Multicenter randomized double masked parallel design exploratory study to assess safety and efficacy of two different doses of intravitreal anti-VEGF treatment with ranibizumab (0.12 mg vs. 0.20 mg) in infants with retinopathy of prematurity (ROP)

Short name: CARE-ROP
Comparing Alternative Ranibizumab dosages for safety and Efficacy in Retinopathy Of Prematurity

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(LKP in accordance with AMG)

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Approval of the Clinical Trial Protocol

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EudraCT No.: 2013-002539-13
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Date
Signature
## Investigator Statement

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<td>Protocol Version No:</td>
<td>2.0 (28.05.2015)</td>
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<th>Trial Center:</th>
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<td>&lt;Name of Investigator&gt;</td>
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I confirm that I have read the Clinical Trial Protocol and hereby commit myself to adhere to all actions and terms as specified in the relevant sections of the clinical, ethical and general paragraphs.
I confirm that I and my colleagues will abide by the local legislation (in Germany, the German Pharmaceutical Law with the appropriate amendments). I further confirm that the Clinical Trial will be carried out in compliance with the Declaration of Helsinki and ICH-GCP guidelines.
I acknowledge that all confidential information in this document, apart from the evaluation of the Clinical Trial will not be used or circulated without the prior written consent of the Sponsor.
Under my supervision, I put copies of this Clinical Trial Protocol and possible updates as well as access to all information regarding the carrying out of this Clinical Trial at the disposal of my colleagues; in particular, I will promptly forward all information from the Sponsor in relation to Pharmaceutical Safety (SUSAR) to my colleagues.
I confirm that I and my colleagues were informed by a responsible scientist about the results and expected risks of the pharmacological and toxicological examination associated with the clinical trial.
I will discuss this Clinical Trial Protocol in detail with my colleagues and ensure that they are comprehensively informed about the trial compound/preparation and the execution of the trial.
Furthermore I commit myself not to commence patient enrollment before the approval of the authorities and acceptance by the relevant/responsible Ethics Committee.

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List of abbreviations
AE        Adverse event
AMD       Age-related Macular Degeneration
AP-ROP    Aggressive posterior ROP
BSL       Baseline
BVA       German Ophthalmologists Association (Berufsverband der Augenärzte Deutschland e.V.)
CRF       Case Report/Record Form
CRA       Clinical Research Associate
CRO       Contract Research Organization
DOG       German Ophthalmic Society (Deutsche Ophthalmologische Gesellschaft)
DME       Diabetic Macular Edema
DSMB      Data safety monitoring board
FAS       Full Analysis Set
FUS       Follow-Up Set
GNN       German Neonatal Network
HA        Health authorities
IB        Investigational brochure
ICH       International Conference on Harmonization
ICU       Intensive Care Unit
IEC       Independent Ethics Committee
IIT       Investigator Initiated Trial
IMP       Investigational Medicinal Product
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tr>
<td>IN</td>
<td>Investigator Notification</td>
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<tr>
<td>IRB</td>
<td>Institutional Review Board</td>
</tr>
<tr>
<td>ITT</td>
<td>Intention to treat</td>
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<tr>
<td>MAH</td>
<td>Market Authorization Holder</td>
</tr>
<tr>
<td>NEO-KISS</td>
<td>Neonatal hospital infections surveillance system (Neonatologisches Surveillance-System für nosokomiale Infektionen)</td>
</tr>
<tr>
<td>PD</td>
<td>Protocol Deviation</td>
</tr>
<tr>
<td>PM</td>
<td>Pathological Myopia</td>
</tr>
<tr>
<td>PPS</td>
<td>Per Protocol Set</td>
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<tr>
<td>Rbz</td>
<td>Ranibizumab</td>
</tr>
<tr>
<td>REB</td>
<td>Research Ethics Board</td>
</tr>
<tr>
<td>RG</td>
<td>German Retina Society (Retinologische Gesellschaft)</td>
</tr>
<tr>
<td>ROP</td>
<td>Retinopathy of Prematurity</td>
</tr>
<tr>
<td>SAE</td>
<td>Serious adverse event</td>
</tr>
<tr>
<td>SAP</td>
<td>Statistical analysis plan</td>
</tr>
<tr>
<td>SESAR</td>
<td>Suspected expected serious adverse reaction</td>
</tr>
<tr>
<td>SUSAR</td>
<td>Suspected unexpected serious adverse reaction</td>
</tr>
<tr>
<td>SCN</td>
<td>Screening</td>
</tr>
<tr>
<td>SmPC</td>
<td>Summary of Product Characteristics</td>
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<td>VEGF</td>
<td>Vascular endothelial growth factor</td>
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## Glossary of terms

<table>
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<th>Term</th>
<th>Description</th>
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<tr>
<td>Assessment</td>
<td>A procedure used to generate data required by the study</td>
</tr>
<tr>
<td>Enrollment</td>
<td>Point/time of patient entry into the study; the point at which informed consent must be obtained (i.e., prior to starting any of the procedures described in the protocol)</td>
</tr>
<tr>
<td>(Core) study</td>
<td>The (core) study will last until the primary endpoint at week 24 post first injection</td>
</tr>
<tr>
<td>Follow-up period</td>
<td>The (core) study is followed by the follow-up period which lasts until the last follow-up visit at year 5 post first injection</td>
</tr>
<tr>
<td>Investigational drug</td>
<td>The study drug whose properties are being tested in the study</td>
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<tr>
<td>Patient number</td>
<td>A number assigned to each patient who enrolls in the study; when combined with the center number, a unique identifier for each patient in the study is created</td>
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<tr>
<td>Period</td>
<td>A minor subdivision of the study timeline; divides phases into smaller functional segments such as screening, baseline, titration, washout, etc.</td>
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<tr>
<td>Phase</td>
<td>A major subdivision of the study timeline; begins and ends with major study milestones such as enrollment, randomization, completion of treatment, etc.</td>
</tr>
<tr>
<td>Plus disease</td>
<td>Pathologic tortuosity of blood vessels in the central retina</td>
</tr>
<tr>
<td>Premature patient withdrawal</td>
<td>Point/time when the patient exits from the study prior to the planned completion of all study treatments and assessments; at this time all study treatments are discontinued and no further assessments are planned</td>
</tr>
<tr>
<td>Randomization number</td>
<td>A unique identifier assigned to each randomized patient, corresponding to a specific treatment arm assignment</td>
</tr>
<tr>
<td>Rescue treatment</td>
<td>Laser photocoagulation or top-up injection of 0.20 mg ranibizumab given within four weeks after a regular injection of study drug due to failure to improve or due to further worsening of ROP. In addition, retinal laser treatment for ROP given at any other time is considered rescue treatment. If after an initial response to the first injection, a second injection is necessary after at least 4 weeks (≥ 28 days) post-injection, this is not regarded as rescue treatment but seen as a re-injection within the study protocol (see secondary endpoints).</td>
</tr>
<tr>
<td>Ridge</td>
<td>Elevated border between vascularized and non-vascularized retina</td>
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<tr>
<td>Study drug</td>
<td>Ranibizumab in two different concentrations (6 mg/ml vs. 10 mg/ml) resulting in the two doses 0.12 mg vs. 0.20 mg</td>
</tr>
<tr>
<td>Variable</td>
<td>Information used in the data analysis; derived directly or indirectly from data collected using specified assessments at specified time-points</td>
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Amendment 1

Amendment rationale

In this study currently 6 patients have been enrolled since 24\textsuperscript{th} March, 2014. The first patient has been randomized in the trial on 06\textsuperscript{th} September, 2014. It is not anticipated that this amendment will affect the treatment or the safety of the study population.

Primary purpose for the amendment is:

- to address feedback from investigators received during the study, e.g. Safety reporting
- to implement changes of SAE handling
- to implement cell pellet storage for further analysis (in addition to plasma sampling)
- to increase data quality for the follow-up visit at years 2 and 5 by additional details

Changes to protocol

The major changes to the previous protocol, version 1.1 from 14\textsuperscript{th} March, 2014, and the sections affected, are detailed below.

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<td>Addition of PD Dr. Stahl as sponsor’s representative</td>
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<td>Addtion of pediatric examination (year 5)</td>
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Protocol synopsis

Title of study:
Multicenter randomized double masked parallel design exploratory study to assess safety and efficacy of two different doses of intravitreal anti-VEGF treatment with ranibizumab (0.12 mg vs. 0.20 mg) in infants with retinopathy of prematurity (ROP).

Study purpose:
This study is designed as an exploratory study to assess safety and efficacy of two different doses of the anti-VEGF agent ranibizumab (0.12 mg vs. 0.20 mg) in the treatment of infants with retinopathy of prematurity. Furthermore it shall help to improve safety in the treatment of ROP and provide explorative data on long-term effects of ranibizumab after intravitreal injection in neonates.

Objectives:
Primary objective:
The primary objective is to assess clinical efficacy of ranibizumab in children with ROP. Efficacy is determined by the number of infants without need for rescue treatment up to week 24 post first injection. Re-injection of study dose is not considered rescue treatment if applied after an initial response to treatment and after at least 4 weeks post injection.

Secondary objectives:
- To assess regression of plus disease during core study
- To assess regression of preretinal vascularized ridge during core study
- To assess progression of peripheral intraretinal vascularization beyond ridge during core study
- Safety determined by number and kind of AEs and SAEs per group during core study
- To compare the changes in vascular endothelial growth factor (VEGF) levels in the systemic circulation during core study
- To assess the number of re-injections of study dose during core study
- To assess the number of patients progressing to stage 4 or 5 ROP during core study
- To assess the number of patients with complete vascularization of the peripheral retina to within one disc diameter of the ora serrata during core study

Explorative objectives:
- To assess the number of late recurrences of ROP during the follow-up period (up to 5 years post first injection)
- To assess the number of patients progressing to stage 4 or 5 ROP after the end of the core study
- To assess the number of patients with complete vascularization of the peripheral retina to within one disc diameter of the ora serrata after the end of the core study
- Long-term outcomes
  a) Ophthalmological development (checked by standard ophthalmic examinations)
  b) Pediatric development (checked by pediatrician)
- Long-term safety of ranibizumab in the treatment of ROP evaluated by number and kind of AEs or SAEs per group between the end of the core study and the end of the follow-up period
Population:
The study population will consist of neonates with retinopathy of prematurity of defined stages (see below). Staging will be performed as defined by the International committee for the classification of retinopathy of prematurity and the German guidelines for ROP screening and staging. 40 patients (20 patients in each treatment arm) meeting eligibility criteria will be enrolled at approximately 10 sites in Germany.

Inclusion/Exclusion criteria:

Inclusion criteria:
1. Bilateral ROP in zone I (stage 1+, 2+, 3+/-, AP-ROP) or ROP in central (=posterior) zone II (stage 3+, AP-ROP). Zone I is defined as twice the distance from the optic disc to the fovea measured temporally, posterior zone II is defined as three times the distance from the optic disc to the fovea measured temporally. Treatment zones will be documented with a RetCam or a comparable imaging system (if available).
2. Legal representatives or their designates willing and able to attend regular study visits with the study infant.
3. Written informed consent to participate in the study (signed by all patient’s legal representatives).

Exclusion criteria:
1. Pediatric conditions rendering the infant ineligible to anti-VEGF treatment or to repeated blood draws as evaluated by a neonatal ICU specialist and a study ophthalmologist.
2. Congenital brain lesions significantly impairing optic nerve function.
3. Severe hydrocephalus with significantly increased intracranial pressure.
4. Advanced stages of ROP with partial or complete retinal detachment (ROP stage 4 and 5).
5. ROP involving only the peripheral retina (i.e. peripheral zone II or zone III).
6. Known hypersensitivity to the study drug or to drugs with similar chemical structures.
7. Contraindications for an intravitreal injection as listed in ranibizumab SmPC.
8. Systemic use of anti-VEGF therapeutics.
9. Use of other investigational drugs - excluding vitamins and minerals - at the time of enrollment, or within 30 days or 5 half-lives prior to enrollment, whichever is longer.

Investigational therapy:
- Ranibizumab: 6 mg/ml solution. 0.020 ml (=20 μl) to be injected intravitreally (containing 0.12 mg ranibizumab)
- Ranibizumab: 10 mg/ml solution. 0.020 ml (=20 μl) to be injected intravitreally (containing 0.20 mg ranibizumab)

Ranibizumab 6 mg/ml is approved for intravitreal injection in adults with DME in the US, ranibizumab 10 mg/ml is approved in the EU. Both concentrations are commercially available.

Patients will be treated with commercial drug in both study arms.

Study design:
In this phase II investigator initiated trial, 40 patients with retinopathy of prematurity will be enrolled. The study is using a randomized, double blind, 2-arm, parallel group design. The study ends with the primary endpoint at week 24 post first injection. Every patient will obligatorily receive one intravitreal injection per eye. If, after an
initial response to the first injection, a second injection is deemed necessary after at least 4 weeks (≥ 28 days) post-injection, this is not regarded as rescue treatment. In this case, the same dose as in the first injection will be reapplied. The same rescue and retreatment criteria then apply as after the first injection.

