	Die Analyse des primären Endpunkts (innerhalb des Full analysis sets der Patienten, FAS) folgt dem Intent-to-Treat-Prinzip und erfolgt mittels einer COX-Regression mit dem Interventionsarm als Haupt-Einflussfaktor und dem Ausgangs-BCVA (≤55 Buchstaben vs. >55 Buchstaben) als fixer Kovariate. Die Annahme proportionaler Hazards wird überprüft und ggf. ein angemessenes alternatives Verfahren eingesetzt. Bisher liegen keine ähnlichen Daten vor. Die Zeit bis zum Behandlungserfolg wird mittels Kaplan-Meier-Kurven (pro Arm) grafisch veranschaulicht. Sekundäre und Sicherheitsendpunkte: Die Anzahl der Ranibizumab-Injektionen, die nach den ersten drei Injektionen erforderlich ist, mittels ANCOVA (Faktor: Behandlungsarm; Kovariate: Stratifikationskriterium); Verläufe von BCVA und CSF mittels gemischter linearer Modelle mit Messwiederholungen (anhand von Messungen zu vorab definierten Zeitpunkten); (S)AE/(S)AR, Neovaskularisationen und andere kritische okulare Ereignisse mittels exaktem Fisher (or Chi²-)Test sowie ggf. multivariater logistischer Regression (falls sinnvoll).
Zeitplan	Einschluss des ersten Patienten bis „last patient out“ (Monate): 59 Studiendauer (Monate): 72 Rekrutierungsdauer (Monate): 30 Behandlungsdauer (Monate pro Patient): 23 und 6 Monate Nachbeobachtungsdauer

Schedule of Assessments and Procedures

Visit	Screening	Baseline	V2	V3	V4	V5	V6	V7	V8	V9	V10	V11	V12	…	V16	…	V20	EoT[i]	FU	EoS
	day -14 to 0	V1																V23	V24	V25
		UPLOADING			MAINTENANCE															
Month	Screening and Baseline can be on the same day	day1 1 +/- 7 days	2 +/- 7 days	3 +/- 7 days	4 +/- 7 days	5 +/- 7 days	6 +/- 7 days	7 +/- 7 days	8 +/- 7 days	9 +/- 7 days	10 +/- 7 days	11 +/- 7 days	12 +/- 7 days	f) +/- 7 days	16 +/- 7 days	f) +/- 7 days	20 +/- 7 days	23 +/- 7 days	24 +/- 7 days	29 +/- 7 days
Eligibility criteria	x																			
Informed consent	x																			
Medical history	x																			
Oph halmic history	x																			
Pregnancy test	x																			
Randomisation	**x**																			
Blood presure and pulse	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
QoL Ques ionnaire		x											x						x	
Related adverse events[d] and Critical ocular events		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x[e]
Concomitant medica ion		x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Visual acuity (BCVA)	x [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [b]	x
Intraocular pressure	x [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Gonioscopy	x												x						x	
Slit lamp bio-microscopy	x [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Visual field					x [b]														x [b]	
OCT [g]	x [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [b]	x
OCT-Angiography [g]	x [b]				x								x						x [b]	x
Oph halmoscopy	x [b]	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x [b]	x
Fundus photography [g]	x [b]			x						x					x				x [b]	
Fluorescein angiography [g]	x [b]			x						x					x				x [b]	
Assess for re-treatment criteria					x	x	x	x	x	x	x	x	x	x	x	x	x	x		
Ranibizumab injection		x	x	x	x [a]	x [a]	x [a]	x [a]	x [a]	x [a]	x [a]	x [a]	x [a]	x [a]	x [a]	x [a]	x [a]	x [a]		
Laser photo-coagulation (experimental arm only)[h]			x		x [c]		x [c]				x [c]									

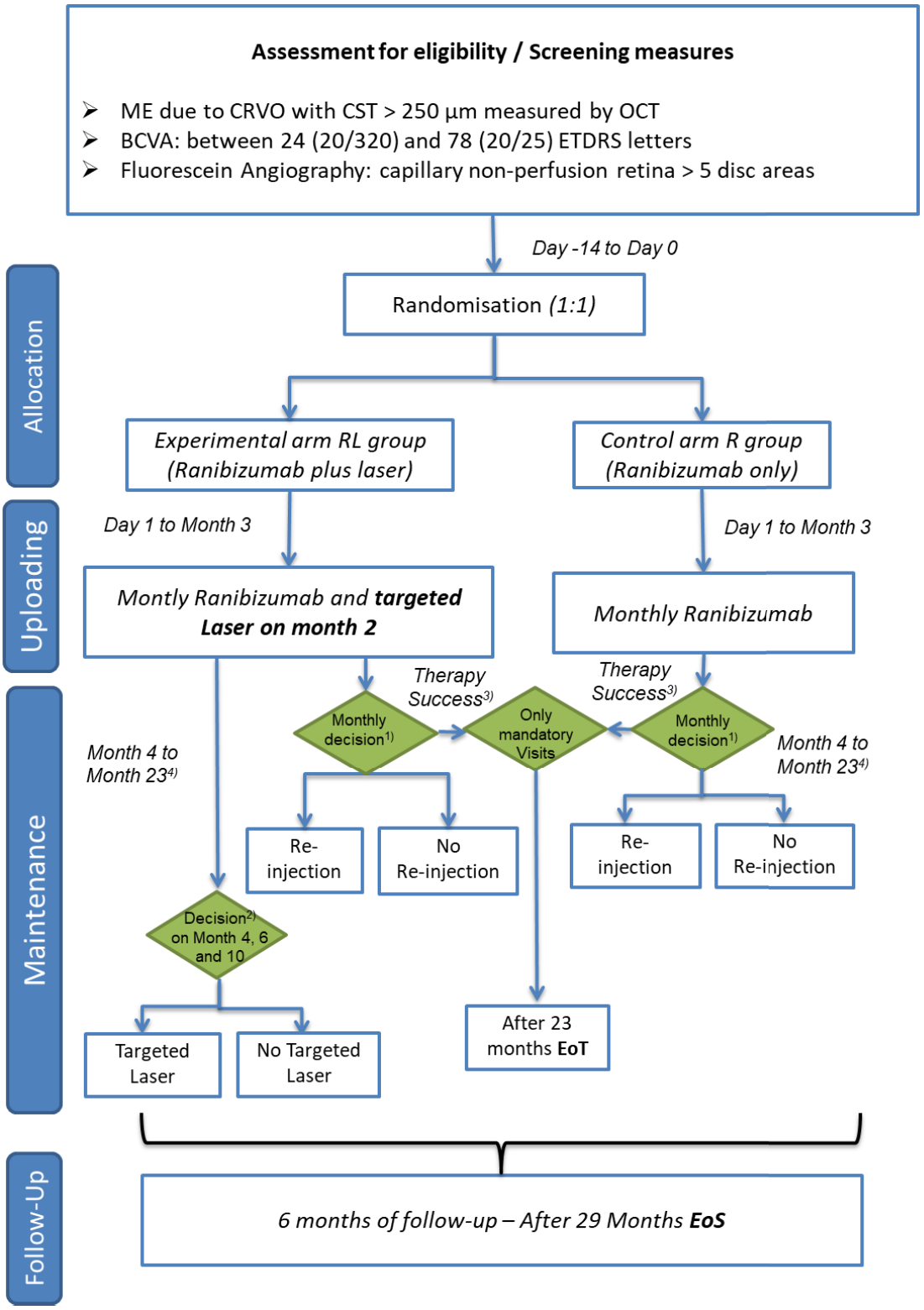
a) if re-treatment criteria met, on he **first day** of each mon h (+/- 7 days is not applicable) b) will be performed in both the study eye and the fellow eye c) if further laser photocoagulation required

d) related (S)AEs/(S)ARs until 4 weeks after the last trial-related intervention **up to Visit 24** and critical ocular events until the end of study visit V25. e) Only critical ocular events

f) During the first 12 months monthly visits will be scheduled. Thereafter visits will be adapted according to success. If success -> mandatory visits only.
-> Patients who are free of intravitreal treatment ≥ 2 months will be seen bi-monthly. **Mandatory Visits 1-12, 16, 20, 24 and 25**
-> If the treatment interval is < 2 months, patients will be followed monthly until the treatment success has been reached or treatment interval is ≥ 2 months for at least 2 consecutive injections

g) Evaluation by CoRaLa II Reading Centre h) Laser treatment according to recomendations of the CoRaLa II Reading Centre i) Study treatment ends at V23 or early if treatment success

Flow Chart



1) Re-treatment criteria for Ranibizumab are described in chapter 6.3 “Description of the Treatment Procedures”
2) Re-treatment criteria for laser coagulation are described in chapter 6.3 “Description of the Treatment Procedures”
3) Treatment success: 6 months without any further need of injections.
4) During the first 12 months monthly visits will be scheduled.
Thereafter visits will be adapted according to success:

⇒ If success -> mandatory visits only.
⇒ Patients who are free of intravitreal treatment ≥ 2 months will be seen bi-monthly.
⇒ If the treatment interval is < 2 months, the patients will be followed monthly until the treatment success has been reached or treatment interval is ≥ 2 months for at least 2 consecutive injection.

1 Rationale

1.1 Medical Background

Retinal vein occlusion (RVO) is the second most common retinal vascular disease leading to visual impairment. Central (CRVO) and branch retinal vein occlusion (BRVO) are distinguished as main types. Prevalence of 5.2/1000 (4.40–5.99) is estimated for RVO and 0.8/1000 (0.61–0.99, 95% CI) for CRVO with significant increase in age [2]. According to the epidemiological data ≈65 to 70 thousand patients suffer from RVO in Germany. Reflecting the burden of the ophthalmological disorders, measured by disability-adjusted life-years (DALYs), acquired in the Global Burden of Diseases (GBD) 2010, 'other vision loss' including CRVO showed the greatest percentage of total DALY 0.25% with increase of +2 DALY %-Change of DALY from year 1990 to 2010. The DALY rank was reported to be 67 of 176 conditions [3].

Main cause for visual impairment in CRVO is macular edema (ME) while neovascularization of the retina and/or the anterior segment is the most serious complication leading to vitreous hemorrhage, retinal detachment and neovascular glaucoma. In serious cases loss of vision is imminent [4]. To date, no causal treatment has been proven to be effective in large trials [1,5] Intravitreal injections of drugs that inhibit the vascular endothelial growth factor (VEGF) and other inflammatory factors [1,6,7] are the current treatments of choice for ME due to CRVO. Two different anti-VEGF drugs (Ranibizumab and Aflibercept), and a biodegradable dexamethasone implant are approved by the EMA [8]. Based on data from confirmatory studies anti-VEGF-drugs are recommended as a treatment of first choice in patients with RVO [9]. The LEAVO Study showed that Aflibercept is noninferior to Ranibizumab. Since Ranibizumab was used in the proof of concept study (CoRaLa I) [10] for the treatment of macular edema, this drug is also used in the multicentre confirmatory study CoRaLa II. All intravitreal drugs provide only a temporary effect with need for re-treatment for recurrences of ME. Mean number of Ranibizumab application needed in CRVO patients was found to be 7.4 to 10.2 injections in 12 months [1,7,9,10]. A significant number of CRVO patients require treatment over several years. Need for repetitive treatments and ophthalmic controls are a major burden for patients (and their relatives who are required for driving the patients to ophthalmologists) despite of only few adverse events and generally well-tolerated injections. Endophthalmitis is the most severe ocular complication which can be eye-sight-threatening. Each injection of anti-VEGF agents such as bevacizumab, ranibizumab, or aflibercept carries a small associated risk of endophthalmitis with a reported incidence of endophthalmitis after anti-VEGF injection between 0.01 and 0.32% [11–17]. The more injections are administered, the higher is the cumulative risk of complications. Due to high costs (>1000 € per injection) treatment with repeated injections over years is of significant socio-economic importance, too. Therefore, treatments concepts which would lead to permanent reduction of ME and/or significantly reduce the number of re-injections over long-term periods are the major currently unmet need in patients with RVO.

Until now, several studies evaluated the impact of the additional pan-retinal laser photocoagulation in patients undergoing the anti-VEGF treatment for the ME due to retinal vein occlusions. However, most of the studies are limited by retrospective design, small number of evaluated patients or lack of the randomisation. None of the available prospective randomized studies had sufficient power to finally clarify the benefit of the additional laser treatment [18–21]. Therefore, there is an unmet need for a large randomized, prospective, multicentric trial.

The proposed study is the first sufficiently powered trial evaluating the long-term effect of targeted laser photocoagulation performed selectively (targeted) in peripheral areas of non-perfusion in combination with standard anti-VEGF treatment (Ranibizumab injections) on the duration of the required intravitreal treatment over time period of 2 years.

Clinical impact: In our randomized proof of concept study (CoRaLa I) [10] we observed faster and more pronounced reduction of ME in patients treated with additional targeted laser (RL arm) compared to patients treated with Ranibizumab only (R-only arm). Gain in visual acuity (VA) and reduction of number of required Ranibizumab injections were observed. After the end of CoRaLa I patients continued their therapy in our department and if ME recurred were retreated and/or switched to Aflibercept and/or dexamethasone implant in single cases. The most recent analysis of long-term courses with 66 [39.5; 87] months of observation (median [1st; 3rd quartile]), and injections if indicated showed a major difference in total numbers of patients who are still under treatment for recurrent ME (1/10 vs 7/12). The total numbers of required re-injections of treatment within 2 years of observation resulted in [(mean(SD)] 18 (7.8) in R-only vs. 9 (6.5) months in RL group. Analysis of changes of the best-corrected visual acuity (BCVA) showed a significant difference between experimental and control group. Patients from the RL group, who received the early targeted photocoagulation, maintained the visual gain over long observational time, however the patients from the control group presented slow but progressive decrease of BCVA after finished first year of the study (see fig. 1).