After 10 patients, the DSMB will review the results of these patients and decide if one of the treatment arms needs to be terminated earlier due to lack of efficacy or safety concerns. In both study arms, rescue treatment is possible at all time-points. In addition, the data review will be triggered earlier (before 10 patients have completed the core study) if more than three patients in one treatment group need rescue treatment (earlier than the first regular interim analysis).

After another 10 patients a second interim data review can be triggered if considered necessary by the DSMB. Here again the DSMB will decide about the continuation of a treatment arm based on these data.

Patients will be assigned to one of the following 2 treatment arms in a ratio of 1:1:

- Ranibizumab 0.12 mg
- Ranibizumab 0.20 mg

**Efficacy assessments:**

Fundoscopy for assessment of:

- Regression of plus disease
- Regression of preretinal vascularized ridge
- Progression of peripheral intraretinal vascularization beyond ridge

**Safety assessments:**

Safety assessments will consist of:

- monitoring and recording of all adverse events (AEs) and serious adverse events (SAEs)
- ophthalmic examinations
- neonatal / pediatric physical examinations
- measurement of vital signs
- measurement of VEGF plasma levels

**Data analysis:**

- Exploratory analyses for ranibizumab 0.12 mg versus ranibizumab 0.20 mg
- After 10 patients or if more than three patients with rescue treatment have been documented in one group the DSMB will review the results of these patients. After another 10 patients a second interim data review can be triggered if considered necessary by the DSMB. In both cases, the DSMB will decide about the continuation of a treatment arm based on the data review.
- Statistical analysis and report writing will be performed when all patients have completed the end of study visit at week 24 post first injection. Follow-up data will be collected from week 24 post injection until year 5 post injection. They will be reported in an appendix to the final study report.
## Responsibilities

<table>
<thead>
<tr>
<th>Role</th>
<th>Name</th>
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### Monitoring

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### Data Management

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### Data Safety Monitoring Board

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1 Background

Retinopathy of prematurity usually occurs in children who are born before 32 weeks gestational age. Since retinal vessels have vascularized the whole retina only at 40 weeks gestational age, the risk for developing ROP increases, the earlier a child is born due to larger areas of non-vascularized retina.

Postnatally, ROP develops in two phases. The first phase, which is induced by a relative hyperoxia at room air compared to intra-uterine environment, is characterized by a slowed growth of physiologic intraretinal vasculature, resulting in avascular retinal areas as described above. Importantly, this hyperoxic environment is present even in infants without iatrogenic supplementation of oxygen. During the third trimester, oxygen partial pressure in utero would be around 30 mmHg, whereas after premature birth it rises up to 60 or even 100 mmHg. At an age of around 32 weeks, the second phase of ROP begins and hyperoxia turns into hypoxia. Reason for this change is maturation and increased metabolic demand of the not fully vascularized retina, which then starts to express VEGF, a hypoxia-induced growth factor, in order to attract more vessels to supply the required amount of oxygen and nutrients. This results, however, not in controlled growth of physiologic blood vessels, but in an uncontrolled and aberrant sprouting of vessels out of the retinal tissue towards the vitreous due to unphysiologically high intravitreal levels of VEGF and associated loss of a guided and organized growth factor gradient that would normally steer retinal vessels towards their targets.

Due to this pathomechanistic understanding of ROP, the first treatment attempts have focused on reducing the amount of avascular retina in order to reduce the expression of angiogenic growth factors. In 1986, the multicenter study CRYO-ROP started. In this two armed clinical trial, ablation of the avascular part of the retina through cryotherapy was tested in one arm, whereas children in the other arm were observed without intervention. Already the preliminary results of the study showed a reduction of incidence of unfavourable outcomes in the cryotherapy arm from 43 to 21.8 %. Nevertheless, the results were far away from an optimal treatment for ROP.

Later on, argon and diode laser treatment were developed and tested in ROP. Similar to cryotherapy, retinal tissue destroyed by ablative laser therapy does not express VEGF anymore and aberrant vessel growth is consequentially reduced. Several randomized clinical trials were able to show that laser was at least as effective as cryotherapy. Results of a 10 year follow-up study directly comparing cryotherapy to laser coagulation show that eyes treated with laser coagulation had superior functional and structural outcome compared to eyes treated with cryotherapy. Based on these and several other results stating that laser is at least as effective as cryotherapy and has a better outcome, photocoagulation became more and more popular and has now completely substituted cryotherapy in most countries. However, the fact remains, that both methods destroy retinal tissue in order to reduce VEGF overexpression. That tissue is forever lost for visual function. In addition, scarring from retinal cryo or laser therapy can lead to retinal traction resulting in macular fold, thus impeding central visual acuity in treated children.
With the advent of intravitreal anti-VEGF therapy, another option to attenuate VEGF-overexpression in retinal diseases has made its way into clinical practice. Initially introduced for exudative age-related macular degeneration (AMD), diabetic macular edema and edema secondary to retinal vein occlusion, anti-VEGF therapy has also been used in ROP infants in now numerous smaller studies and one large clinical trial. The first results from this large trial, the BEAT-ROP study, have compared the efficacy of intravitreal bevacizumab monotherapy (0.065 mg in 0.025 ml) with the efficacy of laser coagulation in reducing the recurrences of ROP 5. Zone I and posterior zone II diseases combined showed a significantly higher rate of recurrences in the laser treated arm than in the bevacizumab treated arm (26 % vs. 6 %) 5. Based on these results, bevacizumab has become an accepted treatment option for ROP that is also embraced by the German Ophthalmic societies DOG, BVA and RG 6. Nevertheless, the BEAT-ROP study leaves several questions unanswered. For example, no dose finding study has ever been performed. Most of the published case reports and also the BEAT-ROP study used half the adult dose of bevacizumab in ROP infants. Corrected for body weight, this results in a much higher systemic exposure of anti-VEGF agent in ROP infants compared to adults. A second shortcoming of the BEAT-ROP study is that systemic effects of bevacizumab were not explored, nor was systemic suppression of VEGF after injection even measured. From adult studies, however, we know that intravitreally injected bevacizumab suppresses systemic VEGF levels for several weeks 7. This poses a potential safety concern in ROP infants where systemic VEGF might be required for normal development of several organs including in particular lung and brain. Ranibizumab, in contrast, has much shorter systemic half-live, thus potentially reducing the risk of systemic side effects after intravitreal anti-VEGF therapy in ROP. In addition, there are also safety concerns with regard to bevacizumab, when a drug is used in this extremely vulnerable population that is not even approved for an intravitreal application in adults. Ranibizumab, in contrast, has been designed for intravitreal use and is approved for adults for the treatment of neovascular age-related macular degeneration, diabetic edema following retinal vein occlusion, diabetic macular edema and CNV due to pathologic myopia.

We therefore designed this study using ranibizumab which is approved for intravitreal use and has superior pharmacokinetic properties compared to bevacizumab. We also aim for using significantly lower doses of anti-VEGF substance than the one used in the BEAT-ROP study. This decision is based on several reports that demonstrate that lower doses of anti-VEGF substance are sufficient to control ROP 8, 9 as well as on experimental data in animal studies demonstrating better physiologic vascularization of avascular retinal areas with lower doses of anti-VEGF agents, while controlling disease activity at the same time 10. The 2-armed design, comparing 0.12 mg with 0.20 mg ranibizumab will help to find the most appropriate dose of ranibizumab for ROP. Allowing re-injections as needed after a 4-week interval will allow a titration of anti-VEGF substance to meet the needs of an individual infant. This is important, since VEGF levels significantly vary between infants 11 and some infants may require only one injection, others two or more. Different from a one-time high bolus treatment given in the BEAT-ROP study, this study design of allowing re-injections of lower doses as needed will help
to avoid overtreatment. In addition, repeated injection of ranibizumab on a four-weekly basis is an accepted and approved standard treatment in adults.

This study will furthermore add novel information on changes in VEGF plasma levels after treatment by measuring systemic VEGF levels at predefined time-points.

Overall, this study has the potential to advance our understanding of ROP pathophysiology while at the same time improving ROP treatment options and potentially increasing the patients’ chances of developing useful visual function despite the presence of a severe and vision-threatening disease. The incorporation of laser-therapy and/or top-up injections as rescue treatment ensures that all infants in the study are treated appropriately according to their individual needs.

2 Study purpose

This study is designed as an exploratory study to assess safety and efficacy of two different doses of the anti-VEGF agent ranibizumab (0.12 mg vs. 0.20 mg) in the treatment of infants with retinopathy of prematurity. Furthermore, it shall help to improve safety in the treatment of ROP and provide explorative data on long-term effects of ranibizumab after intravitreal injection in neonates.

3 Objectives

3.1 Primary objective

The primary objective is to assess clinical efficacy of ranibizumab in children with retinopathy of prematurity. Efficacy is determined by the number of infants without need for rescue treatment up to week 24 post first injection. Re-injection of study dose is not considered rescue treatment if applied after an initial response to treatment and after at least 4 weeks post injection (≥ 28 days).

3.2 Secondary objective(s)

- To assess regression of plus disease during core study
- To assess regression of preretinal vascularized ridge during core study
- To assess progression of peripheral intraretinal vascularization beyond ridge during core study
- Safety determined by number and kind of AEs and SAEs per group during core study
- To compare changes in vascular endothelial growth factor (VEGF) levels in the systemic circulation during core study
- To assess the number of re-injections of study dose during core study
- To assess the number of patients progressing to stage 4 or 5 ROP during core study
- To assess the number of patients with complete vascularization of the peripheral retina to within one disc diameter of the ora serrata during core study

3.3 Explorative objectives

- To assess the number of late recurrences of ROP during the follow-up period (up to five years post first intravitreal injection)
- To assess the number of patients progressing to stage 4 or 5 ROP after the end of the core study
- To assess the number of patients with complete vascularization of the peripheral retina to within one disc diameter of the ora serrata after the end of the core study
- Long-term outcomes
  a) Ophthalmological development (checked by standard ophthalmic examinations)
  b) Pediatric development (checked by pediatrician)
- Long-term safety of ranibizumab in the treatment of ROP evaluated by number and kind of AEs or SAEs per group between the end of the core study and the end of the follow-up period

4 Study design

In this phase II investigator initiated trial, 40 patients with ROP of defined stages will be enrolled. The study is using a randomized, double blind, 2-arm, parallel group design (ranibizumab 0.12 mg vs. ranibizumab 0.20 mg).

The study ends with the primary endpoint at week 24 post first intravitreal injection. The study is followed by a 4.5 year safety and efficacy follow-up period (last visit at 5 years post first injection, see also appendix 3).

Evaluation of efficacy of ranibizumab will be performed by an investigator blinded to treatment dose. Additionally, the development of disease activity will be documented with retinal photographs using a RetCam system or a comparable imaging system before, 1 week and 1 month after injection and at week 24 post first injection if such an imaging system is available.

At visit 1 (screening visit; to occur between day -3 and day -1, see table 7-1), after informed consent is signed by all legal representatives, patients are enrolled into the study. Then procedures to allow assessment of the study eligibility criteria will be performed: ROP stage and zone will be re-evaluated and a neonatologist has to examine the child’s eligibility to participate in the trial. If the neonatologist or the ophthalmologist decides that the child does not meet all inclusion criteria, this child will be seen as a screening failure and will not be randomized. Screened failed patients (screening failures) will not be included in the total
number of patients and screening failures will be replaced with newly enrolled patients until a total number of 40 eligible patients are enrolled.

At the baseline visit on day 0, patients whose eligibility is confirmed will be randomized into one of the two treatment arms. Before medication is applied, retinal photographs will be made to document baseline status of ROP, if RetCam system or a comparable imaging system is available. These baseline images can be taken on the day prior to injection or on the injection day at the discretion of the treating physician. Patients will either receive ranibizumab 0.12 mg or ranibizumab 0.20 mg intravitreally once on day 0 following standard procedures for intravitreal injections adapted for ROP infants as described by the German Ophthalmic Society (DOG), the German Retina Society (RG) and the German Ophthalmologists Association (BVA)\(^6\). The injection and all study exams and documentations will be performed by an ophthalmologist blinded to treatment dose (or where appropriate by a blinded study nurse).

Only children where stage and zone of ROP fulfills the inclusion criteria in both eyes will be included in the study. Therefore, all enrolled children will receive bilateral injection of the study drug. Those two injections should be applied on the same day, but can be applied on two consecutive days (this decision lies at the discretion of the treating ophthalmologist). One vial of ranibizumab will be used per eye. Randomization will be per patient not per eye and the child will be treated with the same concentration of ranibizumab in both eyes. The study therapy consists of one obligatory intravitreal application of ranibizumab per eye. After that treatment, children are monitored on a regular basis (see table 7-1). Clinical signs, laboratory parameters and adverse events will be evaluated as described in table 7-1. If after an initial response to the first injection (which needs to be documented in the efficacy assessments) a second injection is deemed necessary after at least four weeks (\(\geq 28\) days), re-injection of the same dose of ranibizumab can be performed. This is not regarded as rescue treatment and therefore not regarded as missing the primary endpoint. In contrast, rescue treatment is defined as either laser treatment for ROP or an injection of 0.20 mg ranibizumab within four weeks after a regular injection due to lack of initial response or rapid relapse of disease activity. In addition, retinal laser treatment for ROP given at any other time is considered rescue treatment.

A maximum number of 3 re-injections can be applied. If the child needs further treatment thereafter, this is defined as lack of efficacy and rescue treatment needs to be administered. In case a third re-injection is seen necessary by the treating ophthalmologist, the coordinating investigator must be involved in the decision process.

After 10 patients, the DSMB will review the results of these patients and decide if one of the treatment arms needs to be terminated earlier due to lack of efficacy or safety concerns. In addition, the data review will be triggered earlier (before 10 patients have completed the core study) if more than three patients in one group need rescue treatment (earlier than the first regular interim analysis). After another 10 patients, a second interim data review can be triggered if considered necessary by the DSMB. Here again the DSMB will decide about the continuation of a treatment arm based on the reviewed data.
5 Population

The study population will consist of premature infants who develop ROP requiring treatment according to the current guidelines of the German ophthalmic society (DOG)\(^6\)\(^{,12}\). The study is designed as a German multi-center study involving approximately 10 centers nationwide. 40 patients meeting eligibility criteria will be enrolled to achieve 20 evaluable subjects in each treatment arm. No gender ratio has been stipulated in this trial as the results of previous preclinical and clinical studies did not indicate any difference in the effect of ROP treatment in terms of efficacy and safety.

5.1 Inclusion/exclusion criteria

The investigator must ensure that only patients who meet all inclusion and who do not meet any exclusion criteria are offered enrollment in the study. No additional exclusion criteria can be applied by the investigator, in order that the study population will be representative of all eligible patients.
Inclusion criteria:

1. Bilateral ROP in zone I (stage 1+, 2+, 3+/-, AP-ROP) or ROP in central (=posterior) zone II (stage 3+, AP-ROP)\. Zone I is defined as twice the distance from the optic disc to the fovea measured temporally \(^{13}\), posterior zone II is defined as three times the distance from the optic disc to the fovea measured temporally \(^{13}\).

   Treatment zone will be documented with retinal photographs using a RetCam or a comparable imaging system if available.

2. Legal representatives or their designates willing and able to attend regular study visits with the study infant.

3. Written informed consent to participate in the study (signed by all patient’s legal representatives).

Exclusion criteria:

1. Pediatric conditions rendering the infant ineligible to anti-VEGF treatment or to repeated blood draws as evaluated by a neonatal ICU specialist and a study ophthalmologist.

2. Congenital brain lesions significantly impairing optic nerve function.

3. Severe hydrocephalus with significantly increased intracranial pressure.

4. Advanced stages of ROP with partial or complete retinal detachment (ROP stage 4 and 5).

5. ROP involving only the peripheral retina (i.e. peripheral zone II or zone III).

6. Known hypersensitivity to the study drug or to drugs with similar chemical structures.

7. Contraindications for an intravitreal injection as listed in ranibizumab SmPC.

8. Systemic use of anti-VEGF therapeutics.

9. Use of other investigational drugs - excluding vitamins and minerals - at the time of enrollment, or within 30 days or 5 half-lives prior to enrollment, whichever is longer.

5.2 Premature patient withdrawal

Patients must be withdrawn from the study if any of the legal representatives withdraws his/her consent to the study. The investigator may withdraw a subject if, in his or her clinical judgment, it is either in the best interest of the subject or if the subject cannot comply with the protocol. Whenever possible, the tests and evaluations listed for the termination visit should be carried out. The sponsor should be notified of all study withdrawals as soon as possible.
Subjects may discontinue their participation in the trial at any time without prejudice. If a subject’s legal representative withdraws consent, the sponsor will have full access to the subject’s medical records assessed for this trial up to the point of patient withdrawal, including termination information in accordance with the EU data protection laws.

For patients who are lost to follow-up (i.e., those patients whose status is unclear because they fail to appear for study visits without stating an intention to withdraw), the investigator should show "due diligence" by documenting in the source documents steps taken to contact the patient’s legal representatives, e.g., dates of telephone calls, registered letters, etc.

Withdrawn patients will not be replaced by newly enrolled patients unless they are withdrawn due to screening failure.

6 Treatment

6.1 Patient numbering

Each patient is uniquely identified in the study by a combination of his/her center number and patient number. The center number is assigned by the sponsor to the investigative site. Upon signing the informed consent form, the patient is assigned a patient number by the investigator. At each site the first patient is assigned patient number 1, and subsequent patients are assigned consecutive numbers (e.g., the second patient is assigned patient number 2, the third patient is assigned patient number 3 and so on). Once assigned to a patient, a patient number will not be reused. If the patient fails to be randomized for any reason, the reason for not being randomized and the demography data will be entered on the Screening Log.

6.2 Investigational and control drugs

- Ranibizumab: 6 mg/ml solution. 0.020 ml (=20 μl) to be injected intravitreally (containing 0.12 mg ranibizumab)
- Ranibizumab: 10 mg/ml solution. 0.020 ml (=20 μl) to be injected intravitreally (containing 0.20 mg ranibizumab)

Ranibizumab 6 mg/ml is approved for intravitreal injection in adults with DME in the US, ranibizumab 10 mg/ml is approved in the EU. Both concentrations are commercially available.

Patients will be treated with commercial ranibizumab solution in both study arms.

Each vial will be labeled with the appropriate information. Medication labels will comply with the legal requirements and be printed in German. The storage conditions will be described on the label. Ranibizumab is formulated as a sterile solution aseptically filled in a sterile glass vial. Each vial contains ranibizumab in an aqueous solution (pH 5.5) with histidine, trehalose and polysorbate 20. The vial contains no preservative and is suitable for single use only.
Ranibizumab must be stored according to the label instructions and it has to be kept in a secure locked facility.

The MAH will provide sufficient supplies of ranibizumab (in both concentrations) for treatment use to allow for completion of the study (included in this supply are all vials for re-injection or rescue injection of 0.20 mg ranibizumab).

### 6.3 Treatment arms

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

- **Ranibizumab 0.12 mg arm**: one intravitreal injection of 0.020 ml ranibizumab of the 6 mg/ml solution
- **Ranibizumab 0.20 mg arm**: one intravitreal injection of 0.020 ml ranibizumab of the 10 mg/ml solution

If, after an initial response to the first injection (the initial response needs to be documented within the efficacy assessment), a second injection is deemed necessary after at least four weeks (≥ 28 days) post-injection, the same dose as in the first injection can be re-applied in both treatment arms. After re-injection, the same rescue and re-treatment criteria apply as after the first injection. A maximum number of 3 re-injections can be applied. In case a third re-injection is seen necessary by the treating ophthalmologist, the coordinating investigator must be involved in the decision process. Each intravitreal application must be recorded on the paper CRF. During the first 4 weeks following an injection a more frequent follow-up of the patient’s condition is necessary. Therefore, if a reinjection occurs, the visit schedule will be realigned to follow the schedule after the initial injection (see table 7-1 and appendix 2). An additional CRF will be provided in this case with visits numbered R1.3, R1.4 etc. for the first re-injection, R2.3, R2.4 etc. for the second re-injection and so on. If a re-injection is administered less than four weeks before the last visit (i.e. at > 20 weeks after the first injection), this patient is followed-up and documented for at least another 4 weeks with weekly visits. For all patients, the primary endpoint is at 24 weeks after the first injection.

### 6.4 Treatment assignment

Patients will be randomized 1:1 to one of the two treatment arms listed in 6.3.

Stratification by gestational age at birth will be implemented with a cut-off point at 25 weeks gestational age in order to create comparable treatment groups.

The randomization numbers will be generated using the following procedure to ensure that treatment assignment is unbiased and concealed from patients and investigator staff: two randomization lists will be produced, one for each stratum, by or under the responsibility of the sponsor using a validated system that automates the random assignment of treatment arms to randomization numbers in the specified ratio. The randomization numbers will be distributed centrally via an internet application.
At visit 2, if an infant fulfills all inclusion and no exclusion criteria, the unblinded site personnel who will prepare the ranibizumab injection will request a randomization number for the infant of the respective stratum from the internet application. The randomization number assigns the infant to one of the treatment arms and the unblinded site personnel will be informed by the internet application which concentration has to be used. All ophthalmologists and neonatologists participating in study examinations and decisions about necessity of rescue treatment will be blinded to the treatment concentration.

The unblinded site personnel will enter the randomization number received by the internet application in the CRF of the infant, but not the treatment arm or concentration. The treatment arm/concentration will be noted on a Log and this one will be stored in a secure place so that no study personnel except the unblinded staff have access to it. The internet application will be secured by a password that is known only to the unblinded site personnel.

To ensure that emergency unblinding is possible at any time, a set of sealed treatment emergency cards (one card for each randomization number, containing the randomization number printed on the outside and the treatment arm in the sealed inside) will be sent to each study center and to the drug safety department at CROLLL. The process of unblinding using treatment emergency cards is described in section 6.6.6. Unopened treatment emergency cards have to be returned to the monitor at the end of the study.

6.5 Treatment blinding

During the whole trial the blinding of the treatment will be ensured for all involved persons (patients, their parents/legal representatives, persons performing the assessments and data analysts). These persons will remain blind to the identity of the treatment from the time of randomization until database lock of the core phase.

The only exception is the unblinded site personnel and his/her back-up, who will be clearly identified in the site personnel log. The unblinded site personnel will be responsible for preparation of the injection, also in case a re-injection is deemed necessary after an initial response to the injection.

The blinded ophthalmologists and neonatologists will perform all outcome assessments of clinical response as described in the protocol. The ophthalmologist will also determine clinical success or failure of treatment, and make a decision on rescue treatment or on the need for a re-injection. The blinded assessor will also be responsible for the evaluation of all adverse events and their causality. In case rescue treatment is necessary, the blinded ophthalmologist will be unblinded.

6.6 Treating the patient

6.6.1 Dispensing the study drug

Treatment may consist of either 0.12 mg or 0.20 mg ranibizumab intravitreal injection depending on the treatment arm a patient was assigned to. In order to administer this amount
of study drug, 0.020 ml of the following concentrations will be administered: 6 mg/ml concentration, to achieve 0.12 mg, 10 mg/ml concentration to achieve 0.20 mg.

Intravitreal ranibizumab injections will be administered according to standard procedures for intravitreal injection adapted for ROP infants.\(^6\)

If after an initial response to an injection (the initial response needs to be documented within the efficacy assessment), activity of ROP relapses, a second injection with the same study drug amount shall be applied after at least four weeks (≥ 28 days) post-injection. This is not regarded as rescue treatment. After the second injection, the same rescue and re-injection criteria apply as after the first injection. A maximum number of three re-injections can be applied. In case a third re-injection is seen necessary by the treating ophthalmologist, the coordinating investigator must be involved in the decision process.

### 6.6.2 Permitted study drug dose adjustments

No adjustments of the ranibizumab dosing regimen described in section 6.6.1 will be allowed.

### 6.6.3 Rescue treatment and medication

Rescue treatment can be either retinal laser photocoagulation or injection of 0.20 mg ranibizumab. The choice between these two options is at the discretion of the treating ophthalmologist. In both treatment arms, rescue treatment is possible at all time-points. If a child needs further treatment after a third re-injection has been applied, rescue treatment has to be administered.

Rescue treatment is defined as laser treatment or top-up injection given within four weeks after a regular study injection due to failure to improve or due to further worsening of ROP. In addition, retinal laser treatment for ROP given at any other time is considered rescue treatment. If after an initial response to the first injection, a second injection is deemed necessary after at least four weeks (≥ 28 days) post-injection, this is not regarded as rescue treatment if the same dose as in the first injection will be re-applied. The same rescue criteria then apply as after the first injection. Use of rescue treatment in either eye must be recorded on the respective CRF page. All infants requiring rescue treatment will be counted as missing the Primary Endpoint. Nevertheless, the infants should stay in the clinical trial and further evaluation will be performed per infant and per eye. It is also planned that these infants run through the 4.5 year safety and efficacy follow-up phase.

If the blinded ophthalmologist decides that rescue treatment is needed, he or she will be unblinded after that decision is documented. In case a regular re-injection as defined above is deemed necessary by the blinded ophthalmologist, he/she will not be unblinded. Instead, the unblinded site personnel will prepare the same concentration of ranibizumab as in the initial injection and the ophthalmologist will re-inject the same dose of ranibizumab (without being unblinded). If rescue treatment needs to be applied, the child will remain in the trial on an observational basis. Also during the follow-up period, the child shall have all assessments scheduled.
6.6.4 Other concomitant treatment

Use of other investigational drugs is NOT allowed after the start of the study drug and throughout the entire study duration.

The investigator should instruct the patient’s legal representatives to notify the study site about any new medications the patient takes after the start of the study drug. There is no prohibited concomitant medication with the exception of systemic VEGF inhibitors. All medications and significant non-drug therapies (including physical therapy and blood transfusions) administered after the patient starts treatment with study drug and for the duration of the core study must be listed on the concomitant medications/significant non-drug therapies CRF.