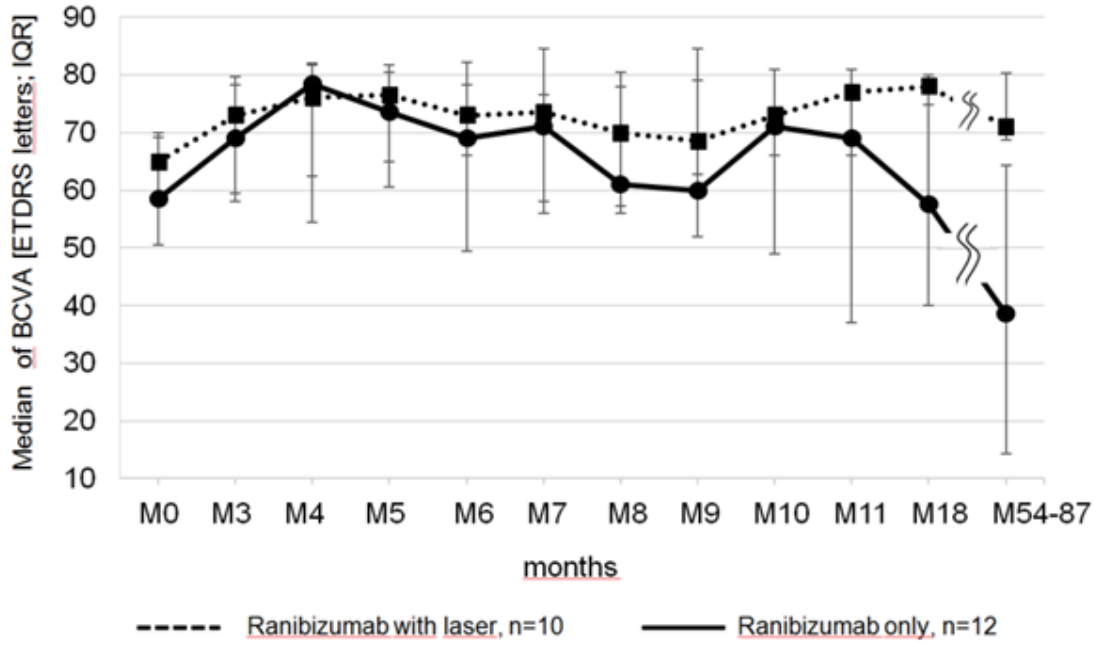


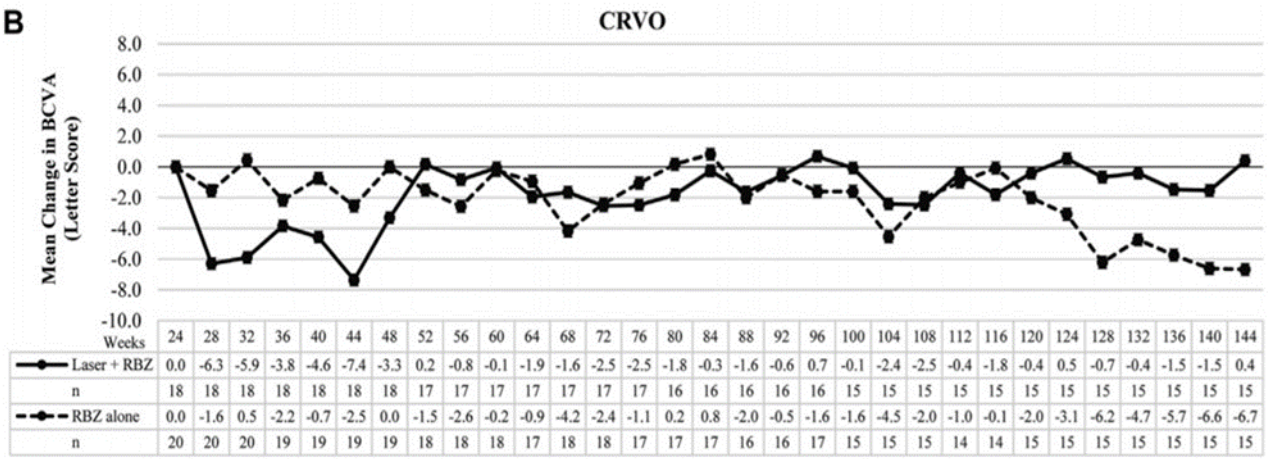
Fig. 1: Median of BCVA (in ETDRS letters) in experimental and control group of CoRaLa I trial with long-time follow-up (54 to 87 months) after baseline (data submitted)

All patients of the R-only group received the laser treatment after the termination of the CoRaLa I study (after month 12). However, this late treatment did not seem to improve the final results. It could be speculated, that the timing of the laser photocoagulation might be an important factor influencing the effect of this additional treatment. Hypothesis that only early laser photocoagulation improves the final results of the anti-VEGF treatment in CRVO patients may be supported by observations of Spaide [22], who evaluated the effect of non-selective laser treatment of peripheral retinal non-perfusion after the initial six monthly Ranibizumab injections were given prior to enrolment into the study (N=22).

The study showed a weak descriptive decrease of BCVA from 54.2(±10.7) to 51.4(±18.8) ETDRS ([means (SD)]; although accompanied by relevant heterogeneity) and no significant difference in the number of Ranibizumab injection during 6 months before and after the photocoagulation (3.4 vs. 3.1 injections). However, 17 of 22 patients in the study had a history of previous intravitreal steroids or of anti-VEGF injections [22].

In the CoRaLa I study we enrolled treatment-naive patients in whom an early selective photocoagulation of peripheral areas of nonperfusion was performed. Recently, further studies described results which are in line with the observations of the CoRaLa I [20,21]. In prospective non-randomized trial Tultseva et al. [20] showed a significantly smaller number of required Ranibizumab injections in CRVO patients treated additionally with scatter laser photocoagulation of peripheral ischemic retina during 24-28 months of trial duration when compared to control group treated with Ranibizumab only [3.5(±1.6) vs 10.6(±2.5) Ranibizumab injections respectively].

Results of the WAVE [18] and RELATE [19] trials which concluded that peripheral laser photocoagulation does not improve final BCVA in RVO patients need to be interpreted with caution. The WAVE study evaluated the effect of target laser photocoagulation in 30 patients, however the laser treated group of 24 eyes included central and branch vein occlusions together and was compared to 6 controls only [18]. The RELATE trial primarily focused on effects of different Ranibizumab concentrations. The effect of additional laser photocoagulation was evaluated in a small subgroup of 38 CRVO patients only. In 18 patients a non-selective pan-retinal scatter laser photocoagulation was performed after 6 months of monthly repetitive Ranibizumab injections [19] - a relevant deviation from the CoRaLa I strategy in our opinion. Furthermore, a cognizable between-group difference in changes of BCVA at week 144 in favour of laser treatment (group means +0.4(±4.3) vs. -6,7(±3.7) ETDRS letters in monotherapy arm – Fig. 2) was observed.



Weeks	24	28	32	36	40	44	48	52	56	60	64	68	72	76	80	84	88	92	96	100	104	108	112	116	120	124	128	132	136	140	144
Laser + RBZ	0.0	-6.3	-5.9	-3.8	-4.6	-7.4	-3.3	0.2	-0.8	-0.1	-1.9	-1.6	-2.5	-2.5	-1.8	-0.3	-1.6	-0.6	0.7	-0.1	-2.4	-2.5	-0.4	-1.8	-0.4	0.5	-0.7	-0.4	-1.5	-1.5	0.4
n	18	18	18	18	18	18	18	17	17	17	17	17	17	17	16	16	16	16	16	15	15	15	15	15	15	15	15	15	15	15	15
RBZ alone	0.0	-1.6	0.5	-2.2	-0.7	-2.5	0.0	-1.5	-2.6	-0.2	-0.9	-4.2	-2.4	-1.1	0.2	0.8	-2.0	-0.5	-1.6	-1.6	-4.5	-2.0	-1.0	-0.1	-2.0	-3.1	-6.2	-4.7	-5.7	-6.6	-6.7
n	20	20	20	19	19	19	19	18	18	18	17	18	18	17	17	17	16	16	17	15	15	15	14	14	15	15	15	15	15	15	15

Fig. 2: The results of the RELATE trial [19] showing the difference in the development of the BCVA in the 3rd year of the study (after week 120). Patients treated with anti-VEGF with additional laser photocoagulation maintained their vision (within ±2 ETDRS letters), however patients treated with Ranibizumab only showed a decrease of BCVA (-6,7 ETDRS letters).

The authors of RELATE concluded that laser treatment does not improve BCVA and is not needed [19]. In contrast we think that the statistical power of the study was too low for such a conclusion. In the RELATE trial the observed between-groups long-term difference in BCVA suggests a laser related benefit which corresponds with the long-term observation of the CoRaLa I study. Against this background we regard it promising to replicate the question addressed within a large enough superiority trial to reach sufficient power for confirmatory

conclusions. Only in this way the expected benefit of additional target laser treatment in CRVO patients can be finally clarified.

Patient benefit: Based on the long-term observation after CoRaLa I study an importantly shorter duration of treatment and a relevant reduction of the total number of re-injections in RL patients is expected in comparison to R-only patients.

The long-term results of anti-VEGF therapy in usual care showed that CRVO patients require the intravitreal injection even in a 3rd year of the treatment [15]. In the RETAIN [23] study, the number of given Ranibizumab injections was 8.0; 4.5; 3.6; 3.4 in the 1st; 2nd; 3rd; and 4th year of the treatment (presented without SD), respectively. Therefore, a reduction of required re-injections as observed in the CoRaLa I trial would decrease the burden of treatment for the individual patient. Furthermore, improved final visual acuity is expected in patients undergoing the laser treatment, which may preserve the reading/ driving ability and improve the quality of life (QoL) compared to the R-only arm.

Socioeconomic impact: The intravitreal injections represent a cost-intensive treatment. For a single application the reimbursement costs are ≈190€ per application (procedure) plus ≈900-1000€ for the drug (following EBM="Einheitliche Bewertungsmaßstab"). Therefore, the reduction of needed re-injections will lead to significant savings of total treatment costs for the health insurance companies/health care system. The need for the follow-up investigations after applications by retinal specialists and general ophthalmologists will also decrease.

1.2 Rationale

1.2.1 Hypothesis and Experimental Aspects of the Clinical Trial

Long-term data of the clinical trial [10] suggest that more than 50% of the patients with R-only, but only a small percentage of RL patients needed treatment beyond 2 years. In fact, in 9/10 patients of experimental group (R+L) treatment was stopped after only 11 months without relapse. The reduction of re-treatments would decrease the burden of treatment for the single patient. Furthermore, improved final visual acuity is expected in patients undergoing the laser treatment, which may preserve the reading/ driving ability and improve the quality of life (QoL) compared to the R-only arm. This forms the rationale for the planned study in which the hypothesis will be tested.

Intravitreal injection of Ranibizumab will be applied in all patients in the CoRaLa II trial (chap.6.3). The experimental group receives additional targeted laser photocoagulation of the peripheral areas of capillary non-perfusion (up to 4 laser treatments if indicated within 1st year of the study). No further additional treatments in study eye will be given in any of the arms of the trial.

To assess a treatment success meaning the time point when 6 months without any further need of injections is stated (based on the predefined criteria) all patients will be seen monthly at the trial site during the first year.

In patients with treatment success within the first trial year, these patients will be followed at "mandatory visits" only.

In the second year, patients who are free of intravitreal treatment ≥ 2 months will be seen bi-monthly. If the treatment interval is < 2 months, the patients will be followed monthly until the treatment success has been reached or treatment interval is ≥ 2 months for at least 2 consecutive injections.

After stating success of treatment (treatment-free interval ≥ 6 months) all patients will be seen at all “mandatory visits” later on in the course of trial. These visits are planned at month 16, 20, 24 and 29. For all patients without earlier “success” last possible Ranibizumab injection within the trial is at month 23 (End of treatment; EoT). Patients, who required further treatment will be treated after month 23 out of trial. All patients will be asked to come for the observational visit at month 29 to assess visual acuity, retinal thickness, the (latest) success possible, and to document the potential late relapses of the edema, which required the treatment out of the trial.

1.3 Risk-Benefit Considerations

The treatment with Ranibizumab in the control group, as well as in the experimental *group* are standard therapies, described in German treatment strategies [5]. Standard care will follow defined re-treatment criteria for Ranibizumab injections according to guidelines [1] .

Laser photocoagulation of the retina is well established treatment technique for ischemic retinal disorders as diabetic retinopathy or retinal vein occlusions. Since decades, panretinal (scatter) laser photocoagulation is used for treatment of the neovascular complications as e.g. vitreous bleeding, neovascular glaucoma or tractive retinal detachment. However, the Central Vein Occlusion Study Group did not find any significant benefit of profilactic panretinal (non-selective) scatter laser photocoagulation in patients with ischemic CRVO [24]. This study focused on ischemic cases only, which have a poor natural prognosis and did not evaluated the visual acuity. Therefore, the implication of these results for current treatment strategy is strongly limited.

Since no established evidence exists on potential benefits of laser therapy as add-on-treatment to usual care (Ranibizumab injections) randomized treatment allocation appears justified.

Intravitreal (IVT) injection of Ranibizumab used in this study will be given according to the label and follow the German treatment strategies [5]. The most serious possible risks of IVT are endophthalmitis and retinal detachment.

The possible risks and side events after retinal laser photocoagulation are the local pain, and temporary increased intraocular pressure. Late side effect of this treatment may be defects in the visual field. In the CoRaLa II trial, the laser photocoagulation will be performed targeted in non-perfused retinal areas only and therefore it is not expected that significant defects of visual field will occur. However, the visual field will be evaluated at the beginning of maintenance phase at month 4 and at end of study to confirm this expectation.

It is expected that the total amount of required IVT can be reduced in the experimental group (combined treatment Ranibizumab and selective laser) compared with controls (Ranibizumab only).