6.6.5 Study treatment discontinuation

Study drug discontinuation (i.e. decision against re-injections) can be triggered both by the patient’s legal representatives and the treating physician. A maximum number of 3 re-injections can be applied. If the child needs further treatment thereafter, rescue treatment has to be administered. ROP treatment will then be performed as medically appropriate by the physician.

Reasons for discontinuation of study treatment are as follows:

- Lack of efficacy (a fourth re-injection is required)
- Injection related endophthalmitis
- Repeat occurrence of other severe adverse events considered likely to be related to injection of study medication

Study treatment discontinuation must not lead to study discontinuation of a patient. If a patient’s legal representatives or the investigator choose to stop treatment, the investigator should encourage the legal representatives to continue study participation on an observational basis, i.e. study examinations only. The last date of study treatment should be entered into the Study Completion CRF and the reason for discontinuing study treatment should be given on the comments page. If a patient who discontinued study treatment performed all scheduled study procedures and measurements, he will be counted as a study completer.

6.6.6 Unmasking of treatment assignment

Regular Unmasking

The unblinded site personnel should adhere to the randomized treatment and ensure that unblinding only happens according to the protocol. The study will be unblinded regularly only after data base lock of the core phase. By that time unblinding codes will be made available to personnel involved in data analysis. Study personnel involved in study assessments shall be kept blinded for infants who still participate in the follow-up phase.
Unmasking in case of rescue treatment

If rescue treatment is seen as medically appropriate by the investigating ophthalmologist, rescue treatment can be applied at every time during the study. After deciding that rescue treatment is necessary, the investigator opens the treatment emergency card with the randomization number of the respective patient printed on the outside. The card contains the information of the treatment arm on the inside. The opened emergency card has to be signed (date of opening and signature) by the opening investigator and stored in the patient file.

Emergency Unmasking

In the event of a life-threatening medical emergency that requires immediate unmasking, or in the event of an unexpected serious adverse event judged by the investigator as related to study drug, unmasking will be implemented following the decision of the investigator that unmasking is necessary. If the decision for unmasking is taken, the investigator opens the treatment emergency card with the randomization number of the respective patient printed on the outside. The card contains the information of the treatment arm on the inside. The opened emergency card has to be signed (date of opening and signature) by the opening investigator and stored in the patient file.

Consequences of emergency unblinding and unblinding in case of rescue treatment for the patient’s treatment

Patient’s treatment with the investigational medicinal product can be continued after unblinding. Further treatment decisions are at the discretion of the investigator. The patient will continue to be followed-up and documented in the CRF (also during the follow-up period).

6.6.7 Study completion and post-study treatment

All subjects entered into this trial will be treated obligatorily with one ranibizumab injection per eye. If, after an initial response to the first injection, a second injection is deemed necessary after at least four weeks (≥ 28 days) post-injection, the same dose as in the first injection can be re-applied. This is not regarded as rescue treatment. The maximum number of re-injections is three. In case a third re-injection is seen necessary by the treating ophthalmologist, the coordinating investigator must be involved in the decision process.

After the end of the study (24 weeks after the first injection of IMP or 4 weeks after the last re-injection whichever occurs later), the treating ophthalmologist will decide on further examinations and intervals as seen medically appropriate. Continuation of treatment after the core study – if necessary – is at the discretion of the treating physician. Any treatment beyond week 24 post first injection (i.e. after the evaluation of the primary endpoint) will happen out of scope of this clinical study. However, possible recurrences of ROP activity and possible treatments given after the end of the core study will be documented during the follow-up period at 1 and 5 years post first injection.
7 Visit schedule and assessments

Table 7-1 lists all assessments and indicates with an “X” the visits when they are performed.

All data obtained from the assessments listed in table 7-1 and described in detail in the subsections below must be supported in the patient’s source documentation. A medical record can also be used as source documentation. Assessments that generate data for database entry and which are recorded on CRFs are listed using the CRF name.
<table>
<thead>
<tr>
<th>Visit number</th>
<th>1</th>
<th>2</th>
<th>3</th>
<th>4</th>
<th>5</th>
<th>6</th>
<th>7</th>
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<th>11</th>
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<td>BSL and treatment</td>
<td>Observation period</td>
<td>End of study</td>
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<td></td>
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<td></td>
<td></td>
</tr>
<tr>
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<td>Day 0 (+1)</td>
<td>Day 1</td>
<td>Day 3 (±1)</td>
<td>Day 7 (±1)</td>
<td>Day 14 (±2)</td>
<td>Day 21 (±2)</td>
<td>Day 28 (±2)</td>
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<td>week 20</td>
<td>week 24</td>
<td></td>
<td></td>
</tr>
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<td>Randomization</td>
<td>X</td>
<td>Injection of study drug</td>
<td>X</td>
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<td>Concomitant medication (incl. supplemental oxygen requirement)</td>
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<tr>
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<td>X</td>
</tr>
<tr>
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<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
<td>X</td>
<td>X</td>
</tr>
<tr>
<td></td>
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<td>X</td>
<td>(X)</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
<td>X</td>
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<td>X</td>
</tr>
</tbody>
</table>

* ophthalmic examinations by indirect ophthalmoscopy including assessment for postoperative intraocular infection where appropriate.
including baseline measurement for efficacy assessment and efficacy assessment after an injection has taken place and including assessment for postoperative intraocular infection on day 1 and 3 after injection.

RetCam documentation shall be done if a RetCam is available. Also other comparable imaging systems able to document ROP stage and zone can be used. The baseline images can be taken at day 0 or day 1 at the discretion of the treating ophthalmologist. An additional retinal photograph to the ones listed in table 7-1 shall be taken in all cases of recurrence and need for rescue treatment or re-injection.

For visits 11-15 patients only need to come to the eye clinics.

All Serious Adverse Events have to be reported immediately after the signing of the Informed Consent. All Adverse Events have to be reported immediately after the first injection.

Assessments marked with an X are obligatory if health condition of the infant allows blood withdrawal, assessments marked with an (X) can be done additionally at the discretion of the treating physician.
The blood draws should be done in combination with other regular blood draws to avoid an additional puncture.

The bilateral injection of ranibizumab can be split to be performed on two consecutive days (at the discretion of the treating ophthalmologist and according to local routine).

At 24 weeks post first injection, the last regular study visit takes place. If a late re-injection is applied, the patient is in all cases at least followed-up with weekly study visits for 4 weeks after injection.

The table above outlines all required study visits. Additional visits can be necessary and performed at the discretion of the treating physician at any time. In this case, the acquired data on ROP disease activity from the additional visits shall be documented within the study CRFs.

If at ≥ 28 days after the first injection a re-injection is necessary, post-injection assessments shall take place exactly like after the first injection (day 1, day 3, then week 1, etc.). In this case, the new assessment schedule replaces the one triggered by the first injection. End of the study, however, remains 24 weeks after the first injection.

At 1 year (+/- 2 months), 2 years (+/- 3 months) and 5 years (+/- 6 months) after the first intravitreal injection, exploratory follow-up visits are planned.
Screening (3 to 1 days prior to drug administration) (visit 1)

According to the normal ROP screening procedures for prematurely born infants, an ophthalmologist checks the prematurely born children for any signs of ROP in line with current screening guidelines. If the ophthalmologist finds a bilateral ROP zone I (stage 1+, 2+, 3+/- or AP-ROP) or a ROP in central zone II (stage 3+, AP-ROP), he/she informs the legal representatives about the possibility of participation in the trial.

If all legal representatives are willing to let the child participate in the trial, the informed consent has to be signed by all legal representatives and the physician. From that moment on, the child is enrolled in the study.

After Informed Consent has been obtained, the infant should have the following procedures performed before randomization:

- Documentation of medical history and prior medication including type and duration of supplemental oxygen requirement since birth
- Documentation of concomitant medication
- Documentation of the demographics including gestational age at birth and birth weight, height and head circumference at birth
- Examination of all inclusion/exclusion criteria
- Anterior segment exam (ophthalmic examinations by indirect ophthalmoscopy)
- Fundoscopy and staging of ROP
- Physical examination: weight, height, head circumference
- Vital signs: blood pressure, pulse, respiratory rate
- Evaluation of serious adverse events

**Baseline and treatment (visit 2)**

The following procedures should be performed before study drug administration if not indicated otherwise:

- Documentation of medical history and prior medication
- Documentation of concomitant medication including type and duration of supplemental oxygen requirement since last assessment
- Re-evaluation and documentation of inclusion/exclusion criteria
- Randomization (the blinded ophthalmologists or neonatologists must not be involved in this process!)
- Anterior segment exam (ophthalmic examinations by indirect ophthalmoscopy)
- Fundoscopy and staging of ROP (including baseline measurement for efficacy assessment)
- Documentation with retinal photographs using the RetCam photographic system or a comparable imaging system if available (can be performed on the day prior to injection or on the injection day at the discretion of the treating physician)
- Physical examination: weight, height, head circumference
- Vital signs: blood pressure, pulse, respiratory rate
- Evaluation of (serious) adverse events
- Blood sample collection for plasma sample and cell pellet storage (at least 200 µl full blood executed in combination with regular blood draws to avoid an additional puncture; details regarding sample acquisition and handling will be provided separately in the lab manual)

**Randomization**

After enrollment into the study, the unblinded site personnel receives randomization information via an online tool. The blinded ophthalmologists and neonatologists who will
perform the treatment and the study exams after treatment must not be involved in this process and will be informed about the randomization number only.

**Application of study drug**

The study drug injection is prepared by an unblinded site staff. Study drug injection is performed by a blinded ophthalmologist according to standard procedures for intravitreal injection adapted for ROP infants.

**During Observation period (according to study schedule, see table 7-1)**

- Documentation of concomitant medications including type and duration of supplemental oxygen requirement since last assessment
- Anterior segment exam (ophthalmic examinations by indirect ophthalmoscopy)
- Fundoscopy and staging of ROP including efficacy assessment
- Assessment of clinical signs and symptoms of postoperative intraocular infection as assessed by anterior segment exam and fundoscopy. The location, size and description of a possible lesion must be recorded in detail in the CRF
- Documentation with retinal photographs using the RetCam photographic system or comparable imaging system (if RetCam/comparable imaging system is available) 1 week and 1 month after the injection
- Physical examination: weight, height, head circumference
- Vital signs: blood pressure, pulse, respiratory rate
- Evaluation of (serious) adverse events
- Blood sample collection for plasma sample and cell pellet storage (at least 200 μl full blood) 1 week, 3 weeks and 5 weeks after injection are obligatory if health condition of the child allows. At week 2, 4 and 6, additional blood sample collection is optional and at the discretion of the treating physician (details regarding sample acquisition and handling will be provided separately in the lab manual). All samples should be taken in combination with regular blood draws to avoid an additional puncture.

Table 7-1 outlines all required study visits. Additional visits can be necessary based on the patient’s clinical condition and will be performed at the discretion of the treating physician. In case of additional exams, the acquired data on ROP disease activity shall be documented within the study CRFs.
End of Study Visit (at week 24 post first injection)

- Assessment of concomitant medications including type and duration of supplemental oxygen requirement since last assessment
- Anterior segment exam by indirect ophthalmoscopy
- Fundoscopy and staging of ROP including efficacy assessment
- Documentation with retinal photographs using the RetCam photographic system or a comparable imaging system if available
- Physical examination: weight, height, head circumference
- Vital signs: blood pressure, pulse, respiratory rate
- Evaluation of (serious) adverse events

The core study ends when the visit at week 24 post first injection has taken place. After a possible re-injection, the follow-up visits will be re-aligned to follow the timeline given in table 7-1, again starting with visit number 3 (see appendix 2). This means that after re-injection, the first follow-up visits will be on day 1 and 3 followed by initially weekly visits irrespective of the timeline for follow-up visits resulting from the first injection. In other words, the follow-up visit schedule triggered by the first injection will be replaced by the new follow-up schedule triggered by the re-injection. In case of a re-injection, the patient will be controlled and documented for at least another 4 weeks with weekly study visits.

Follow-up – 1, 2 and 5 years after intravitreal injection

The core study ends with the primary endpoint at 24 weeks post first injection followed by an exploratory follow-up period of about 4.5 years (for detailed visit schedule see also appendix 3):

At 1 year (+/- 2 months), 2 years (+/- 3 months) and 5 years (+/- 6 months) after the first intravitreal injection follow-up visits are planned.

At the follow-up visit at year 1 the following examinations will be done:
- Ophthalmological observation (determination of the orthoptic status, cycloplegic retinoscopy, refraction, slit lamp exam, IOP and fundoscopy; optionally a documentation with retinal photographs can be performed)
- Documentation of late recurrences and any possible ROP treatments of late recurrences between the end of the core study and the 1 year follow-up visit

For the follow-up visit at year 2 the results of the Bayley-Test, which is regularly measured at this age by neonatologists and information on the presence or absence of cerebral palsy, deafness or blindness will be gathered. No additional examination will take place. The data
needs to be retrieved from the neonatal source documentation. The Bayley-Test is usually done by the trial site where the child was hospitalized after birth.

At the follow-up visit at year 5 the following examinations will be done:

- Ophthalmological observation (visual acuity, determination of the orthoptic status, cycloplegic retinoscopy, refraction, slit lamp exam, IOP, fundoscopy, if possible also OCT and fundus photographs)

- Pediatric examination will be performed in analogy to the protocol of the 5 year follow-up examination of the German Neonatal Network (GNN)\(^\text{14}\) and will be carried out in a standardized fashion by a team of investigators trained by the GNN. This standardized testing will help to increase data quality.

The ophthalmological assessments can be performed at any of the trial sites or at the site where the child was hospitalized after birth using a physician’s letter as source data. The pediatric assessments are performed by a team of travelling GNN investigators at sites convenient to the parents.

In case of moving, parents are asked for their consent to follow them up at the Residents’ Registration Office and/or the responsible health insurance in order to keep participation rate of follow-up visits at a high level (less loss to follow up). Also a postcard will be handed over to the parents for an easy notification about relocation.

In order to remind patients about the follow-up visits, the trial site will contact them through a letter. A reminder will be sent to the sites by the CRO responsible for monitoring.

### 7.1 Information to be collected on screening failures

If a subject was screened but not randomized to a treatment arm, the reason for this screening failure and demographic data have to be recorded in the Screening Log. The screening failures will not be counted for the total number of patients. The enrollment of patients in this trial will be continued until 40 analyzable patients are included.

### 7.2 Patient demographics/other baseline characteristics

The following patient data must be recorded in the CRF at the screening visit (V1):

- Date of birth*
- Gestational age at birth
- Gender
- Ethnic group
- Weight, height, head circumference at birth and at screening visit
- Vital signs: blood pressure, pulse, respiratory rate
- Past medical history and current medical conditions
- Prior medication including type and duration of supplemental oxygen requirement since birth
- Concomitant medication
- Staging of ROP per eye
- APGAR scores

* Retinopathy of prematurity is a disease in which the age of the child is extremely important since weeks and even days can change the situation in a great manner. Therefore, it is very important to document the exact date of birth in order to be able to calculate the exact age (in weeks and days) when the child develops ROP and when treatment and observation visits take place.

7.3 Treatment exposure and compliance

Regarding the study drug, the following parameters will be collected on the standard CRFs:

- Date and reason of administration (in case of re-injections, the dates and reasons of re-injections have to be documented)

This includes the primary injection, regular re-injections and rescue injections. Any deviation from the protocol in the administration of ranibizumab injections must be described in the CRF. The applied dosage per randomization number will be held in a separate folder by the unblinded site personnel.

Regarding laser treatment applied as rescue treatment, the number of applied laser spots will be documented.

Prior and concomitant medications and significant non-drug therapies including type and duration of supplemental oxygen used/required since birth and throughout the core study will be recorded in the CRFs.

7.4 Efficacy

The following assessments will be performed by an ophthalmologist blinded to treatment dose to assess the efficacy of ranibizumab injection. This assessment is part of the fundoscopy and staging of ROP assessment as outlined in table 7-1:

Efficacy assessment will be carried out by a blinded ophthalmologist experienced in ROP screening for the following characteristics:

- Regression of plus disease
- Regression of preretinal vascularized ridge
- Progression of peripheral intraretinal vascularization beyond ridge

The results of this assessment will be documented in a semi-quantitative manner on paper CRFs and in addition with retinal photographs using (if available) the RetCam photographic
system or a comparable imaging system before, one week and one month after injection, as well as at the visit at week 24 post first injection (see table 7-1). Criteria for re-injections of the study dose after an initial treatment response lasting at least 4 weeks (≥ 28 days) are the same as for the initial injection.

7.5 Safety

Safety assessments will consist of monitoring and recording of all adverse events (AEs) and serious adverse events (SAEs), ophthalmic examinations, physical examinations, checking of vital signs and laboratory evaluations (see table 7-1).

7.5.1 Adverse events

An adverse event is the appearance or worsening of any undesirable sign, symptom, or medical condition occurring after starting the study drug even if the event is not considered to be related to the study drug. Medical conditions/diseases present before starting the study drug, or that are commonly present among other prematurely born babies not receiving ranibizumab are only considered adverse events if they worsen significantly after starting the study drug. Abnormal laboratory values or test results constitute adverse events only if they induce clinical signs or symptoms, are considered clinically significant, or require therapy.

The occurrence of adverse events should be sought by non-directive questioning the legal representatives of the patient when present at a visit during the study. Adverse events also may be detected when they are volunteered by the patient’s legal representatives during or between visits or through physical examination of the infant, laboratory tests, or other assessments.

All adverse events have to be recorded on the adverse events CRF with the following information:

1. the severity grade (mild, moderate, severe)
2. its relationship to the study drug(s) (suspected/not suspected)
3. its relationship to the ocular injection (suspected/not suspected)
4. its duration (start and end dates or if continuing at final exam)
5. whether it constitutes a serious adverse event (SAE)

An SAE is defined as an event which:

- is fatal or life-threatening,
- results in persistent or significant disability/incapacity,
- requires inpatient hospitalization or prolongation of existing hospitalization, unless hospitalization is for:
- routine treatment or monitoring of the studied indication, not associated with any deterioration in condition
- elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the study drug start
- treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of an SAE given above and not resulting in hospital admission
- social reasons and respite care in the absence of any deterioration in the patient’s general condition,
- is a congenital anomaly/birth defect, or
- is medically significant, i.e., defined as an event that jeopardizes the patient or may require medical or surgical intervention to prevent one of the outcomes listed above

Due to the fact that retinopathy of prematurity is a disease, which mainly occurs in very prematurely born infants, diseases or complications of prematurity that may be classified as medically significant including death must be expected independent of any study intervention. Due to their high frequency of occurrence in this high risk study population, however, the vast majority of the events listed below will not be related to the investigational medical intervention. For these reasons, the below listed AEs will not be reported separately as SAEs (except death), but their occurrence has to be documented in the source data and CRF files. In case of a heavy or unexpected event, however, an investigator can always decide to deviate from this agreement and file an SAE report for any of the below listed conditions. In this case, an SAE form should be filled out as usual and the SAE should be reported according to protocol.

In our study cohort, the following AEs must be expected with an occurrence rate of >10%:
- hospitalization for re-treatment with study medication
- nosocomial infections (including blood culture positive sepsis, clinical sepsis, and pneumonia according to the NEOKISS definition)
- chronic lung disease of prematurity
- ventriculomegaly

The following AE must be expected with an occurrence rate of 5-10%:
- death
- necrotizing enterocolitis > 2°

The following AEs are expected with an occurrence rate of <5%:
- newly diagnosed (not pre-existing) patent ductus arteriosus requiring therapy
- periventricular leukomalacia
- porencephalic cyst
- blood transmitted infection
- transfusion reaction
- pneumothorax
- pulmonary interstitial emphysema
- pulmonary hypertension
- volvulus
- posthemorrhagic hydrocephalus / ventricular dilatation requiring shunt operation
- ventriculoperitoneal shunt infection
- systemic cytomegalovirus (CMV) infection

All AEs (common, rare and very rare) listed above will be documented in the source data and CRF files, entered in the database, and regularly evaluated by the DSMB (regardless of their casual relationship to the investigational intervention).

Documentation and reporting of these AEs as SAEs even if characterized as serious, however, is not required as they are all foreseeable events within this patient population. For the final DSMB analysis, all these SAEs will be classified as suspected expected serious adverse reactions (SESARs).

Unlike routine safety assessments, all SAEs not listed in the section above are monitored continuously and have special reporting requirements; see section 9.1.

All adverse events (whether expected or unexpected) should be treated appropriately. Treatment may include but is not limited to one or more of the following: no action taken (i.e., further observation only); concomitant medication given; non-drug therapy given; patient hospitalized/patient’s hospitalization prolonged. The action taken to treat the adverse event should be recorded on the Adverse Event CRF.

Once an adverse event is detected, it should be followed until its resolution or until it is judged to be permanent, and assessment should be made at each visit (or more frequently, if necessary) of any changes in severity, the suspected relationship to the study drug, the interventions required to treat it, and the outcome.

Information about common side effects already known about the investigational drug can be found in the Investigator Brochure (IB) or will be communicated between IB updates in the form of Investigator Notifications (IN) provided by the MAH. This information will be included in the patient informed consent and should be discussed with the patient’s legal representatives during the study as needed.

### 7.5.2 Physical examination

The following parameters will be documented during physical examination as indicated in the Assessment Schedule (Table 7-1):

- Weight
- Height
- Head circumference
- General physical examination
7.5.3 Vital signs

The following vital signs will be measured as indicated in the Assessment Schedule (Table 7-1):

- Blood pressure
- Respiratory rate
- Pulse

7.5.4 Laboratory evaluations

For laboratory evaluations blood should be taken as indicated in the Assessment Schedule (Table 7-1) in combination with regular blood draws to avoid an additional puncture. After centrifugation of the collected plasma samples, the supernatant will be stored for VEGF measurements; the remaining cell pellet will also be stored for further analysis. A central laboratory will analyze all samples. VEGF levels will be measured from plasma. If technically possible also IGF-1 or other biomarkers, that are discussed to be related to ROP, will be measured from plasma samples or cell pellets.

Instructions for the collection and shipment of samples and details on reporting of results by the central laboratory will be provided separately.

7.5.5 Ophthalmic examinations

Ophthalmic examinations include anterior segment exam (screening for corneal/lens abnormalities or persistent fetal vasculature/membranes by indirect ophthalmoscopy), fundoscopy (screening for signs of treatment-associated immediate local complications such as endophthalmitis, lens damage, retinal detachment, bleeding, media opacities, insufficient treatment response) and staging of ROP. Documentation with retinal photographs using a RetCam system or a comparable imaging system will be done if RetCam/comparable imaging system is available. They will be performed as indicated in the Assessment Schedule (Table 7-1).

The pupils will be dilated with eye drops (e.g. tropicamide). The test results will be recorded in the source documents and clinically significant abnormalities will be recorded on the Adverse Event CRF.

7.5.6 Clinically notable laboratory values and vital signs

Laboratory values will vary between individual preterm infants due to the various accompanying systemic disorders that are frequently present in these infants (e.g. sepsis, hemorrhage etc.). Laboratory values and vital signs will therefore be continuously checked by a neonatal ICU specialist during the hospitalization period and by the treating pediatrician as seen medically needed after discharge from inpatient treatment. Except for blood samples for VEGF measurements (and if technically possible other ROP biomarkers from the same sample) no extra laboratory values are documented for this study. If an adverse event, however,
manifests itself with significant changes in standard laboratory values, these changes shall be documented together with the adverse event on the paper CRFs.

### 7.6 Tolerability/acceptability

Tolerability of the treatment will be assessed through adverse event reporting in this study.

### 7.7 Resource utilization

Not applicable.

### 7.8 Health-related Quality of Life

Not applicable.

### 7.9 Pharmacokinetics

Not applicable.

### 7.10 Pharmacogenetics/pharmacogenomics

Not applicable.

### 7.11 Other biomarkers

If technically possible also other factors relevant in the context of ROP, for example insulin-like growth factor 1 (IGF-1) will be measured from the same blood samples as VEGF or from the cell pellets.

### 8 Investigational medicinal product

#### 8.1 Investigational medicinal product

Ranibizumab 6 mg/ml is approved for intravitreal injection in adults with DME in the US, ranibizumab 10 mg/ml is approved in the EU. Both concentrations are commercially available. Patients will be treated with commercial drug in both study arms.

Intravitreal injection will be 0.020 ml (=20 μl) in both treatment arms, resulting in 0.12 mg in the 6 mg/ml treatment arm and in 0.20 mg in the 10 mg/ml treatment arm.

Ranibizumab is formulated as a sterile solution aseptically filled in a sterile glass vial. Each vial contains ranibizumab in an aqueous solution (pH 5.5) with histidine, trehalose and polysorbate 20. The vial contains no preservative and is suitable for single use only.
8.2 Packaging and labeling

Medication labels will be in German and comply with the legal requirements. They will include storage conditions for the drug but no information about the patient.

8.3 Supply and ordering

The MAH will provide sufficient supplies of ranibizumab (in 6 mg/ml and 10 mg/ml concentration) for treatment use to allow for completion of the study (included in this supply are all vials for re-injections and rescue injections). Address and order sheet for ordering of ranibizumab will be provided in the investigator folder at each site.

8.4 Receipt and storage

Ranibizumab must be received by a designated person at the study site, stored according to the label instructions and be kept in a secure locked facility to which only the unblinded site personnel and designees have access. The investigator is responsible for ensuring the correct storage and sufficient stocks of the investigational medicinal product at the site. Where required, the investigator may entrust the investigational medicinal product, in whole or in part, to an appropriate pharmacist (to be designated in advance) or another appropriate individual who is under the supervision of the investigator. This is at the investigator’s discretion. The investigator or another appropriate individual who is designated by the investigator should maintain records of the delivery and use of the investigational medicinal product and the stocks at the study site on a drug accountability log. Monitoring of drug accountability will be performed by the field monitor during site visits and at the completion of the trial.

8.5 Preparation and dispensing

According to the assigned treatment group, 0.020 ml (=20 μl) of either the 6 mg/ml solution containing 0.12 mg ranibizumab or of the 10 mg/ml solution containing 0.20 mg ranibizumab will be injected intravitreally. The solution is for single use only.