Patients who develop neovascularization of the retina or in the anterior segment (rubeosis iridis) will be withdrawn from the study and receive a rescue panretinal laser photocoagulation (PRP) as a full scatter.

2 Objectives

2.1 Primary Objective

The primary objective is to evaluate whether or not the duration of guideline-conform [1] periodic ranibizumab injections may be shortened or even be successfully terminated in

patients with macular edema due to central retinal vein occlusion if early targeted peripheral laser photocoagulation is applied in parallel.

2.2 Secondary Objectives

Secondary objectives are to evaluate the visual acuity during and after the course of intervention, quality of life associated aspects and possible problems which might possibly be associated with the trial's intervention.

Secondary endpoints (sEP) are:

- the best corrected visual acuity (BCVA)
- central subfield thickness (CST)
- the number of ranibizumab injections required until treatment success and up to the end of observation.

Complementary outcomes of interest are:

- the proportion of subjects developing neovascularization(s) over total observation period.
- health-related quality of life (HrQoL)
- the area of non-perfusion
- vessel density & areal of fovelar avascular zone
- potential visual field loss
- development of collaterals
- the number of laser treatments and the laser spots given in the experimental group (RL-arm)

Furthermore, the safety profile of the combined intervention will be compared to that of the guideline-based standard intervention in terms of (S)AEs/(S)ARs occurrence until 4 weeks after the last trial-related intervention. Critical ocular events will be evaluated until the end of study.

3 Trial design and description

3.1 Trial Design

The trial is a multi-centric, prospective, randomized, interventional, clinical trial with two parallel groups, phase IIIb and randomisation ratio of 1:1. Basic treatment for all patients (of control/R-only and experimental/ RL group) consists of three monthly intravitreal injections (0.5 mg Ranibizumab). Thereafter, up to 20 further injections if indicated by pre-defined criteria (in pro re nata (PRN) regimen as described in chapter 6.3 "Description of the Treatment Procedures") until month 23 may be applied (maintenance phase).

Experimental/RL group: During the first year of the study the targeted laser photocoagulation will be performed successively up to 4 times (as accessible after resolution of the retinal haemorrhages) along with Ranibizumab injections. It will be restricted to peripheral retinal areas of capillary non-perfusion (detected by ultra-wide field fluorescein angiography [FA]) outside the macula. Control fluorescein angiography (FA) is scheduled at month 3 and 9. If new areas of capillary non-perfusion will be detected, further targeted laser photocoagulation will be performed.

3.2 Requirements at the Trial Sites regarding Personnel and Equipment

3.2.1 Qualification of investigator and medical staff in the study team

The trial will be performed as multicentric study coordinated by Prof. MUDr. Matus Rehak of the Department of Ophthalmology, Justus-Liebig University, Gießen.

Qualification of investigator/deputy and medical staff in the trial team

This chapter defines general requirements for trial staff in the CoRaLa II trial as required by GCP. Trial specific and/or national requirements regarding the qualification of the trial sites and trial staff are specified in the qualification documents used for application to the institutional review board and/or responsible authorities in more detail.

Coordinating Investigator/Principal Investigator

The **coordinating investigator in multicentre trials** and his deputy are licenced to practice medicine, are medical specialists and have at least two years of working experience in the study specific indication. They have theoretical and practical experience in conducting clinical trials.

Principle Investigator/ Investigator

Principal Investigator and Investigators are licenced to practice medicine and are medical specialists in ophthalmology and have experience in the treatment of macular edema due to central retinal vein occlusion.

The Investigator is responsible for selecting and assembling the trial team members (especially the medical staff) according to the requirements of this trial protocol and the specifications in the qualifications documents the sponsor will provide to each trial site. Furthermore, the investigator is responsible for training and supervision of the trial team and providing all necessary information during the course of the trial. This has to be documented accordingly.

All sites will appoint **a blinded BCVA assessor**, who will perform the assessment of BCVA investigation.

3.2.2 Required Equipment

All participating centres are established, well experienced study sites with a long tradition of participation on clinical trials. All centres provide the necessary equipment required as ETDRS charts, slit lamps, applanation tonometry, ultra wide-field fundus photography and angiography devices as well as OCT and OCT-angiography devices to carry out the CoRaLa II study.

A Central Reading Center (“CoRaLa II Reading Center”) of experienced ophthalmologists will review colour fundus images, and FA images from all patients. Two independent readers will independently define the areas of capillary non-perfusion as a target for the laser photocoagulation, which will be performed in each study side according to the standardized protocol. In the case of differences of opinion between two grades a third one will perform an additional independent grading. A consented plan will be transferred to the patient´s site and recommend on details of the laser treatment (see chapter 12). Additionally the OCT-scans from all visits will be transferred to the CoRaLa II Reading Center for the evaluation and statistical analysis of the CST values, according to the imaging protocol.

3.3 Trial Sites and Number of Trial Subjects

13 trial sites participate into the study at the time of the amendment. If necessary further sites

may be approached in case of too slow recruitment.

The assumptions concerning the number of patients needed, is described in chapter 8.4. “Sample Size Discussion”:

- to be assessed for eligibility: 130
- to be allocated to trial: 110
- to be analysed: 110

3.4 Expected Duration of Trial

Recruitment started with the initiation of the first trial site in August 2020 and will stop after the planned recruitment period (30 months) and/or number of patients is reached.

Start of the study is defined as date of the first randomisation. End of study correlates to last patient last visit/last patient out (LPLV/LPO).

First patient in to last patient out (months): 59

Duration of the entire trial (months): 72

Recruitment period (months): 30

Treatment period (months per patient): **23** months treatment and 6 months follow-up

Total Duration per patient (observation period): up to 29 months (for primary endpoint)

3.5 Premature Termination of the Trial

3.5.1 Termination of the Trial at a Single Site

The trial can be aborted at a single site if

- the protocol is not adhered to,
- the quality of data is deficient,
- there is inadequate recruitment.

The coordinating investigator decides whether or not to exclude the site, together with biometrician if appropriate.

Investigators and sites no longer participating in the trial must inform the coordinating investigator immediately and should provide justification for the decision. Further treatment of patients still involved in the study is to be arranged together with the coordinating investigator.

3.5.2 Termination of the Whole Trial or of Individual Arms of the Trial

The trial can be terminated prematurely by the coordinating investigator in the event of

- marked increase of clinical events in the experimental arm
- changes in the risk-benefit considerations, e.g. as a result of unexpected adverse events
- new insights from other trials
- an insufficient recruitment rate.

The final decision regarding the premature termination of the trial will be made by the coordinating investigator based on recommendations of the DSMB and the biometrician.

4 TRIAL SUBJECTS

4.1 Inclusion Criteria

Patients must meet ALL of the following 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 78 letters (20/25) measured in ETDRS chart
5. History of CRVO no longer than 6 months
6. Presence of capillary non-perfusion in peripheral retina larger than 5 disc areas documented in ultra wide-field fluorescein angiography
7. Ability and willingness to attend all scheduled visits and assessments

Only one eye per subject will be enrolled in the study. For subjects who meet eligibility criteria in both eyes, the eye with the worst visual acuity will be selected as the study eye. If both eyes have equal visual acuity, the eye with the greater central retinal thickness will be designated as the study eye.

If a subject fails screening (i.e. does not meet all inclusion criteria or meets one or more of the exclusion criteria), the subject can be re-screened once, if the reason(s) for the screening failure is (are) resolved.

4.2 Exclusion Criteria

Patients will be excluded for ANY ONE of the following reasons:

1. CRVO with ischemic maculopathy defined as diameter of the foveolar avascular zone larger than 2 optic disc diameters
2. Macular edema due to another etiology than retinal vein occlusion (e.g. diabetic maculopathy, uveitis, age related macular degeneration, Irvine-Gass syndrome)
3. History of idiopathic central serous chorioretinopathy
4. Presence of vitreoretinal interface disease (e.g. vitreomacular traction, epiretinal membrane), either on clinical examination or in OCT
5. 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
6. Aphakia in the study eye
7. Scatter laser photocoagulation or macular photocoagulation in the study eye prior to study entry
8. Intraocular or periocular injection of steroids in the study eye prior to study entry
9. Previous use of an anti-VEGF drug in the study eye
10. Cataract surgery or any other intraocular surgery in the study eye within 3 months prior to study entry
11. Uncontrolled glaucoma (defined as intraocular pressure ≥ 30 mm Hg despite treatment with maximal anti-glaucoma medications)
12. History of stroke, myocardial infarction, transient ischemic attacks within 3 months prior to the study
13. Pregnancy (positive urine pregnancy test) or lactation

14. The presence of active malignancy, including lymphoproliferative disorders.
15. History of allergy to fluorescein or any component of the ranibizumab formulation
16. Active intraocular infection
17. Participation in another simultaneous interventional medical investigation or trial
18. 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.

4.3 Justification for the Inclusion of vulnerable populations

This clinical trial will not include particularly vulnerable individuals as defined by § 40 chapter 4 and § 41 chapters 2 and 3 AMG.

4.4 Participation in more than one Clinical Trial

During the verification of the inclusion and exclusion criteria the investigator/his deputy or authorised medical staff of the trial team checks if the patient is currently participating in any other interventional clinical trial(s). Should this be the case, the patient will not be included.

Moreover, by signing the informed consent form, the patient confirms that he is not participating in any other interventional clinical trial simultaneously.

4.5 Statement on the Inclusion of Dependent Individuals

During the screening procedure, all patients will be interviewed concerning any potential relationship to the investigator/ his deputy or to medical staff of the trial team or the coordinating investigator or the sponsor.

In case of a potential benefit of the trial for the patient he should not be excluded from the trial, if any dependency exist, the patient cannot be included by the person he is dependent on.

4.6 Rationale for Gender Distribution

A difference of the prevalence for CRVO depending on the patient’s gender is not expected and therefore not considered in this study.

5 Investigational Product

5.1 Trial Drug

Commercially available, approved medication will be used. According to § 42 AMG and § 5 GCP-V, a special labelling for the trial is not necessary.

Documentation permitting the traceability and identification of the medication used in the clinical trial will track the correct administration of the medication as part of the eCRF, guaranteeing participants' safety (e. g. in case of IMP recalls).

Generic Name:	Ranibizumab
Trade Names and manufacturer:	e.g. Lucentis®
Drug allocation:	Supplied by the pharmacies at the trial sites
Potency, Dosage Form	0.5 mg Ranibizumab (labelled as 2.3 mg/ 0.23ml)
Packaging:	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 will be administered after withdrawn to a syringe as intravitreal injection. The vial contains no preservative and is suitable for single use only.
Storage conditions:	Exposure of the material to temperatures outside the range of 2-8 °C, except for warming prior to administration, is not recommended and may result in loss of activity.
Preventive measures/Incompatibility:	**For further information, please refer to the SmPC of Ranibizumab.**

5.2 Drug Accountability

Ranibizumab is part of the routine treatment of patients with CRVO according to current guidelines. Thus, the IMP will be prescribed according to local practice and received from the pharmacy of the treating institution.

For a comprehensive documentation of the used IMP, the eCRF will contain data regarding drug application for each patient:

- date and time of application start
- number of applied Ranibizumab injections (as described in chapter 9.5.2).

5.3 Administration of Trial Drug

5.3.1 Procedures

The study drug will be prepared at the study site by an individual qualified to prepare the drug for IVT injection. The intravitreal injection will be done by experienced study physicians in line with national recommendation for IVT application [25,26].

Treatment with IVT injections of Ranibizumab 0.5 mg is initiated with a fixed loading phase of one injection per month for three consecutive months. Further treatment with Ranibizumab will be performed according to treatment guidelines if re-treatment criteria are identified.

5.3.2 Compliance

Study interventions will be administered on the study site; therefore, compliance with the dosing of study drug will be monitored by a review of clinical records.

5.3.3 Dealing with Side-effects

The most common side effects of Ranibizumab (seen in more than 1 in 10 patients) are increased intraocular pressure, headache, vitritis, retinal haemorrhage, visual disturbance, eye pain, vitreous floaters, conjunctival haemorrhage, eye irritation, sensation of a foreign body in the eye, increased lacrimation, blepharitis, dry eye, ocular hyperaemia, eye pruritis, arthralgia and nasopharyngitis. For the full list of all side effects reported for Ranibizumab, see the prescribing information.

Rarely, endophthalmitis, serious eye inflammation, damage to the retina and cataract can occur after treatment with Ranibizumab. It is important to treat these problems as soon as possible. Their symptoms and instructions about what to do if a patient suffers from them are explained in the prescribing information.

Ranibizumab must not be used in patients who are hypersensitive (allergic) to Ranibizumab or any of the other ingredients. It must not be used in patients who may have an infection of the eye or the area around the eye, or who have severe inflammation within the eye.

5.3.4 Alternative Medication

Patients may not receive any treatment (approved or investigational) for their CRVO in the study eye other than the study treatment with Ranibizumab. Patients without response to Ranibizumab will be switched to an alternative intravitreal drug (Aflibercept or Dexamethasone implant), which will be given out of the study (see chapter 6.5).

5.3.5 Counterindicated/Forbidden Concomitant Medication

Drug interaction studies have not been conducted with Ranibizumab.

5.3.6 Overdose and Abuse

The study drug will be prepared and administered at the trial sites by an individual qualified to prepare and apply the drug for the intravitreal injection. The overdose or abuse of the study drug is not possible.

5.4 Laser Photocoagulation

The laser photocoagulation is a well-known and established therapy for ischemic complications of retinal vein occlusions and will be applied in accordance with its specific medical purpose.

The experimental group will receive additionally to the Ranibizumab therapy a targeted laser photocoagulation of the peripheral areas of capillary non-perfusion (up to 4 laser treatments within 1st year of the study). Based on the FA images evaluated by the grades of the CoRaLa II

Central Reading Center, who will identify and mark the areas of non-perfusion for the target laser photocoagulation, the 1st laser treatment could be applied at month 2 after randomisation. Re-treatment criteria for laser coagulation are new areas of capillary non-perfusion detected with fundus photography and FA at 3 and 9 months after randomisation. Further laser coagulation will be performed if needed at Months 4, 6 and 10.