Injection procedure will be according to local practice for intravitreal injection adopted for ROP infants in line with the current statement of the German Ophthalmic Society (DOG), the German Retina Society (RG) and the German Ophthalmologists Association (BVA) 6.

8.6 Return and destruction

At the conclusion of the study and as appropriate during the course of the study, all unused investigational medication can be destroyed at the study site or can be sent back to the MAHs depot at Wehr, Germany (address provided in the investigator folder at each site) for destruction, as appropriate according to SOP and/or local regulations.
The investigator or another appropriate individual who is designated by the investigator should maintain records of the destruction and return of unused investigational medicinal products to the sponsor or their disposal.

### 8.7 Drug compliance and accountability

The investigator or designee must maintain an accurate record of the shipment and use of investigational product in a drug accountability log. Drug accountability will be checked by the field monitor during site visits and at the completion of the trial.

At the conclusion of the trial, and, as appropriate during the course of the trial, the investigator will return/destruct all used and unused investigational product, packaging/labels.

The investigator or another appropriate individual who is designated by the investigator, should maintain records of the delivery of the investigational medicinal product, the stocks at the study site, the use by the individual trial patients, and the return of unused investigational medicinal products to the sponsor or their disposal. The investigator should ensure that the investigational medicinal product is only used according to this protocol.

The investigator bears the responsibility for the proper storage in an appropriate place to which unauthorized persons have no access.

The investigator may only apply the investigational medicinal product to patients who have been enrolled in the study. The dispensing of the investigational medicinal product to patients outside of this clinical trial is not permitted.

### 9 Safety monitoring

#### 9.1 Serious adverse event reporting

To ensure patient safety, every serious adverse event (SAE) (apart from those listed in 7.5.1), regardless of suspected causality, occurring after the patients' legal representatives have provided informed consent and until 4 weeks after the patient has completed the core study must be reported to pharmacovigilance management at the CRO CROLLL within 24 hours of learning of its occurrence (see appendix 1).

Any SAEs experienced after this 4-week period should only be reported to the pharmacovigilance management at the CRO CROLLL if the investigator suspects a causal relationship to the study drug.

Recurrent episodes, complications, or progression of the initial SAE must be reported as follow-up to the original episode, regardless of when the event occurs. This report must be submitted within 24 hours of the investigator receiving the follow-up information. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.
Information about all SAEs is collected and recorded on the Serious Adverse Event Report Form. The investigator must assess the relationship to study drug, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the pharmacovigilance management at the CRO CROLLL. The telephone and fax number of the contact persons are listed in the investigator folder. The original copy of the SAE Report Form and the fax confirmation sheet must be kept with the case report form documentation at the study site.

Follow-up information has to be sent to the same person to whom the original SAE Report Form was sent, using a new SAE Report Form stating that this is a follow-up to the previously reported SAE and giving the date of the original report. The follow-up information should describe whether the event has resolved or continues, if and how it was treated, and whether the patient continued or withdrew from study participation.

All the AEs (common, rare, and very rare) listed in section 7.5.1 will be documented in the CRF, entered in the database, and regularly evaluated by the DSMB.

If the SAE is not previously documented in the Investigator’s Brochure or Package Insert (new occurrence) and is thought to be related to the study drug, the MAH may urgently require further information from the investigator for Health Authority reporting. The MAH may need to issue an Investigator Notification (IN) to inform all investigators involved in any study with the same drug that this SAE has been reported. In every case, the MAH may issue queries to obtain further information on SAEs. These queries have to be answered by the investigator and sent by fax to the pharmacovigilance management at the CRO CROLLL.

9.2 Data and Safety Monitoring

Copies of all SAE forms have to be sent to the responsible persons (determined by the sponsor) for data and safety monitoring. The responsible person reviews the safety data and provides recommendations regarding study modification, continuation or termination.

Data and Safety monitoring will additionally be performed by the Data Safety Monitoring Board according to the DSMB Charter. The DSMB will receive all SAE forms before their meetings.

9.3 Data Safety Monitoring Board

A Data Safety Monitoring Board (DSMB) will be established that will review the data after 10 patients have completed the core study. Based on these results, the DSMB will decide if any of the treatment arms will be terminated early due to lack of efficacy or safety concerns.

In addition, the data review will be triggered early (before 10 patients have completed the core study) if more than three patients with rescue treatment have been documented in one group. A second review of data after another 10 patients can be triggered if considered necessary by the DSMB after reviewing the data of the first 10 patients. Here again the DSMB will decide about the continuation of a treatment arm based on these data.
The DSMB also reviews the photographs taken with a RetCam photographic system or a comparable imaging system. For this purpose, images will be sent to all three members of the DSMB within 7 days after baseline to confirm inclusion criteria and staging of ROP. The DSMB will confirm the inclusion within 10 days after receipt of the images. If the DSMB does not confirm the inclusion criteria of a child, this child will be withdrawn from the study and seen as a screening failure but will be followed-up on an observational basis for safety reasons. In addition, all available images (baseline and follow-ups) will be provided to the DSMB for the interim analysis.

Procedures and criteria for termination of treatment arms or the whole trial are outlined in detail in the Data Safety Monitoring Board Charter.

10 Discontinuation criteria

10.1 Premature termination of one of the treatment arms or the entire trial

The sponsor/coordinating investigator is under obligation to monitor the progress of the clinical trial with regard to safety-relevant developments and, if necessary, initiate the premature termination of a treatment arm or the entire clinical trial. If one treatment arm is terminated early, all remaining patients will be included in the other treatment arm until a total of 40 patients is reached. The sponsor/coordinating investigator will be supported in this responsibility by the DSMB, if necessary.

Unless clear reasons outside the study treatment exist that would explain the need for rescue treatment a treatment arm or the entire clinical trial must be terminated prematurely if:

- during the first regular interim analysis (after 10 patients completed the core study) it is discovered that at least 4 patients of the same treatment arm needed rescue treatment. Furthermore, the DSMB can already advice the sponsor to stop one treatment arm, if there are fewer rescue cases within one treatment arm,
- during a second interim analysis it is discovered that 60% or more patients with completed core study, in one treatment arm required rescue treatment. Furthermore, as in the first interim analysis, the DSMB can already advice the sponsor to stop one treatment arm, if there are fewer rescue cases within one treatment arm.

A treatment arm or the entire clinical trial must also be terminated if in the interim analysis indications arise that the trial patients' safety is no longer guaranteed or the benefit-to-risk ratio for the patient changes markedly, e.g. accumulation of high rates of serious adverse events, for example:

- cumulative cases of endophthalmitis
- cumulative cases of patient death, considered likely related to study treatment

In addition the sponsor/coordinating investigator (German LKP) or the DSMB considers whether the termination of the trial or one treatment arm is necessary if:
• the question(s) addressed in the trial can be clearly answered on the basis of an interim analysis,
• the question(s) addressed in the trial can be clearly answered on the basis of results of another trial on the same subjects,
• an insufficient recruitment rate makes a successful conclusion of the clinical trial appear impossible.

If the clinical trial is prematurely terminated or suspended for any reason, the investigator should promptly inform the trial patients and ensure appropriate therapy and follow-up for the patients. Where required by the applicable regulatory requirements, the competent authority(ies) and the ethic committee(s) will also be informed (this is usually done by the sponsor).

10.2 Premature termination of the trial at one of the trial centers

Both the investigator and the sponsor have the right to terminate the trial at one of the centers. The clinical trial can also be terminated prematurely at his center by the investigator if, for instance unforeseeable circumstances have arisen at the trial center which preclude the continuation of the clinical trial, the investigator considers that the resources for continuation are no longer available, the investigator considers that the continuation of the trial is no longer ethically or medically justifiable.

The Sponsor can initiate the exclusion of a center from further participation if, for instance, patient recruitment is inadequate, serious problems arise with regard to the quality of the collected data which cannot be resolved.

Premature termination at one of the trial centers does not automatically mean a termination of the trial for already enrolled trial patients. A separate decision on further treatment must be made for each patient, depending on the overall situation. Adequate further treatment and follow-up of already enrolled trial patients must be ensured. The documentation of already enrolled trial patients will be reviewed for completeness and plausibility. Queries may be raised for further clarification before the center is closed. These queries must be answered properly by the center. The competent authority(ies) and ethics committee(s) must be duly notified of the center's closure, including reasons, within the specified period. The trial center concerned will be closed in stages by the CRA when a decision has been made on the further treatment of the patients concerned.

10.3 Discontinuation for individual trial patients

A maximum number of 3 re-injections can be applied. If the child needs further treatment thereafter, rescue treatment needs to be administered.

If a child has suffered from an injection related endophthalmitis, no further (re-)injection shall be applied.
In the case trial treatment of a patient has been stopped prematurely, further follow-up visits and the assessment of the trial endpoints are essential to enable an analysis of the full analysis set according to the intention-to-treat principle. Further visits, follow-up and documentation should always be striven for/ensured in this case. This includes the follow-up of AEs, the time of termination, the results available at that time and, if known, the documentation of the termination of treatment on the CRF and in the medical record, giving reasons, a final examination and documentation according to the protocol (if possible).

The documentation should be completed as far as possible under these circumstances, e.g. a final examination and documentation according to the protocol (if possible), a documentation of the premature trial termination on the CRF and in the medical record, giving reasons, appropriate further treatment and follow-up outside the trial should be ensured.

11 Data review and database management

11.1 Site monitoring

Before study initiation, the study monitor will review the protocol, the CRFs and specific study procedures with the investigators and their staff at a Site Initiation Visit.

During the study, the study monitor will contact or visit the site to check the completeness of patient records, the accuracy of entries on the CRFs, the adherence to the protocol and to Good Clinical Practice, the progress of enrollment, and to ensure that study drug is being stored, dispensed, and accounted for according to specifications. Key trial personnel must be available to assist the monitor during these visits. About once a year there will be also an unblinded monitoring visit at all active trial sites for drug accounting.

The investigator must give the monitor access to all relevant source documents to confirm their consistency with the CRF entries. The monitoring standard requires full verification for the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of SAEs, and the recording of data that will be used for all primary and safety variables. Additional checks of the consistency of the source data with the CRFs are performed according to the study-specific monitoring plan. No information in source documents about the identity of the subjects will be disclosed.

The investigator must maintain source documents for each patient in the study, consisting of case and visit notes (hospital or clinic medical records) containing demographic and medical information, laboratory data, and the results of any other tests or assessments. All information on CRFs must be traceable to these source documents in the patient’s file. Data not requiring a separate written record will be defined before study start in the Monitoring Plan and will be recorded directly on the CRFs, which will be documented as being the source data. The investigator must also keep the original informed consent form signed by the patient’s legal representatives (a signed copy is given to the patients’ legal representatives).
11.2 Data collection

Designated investigator staff must enter the information required by the protocol onto the CRFs that are printed on 3-part, non-carbon-required paper. Of the 3 copies, the original CRFs are forwarded to the data managing CRO (Winicker Norimed) by the clinical monitor, one copy is retained at the investigational site, and one copy is kept by the monitor. Once the CRFs are received by Winicker Norimed, their receipt is recorded, CRFs are placed in Central Files and processed for data management.

11.3 Database management and quality control

Data from the CRFs are entered into the study database by data management staff using double data entry and are transmitted in a coded way.

Subsequently, the entered data are systematically checked by data management staff, using error messages printed from validation programs and database listings. Obvious errors are corrected by data management personnel. Other errors or omissions are entered on Data Query Forms, which are returned to the investigational site for resolution by the CRAs. The signed original and resolved Data Query Forms are kept with the CRFs at the investigator site, and a copy is sent to the CRO Winicker Norimed so that the resolutions can be entered into the database. Quality control audits (1:1 check of all variables between CRF and database in a subset of 7 patients) are made prior to locking the database.

Concomitant medications entered into the database will be coded using the WHO Drug Reference List, which employs the Anatomical Therapeutic Chemical classification system. Medical history/current medical conditions and adverse events will be coded using the Medical dictionary for regulatory activities (MedDRA) terminology.

Laboratory samples will be processed centrally and the results will be sent to the CRO Winicker.

At the conclusion of the study, the occurrence of any protocol violations will be determined. After these actions have been completed and the database has been declared to be complete and accurate, it will be locked and made available for data analysis.

12 Data analysis

All analyses will be performed by the sponsor, his delegates or the CRO Winicker Norimed GmbH. Any data analysis carried out independently by the investigator(s) must be approved by the sponsor prior to publication or presentation.

Descriptive statistics include n, mean, standard deviation, median, quartiles and ranges for continuous variables and frequencies and percentages for categorical variables and will be provided by treatment arm unless otherwise specified. As baseline value the screening value or the values achieved at visit 2 will be considered, whichever is later and available. If statistics are presented by visit, post-re-injection visits will be analyzed separately.
Further technical details will appear in the Statistical Analysis Plan, which will be finalized prior to database lock.

12.1 Populations for analysis

The Full Analysis Set (FAS) will consist of all patients who were randomized, in whom the study indication is present (i.e. who were not included by mistake), and who received at least one obligatory dose of study therapy. No data will be excluded from the FAS analyses because of protocol deviations. Patients will be analyzed as randomized, i.e. in the treatment arm they were randomized to.