Laser photocoagulation using green argon laser (532 nm) or a yellow Laser (577 nm) is applied in peripheral areas of capillary non-perfusion defined by the central reading center. The laser treatment could be performed on the same day as the Ranibizumab injection. In this case the laser needs to be done previously to the intravitreal injection.

The laser photocoagulation will be performed after topical anaesthesia using a Wide-Field-Contact-Lens, and with following specification: spot size of 300-400µm; time of exposition: 0.1-0.2 s; burns spaced about one half burn apart; the starting energy of 80 mW is increased by 25 mW until a grey-white burn of gentle intensity is produced. The number of laser treatments depends on the area of ischemic retina and presence of retinal hemorrhages. As large retinal hemorrhages do not allow the assessment of the perfusion status and make photocoagulation impossible, no laser treatment will be done in these areas. The resorption of the hemorrhages will have to be awaited for and a reassessment will be done by FA at months 3 and 9. As mentioned above, the newly detected areas of non-perfusion will be photocoagulated at months 4, 6 and 10. No laser photocoagulation will be performed in the central retinal area (inside the vessels arcades).

5.4.1 Side effect of laser photocoagulation

Possible side effects of laser photocoagulation are: subjective pain during the treatment, transient increase of intraocular pressure and development of extensive retinal scars in the areas of laser spots. If large retinal areas are involved, this could lead to the impairment in the visual field. A rare complication after laser photocoagulation is the development of macular pucker leading to macular edema and decrease of visual acuity. The treatment of this complication (in case of significant visual impairment) is the vitrectomy with peeling of pucker membrane.

6 INDIVIDUAL TRIAL PROCEDURES

6.1 Patient Information and Informed Consent

An authorised trial physician will seek the patient’s consent before performing any trial specific medical procedures with the patient. Patients who are considered not competent to consent to participate, e.g. due to an insufficient level of understanding, cannot participate in the trial.

In accordance with international guidelines, the informed consent of trial participants will be in writing (written, dated and signed by the person performing the interview referred to below, and by the subject).

The patient’s consent must refer explicitly to the collection and processing of health-related data. Therefore, the patient should be informed explicitly about the purpose of collecting the data and scope of what is to be collected and that personal data, including health related data, will be stored and used for analyses in a pseudonymized form.

Before obtaining informed consent, the potential trial participant will receive information regarding the clinical trial in an interview. It will be performed by a qualified medical member of the trial group authorised by the investigator for this task.

The interview has to cover the following items:

- the nature, objectives, benefits, implications, risks and potential inconveniences of the clinical trial
- the expected duration of the subject's participation in the clinical trial
- the information that the patient may withdraw his consent to participate at any time without giving reasons. The patient is to be informed that in case of revocation of his consent, the stored data may be used further, as may be necessary to
    - assess effects of the medicinal product being tested,
    - guarantee that the patient’s personal interests are not adversely affected,
    - comply with the requirement to provide complete authorisation documentation.
- potential treatment alternatives
- follow-up measures in case of early termination of the trial for the patient or overall
- the applicable damage compensation system in case of damage to a patient
- the right on data access, rectification and withdrawal of personal data

The subject will have the opportunity to ask questions at any moment.

Adequate time will be provided for the subject to consider his or her decision.

6.1.1 Withdrawal of Informed Consent

Patients may withdraw their consent to participate at any time without giving reasons. Nevertheless, the patient should be asked for the reason of the premature termination after being informed that he does not need to do so. Information as to when and why a patient was registered/ randomised and when he withdrew consent must be retained in the documentation.

The patient is to be informed that in case of revocation of his consent, the stored data may be used further (according to § 40 lit 2a sublit 3 to 5 German Medicinal Products Act), as may be necessary to

- assess effects of the combination of the laser and drug being tested,
- guarantee that the patient’s personal interests are not affected adversely,
- comply with the requirement to provide complete authorisation documentation.

Data no longer required for the aforementioned purposes shall be deleted immediately.

6.2 Enrolment in the Trial

All patients with suspected CRVO attending one of the participating trial sites will be screened for eligibility. If a patient fails screening, i.e., does not meet all inclusion criteria or meets one or more of the exclusion criteria, the patient can be re-screened within 30 days once, if the reason(s) for the screening failure is (are) resolved.

If all inclusion criteria and no exclusion criteria apply and the patient provides written informed consent, a web-based randomisation (Day -14 to 0) will be performed and the patient will be assigned to a treatment arm. The patient ID has to be entered in the patient identification list (PIL) in the investigator site file together with the patient‘s name and date of birth. The randomisation result will be shown online by the randomisation tool and an automatic e-mail will be sent to the trial site for filing in the investigator site file (ISF). If a trial site prefers an automatic fax, this could also be implemented.

In cases, when the randomisation cannot be performed using the internet-based tool (server shut down, internet connection blocked …), the randomisation page of the eCRF can be filled in by hand and sent to the ZKS Leipzig by e-mail (scan) or fax. There will be a randomisation list at the ZKS Leipzig allowing database independent randomisation during regular office hours (Monday – Friday, between 8:00 am and 5:00 pm). After such a randomisation, the patient will be entered to the database by the ZKS Leipzig as soon as the database is functional again.

Randomisation results and allocated treatment has to be documented in the patient’s medical record.

The assessments and procedures essential for trial inclusion are described below.

6.2.1 Discovery of a Violation of the Eligibility Criteria after the Fact

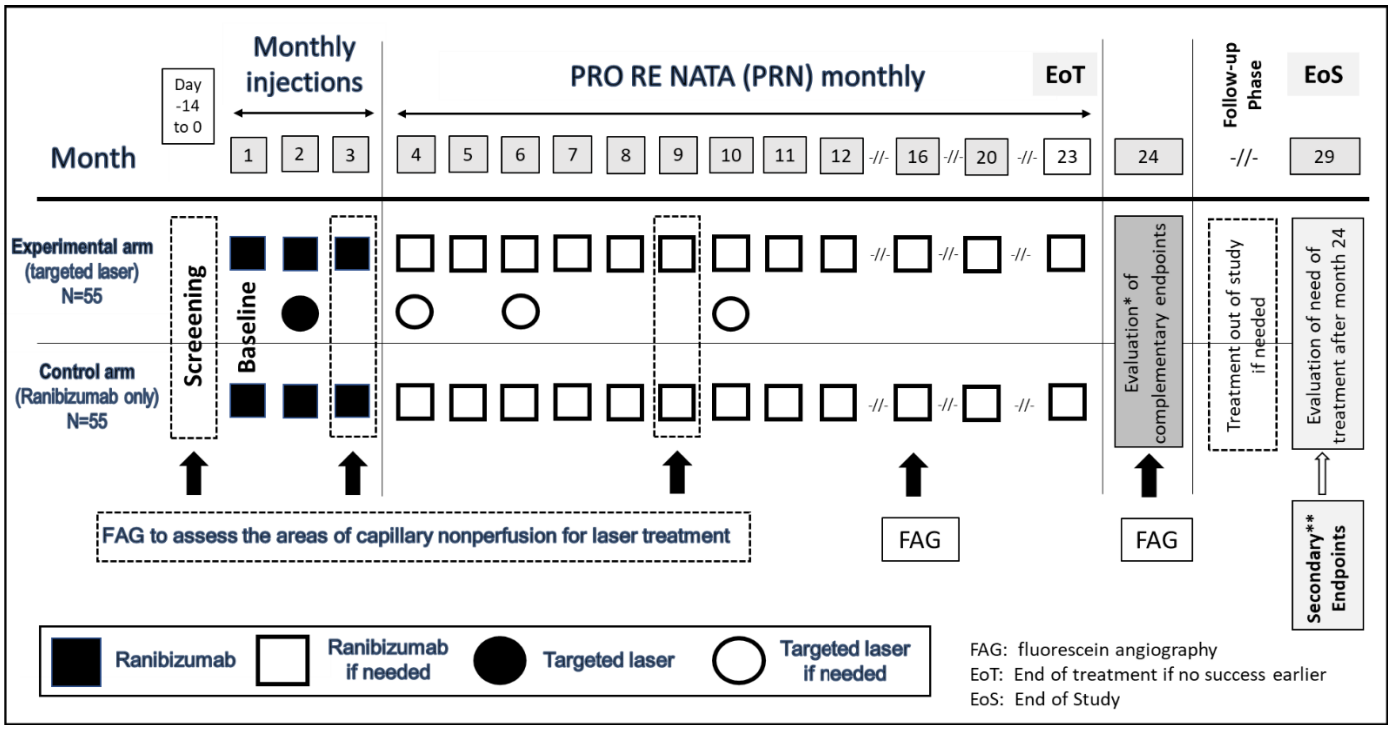
If a violation of a selection criterion is discovered after randomisation of a patient, this has to be documented in the eCRF, which will result in an automatic report to the responsible trial team members at the ZKS Leipzig.

After consultation with the coordinating investigator/biometry / project management of the ZKS Leipzig the project manager informs the investigator immediately regarding the further treatment of the patient. The patient’s data will continue to be recorded unless the patient revokes his informed consent. For procedures after premature trial termination of a single patient see chapter 6.5.

6.3 Description of the Treatment Procedures

Intravitreal injections of Ranibizumab will be applied in all patients according to treatment guidelines. The experimental group will receive an additional targeted laser photocoagulation of the peripheral areas of capillary non-perfusion (up to 4 laser treatments within 1st year of the study). No further additional treatments of the study eye will be given in any of the arms of the trial.

Intervention scheme of CoRaLa II Trial



* complementary endpoints in all patients at month 24.

** secondary endpoints in patients with success at that visit when success is stated; in patients without treatment success prior to visit 24, secondary endpoints will be assessed at month 29; if a patient needs treatment after success, this treatment is no longer a study treatment and therefore no further AE/SAE documentation is needed.

Based on the results of optical coherence tomography (OCT) the **diagnosis of ME** will be established and Ranibizumab injections will be indicated.

Pre-defined re-treatment criteria will be applied according to treatment guidelines in order to identify a further need of re-injections at the monthly visits.

Re-treatment with Ranibizumab is needed if the following criteria are met:

a) persisting ME or
b) recurrence of ME
defined as presence of intra-/sub-retinal fluid and /or central subfield thickness **(CST) of ≥250 µm** assessed by OCT

Re-treatment criteria for laser photocoagulation: new areas of capillary non-perfusion detected with fundus photography and FA at 3 and 9 months after randomisation. Experienced graders of the CoRaLa II Central Reading Center will evaluate all fundus and FA images taken with the Zeiss 700 device and define the non-perfused retinal areas for laser photocoagulation. Laser photocoagulation will be performed at Month 2 and if needed at Months 4, 6 and 10.

Parameters needed for end-point evaluations:

- Only if no ME can be identified by OCT over 6 months of follow-up **treatment success** is stated and the time until this visit will be used in confirmatory analysis.

- **The number of Ranibizumab injections** depends on the valid assessment of presence/ or absence of ME in all monthly visits and will be counted until defined success (if applicable) and at the end of study.
- **The best-corrected visual acuity (BCVA)** will be assessed in ETDRS letters. After "success" is reached (treatments free interval ≥ 6 months) all patients will be seen at "mandatory visits" only. These visits are planned at: months 1 to 12, 16, 20, 24, and 29.
- **Visual field** measures are performed at month 4 and month 24 (at both visits in both eyes).

Objective assessment BCVA investigation will be performed by blinded BCVA assessors, who are independent of decisions regarding further re-treatment or other study procedures.

- **Neovascularisations** will be identified by gonioscopy, slit lamp bio-microscopy, ophthalmoscopy and/or FAG. A single occurrence during the entire duration of observation per patient will already contribute to the rate per arm, which will be compared between groups.
- **OCT-angiography** parameters as perfusion density and size of central avascular zone measurements will be at the baseline at month 4, 12, 24 and at month 29
- Patients will complete the **QoL questionnaire** before the ophthalmologic investigation will be performed at the baseline at month 12 and at month 24. Because QoL is a complementary aspect of the trial intervention only.

It is recommended to perform the ocular assessments in the order they are listed in each visit description.
Ocular assessments at the screening visit will be performed in both the study eye and the fellow eye (exception: gonioscopy).
All other ocular assessments at all other visits will only be performed in the study eye with exception of visual field (V4 and V24) and ophthalmoscopy at V24.

⇒ **For blood pressure, OCT, OCT-A, visual field and intraocular pressure (IOP) measurements, the same method must be used for all measurements throughout the study.**

6.3.1 Screening visit (Day -14 to Day 0)

- Signed informed consent
- Medical history and ophthalmic history
- Assessment for women of childbearing potential: urine pregnancy test
- Blood pressure and pulse
- Ocular assessments (study eye and fellow eye):

  - Investigation of BCVA using ETDRS chart **performed by a blinded assessor**
  - IOP
  - Gonioscopy (exception: study eye only!)
  - Slit lamp biomicroscopy
  - OCT (in addition OCT will be evaluated by the CoRaLa II Central Reading Center)

- OCT-Angiography (in addition OCT-Angiography will be evaluated by the CoRaLa II Central Reading Center)
- Ophthalmoscopy
- Fundus photography and Fluorescein angiography (FAG) performed according to the imaging protocol and evaluated by the CoRaLa II Central Reading Center.

⇒ If all inclusion criteria and no exclusion criteria apply randomisation is performed.
⇒ **The screening visit may be performed together with Baseline Visit on the same day.**

6.3.2 Day 1 – Visit 1 (Baseline), Visit 2 (month 2 +/- 7 days) and Visit 3 (month 3 +/- 7 days)

- Blood pressure and pulse
- QoL (Visual Function Questionnaire) only at Baseline
- Documentation of Adverse events, critical ocular events and Concomitant medication
- Ocular assessment (assess prior to injection, assess in the study eye only):
  - Investigation of BCVA using ETDRS chart **performed by a blinded assessor**
  - IOP
  - Slit lamp biomicroscopy
  - OCT (in addition OCT will be evaluated by the CoRaLa II Central Reading Center)
  - Ophthalmoscopy
  - Fundus photography and Fluorescein angiography (FAG) performed according to the imaging protocol and evaluated by the CoRaLa II Central Reading Center, **only at Visit 3.**

➢ Control group:
Ranibizumab injection at Baseline, Visit 2 and Visit 3.

➢ Experimental group:
Ranibizumab injection at Baseline, Visit 2 and Visit 3.
ONLY at Visit 2 (Month 2) laser photocoagulation will be performed in the experimental arm before injection of Ranibizumab.

6.3.3 Visit 4 (month 4 +/- 7 days) Start of Maintenance dosing phase monthly Visits up to Visit 12 (month 12 +/- 7 days)

- Blood pressure and pulse

- QoL (Visual Function Questionnaire) only at Visit 12 before the ophthalmologic investigation will be performed
- Documentation of Adverse events, critical ocular events and Concomitant medication
- Ocular assessment (assess prior to injection, assess in the study eye only, see exceptions in text below):
  - Investigation of BCVA using ETDRS chart **performed by a blinded assessor**
  - IOP
  - Gonioscopy only at Visit 12
  - Slit lamp biomicroscopy
  - Visual field performed only at Visit 4 in both eyes
  - OCT (in addition OCT will be evaluated by the CoRaLa II Central Reading Center)
  - OCT-angiography only at Visit 4 and Visit 12 (in addition OCT-Angiography will be evaluated by the CoRaLa II Central Reading Center)
  - Ophthalmoscopy
  - Fundus photography and Fluorescein angiography (FAG) performed according to the imaging protocol and evaluated by the CoRaLa II Central Reading Center **only at Visit 9.**

Assesement of re-treatment criteria

- Control group and experimental group: **if re-treatment criteria are met**, then Ranibizumab injection will be performed.
- Experimental group ONLY at the Visits 4, 6 and 10 laser photocoagulation will be performed, **if required**.

6.3.4 **Visit 13** (month 13 +/- 7 days) **to Visit 23** (End of treatment) month 23 +/- 7 days)

⇒ If patient has reached already treatment success, only the mandatory study visits (16 and 20) will be performed.

⇒ If patient still needs re-injections, study visits will be performed monthly.

⇒ Patients who are free of intravitreal treatment ≥ 2 months will be seen bi-monthly.

⇒ If the treatment interval is < 2 months, the patients will be followed monthly until the treatment success has been reached or treatment interval is ≥ 2 months for at least 2 consecutive injections

Nevertheless Visits 16 and 20 are mandatory for all patients to assess endpoint- relevant parameters.

- Blood pressure and pulse
- Documentation of Adverse events, critical ocular events and Concomitant medication

- Ocular assessment (assess prior to injection, assess in the study eye only):
  - Investigation of BCVA using ETDRS chart **performed by a blinded assessor**
  - IOP
  - Slit lamp biomicroscopy
  - OCT (in addition OCT will be evaluated by the CoRaLa II Central Reading Center)
  - Ophthalmoscopy
  - Fundus photography and Fluorescein angiography performed according to the imaging protocol and evaluated by the CoRaLa II Central Reading Center **only at Visit 16.**

Assessment of re-treatment criteria,

- Control group and experimental group**: if re-treatment criteria are met**, then Ranibizumab injection will be performed.

6.3.5 Visit 24 (month 24 +/- 7 days) is a mandatory visit for all patients

Safety visit and end of (S)AE report period (4 weeks after EoT) for patients who still need monthly intravitreal injections (no success reached).

- Blood pressure and pulse
- QoL (Visual Function Questionnaire) before the ophthalmologic investigation will be performed
- Documentation of Adverse events, critical ocular events and Concomitant medication
- Ocular assessment (assess prior to injection, assess in the study eye only, see exceptions in text below):

- Investigation of BCVA using ETDRS chart **performed by a blinded assessor in both eyes**!
- IOP
- Gonioscopy
- Slit lamp biomicroscopy
- Visual field performed **in both eyes**!
- OCT **in both eyes!** (in addition OCT will be evaluated by the CoRaLa II Central Reading Center)
- OCT-Angiography **in both eyes!** (in addition OCT-Angiography will be evaluated by the CoRaLa II Central Reading Center)
- Ophthalmoscopy performed **in both eyes**!

- Fundus photography and Fluorescein angiography (FAG) **in both eyes!** performed according to the imaging protocol and evaluated by the CoRaLa II Central Reading Center.

- Documentation if an injection with Ranibizumab was needed. (Injections of Ranibizumab after Months 23 are no longer documented as study treatment.)

6.4 Follow-up Visit 25 (month 29 +/- 7 days) EoS is a mandatory visit for all patients

Ocular assessment (study eye only) providing the final assessment of all secondary endpoints and any potentially late occurrence of critical ocular events.

- Blood pressure and pulse
- Critical ocular events and Concomitant medication
- Ocular assessments in study eye only:
  - Investigation of BCVA using ETDRS chart **performed by a blinded assessor**
  - IOP
  - Slit lamp biomicroscopy
  - OCT (in addition OCT will be evaluated by the CoRaLa II Central Reading Center)
  - OCT-Angiography (in addition OCT-angiography will be evaluated by the CoRaLa II Central Reading Center)
  - Ophthalmoscopy

- Documentation how many injections with Ranibizumab were needed. (Injections of Ranibizumab after Months 23 are no longer documented as study treatment.)

6.5 Premature Termination of the Therapy and Follow-up for Individual Patients

6.5.1 Premature Termination of the Therapy for Individual Patients

Each premature termination of the trial therapy has to be documented by the responsible investigator. If possible, date, circumstances of and reason for the termination should be documented in detail and communicated to the ZKS Leipzig Data Management. Premature termination should be avoided.

The premature termination of trial therapy for an individual patient may be considered for the following aspects:

- progress of neovascular complication (Increase of NVE´s or NVD´s, neovascular glaucoma) (see rescue treatment)
- persisting macular edema without response to Ranibizumab
- protocol violations if they indicate a significant risk to the patient's safety
- non-compliance
- pregnancy

- at the discretion of the investigator
- for reasons of medical prudence based on DSMB recommendations or
- withdrawal of consent

All patients with premature therapy termination (except in case of consent withdrawal) will, however, be instructed to return for a safety follow-up visit 4 weeks after last study treatment. Further, all patients (except in case of consent withdrawal) will be offered the visit in Month 29, because at this visit the primary endpoint is documented as well as the major secondary endpoints.

6.5.2 Rescue Treatment

Patients with progress of neovascular complication (Increase of NVE´s or NVD´s, neovascular glaucoma) will receive rescue treatment with pan-retinal photocoagulation (PRP) outside the study intervention.

Patients with persisting macular edema without response to Ranibizumab will be treated with intravitreal Aflibercept (Eylea) or dexamethasone implant (Ozurdex) out of the study.

6.6 Plan for Further Treatment

In case the patients will suffer from a recurrence of macular edema with impaired BCVA after month 23 (End of treatment visit) of the study, further treatment with anti-VEGF drugs (Ranibizumab or Aflibercept) or other treatment methods (e.g. application of Dexamethasone implant = Ozurdex) will be offered depending on investigators decision.

7 METHODS OF DIAGNOSTICS AND DATA SAMPLING

⇒ **Best Corrected Visual Acuity (BCVA)**

BCVA of the study eye (at screening performed in both eyes) will be assessed using the ETDRS chart (The Early Treatment Diabetic Retinopathy Study Group, 1985). The BCVA examiner will remain blinded to treatment allocation of a patient. A detailed protocol for conducting BCVA testing and refraction will be filed in the investigator site file. BCVA will be performed at all study visits.

⇒ **Central subfield thickness (CST) measured by Optical Coherence Tomography (OCT)**

Macular edema characteristics will be evaluated using OCT. All OCT images will be captured using the spectral domain (SD) OCT device and will be electronically archived. To ensure consistency and quality in image acquisition only experienced technicians will perform the OCT investigation using dense volume scans. OCT will be done at every study visit. A detailed protocol for OCT capturing and data transfer will be filed in the investigator site file. The measurement of the central subfield thickness (CST) and the total macular volume will be done by the CoRaLa II Central Reading Center.

⇒ **Vessel Density (VD) and area of foveal avascular zone (FAZ) measured by Optical Coherence Tomography Angiography (OCT-A) – complementary outcomes**

OCT-A imaging was performed after pupil dilatation. The same OCT-A device will be used for all single patients over all study visits. The macula will be imaged using 6×6 mm2 scans. Additionally, peripheral OCT-A scans will be captured, too. A detailed protocol for OCT-A imaging will be filed in the investigator site file. The captured scans will be transferred to the CoRaLa II Central Reading Center, which will analyse the segmentation quality and measure the VD and the area of the foveal avascular zone (FAZ) in the superficial and deep vascular plexus.

⇒ **Peripheral Areas of non-perfusion (pANP – complementary outcome)**

Peripheral areas of non-perfusion will be measured by CoRaLa II Central Reading Center using the early stages of the FA images (arterial phase) captured by Clarus 700 device. The entire area will be measured in mm^2 using the device internal software based or the ratio of the peripheral non-perfusion to the area of the optic disc. Further, Greatest line dimension (GLD) of horizontal and vertical reference area (optic disc) will be calculated to ensure a valid assessment of area measurements over all measures performed in the course.

⇒ **Defects of peripheral Visual fields (VF – complementary outcome)**

The visual field defects will be captured by assessing the retinal sensitivities of various points in the mid-peripheral and peripheral visual fields at month 4 and 24 in both eyes. Eyes with excessive false positive response or excessive fixation loss will be excluded from analysis.

A false positive response is defined as a response to a false positive test, i.e. a projector movement (or other external stimulus) when no stimulus is presented. Excessive false positive response is defined as [(# false positive responses) ÷ (# false positive tests)] *100 >33%.

A fixation loss is defined as a response to a fixation loss test, i.e. a stimulus presented to the blind spot. Excessive fixation loss was defined as [(# fixation losses) ÷ (# fixation loss tests)]*100 > 33%. Outlying values will be truncated at ±3 standard deviation from the mean to minimize the effect of potential outliers.

⇒ **Number of Ranibizumab injections**

All patients will receive 3 intraocular injections. The application of further injections is guided by standardized retreatment criteria. The number of injections required will be recorded for every patient.

⇒ **The progression to neovascularization of the retina or anterior segment**

Patients will be evaluated for the development of neovascularization of the iridocorneal angle by gonioscopy in conjunction with slit lamp biomicroscopy at screening visit and further at month 12 and 24. The examination should be performed after OCT and before funduscopy, fundus photography, and fluorescein angiography.

All patients will be investigated for the development of neovascularization of the optic disc or of the retina elsewhere by ophthalmoscopy in mydriasis at every visit. The presence of neovascularization will be documented by fundus photography. If suspected lesion could not be surely distinguished between neovascularization or shunt vessels by ophthalmoscopy, a fluorescein angiography will be performed.

Patients in whom a neovascularization will be found will undergo panretinal scatter laser photocoagulation as a rescue treatment according the recommendations of CRVO study group [24].

8 ADVERSE EVENTS (AE/SAE)

8.1 Adverse Events

8.1.1 Definition AE

An Adverse Event is any untoward medical occurrence in a patient or clinical investigation subject administered a pharmaceutical product and which does not necessarily have to have a causal relationship with this treatment.

An Adverse Event (AE) can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medicinal product and/or laser treatment, whether or not considered related to the medicinal product. (ICH Guideline E2A).

8.1.2 Adverse Drug Reaction (ADR)

An adverse drug reaction of a medicinal product **carrying a marketing authorization** is defined in Article 2(n) of Directive 2001/20/EC as all “untoward and unintended responses to an investigational medicinal product which occurs at doses normally used”.

8.1.3 Documentation and Reporting

Adverse events will be documented on special AE-forms electronically in eCRF from first Ranibizumab administration until 4 weeks after the last trial-related intervention.

At each visit, the patient will be asked a non-leading question such as “Have you had any health problems since the last visit”. In this study **ONLY** AEs related to the study procedures and AEs related study drug and critical ocular events will be recorded. In case of endophthalmitis, it will be documented on the AE-form which kind of ranibizumab preparation was used (pre-filled syringe or syringe prepared at the pharmacy or syringe prepared intraoperatively).

If an AE fulfils any of the criteria for an SAE (see chapter 8.4.1 for SAE-definition), both the AE pages of the eCRF **and** the paper based SAE form must be completed. This also applies ONLY to events **considered to be related to trial treatment.**

For both serious+related and non-serious+related AEs, documentation should be supported by an entry in the patient’s health record. Required information in the patient’s health record should include:

- type of AE
- grade/severity/intensity acc. to e.g. CTCAE
- seriousness (see also section 18.1)
- onset date
- end date
- actions required
- outcome
- **assessment of its relationship to trial treatment**

Adverse Events are classified by their seriousness, intensity/severity and relationship to the trial treatment (see also *18.1*)

8.1.4 AEs related to the trial treatment

AEs related to the trial treatment are:

- adverse drug reactions of the study drug
- adverse events due to the injection of the study drug
- adverse device effects of photocoagulation

8.1.5 Critical ocular events

Critical ocular events will be documented on the AE eCRF during the complete study participation.

Following events are defined as critical ocular event:

- Any intraocular inflammatory response regardless of suspected etiology.
- Any case of new onset of a clinically significant increase in IOP, at any time, that required treatment.
- Any abrupt, clinically significant decrease in BCVA ≥ 15 letters
- Any new onset of retinal vein occlusion (central or branch) with new macular edema (ME) requiring the treatment with intravitreal drugs. The CRVO or BRVO will be defined as a new event if the macular edema occurs later than 2 months after the last intravitreal injection AND new intraretinal bleedings or microaneurysms will be detected and/or new venous dilatation will be detected when compared with visit prior to new detection of ME.
- An event that may - in the opinion of the investigator - require medical intervention to prevent permanent loss of sight.