The Per Protocol Set (PPS) will consist of all patients in the FAS who received study treatment as randomized and who completed the trial without any major protocol deviations.

Protocol deviations will be assessed as 'major' if they are assumed to influence the primary efficacy variable. Criteria for assessing protocol violations will be defined before unblinding.

The Safety Set will consist of all enrolled patients who received at least one obligatory dose of study treatment and had at least one post-baseline safety assessment. Patients will be analyzed according to the treatment received. The statement that a patient had no adverse events also constitutes a safety assessment.

The Follow-Up Set (FUS) will consist of all patients in the FAS, who were examined at least one follow-up visit.

12.2 Patient demographics/other baseline characteristics

Demographic and background information will be summarized for the FAS by descriptive statistics. Background information includes demographics, a description of the study indication and past/current medical conditions at baseline.

12.3 Treatments (study drug, rescue medication, other concomitant therapies)

Descriptive statistics on treatment will be provided for the FAS and the Safety Set (separate tables will be provided only if the analysis sets differ).

Study treatment

The number of ranibizumab regular (re-)injections during the core study as well as the time to (regular) re-injections will be presented descriptively per infant and per eye. The analyses will be presented in total and separated by infants/eyes having received no rescue treatment, infants/eyes having received laser treatment, and infants/eyes having received a ranibizumab injection as rescue treatment.

Similar tables will be presented for ranibizumab re-injections during the follow-up period for the FUS.

Rescue treatment
The number of rescue treatments as well as the time to rescue treatment after the last regular injection will be presented descriptively per infant and per eye. The analyses will be presented in total and separated by the number of previous regular (re-)injections per infant/eye, and by the kind of rescue treatment (laser treatment or early ranibizumab re-injection). Further analyses for the primary objective are presented in section 12.4.

Similar tables will be presented for rescue treatment during the follow-up period for the FUS.

**Prior/concomitant therapies**

The number and percentage of patients receiving prior/concomitant therapies will be summarized by preferred term according to the WHO Drug Reference List dictionary. Summaries will be presented separately for prior medications (received prior to the start of treatment) and for concomitant medications (received during the observational period).

Type and duration of supplemental oxygen will be summarized over the duration of the core study for each infant and analysed descriptively.

### 12.4 Analysis of the primary objective(s)

#### 12.4.1 Variable

The primary endpoint is the number of infants without need for rescue treatment up to week 24 post first injection. Re-injection of study dose is not considered rescue treatment if applied after an initial response to treatment and after at least 4 weeks post injection.

#### 12.4.2 Statistical hypothesis, model, and method of analysis

Since this is an exploratory study, the focus is not on hypothesis testing but on an estimation of differences between treatments. Still, confidence intervals and the usual p-values will be provided as a descriptive tool.

The differences between treatment groups will be analyzed by Cochran-Mantel-Haenszel controlled by gestational age at birth (cut-off point as defined for the stratification) and, depending on the number of infants receiving re-injection(s), by whether re-injection(s) were administered or not.

For total and each age group (and re-injection group if applicable), incidences will be calculated with exact confidence intervals. Additionally, the odds ratios with confidence intervals will be calculated.

The homogeneity of the odds ratios between the age groups will be calculated by Breslow-Day.

#### 12.4.3 Handling of missing values/censoring

Missing values of the primary endpoint due to premature patient withdrawal or due to death of the infant will be replaced by a failure of the primary endpoint, i.e. as if the infant had
received rescue treatment. Handling of missing values in secondary and exploratory endpoints will be specified in the statistical analysis plan (SAP).

12.4.4 Supportive analyses
The primary analysis will be repeated for the PPS.

12.5 Analysis of secondary efficacy objectives

12.5.1 Number of infants with regression of plus disease, regression of preretinal vascularized ridge, and progression of peripheral intraretinal vascularization beyond ridge during core study

Endpoints will be defined as the number of infants with improvement of the respective condition by at least one grade in both eyes from baseline to week 24. An additional endpoint will be the number of infants with initial response in both eyes. Analyses of these endpoints will be performed like the primary analysis using the FAS, separated by 'rescue treatment' (yes/no). In addition, grading of the conditions will be summarized descriptively for each visit and changes between baseline and week 24 will be presented by shift tables. These tables will be given per infant and per eye, separated by 'rescue treatment' (yes/no).

12.5.2 Number of patients progressing to stage 4 or 5 ROP during core study
For the number of patients progressing to stage 4 or 5 ROP in at least one eye during the core study, the analysis will be performed as in 12.5.1.

12.5.3 Number of patients with complete vascularization of the peripheral retina to within one disc diameter of the ora serrata during core study
For the patients with complete vascularization of the peripheral retina to within one disc diameter of the ora serrata in at least one eye during the core study, the analysis will be performed as in 12.5.1.

Analyses of the secondary objective "number of re-injections of study dose during core study" are described under 12.3 "Treatments (study drug, rescue medication, other concomitant therapies)".

12.6 Analysis of exploratory objectives (follow-up period)

12.6.1 Number of late recurrences of ROP needing re-injections and/or laser treatment after the core study period (to be evaluated after one year and after 5 years)
The analysis will be performed like the primary analysis, using the FUS separated by whether infants had received rescue treatment during the core study or not.
12.6.2 **Number of patients progressing to stage 4 or 5 ROP after the end of the core study (to be evaluated after one year and after 5 years)**

The analysis will be performed as in 12.5.1, using the FUS separated by whether infants had received rescue treatment during the core study or not.

12.6.3 **Number of patients with complete vascularization of the peripheral retina to within one disc diameter of the ora serrata after the end of the core study (to be evaluated after one year and after 5 years)**

The analysis will be performed as in 12.5.1, using the FUS separated by whether infants had received rescue treatment during the core study or not.

All other long term outcomes (ophthalmological and pediatric development) will be summarized descriptively.

12.7 **Analysis of secondary and exploratory safety objectives**

12.7.1 **Number and kind of AEs, SAEs and other safety variables**

- Safety determined by number and kind of AEs and SAEs per group during the phase of the interventional core study
- Long-term safety or ranibizumab in the treatment of ROP evaluated by number and kind of AEs or SAEs per group between the end of the observational core study and the end of the follow-up period (up to 5 years post first injection)

The analyses will be done using the Safety Set. Subjects will be analyzed according to the study drug dose received. In case of a re-injection, patients will also be analyzed according to the number of study drug injections received (see secondary endpoints). All patients at all time-points can receive rescue treatment if deemed necessary by investigator.

Safety variables are:

- Treatment emergent adverse events
- Ophthalmic examination results
- Vital signs
- Laboratory variables
- Growth

Adverse event terms recorded on the CRFs will be mapped to preferred terms using the MedDRA® dictionary. All adverse events will be summarized by treatment group, according to the system organ class and preferred term within the organ class. Adverse events will be compiled for reporting of overall incidence, worst reported severity, and relationship to study drug for each preferred term per subject. Serious adverse events will be similarly summarized. The incidence of adverse events will be compared between
treatment groups using Fisher’s exact test. Listings of deaths, serious adverse events, and adverse events will also be provided.

The analysis will be performed for the interventional core study period in the Safety Set and for the follow-up period in the FUS.

Vital signs and changes of vital signs from baseline will be presented descriptively for each visit.

Laboratory variables will be examined descriptively using absolute values and changes from baseline to various time points for each treatment group. Shift tables will be presented to show the number and percentage of subjects with high, normal, and low (or normal/abnormal) laboratory results at baseline and last measurement available.

Growth of infants will be presented descriptively as mean increase in weight, height and head circumference per day since the last visit for each visit.

12.7.2 Changes in vascular endothelial growth factor (VEGF) levels in the systemic circulation during core study

For VEGF levels, absolute values and changes from baseline as well as the number and percentage of infants with complete suppression below detection limit will be presented descriptively at each visit for each treatment group. In addition, shift tables will be presented to show changes in the number and percentage of subjects with complete suppression below detection limit between baseline and the last measurement available.

12.7.3 Tolerability

Tolerability will not be assessed separately and will be included in the adverse event reporting.

12.8 Resource utilization

Not applicable.

12.9 Health-related Quality of Life

Not applicable.

12.10 Pharmacokinetics

Not applicable.

12.11 Pharmacogenetics/pharmacogenomics

Not applicable.
12.12  **Biomarkers**

If technically possible other factors relevant in the context of ROP, for example insulin-like growth factor 1 (IGF-1) will be measured from the same plasma samples as VEGF or from the cell pellets. If applicable, descriptive analyses of these factors will be defined in the SAP.

12.13  **PK/PD**

Not applicable.

12.14  **Interim analysis**

After 10 patients have completed the study, the DSMB will review the results of these patients and decide if one of the treatment arms needs to be terminated early due to lack of efficacy or safety concerns. In both study arms, rescue treatment is possible at all time-points (see above). In addition, the data review will be triggered earlier (before 10 patients have completed the study) if more than three patients in one treatment group need rescue treatment (earlier than the first regular interim analysis). After another 10 patients, a second interim data review can be triggered if considered necessary by the DSMB. Here again the DSMB will decide about the continuation of a treatment arm based on these data. A treatment arm must be discontinued if at time of the first regular interim analysis 4 or more patients of this treatment arm needed rescue treatment. The same applies if at the second interim analysis 60% or more patients in one arm needed rescue treatment.

12.15  **Sample size calculation**

In Germany about 400 to 600 cases of ROP that need treatment are registered per year. 40 patients is therefore a realistic number of ROP patients to be enrolled in this exploratory study at participating centers during enrollment time.

12.16  **Power for analysis of critical secondary variables**

Not applicable.

13  **Discussion and rationale for study design features**

13.1  **Objectives**

Since the 1990s the standard treatment of ROP has consisted of laser photocoagulation of avascular retinal areas. Laser photocoagulation, however, is a destructive therapy with potential side effects like macular traction and restriction of the visual field. When the results of the BEAT-ROP study were published in 2011, a new treatment option resulted. Compared to infants receiving laser photocoagulation, infants treated with a single intravitreal injection of the anti-VEGF antibody bevacizumab showed a reduced number of ROP recurrence. In the
BEAT-ROP study, however, several questions remained unanswered. The influence of the anti-VEGF treatment on the systemic VEGF-levels was not tested at all. Also no dose finding has ever been conducted and long-term effects of bevacizumab are not known yet. Additionally, the CATT trial, in which ranibizumab and bevacizumab were compared for the treatment of AMD in adults, showed significantly more adverse events in the bevacizumab arm compared to the ranibizumab arm 17.

From head-to-head comparative studies in adults, similar ocular efficacies of bevacizumab and ranibizumab in treating neovascular eye disease were reported 17, 18. In contrast to bevacizumab, however, ranibizumab is approved for intravitreal injection in adult patients. Also different from bevacizumab, ranibizumab is excreted rapidly from the systemic circulation, thus potentially reducing unwanted systemic VEGF inhibition. For these reasons, ranibizumab is expected to show ocular efficacies in ROP infants that are comparable to bevacizumab with the advantage of using a drug that is approved and manufactured for intraocular injection and showing preferable characteristics concerning unwanted systemic exposure to anti-VEGF medication. In addition, this study will explore the differences between two doses of ranibizumab. If our results show equal efficacy with the lower dose, this finding would implicate that lower doses of anti-VEGF medication can be used to achieve the desired ocular effects in ROP thus further reducing potential side effects.

Additionally, the effects of the intravitreal application of ranibizumab on the systemic VEGF-levels in ROP infants will be tested as a safety variable and this study will furthermore assess long-term effects with the follow-up examinations at year 1, 2 and 5.

### 13.2 Population criteria

The study population will consist of children with retinopathy of prematurity as defined by the International Committee of Classification of ROP 19. The recruitment target of 40 patients will be achieved by involving approximately 10 sites within Germany.

The risk of patients in this trial will be minimized by adherence to the inclusion/exclusion criteria, close clinical monitoring and a Data Safety Monitoring Board.

### 13.3 Study drug dose

In this study, two different doses (0.12 mg vs. 0.20 mg) of ranibizumab will be compared regarding safety and efficacy in ROP.

The 0.20 mg arm will use 40 % of the 0.50 mg ranibizumab dose, which is approved for intravitreal use for adults in AMD, DME, PM and RVO. This is concordant with the BEAT-ROP study which used about half the adult dose of bevacizumab per eye 5. From data in adults, comparable results regarding ocular efficacy can be expected for ranibizumab and bevacizumab in these doses 17, 18.
However, since no dose-finding studies have been performed for bevacizumab or ranibizumab in ROP, we do not know if lower doses could potentially be similarly effective in halting ROP progression.