8.2 Further safety-relevant issues

During the course of the trial, every patient will be monitored closely to identify the

- Presence of rubeosis iridis or neovascularization in iridocorneal angle
- Presence of neovascularization of optic disk (NVDs) or retinal neovascularizations elsewhere (NVEs) at every visit if present.

8.3 Concomitant Diseases

Concomitant diseases will be recorded at *baseline (Day 1).* Changes will be assessed at the regular trial visits and recorded if present. Any worsening of concomitant diseases will be regarded as adverse event, but will only be documented in the eCRF, if related to the trial treatment.

8.4 Serious Adverse Events

8.4.1 Definition SAE

A Serious Adverse Event (experience) or reaction is (according to ICH-Guideline E2A) any untoward medical occurrence that at any dose:

- **results in death**,
- **is life-threatening**,

  Note: The term “life-threatening” in the definition of “serious” refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death had it been more severe.
- **requires in-patient hospitalisation or prolongation of existing hospitalisation**[1],
- **results in persistent or significant disability/incapacity or**
- **is a congenital abnormal/birth defect**

Medical and scientific judgement should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalisation but may jeopardise the patient or may require intervention to prevent one of the other outcomes listed in the definition above. These should also usually be considered serious.

In the CoRaLa-II study **ONLY** adverse events related to the study procedures will be recorded as SAE if they fulfil any SAE-criteria (SAR).

*A*dditionally*,* any untoward medical occurrence that caused or threatened significant loss of visual acuity defined as ≥ 30 ETDRS letters will be considered as SAE.

8.4.2 Documentation and Reporting Obligations: INVESTIGATOR

Serious Adverse Events have to be documented on the SAE-forms and the investigator must report them to the sponsor immediately. If more information about the SAE becomes available later, it must also be reported to the sponsor immediately.

SAE reporting will be performed from first injection of the study drug (Visit 1) up to 4 weeks after the last trial-related intervention, which is (at latest) Visit 24.

In the event of a patient’s death, the investigator/deputy or the authorised medical staff provides the leading ethics committee(s), all involved ethics committees in multi-centred trials, the responsible federal authorities and the sponsor with all further information needed to fulfil their tasks **upon request**.

In all the reports, personal data are to be pseudonymized by using the patient’s identification code. It must be possible to relate the initial and all follow-up reports to each other by means of the patient identification number.

1 In general, hospitalisation means that the patient stays (usually at least an overnight stay) at the hospital or emergency ward for observation and/or treatment. Complications that occur during the stay are AEs. If a complication prolongs hospitalisation or fulfills any other serious criteria, the event is serious.
Hospitalisation for elective treatment of a pre-existing condition that did not worsen from baseline is not considered an AE.

The investigator, the deputy or the authorised medical staff must report every Serious Adverse Event as soon as getting knowledge of it to the following address:

ZKS Leipzig/Pharmacovigilance
Universität Leipzig
Zentrum für Klinische Studien Leipzig
Haertelstr. 16-18, 04107 Leipzig
Phone: +49/341/97-16129
E-mail: pharmacovigilance@zks.uni-leipzig.de

Fax: +49/341/97-16278

8.4.3 Documentation and Reporting Obligations: SPONSOR

After the ZKS Leipzig receives the SAE, it is immediately passed on to the coordinating investigator/responsible person for medical assessment.

The coordinating investigator/responsible person forms a second medical opinion of the SAE with respect to causal relationships and the decision as to whether or not it was expected, as described in chapter 18.1.3 and 18.1.4 and forwards the second opinion to the ZKS Leipzig within two days of its arrival.

In the ZKS Leipzig the SAE data are entered into the SAE database immediately and the MedDRA coding takes place simultaneously.

Then forwarding as per law and as described in Chapter 8.5 only for Suspected Unexpected Serious Adverse Drug Reactions (SUSARs) takes place.

Details of the sponsor's documentation and reporting obligations will be specified in a special, trial-specific pharmacovigilance plan, which will be written and finalised alongside with this protocol, if possible.

8.4.4 Annual Safety Report

According to German Medicinal Products Act the sponsor writes a safety report annually (Annual Safety Report, ASR[2]) and sends this report to the leading ethics committee(s) and the federal authority/i*es*.

The key date is the date of the first authorization of the clinical trial by a federal authority. All data obtained up to this date (each year) will be included in the ASR. Beginning with the key date, there is a time-limit of 60 days for the preparation and submission of the ASR.

The ASR will be prepared by the ZKS Leipzig (project manager, responsible biometrician and PV data manager) acc. to the national requirements deadlines regarding the ASR based on the German Medicinal Products Act. The final report will be released in co-operation with the sponsor's representative.

2 See "Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use").

8.5 Suspected Unexpected Serious Adverse Reactions (SUSAR)

8.5.1 Documentation und Reporting Obligations

Information for SPONSOR

The sponsor submits all information available about a SUSAR immediately to the leading ethics committee, the responsible federal authorities, and to all participating primary investigators, at the latest within 15 calendar days after the event becomes known.

For every SUSAR that results in death or a life-threatening condition, the leading ethics committee, the federal authority, and all participating investigators must be informed by the sponsor within 7 calendar days after the event becomes known. Additional information has to be given within 8 further calendar days.

Details of the sponsor's documentation and reporting obligations will be specified in a trial-specific pharmacovigilance plan, which will be written and finalised alongside with this protocol.

Information for INVESTIGATOR

The investigator passes down all relevant information concerning the SUSAR to all participating trial staff at his trial centre. This has to be confirmed by the investigator by signing an acknowledgement document.

8.6 Dealing with Pregnancy

Every pregnancy that occurs while taking part in the trial must be reported to the ZKS Leipzig by the investigator/deputy or the authorised medical staff within 24 hours of having learned of it by informal communication:

ZKS Leipzig / Pharmacovigilance
Universität Leipzig
Zentrum für Klinische Studien Leipzig
Härtelstr. 16-18, 04107 Leipzig
Telefon: +49/341/97-16129
Fax: +49/341/97-16278
E-mail: pharmacovigilance@zks.uni-leipzig.de

The ZKS Leipzig will then supply the essential forms for documentation to the investigator/deputy investigator without unduly delay. Pregnancies that occur in female trial subjects have to be reported by using the form: "Report on the arising of a pregnancy during exposition to a trial medication". Severe side effects and complications during a pregnancy as well as congenital birth defects are Serious Adverse Events by definition and therefore also have to be reported on the Serious Adverse Event form according to the reporting procedures described above.

The outcome of a pregnancy has to be reported on the form "Report on the outcome of a pregnancy during/after exposition to a trial medication". This form will document the outcome of the pregnancy, including a spontaneous or voluntary abortion, details of the birth process, the presence or absence of congenital malformations and birth defects, maternal or foetal complications and the potential relationship to the trial drug.

Collecting data concerning the outcome of a pregnancy is only permitted if the trial subject puts down her permission in writing beforehand. The collection of data on the child's health requires the prior information and consent of the guardian/parents (usually both).

9 BIOMETRY

9.1 Biometrical Aspects of the Trial Design

This is a randomized parallel-group trial with two arms:

- Experimental group, in which patients will receive injections of Ranibizumab and additional targeted laser photocoagulation in areas of non-perfusion at pre-specified time points if indicated.
- Control group, in which patients will receive the standard intravitreal injections of Ranibizumab as per current treatment guidelines only.

All patients will be followed for 29 months after randomisation to identify a treatment success, in case the first time without need for re-injection is the last visit with planned re-injection (EoT, at month 23), and to evaluate the long-term development of BCVA and CST.

9.1.1 Measures to Prevent Bias

Remote computerised randomisation 1:1 via internet will be provided. Randomisation will be stratified by baseline BCVA (≤55 letters vs 55>letters) as sole patient-centred criterion. The stratification according to baseline BCVA reflects the differences in the natural prognosis of CRVO patients treated with Ranibizumab [27].

Handling bias should be negligible because maintenance injections will follow pre-defined re-treatment criteria guided by morphologic OCT criteria.

To achieve the highest possible standardization of the laser photocoagulation, the evaluation of FA images and indication of the peripheral retinal areas for laser treatment will be performed centrally by the CoRaLa II Central Reading Center (see chapters 3.2). A consented plan containing the localisations will be transferred to the patient’s site, where the laser treatment is performed.

ITT analysis within the full analysis set of patients (FAS) acc. to ICH E9 guideline [20] will ensure an unbiased analysis. Regular supervision of study documentation and established query management will ensure data quality and completeness [21].

9.2 End Points

9.2.1 Primary End Point

Primary efficacy endpoint is the time to treatment success, defined as time from randomisation until the date of last criteria-based intravitreal injection in case that thereafter a treatment-free period for (at least) 6 months was observed.

Objective criteria for further treatment indication (according to details in section 6.3) have to be fulfilled for decisions regarding further re-treatment.

Drop-outs/deaths without earlier success will be censored at the end of their observation time and all other patients without documented success at month 24 or 29 after randomisation (in case of no treatment indication at the last regular visit to state or deny a late success).

9.2.2 Secondary End Points

Secondary endpoints (sEP) are:

1) the best corrected visual acuity (BCVA) in BCVA letter scores (EDTRS charts) per visit;
2) central subfield thickness (CST) measured by OCT per visit;
3) the number of Ranibizumab injections required (after three initial monthly injections) according to re-treatment criteria (see 6.3) until “success” is reached as well as up to month 29 after randomisation (the entire period of observation, in case of late recurrence of ME);

All these items are measured at every mandatory visits, at latest at Month 29.

9.2.3 Further complementary outcomes including quality of life

- proportion of subjects developing neovascularization(s) of retina, optic disc, and/or in anterior segment over the total period of observation.
- patient-reported health-related quality of life (QoL) will be investigated at BL and at the end of study. It is measured by the Visual Function Questionnaire VFQ25 [28], which focuses on functional aspects in case of impaired visual acuity. It has been proven to have satisfying properties regarding validity, reliability and sensitivity to change in English and German. Patients will complete the questionnaire before the ophthalmologic investigation will be performed at the baseline and at month 12 and 24. We expect most patients to understand the questions in the questionnaire.

  Because QoL is a complementary endpoint only we refrain from having an exclusion criterion on language. The pre-post change in the QoL will be analysed.

- vessel density (assessed by OCT-angiography, see also sec. 7) will be quantified by a metric measure with the range [0;1].
- area of the foveal avascular zone (FAZ, assessed by OCT-angiography, see also sec. 7, in [mm²])
- the area of non-perfusion (assessed by FA) will be quantified as sum of all areas identified (see also sec. 7);
- a potential visual field loss will be quantified as follows: for each patient the retinal sensitivities over all points tested will be summed-up and divided by the number of points investigated. The harmonized mean per group will be calculated per group and visit. The change between the two timepoints (Months 4 and 24) per arm will be used to characterize the both groups and be compared between treatment arms (see also sec. 7);
- the number of visits with applied laser treatment and the laser spots applied in the experimental group (RL-arm) will be counted for descriptive reasons and be compared between treatment arms.

9.2.4 Safety characteristics

(Serious) adverse reactions (S)ARs and critical ocular events will be compared between the

arms to describe the safety profiles of the combined intervention.

9.3 Statistical Description of the trial hypothesis

9.3.1 Statistical Hypotheses/Statistical Estimation Method

It is to be assessed whether there is a difference in the times to reach treatment success as defined in the primary. The statistical hypotheses are:

- H_0: Time to success (experimental group) = Time to success (control group)
- HA: Time to success (experimental group) ≠ Time to success (control group)

9.4 Sample Size Discussion

Long-term review of CoRaLa I [10] patients (as reported in 1.2) showed that a proportion of $p_{R\text{-}only}$=0.58 had to be treated longer than 2 years, while for all but one patient (p_{RL}=0.1) the combined therapy could be terminated after median [quartiles] of 10 [3;11] months but total observation times of 18 [16; 20] months.

Assuming 2 years to treatment success, rates of 50% with R-only and (conservative) 20% with RL, setting a two-sided significance level α at 5%, and requiring 90% power we need a total of N=92 cases with a log rank test.
With regard to the number of injections applied within two years (without the three initial monthly injections), we observed 5.6 (4.9) injections (mean (SD)) in the R-only, but 2.8 (2.7) in the RL-group. Based on these means (SD), we need n=46 patients per group with an α level of 5% (2-sided) and for a power of 90%.

Non-compliance and dropout rates are expected to be rather low with regard to the massive impact of impaired visual acuity on activities of daily and social living. Regarding the CoRaLa I patients one participant (of 22) was lost (after 15 months) and 2 per arm died after long-term observation of more than 4 years. Although (extended) oversampling is not needed with regard to the confirmatory analysis within the FAS and a time-to-event primary endpoint, a major interest of the trial focuses on mid-/long-term differences between the treatments, too. Therefore, we amply plan with 20% dropouts and intend to include at least 110 patients to learn as much as possible on the effect of the additional laser treatment on the further need of regular Ranibizumab injections in long-term and ensure sufficiently precise estimations after two year of observation.

9.5 Statistical Methods

9.5.1 Analysis Population

Full analysis set

The full analysis set (FAS, based on the intention-to-treat (ITT) strategy) is defined by all randomized patients with valid informed consent and (at least) a single study intervention performed.

Per protocol set

The per-protocol (PPS) set is defined by all patients belonging to the FAS without major violations of the study protocol.
The following protocol violations are classified as major:

- Violation of an eligibility criterion;

- Patients who did receive less than 75% of the intended treatment days without earlier success or other *relevant clinical* r*easons (including clinical reasons which require a postponed injection or a (timely) interruption of the series, death, (serious) adverse events) which may require a premature termination of the intervention*

This is not an exclusive list. In the light of protocol violations which actually may occur during study conduct, all major protocol violations will be defined, e.g. as part of the statistical analysis plan. The completed list will be finalised before database closure and start of the final analysis.