If so, lower doses would be highly desirable to reduce potential ocular and/or systemic side effects of intravitreal anti-VEGF therapy in ROP. Therefore a lower dose (0.12 mg) of ranibizumab will also be investigated in this trial. In the oxygen-induced retinopathy model of dogs, Lutty et al. found that high doses of anti-VEGF agents may inhibit the desirable peripheral vascularization of the retina. In contrast, lower doses can inhibit pathologic disease activity while at the same time allowing the desired peripheral vascularization of the retina. Concordant with these findings, this study design uses a low-dose arm. Since it might be that ROP activity relapses when ranibizumab is not present in the vitreous anymore, the study design allows re-injections of the same concentration of ranibizumab if there had been an initial response to the first injection that was of some but not sufficient duration (i.e. at least controlling disease activity for 4 weeks). If, after ≥ 28 days, disease activity recurs, a re-injection is possible. It is conceivable that this protocol can achieve superior outcomes over a single high-dose injection since it would (a) allow titration of anti-VEGF dosing with one infant potentially needing only one injection, another however several injections, thus avoiding over- and under treatment and (b) this study design might achieve superior vascularization of the peripheral retina based on the experimental data from Lutty et al.

After 10 patients, the DSMB will review the results of these patients and decide if one of the treatment arms needs to be terminated early due to lack of efficacy or safety concerns. In both study arms, rescue treatment is possible at all time-points. In addition, the data review will be triggered early (before 10 patients have completed the core study) if more than three patients in one treatment group need rescue treatment (earlier than the first regular interim analysis). After another 10 patients, a second interim data review can be triggered if considered necessary by the DSMB. Here again the DSMB will decide about the continuation of a treatment arm based on these data.

The ranibizumab formulation that is used as study drug in order to apply the stated amount of active ingredient is commercially available and approved for intravitreal use in adults. Overall, the expected safety profile of ranibizumab is highly favorable over bevacizumab due to the significantly faster excretion of ranibizumab from the systemic circulation. From data in adults and first case reports in infants we know that intravitreal bevacizumab suppresses systemic VEGF-levels for up to several weeks. Ranibizumab, in contrast, has much faster systemic clearance rates from the systemic circulation with a systemic half-life of hours vs. days for bevacizumab. At the same time, ranibizumab is approved for intraocular injections in adult patients while bevacizumab is not. This trial is therefore designed to investigate if similar beneficial results as the ones reported for bevacizumab can be obtained with ranibizumab. At the same time, this trial will go beyond the BEAT-ROP study with regard to dose finding and investigation of ocular and systemic safety. By comparing two doses of ranibizumab, this trial will establish whether lower doses than the currently used half adult
dose are sufficient in premature infants to control ROP and if maybe a different dosing scheme for the lower doses would be preferable.

By adding VEGF measurements from systemic blood samples, a potential correlation between ranibizumab dose and VEGF suppression can be investigated. Long-term data will be exploratively collected on pediatric and ophthalmic exams at one, two and five years of age.

13.4 Blinding

With the exception of the site personnel who prepares the study drug for injection, all personnel and legal representatives involved will be blinded to treatment. The double blind study design and the DSMB which will re-evaluate ROP gradings, will minimize any potential bias. Furthermore, objective endpoints such as VEGF plasma levels are part of the assessment.

13.5 Assessments

All measurements performed in the study are standard measurements and will be carried out by the investigative site using the accepted methodology at that site unless otherwise specified.

13.6 Data analysis

Due to the limited realistic number of ROP patients requiring treatment no formal hypothesis testing is possible. Thus this is an exploratory study.

14 Ethical and legal principles

14.1 Regulatory and ethical compliance

This clinical trial was designed, shall be implemented and reported in accordance with the ICH Harmonized Tripartite Guidelines for Good Clinical Practice, with applicable local regulations (including European Directive 2001/20/EC and US Code of Federal Regulations Title 21, and Japanese Ministry of Health, Labor and Welfare), and with the ethical principles laid down in the Declaration of Helsinki.

14.2 Responsibilities of the investigator and IEC

The protocol and the proposed informed consent form must be reviewed and approved by a properly constituted Independent Ethics Committee (IEC) before trial start. A signed and dated statement that the protocol and informed consent have been approved by the IEC must be given to the sponsor before initiation of the trial. Prior to start of the trial, the investigator is required to sign a protocol signature page confirming his/her agreement to conduct the trial in accordance with these documents and all of the instructions and procedures found in this protocol and to give access to all relevant data and records to sponsor monitors, auditors, sponsor Clinical Quality Assurance representatives, designated agents of sponsor, IECs and
regulatory authorities as required. If an inspection of the clinical site is requested by a regulatory authority, the investigator must inform the sponsor immediately that this request has been made.

14.3 Informed consent procedures

Before enrolment in the clinical trial, the patient’s legal representatives will be informed that participation in the clinical trial is voluntary and that they may withdraw their child from the clinical trial at any time without having to give reasons and without penalty or loss of benefits to which the patient is otherwise entitled.

The treating physician will provide the patients’ legal representatives with information about the treatment methods to be compared and the possible risks involved. At the same time, the nature, significance, implications, expected benefits and potential risks of the clinical trial and alternative treatments will be explained to the patient’s legal representatives. During the informed consent discussion, the patient’s legal representatives will also be informed about the insurance cover that exists and the insured’s obligations. The patient’s legal representatives will be given ample time and opportunity to obtain answers to any open questions. All questions relating to the clinical trial should be answered to the satisfaction of the patient’s legal representatives. In addition, they will be given a patient information sheet which contains all the important information in writing.

| The patient's legal representatives' written consent must be obtained before any trial-specific tests/treatments. |
| For this purpose, the written consent form will be personally dated and signed by the trial patient’s legal representatives and the investigator conducting the informed consent discussion. |

By signing the consent form, the patient’s legal representatives agree that their child voluntarily participates in the clinical trial and declare their intention to comply with the requirements of the clinical trial and the investigator's instructions during the clinical trial. By signing the form, the patient’s legal representatives also declare that they agree to the recording of personal data, particularly medical data, for the trial, to their storage and codified (“pseudonymised”) transmission to the sponsor or to the competent authority, and further agree that authorised representatives of the sponsor, who are bound to confidentiality, and national or foreign competent authorities may inspect the personal data, particularly medical data, which are held by the investigator. Furthermore, the parents also give their consent for the anonymized publication of RetCam images. They also declare that in case of moving, a follow-up at the Resident Registration Office and/or at the responsible health insurance can be performed in order to obtain the new address. After signing, the legal representatives will be given one copy of the signed and dated written consent form and any other written information to be provided to them.
In the case of substantial amendments, the patient’s legal representatives must be informed with an appropriate revised patient information/consent form. Changed trial procedures can only be carried out if they have been approved by the competent authority and the leading Ethics Committee, and if the patient has been appropriately informed and has given his/her written consent.

*ICH-GCP 4.8.9: If a patient is unable to read or if a legal representative is unable to read, an impartial witness should be present during the entire informed consent discussion. After the written informed consent form and any other written information to be provided to patients is read and explained to the patient or the patient’s legal representative, and after the patient or the patient’s legal representative has orally consented to the patient’s participation in the trial and, if capable of doing so, has signed and personally dated the informed consent form, the witness should sign and personally date the consent form. By signing the consent form, the witness attests that the information in the consent form and any other written information was accurately explained to, and apparently understood by, the patient or the patient’s legal representative, and that informed consent was freely given by the patient or the patient’s legal representative.*

**14.4 Patient insurance**

Subject insurance according to AMG and a travel accident insurance have been taken out for all subjects participating in the clinical trial. For legal representatives also a travel accident insurance starting when the child is discharged from hospital has been taken out.

The investigator, or an individual who is designated by the investigator, will inform the subject’s legal representatives of the existence of the insurances, including the obligations arising from them. The trial subjects’ legal representatives must be afforded access to insurance documents and provided with copies of the general conditions of insurances on request.

**14.5 Confidentiality of trial documents and patient records**

The investigator must ensure anonymity of the patients; patients must not be identified by names in any documents submitted to the sponsor. Signed informed consent forms and patient enrolment log must be kept strictly confidential to enable patient identification at the site.

**14.6 Financial disclosure**

Financial disclosures should be provided by trial personnel who is directly involved in the treatment or evaluation of patients at the site prior to trial start.
15 Protocol adherence and amendments

15.1 Protocol adherence

Investigators ascertain they will apply due diligence to avoid protocol deviations. Under no circumstances should the investigator request approval of a protocol deviation, as no authorized deviations are permitted. If the investigator feels a protocol deviation would improve the conduct of the trial this must be considered a protocol amendment, and unless such an amendment is agreed by the sponsor and approved by the IEC it cannot be implemented.

15.2 Amendments to the protocol

Any substantial change or addition to the protocol can only be made in a written protocol amendment that must be approved by the sponsor and the IEC. Only changes of the protocol that are required for patient safety may be implemented prior to IEC approval. Notwithstanding the need for approval of formal protocol amendments, the investigator is expected to take any immediate action required for the safety of any patient included in this trial, even if this action represents a deviation from the protocol. In such cases, the sponsor should be notified as soon as possible of this action; the IEC should be informed correspondingly.

15.3 Protocol deviations

As outlined above, the investigators ascertain their adherence to the study protocol. If a protocol deviation is noticed, a protocol deviation form needs to be filled in and sent to the responsible clinical monitor. Then the severity of this protocol deviation is evaluated by the coordinating investigator and a decision is taken on the course of action and the implications for the patient. The data management will be informed about all protocol deviations. No protocol deviation form is necessary if the deviation can be detected in the CRF by the data management.

Before database lock, all PDs need to have been evaluated regarding their implications for the results.

16 Administrative Agreements

16.1 Financing of the trial

The clinical trial will be financed by the university hospital Freiburg with financial support and support of medication of the MAH. The MAH does not have any influence on the content of the study. Additional funding can be applied for from other sources, e.g. from public or private research-funding organizations.


16.1.1 Trial agreement/investigator compensation

According to ICH-GCP 4.9.6, a trial agreement on the conduct of the clinical trial and the compensation for conducting the trial will be signed between the sponsor of the clinical trial and the investigators at their respective centers including their heads of administration.

16.1.2 Reimbursement of trial patients

Travel expenses for study visits after the child has left the hospital will be reimbursed. The cheapest way of travelling has to be used.

16.2 Trial language

The trial will be conducted in German. Therefore, all patient communication will be in German. Amongst each other, investigators, trial personnel, sponsor etc. may communicate in German or English, additionally the documentation on the CRFs will be in English.

16.3 Trial reports

After completion of the analysis by the responsible biostatistician, the coordinating investigator will prepare and sign the final integrated medical and statistical report jointly with the biostatistician.

The final trial report will be written and signed in co-operation between the coordinating investigator and the CRO responsible for data analysis at the end of the study, i.e. after the primary endpoint at week 24 post first injection is reached for all infants. Follow-up data will be analyzed and reported in appendices to the final study report.

16.4 Clinical trials registry

This clinical trial will be registered in the public database clinicaltrials.gov after approval of the IEC and the HA but before the first patient is randomized for the study.

16.5 Publication of trial protocol and results

The sponsor assures that the key design elements of this protocol will be posted in a publicly accessible clinical trials registry such as clinicaltrials.gov. In addition, upon trial completion the results of this trial will be submitted for publication and/or posted in a publicly accessible database of clinical trial results. All personal data including RetCam images that will be included in a publication will be anonymized.

Each publication of trial results will be in best possible mutual agreement between the principal investigator and the other investigators involved. All data collected in connection with the clinical trial will be treated in confidence by the coordinating investigator and all others involved in the trial, until publication. Interim data and final results may only be published (orally or in writing) with the agreement of the coordinating investigator.
17 References


Appendix 1: SAE/SUSAR-flow chart

Investigator → reports SAE

within 24 h

within 1 working day

SUSAR-Evaluation
PD Dr. Andreas Stahl
(or substitute)
E-mail: andreas.stahl@uniklinik-freiburg.de
Weil@CARE-ROP.uniklinik-freiburg.de
Fax +49 761-201 4064

Pharmaceutical
Manufacturer

Investigators

CROLL
Fax +49 911-252688-46

SAE report

within 1 working day

SUSAR evaluation

Pharmaceutical manufacturer: Novartis
Fax +49 911-275 12099

CROLL
(SUSAR-forwarding)
(7/15 days)

DEMS-Form (FUGA)

Ethics
Committee

Competent
Authority

* To observe the time limit according to GDPR §13, the SUSAR evaluator has to be informed about the occurrence of an SAE on weekends and holidays by phone:
+49 761-275 12099 or +49 151-9700349
Appendix 2: Reinjection Overview

Visit schedule after re-injection:

Whenever ≥ 28 days after the first injection, a re-injection is performed, all post-injection assessments shall take place exactly as after the first injection.

In case of a re-injection, the new assessment schedule therefore replaces the one triggered by the first injection.

All re-injections are followed-up with at least 4 weekly study visits. The primary study endpoint, however, remains at 24 weeks after the first injection for all infants.

Example 1: Re-injection 5 weeks after initial injection

Example 2: Re-injection at 22 weeks after initial injection
Appendix 3: visit schedule follow-up period

End of core study visit: 24 weeks post first injection

Follow-up at year 1 (+/- 2 months): ophthalmological assessment

Follow-up at year 2 (+/- 3 months): pediatric Bayley-Test, assessment of cerebral paresis, deafness, blindness

Final follow-up at year 5 (+/- 6 months): ophthalmological assessment and pediatric assessment along the GNN 5 year FU study protocol