Safety analysis set

The safety population is defined by all randomized patients belonging to the FAS. In safety analyses, patients will be classified whether or not they received at least a single laser therapy, irrespective of the randomized group allocation.

In analyses of *secondary and complementary* endpoints all patients will be excluded in whom a new onset of RVO was found after a previous success since this would cause a bias.
The aspects of relapses and recurrence of ME after a reported success will be reported separately.

9.5.2 Planned Methods for Analysis

Analysis of the *primary endpoint* (within the FAS, [31]) will follow the intent-to treat principle and will be based on COX regression with the stratification factor baseline BCVA (≤55 letters vs >55 letters) as fixed covariate for confirmatory analysis.

Further models will include potentially prognostic factors and compliance for sensitivity reasons. The assumption of proportional hazard may be justified although no similar data are available by now. It will be checked and otherwise adequately dealt with. Kaplan-Meier curves provide time without treatment success per arm.

The *number of Ranibizumab injections* required after the initial three injections will be analysed by an ANCOVA *model* including treatment as factor and baseline BCVA as covariate (also used for stratification); for sensitivity reasons, further models may include the same prognostic factors of potential relevance as selected for analyses of the primary endpoint.

To adequately analyse the long-term *courses of BCVA and CST* at the end of study we require that patients with early treatment success have further mandatory visits beyond success since - based on CoRaLa I data - we expect rather different event times with regard to the chosen primary endpoint. Given the 6 monthly visits to determine “success”, we assume that this will lead to only few additional visits per patient

In each patient, BCVA and CST will be analysed at 6 time points: at baseline visit, and after 12, 16, 20, 24 and 29 months. Analyses of both secondary endpoints are identically structured: mean changes from baseline mean will be analysed using a repeated measurement linear mixed model without intercept containing the fixed, categorical effects of

- visit (as named),
- treatment (RL vs R-only),
- treatment by visit interaction,
- low BCVA pre-treatment value (yes / no) as well as
- a patient-specific, visit random effect.

An unstructured (co-)variance structure will be used to model the residual within-patient errors. If this analysis fails (does not converge), a compound symmetry structure corresponding to a constant correlation will be used. The analysis will be based on restricted maximum likelihood

(REML). The contrast of interest is the treatment by visit interaction at 29 months. Respective inference will be based on Wald type confidence intervals and respective p-values.

As described above, we expect a low rate of patients with missing information on both endpoints. We expect that missing endpoints will be missing at random given the specified model structure. The above model can deal with patients with incomplete data as long as at least one valid measurement is documented.

The extended observation period for all patients will further provide the opportunity to identify a late recurrence of ME after success (if present).

The *rates of neovascularizations*, of *developed collaterals*, of *critical ocular incidents* and (S)AE/(S)AR (as per MedDRA-coded Preferred Terms or higher aggregation levels up to System Organ Classes) will be analysed by the exact Fisher (or Chi²) test as well as with multivariate logistic regression models (if numbers permit) to consider the impact of covariates.

Vessel density, areas of the foveal avascular zone and of non-perfusion will be compared between the arms by ANCOVA models, too, with baseline measures (if available) and high/low visual acuity at BL as a covariates.

The same will be done for analysing a potential *visual field loss* with adjustment for BL visual field score, high/low visual acuity at BL and BL CST. Change values were truncated at ± 3 standard deviations from the mean change to minimize the effect of outliers (if applicable).

Neither imputation of missing values nor an adjustment for multiple testing is planned for secondary/safety or complementary endpoints. No interim analysis is scheduled.

For all major statistics 95% confidence limits will be provided.

9.6 Statistical Monitoring

Regular monitoring visits and timely supervision of study documentation including a regular query management will be performed to ensure data quality and completeness acc. to ZKS Leipzig SOPs; it will be based on a risk-adapted monitoring concept.

The on-site monitoring (see chapter 13.2) will be supported by a regular central (statistical) off-site monitoring. The objectives are

- to detect safety relevant signals as soon as possible
- to detect non-compliance and relevant protocol violations and to prevent their future occurrence by prompt reaction

Central statistical monitoring will start 10 months after inclusion of the first patient in front of the analyses for 1st annual safety report if statistically sufficient numbers of patients were already included to enable statistical statements. Findings will be queried for clarification with the centres.

Non-compliance and/or PVs identified will be discussed at the ZKS Leipzig study team, with the coordinating investigator and with the respective centre(s).

The risk factors defined by the risk analyses during trial planning and implementation will be supervised during trial implementation at regular intervals.

For example, activities of central monitoring may refer to:

- data quality (completeness, timely documentation, consistency, …)
- recruitment rate and screening-failures (overall, per site and between-sites

comparisons)
- incidence of AEs/SAEs (overall, per site and between-sites comparisons)
- surveillance and evaluation of drop-outs (reasons and frequencies; overall, per site and between-sites comparisons)
- surveillance and evaluation of protocol violations (reasons and frequencies; overall, per site and between-sites comparisons)

9.7 Final Analysis

Final analysis will be performed when the data of all enrolled patients have been collected, all DM procedures have been finalised and the database has been cleaned for analysis.

In case of a premature termination of the whole trial (due to organisational, financial or other reasons) a limited analysis of the data available up to then may be suitable if at least 2 thirds of sample size finished the trial. A power analysis may add information regarding the study results and for future trials.
The decision on its extent and timely priority will be made in common voting of the ZKS Leipzig und the coordinating investigator.

No scheduled interim analysis is planned.

10 ETHICAL, LEGAL AND ADMINISTRATIVE ASPECTS

10.1 GCP-Statement

All persons participating in the conduct of the trial (sponsor, authorised representative of the sponsor, investigators, etc.) commit themselves to observe the Declaration of Helsinki of the WMA (in its current version), as well as all pertinent national laws and the ICH guideline for Good Clinical Practice (GCP) ICH E6(R2) (EMA/CHMP/ICH/135/1995) issued in June 2017.

10.2 Initial Submission

10.2.1 Submission to the Ethics Committee and Federal Authority

Prior to submitting the trial related documents to the leading (and involved) ethics committee(s) and the responsible federal authority, the sponsor must enter the trial information into the European database for clinical trials (EudraCT).

Afterwards, the protocol and all other associated documents according to GCP-V §7 will be submitted to the leading ethics committee for approval. Parallel to the submission to the leading ethics committee (EC), each participating EC is informed of the submission and also receives a copy of the documents including those of the trial sites, which they have to approve. At the same time the study documents will be submitted to the responsible federal authority (PEI) according to the requirements of GCP-V §7.

The trial can start only after obtaining a positive review by the leading ethics committee and approval from the responsible federal authority. The written approval of the EC must be filed in the trial master file (TMF). Additionally, every participating centre must receive a copy of these documents to be filed in the investigator site file (ISF).

10.3 Protocol Amendments

Changes to an approved trial protocol have to be submitted to EC and CA and positively appraised before implementation of the changes, if the changes are such that they may affect the subjects' safety, e.g.:

- that they may affect the subjects' safety, (e. g. fundamental changes to the therapeutic procedures),
- result in further data collection that requires changes to the patient information and/or informed consent form,
- affect the interpretation of the scientific documents upon which the trial is based or the significance of the results of the trial,
- that they significantly affect the leadership or conduct of the trial.

Changes to the protocol may only be performed by the co-ordinating investigator in co-operation with the biometrician and/or DSMB.

After approval of the trial changes, all participating trial sites have to be informed about the changes in writing and supplied with potentially changed documents.

The whole process has to be documented in the Trial Master File (TMF).

11 DOCUMENTATION

11.1 General information and Access Rights

The Case report Form (CRF) in the context of a database for electronic data capture only will be designed by the ZKS Leipzig in cooperation with the Coordinating Investigator and provided as electronic form (eCRF). In order to facilitate the documentation as per protocol in case of malfunction of the electronic system or any of its components, a paper version of the CRF will be provided in the ISF (investigator site file). The content of this paper version will be transferred to the eCRF as soon as the electronic system is available again.

Special CRF forms will be provided as paper CRF:

- **SAE-forms**, because these have to be sent to the ZKS Leipzig in a printable version for submission to the relevant authorities

An eCRF will be provided for each patient. The patient will be identified as per Patient-ID only. The eCRF must be filled in shortly after each trial visit according to ICH Guideline E6 chapter 4.9.1 and to enable central monitoring of the trial data.

Access to the data base will be limited to authorised staff only. Authorisation is granted by the site’s investigator using the trial specific staff signature and delegation log. Based on the staff signature and delegation log access to the eCRF will be granted by the responsible staff at the ZKS Leipzig.

Authorised staff members on site will be able to enter and update data as well as finalise data by electronic signature during the conduct of the trial according to a trial specific concept for documentation. This concept is based on the internal Standard Operating Procedures implemented by the ZKS Leipzig and follows the ICH Guideline E6. All entries and data changes will be tracked automatically including date, time and person who entered/changed information (audit trail). Major correction(s) or major missing data have to be explained.

11.2 Patient File and Source Data

All information required by the protocol and therefore collected during the clinical trial must be recorded by the Investigator or an authorised member of the trial team as source data in the source documentation for the trial (e. g. patient file).

Source data according to ICH Guideline E6 are defined as any information in original records and/or certified copies of original records of clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents.

The Source Data Agreement is defining source data and their location for respective CRF entries. It will be filled in at the initiation visit, signed by the investigator or deputy investigator and filed in the trial master file.

In order to confirm the completeness, accuracy and consistency of the data with the data in the source documents the investigator or deputy investigator has to electronically sign each patient's CRF after his individual end of trial participation.

11.3 Data Management

For creation of the trial database the EDC tool secuTrial®, developed and distributed by interActive Systems GmbH (iAS), will be used. The database will be validated according to the Standard Operating Procedures (SOPs) of the ZKS Leipzig prior to data capture.

The information entered into the eCRF by the investigator or an authorised member of the trial team is systematically checked for completeness, consistency and plausibility by routines implemented in CDMS such that discrepancies can be dealt with at data entry. Errors and Warnings are listed in a validation report and can be resolved at any time during entry process. On completion of the data entry the site staff flags the eCRF-pages as 'data entry completed' (DEC).

During on-site monitoring or central/statistical monitoring, the monitor or the data manager at the Clinical Trial Centre may create a manual query for discrepancies that are identified after DEC. All eCRF-pages with queries are marked in the system and a report with all queries listed is available. The site staff is responsible for data correction and can resolve queries directly in the eCRF-page.

The ZKS Leipzig will supervise and support the solution of queries and will close all correctly resolved queries. In case a query cannot be solved, the data management staff may close the query in agreement with the trial biometrician.

During the whole course of the trial, a backup of the data is made on a daily basis according to the backup policies of the ZKS Leipzig. Unauthorised access to patient data is prevented by the access concept of the trial database which is based on a strict hierarchy and role concept. Any change of data (e.g. when data is changed in the database during query management) is recorded automatically via audit trail within the database.

At the end of the trial, once the database has been declared complete and accurate, the database will be locked. Thereafter, any changes to the database are possible only by joint written agreement between sponsor/sponsors authorised representative/coordinating investigator, biometrician and data manager.

11.4 Archiving

All relevant trial documentation (Trial Master File), the electronically stored data, the original CRFs and the final report will be stored for at least 10 years at the coordinating investigator / sponsor after the trial's completion.

At the investigating sites, the investigators' files, patient identification lists, signed written consent forms, copies of all CRFs and the patients' files will be stored for at least 10 years after the trial's completion. If local rules or other legal requirements (e.g. Strahlenschutzverordnung, Röntgenverordnung) require longer periods of archiving, then these are to be met.

12 Reference evaluations

A **Central Reading Center** (CoRaLa II Reading Center) of experienced ophthalmologists will review coloured fundus images and FA images from all patients. Two independent graders will independently define the areas of capillary non-perfusion as a target for the laser photocoagulation, which will be performed in each study site according to the standardized protocol. In the case of divergent opinions between two grades a third one will perform an additional independent grading. A consented plan will be transferred to the patient´s site and recommend on details of the laser treatment, according to the imaging protocol.

13 Supervision of the clinical trial

13.1 Access to Source Data

According to ICH-GCP and the applicable German laws, the investigator must permit all authorized third parties access to the trial site and the medical records of the trial subjects (source data). These include the clinical trial monitors, auditors and other authorized employees of the sponsor, as well as members of the local or federal authorities. All these persons are sworn to secrecy.

13.2 Monitoring

The ZKS Leipzig will be responsible for trial monitoring. Pre-study, initiation, regular and close-out visits will be performed in all centres. A risk-based quality management approach will be implemented according to the SOPs of the ZKS Leipzig and the ICH guideline E6 (R2) [32]. During trial conduct, central monitoring procedures will be combined with on-site monitoring visits in order to achieve high protocol compliance (especially regarding the re-treatment criteria) and data quality, as well as to ensure patients' safety and rights. A first monitoring visit at a centre will be scheduled after the three initial monthly Ranibizumab injections of the first patient in every centre, checking protocol compliance and preventing further systematic errors due to misunderstandings. All trial sites will then be visited regularly. The frequency of further monitoring visits will depend on the trial site's recruitment rate and on whether problems have been detected with the site, either by prior on-site visits or by central monitoring. However, trial sites will be visited at least every 12 months. During the visits, the monitor will

During the visits the monitor will:

- check informed consent forms of all patients enrolled
- perform source data verification of the key data (selected baseline parameters, therapy delivery, serious adverse events, follow-up) in a random sample of the site's patients
- perform targeted source data verification for patients with possible deviations
- discuss open queries raised by data management
- check essential parts of the investigator site file (see monitoring plan)
- check source data for AEs /SAEs, which have not been properly reported in the eCRF
- check for major GCP-breaches and/or protocol violations

according to the trial specific monitoring plan.

13.3 Audits

In order to guarantee that the conduct of the study is in accordance with ICH-GCP and the national laws, the co-ordinating investigator may initiate for cause or random audits at the trial sites, core labs or involved institutions carried out by an independent auditor.

The investigator agrees to give the auditor access to all relevant documents for review.

13.4 Inspections

According to German drug law (AMG) and the corresponding GCP-guidelines (GCP-V), inspections of the trial sites may be performed by the local or federal authorities at any time during or after completion of the trial.

The investigator agrees to give the inspectors access to all relevant documents for review.

13.5 Steering Committee (SC)

A Steering Committee (SC) supervised the development of the trial protocol and recommended on improvements. It will be consulted as well in relevant issues, e.g. if amendments may be necessary, or in futures aspects of analyses which may go beyond the predefined concept within the protocol.

Further, SC will advise the members of the CoRaLa II Reading Center regarding the preparation of the standardised protocol for the detection of retinal areas of non-perfusion. The SC also takes responsibility for the scientific validity and quality of the study as well as for the scientific interpretation of the results and quality of the final study report. It will consist of one chairperson and at least three further experts in field of medical retina. One member of the committee should be a representative of the ProRetina organization.

13.6 Independent Supervision of the Trial

An independent Data Safety and Monitoring Board (DMSB) will be installed and consists of experienced scientists (ophthalmologists and a biostatistician). It will annually assess the progress of the trial and the safety of the participants.

Prof. Dr. med. Salvatore Grisanti has been approached as the senior clinical member, and he will recommend (at least) an additional clinician. The DMSB will assess the progress of the trial and evaluate all safety data, trial's performance and general adherence to the protocol based on statistical monitoring reports in annual intervals. It will recommend to the coordinating investigator whether to continue, modify, or stop the trial. Procedures will be described in a DSMB Charter.

14 Data protection and Confidentiality

The sponsor, together with ZKS Leipzig and the trial sites, is responsible for the implementation and data processing in accordance with Article 4(7) of the EU Data Protection Basic Regulation 2016/679 in this trial. The ZKS Leipzig is responsible for implementation of procedures for data collection, storage, protection, retention and destruction. The ZKS Leipzig has implemented a data safety and security concept according to the requirements of the German Federal Office for Information Security (www.bsi.bund.de).

All data will be initially collected by investigators in the recruiting trial sites. Together with information on the trial, eligible patients will be informed about data capture, transmission, analysis processes and their rights according to the General Data Protection Regulation (GDPR). Once a patient is eligible and has given his informed consent to trial participation and data collection, the investigator will assign the patient a unique patient identification code. Patient identification code lists will be generated in advance by ZKS Leipzig and forwarded to the recruiting sites. These lists are part of the investigator site file and remain at the recruiting site. These lists are the only documents that allow for re-identification of the patients.

All clinical data entered by the investigators (or their designated staff) into eCRFs will be recorded in a pseudonymized form (i.e. without reference to the patient's name and date of birth) exclusively using the patient's identification code.

Clinical monitors appointed by ZKS Leipzig will regularly visit the recruiting sites and verify the informed consent forms. Data will only be used for analysis after it has been verified by monitors that the patient has unambiguously given his or her consent for trial participation as well as for data capture, transmission and analysis. The patients are informed of this fact and agree to the procedure with the patient information/informed consent.

In the event of withdrawal of consent, the necessity for storing data will be evaluated. While the General Data Protection Regulation (EU) 2016/679 strengthens personal data protection rights, encompassing the right to access, rectification and withdrawal of data, it also specifies the situations when restriction on those rights may be imposed. The withdrawal of informed consent should not affect the results of activities already carried out, such as the storage and use of data obtained on the basis of informed consent before.

14.1 Declaration regarding Data Protection

We hereby confirm that all clinical trial information will be recorded, processed, handled and stored by ZKS Leipzig, Härtelstr. 16-18, 04107 Leipzig, Germany on behalf of the sponsor.

Data captured by the investigators will be processed in such a way that it can be accurately reported, interpreted and verified while the confidentiality of records and the personal data of the subjects remain protected. Data capture and processing will be in accordance with the applicable law on personal data protection and with the "General Data Protection Regulation" (EC) 2016/679 of the European parliament and of the council.

Access to the data is strictly limited to authorised persons. Data are protected against unauthorised access.

14.2 Declaration regarding the Pseudonymized Transfer of Personal Data

The sponsor certifies herewith that the transfer of pseudonymized personal data will take place according to the documentation and communication regulations in §§ 12 und 13 of the GCP-guidelines (GCP-V) [33]. Moreover, the sponsor certifies that trial participants who do not permit the transfer of data will not be admitted to the trial. This will be ascertained by including the relevant information in the patient information/informed consent.

14.3 Anonymisation of Data after the end of Archiving

After the end of the archiving period, all clinical data present at the ZKS Leipzig will be stored in an anonymous form.

All data will be subject to an anonymization process removing personalised data as far as possible, i.e. without endangering the possibility to answer scientific questions related to the trial. Anonymised data will be relocated to a separate, access restricted, file location and secondary data sources will be deleted.

Non clinical data (like contact information) will be deleted after the end of the archiving period.

15 Administrative agreements

15.1 Adherence to the Protocol

The study will be conducted in accordance with the protocol, GCP and applicable regulatory requirements.

Protocol violations are all deviations from the procedures outlined in this document, e.g.

- examinations that are missed or that take place at the wrong time
- non-compliance

After a patient has been enrolled, it is the investigator's responsibility to avoid protocol violations in order to obtain unbiased data for the trial.

Those protocol violations deemed to be major are defined by the risk analysis performed before and during trial implementation and will be further detailed in separate documents belonging to the risk assessment/monitoring plan. This list can be augmented in the course of the trial. Major protocol violations will be reported to the ZKS Leipzig, which will inform the coordinating investigator.

All protocol violations will be documented and discussed with the responsible biometrician before closing the data base and carrying out the statistical analysis. This is done without revealing the group that the patient is a member of.

The investigator must ensure that the recorded data are documented as per protocol. Minor variations are an inevitability, but must be documented together with a justification.

15.2 Funding and Insurance

This trial is funded by the “Bundesministerium für Bildung und Forschung (BMBF).

For all participating patients a travel accident insurance was concluded.

Contact data of the insurance company:

HDI Global SE, Theodor-Heuss-Platz 7, 14052 Berlin

This insurance covers health damages caused by accidents, which occur during the journey to and from the test centre and during the stay in the test centre. The insurance number of this travel accident insurance is 28138971-03722.

Insurance of patients against health impairment occurring as a result of participation in the clinical trial will be set up by the coordinating investigator only for patients in the intervention arm who have had an event recorder implanted.

Patients are insured by the insurance company:

HDI Global SE, Niederlassung Leipzig, Eisenbahnstr. 1 – 3, 04315 Leipzig

The number of the insurance police is 28-138971 03302. A copy of the insurance policy and the insurance conditions will be filed in the investigators file. A copy of the insurance conditions has to be handed over to the patient.

15.3 Notification of Local Authorities

Prior to enrolment of the first patient in the trial, the sponsor, his legal representatives/ contractors and all investigators and their deputies are responsible according to German Medicinal Products Act AMG § 67 (1) and the requirements of the GCP-V §§ 12 and 13 for notifying the local regulatory authority of their participation in the trial.

According to § 67 (3) AMG and §§ 12,13 GCP-V the sponsor, his legal representatives/ contractors and all investigators and their deputies are also responsible for notifying the local regulatory authority of amendments, premature termination of trial arms or of the whole trial and the regular trial termination.

15.4 Publication Policy and Registration

The results of this trial will be submitted for publication in a peer-reviewed, international English-language journal of appropriate aim and scope. Accordingly, the clinical trial will be registered at the ClinicalTrialsGov register before recruitment starts. According to the results of main and concomitant studies, the results may be submitted in separate or combined manuscripts; decisions about the form and scope of individual manuscripts will be discussed among all persons participating in the design, conduct and analysis of the trial who qualify for authorship. The coordinating investigator together with the biometrician(s) is responsible for drafting and circulating manuscripts and for discussing and handling requests by co-authors or/and sponsors to edit the text.

The authorship will follow the criteria for authorship developed by the International Committee of Medical Journal Editors (ICMJE), including those that distinguish authors from other contributors.

The ICMJE recommends that authorship be based on the following 4 criteria:

- Substantial contributions to the conception or design of the work; or the acquisition, analysis, or interpretation of data for the work; AND
- Drafting the work or revising it critically for important intellectual content; AND
- Final approval of the version to be published; AND
- Agreement to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

All those designated as authors should meet all four criteria for authorship, and all who meet the four criteria should be identified as authors. Those who do not meet all four criteria will be acknowledged in the manuscript.

The scientific use of data resulting from this trial by local trial sites is ruled by the site contracts between the sponsor and the local trial sites. Generally, sites might use data for own scientific questions (independent from the questions discussed in this trial protocol) and publication after consultation with the sponsor.

15.5 Data Sharing Statement

According to the recommendations on data sharing by the International Committee of Medical Journal Editors (ICMJE) data resulting from the CoRaLa II-trial will be made available to the scientific community as follows:

After publication of the major results and upon reasonable request from researchers performing an individual patient data meta-analysis, individual patient data that underlie published results will be shared after de-identification. This requires approval by the local Institutional Review Board (IRB) of the researcher requesting the data along with public registration of the meta-analysis.

Summary statistics that go beyond the scope of published material will be made available to researchers for meta-analysis upon reasonable request and if the necessary data analysis is not unduly time-consuming. Together with publication of the main results, the trial protocol in full will be made publically available as well as the statistical analysis plan.

16 Protocol signatures

Confirmation of the Final Protocol

We hereby certify that this is the final version of the protocol:

Coordinating Investigator:

Prof. MUDr. Matus Rehak

Date	Signature

Authorised representative of the sponsor:

[redacted]

[redacted]

Biometrician:

[redacted]

[redacted]

17 Protocol agreement

Herewith I declare that I have read and understood the present protocol and agree to take into account and follow each part of it. I will ensure that all trial patients enrolled in this trial site will be treated, observed and documented in accordance with this protocol. I will ensure that all persons assisting with the trial under my supervision are adequately informed about the protocol, the investigational product and their duties.

I further declare that I do not have any financial and other competing interests in this trial.

Centre-ID	_____ - __/__/__/
Address trial site (stamp)	

Date

Signature Principal Investigator

Date

Signature Deputy Investigator

18 APPENDIX

18.1 Classification of Adverse Events

18.1.1 Degree of Seriousness

The degree of seriousness of an Adverse Event will be determined in accordance with the definitions in 8.4.

18.1.2 Assessment of Intensity/severity

The assessment of the intensity/severity accords with CTCAE V5.0

Mild Adverse Event	• asymptomatic or mild symptoms; • clinical or diagnostic observations only; • intervention not indicated.
Moderate Adverse Event	• minimal, local or noninvasive intervention indicated; • limiting age-appropriate instrumental ADL*[3].
Severe Adverse Event	• medically significant but not immediately life-threatening; • hospitalization or prolongation of hospitalization indicated; • disabling; • limiting self care ADL**
Life-threatening Adverse Event	• Life-threatening consequences; • urgent intervention indicated
Death related to Adverse Event	

18.1.3 Determining the Causal Relationship

The investigator/ the deputy or the authorized medical staff must assess whether or not the Adverse Event is causally related to the trial treatment. The following classification is to be used.

- Reasonable possibility
- No reasonable possibility

A reasonable possibility exists, if one of the following WHO-UMC criteria is met:

3 **Activities of Daily Living (ADL):**
*Instrumental ADL refer to preparing meals, shopping for groceries or clothes, using the telephone, managing money, etc.
**Self care ADL refer to bathing, dressing and undressing, feeding self, using the toilet, taking medications, and not bedridden.

- occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacological or phenomenological, using a satisfactory rechallenge procedure if necessary.
- with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfil this definition.
- with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- more data is essential for a proper assessment or the additional data are under examination
- cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified

No reasonable possibility exists, if the following WHO-UMC criterion is met:

- with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.

18.1.4 Expected/Unexpected

Adverse Events are unexpected if they do not occur in the manner or with the intensity described in the *SmPC* of Ranibizumab (see investigator's files).

18.1.5 Outcome of an Adverse Event

The outcome of an Adverse Event is classified as follows:

- recovered/resolved
- recovering/resolving
- not recovered/not resolved
- recovered/resolved with sequelae
- fatal*
- unknown

*Note: A patient's death is not in itself an event, but the consequence of one. The event that led to the patient's death must be documented completely and reported even if death occurs four weeks after stopping medication and independent of whether or not there is a relation to the therapy or not.

18.2 Definitions

18.3 Acronyms

AE Adverse Event

AMG	Arzneimittelgesetz
BCVA	Best Corrected Visual Acuity
BRVO	Branch Retinal Vein Occlusions
CRF	Case Report Form
CRVO	Central Retinal Vein Occlusion
CST	central subfield thickness
CTCAE	Common Terminology Criteria for Adverse Events
EK	Ethikkommission
EoS	End of Study
EoT	End of Treatment
ETDRS	Early Treatment Diabetic Retinopathy Study
FAG	Fluorescein angiography
GCP	Good Clinical Practice
GCP-V	GCP-Verordnung
ICH	International Conference on Harmonisation
ISF	Investigator Site File
IOP	intraocular pressure
IVT	Intravitreal
ME	macular edema
NVD	neovascularization of the optic disc
OCT	optical coherence tomography
PEI	Paul-Ehrlich-Institut
PRN	Pro Re Nata
QoL	Quality of Life
SAE	schwerwiegendes unerwünschtes Ereignis (serious adverse event)
SAR	schwerwiegende Nebenwirkung (serious adverse reaction)
SmPC	Summary of medicinal Product Characteristics
SUSAR	Unerwartete, schwerwiegende Arzneimittelnebenwirkung (suspected unexpected serious adverse reaction
TMF	Trial Master File
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
WHO-UMC	World Health Organization – Uppsala Monitoring Centre

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