CharitéCentrum für Audiologie / Phoniatrie, Augen und HNO-Heilkunde

TRIAL PROTOCOL

Sponsor

Charité – University Medicine Berlin
Charitéplatz 1
10117 Berlin
Germany

Principal Coordinating Investigator (PCI):

Prof. Dr. Antonia M. Joussen
Charité, University Medicine Berlin
Department of Ophthalmology, CBF
Hindenburgdamm 30
12200 Berlin
Germany

Trial protocol code: **DORO001**

Trial title: **Influence of diabetes control on treatment of diabetic macular edema with ranibizumab**

DRKS: 00004731

EudraCT number: 2012-003943-32

Version of 23 July 2015, Version Final

Signatures

Protocol authorization signature page

Trial code: **DORO001**

Title: **Influence of diabetes control on treatment of diabetic macular edema with Ranibizumab**

EudraCT-No: **2012-003943-32**

Approved by the following

Prof. Dr. med. Antonia M. Joussen
(Principal Coordinating Investigator, PCI)
Charité, Department of Ophthalmology, Berlin;
Acting on behalf of the sponsor

Signature Date

[redacted]

Signature Date

[redacted]

Signature Date

I. Synopsis

Sponsor:	Charité, University Medicine Berlin Charitéplatz 1 10117 Berlin Germany Represented by: Prof. Dr. med. Antonia M. Joussen Charité University Medicine Berlin Department of Ophthalmology, CBF Hindenburgdamm 30 12200 Berlin Germany
Principal Coordinating Investigator:	Prof. Dr. med. Antonia M. Joussen
Title of the clinical trial:	Influence of diabetes control on treatment of diabetic macular edema with ranibizumab
Indication:	Diabetic Macular Edema
Phase:	IV, therapeutic-exploratory trial
Type of trial, trial design, methodology:	Monocentre, two-arm, randomised, parallel-group controlled clinical trial in Germany
Number of subjects:	60 patients per treatment arm (total 120)
Primary trial objective:	To evaluate the influence of an intensified diabetes control programme on treatment of diabetic macular edema with ranibizumab.
Study endpoints:	Primary endpoint: • Change of best corrected visual acuity in ETDRS letters score at month 12 when compared with baseline (measured by the difference in ETDRS letters score between month 12 and baseline) Secondary endpoints: • Number of treatments with ranibizumab up to 6, 12, 18 and 24 months of treatment respectively • Mean average change in BCVA at 6, 12, 18 and 24 months after initial treatment • Macular thickness (as measured with OCT) at 6, 12, 18 and 24 months after initial treatment • Time to reach target HbA1c • Number of neovascular complications: need for panretinal laser photocoagulation (PRP) • Rates of ocular and of systemic AEs (retinal detachment, central retinal artery occlusion, endophthalmitis; rates of stroke, myocardial infarction, severe hypoglycemia)

Medical condition:	Diabetic patients with visual impairment due to diabetic macular edema (DME)
Principal inclusion criteria:	• Patients with diabetic macular edema relevant to visual acuity • OCT central retinal thickness ≥ 250µm • HbA1c > 6,5% at initial visit • BCVA ≤ 0.8 and ≥ 0.05 • Age ≥18 years • Written patient informed consent given
Principal exclusion criteria:	• Previous treatment with intravitreal drugs in last 6 months • Vitreous hemorrhage as a consequence of proliferative retinopathy • Pregnancy • Blood pressure of ≥ 180/100 (or uncontrolled pressures under pharmacological therapy) • Chronic systemic or ocular inflammatory/autoimmune diseases (e.g. inflammatory bowel disease, Addison´s disease, Cushing Syndrome, Uveitis) • Systemic cortisone or anti-VEGF therapy • Acute systemic or ocular infectious diseases
Name of investigational medicinal product (IMP):	Ranibizumab (Lucentis®)
Investigational medicinal product – dosage and method of administration:	Ranibizumab – three initial monthly intravitreal injections (0.05 mg) and subsequent injections until visual acuity reached maximum (maximum of visual acuity defined as stable visual acuity under treatment with ranibizumab on three consecutive monthly control visits)
IMP or therapy used as a comparator – dosage and method of administration:	not applicable
Duration of treatment:	12 months treatment period with Ranibizumab Total follow-up is 12 months (with PRN treatment option)
Time plan:	First patient first visit (FPFV): 01 August 2015 Last patient first visit (LPFV): 31 May 2018 Last patient last visit (LPLV): 31 May 2020 Final study report: 31 April 2021
Statistician:	[redacted]

Statistical methods:	For the comparison of means between two arms ANCOVA is used (normality assumption is assessed graphically and if necessary, will be tested by Shapiro-Wilk statistic. If the normality assumption is violated a nonparametric test is applied). Repeated measurement analysis for BCVA and central retinal thickness. Log-rank test and Cox model for time to reach target HbA1c Chisquare test for the number of neovascular complications and AE comparisons if applicable, otherwise the Fishers exact test will be performed. Descriptive statistics in terms of mean, standard deviation (SD), median, 25^{th} and 75^{th} percentiles, 95% confidence Intervals and frequency tables.
GCP conformance:	The present trial will be conducted in accordance with the valid versions of the trial protocol, ICH Good Clinical Practice Guidelines (ICH-GCP) and applicaple local regulatory requirements.
Financing:	This investigator initiated trial is financially supported by Novartis Pharma, Nürnberg, Germany. Trial Sponsorship is taken over by Charité University Medicine Berlin.

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II. Abbreviations

Abbreviation	Meaning
AE	Adverse Event
AN(C)OVA	Analysis of (Co)Variance
CRF	Case Report Form
CRT	Central Retinal Thickness
DMC	Data Monitoring Committee
DME	Diabetic macula edema
IMP	Investigational medicinal product
LKP	Principal Coordinating Investigator (Leiter der klinischen Prüfung)
PEI	Paul-Ehrlich-Institut
PRN	pro re nata (as needed = when necessary)
PRP	pan retinal photocoagulation
RR	Blood Pressure
SAE	Serious Adverse Event
SmPC	Summary of product characteristics
SUSAR	Suspected Unexpected Serious Adverse Reaction
UWFFA	Ultra wide field fluorescein angiography
VEGF	Vascular Endothelial Growth Factor

1. Introduction

Diabetic macular edema (DME) is the leading cause of blindness in young adults in developed counties, affecting 12 % of type 1 and 28% of type 2 diabetic patients (Kiire et al. 2013). The gold standard DME treatment should be based on a good control of glycemia along with control of lipids and hypertension function. However, despite the systemic metabolic control values being essential for patients with diabetic retinopathy, it has proven to be insufficient for DME if it appears. With these patients, additional measures are needed in order to avoid the subsequent loss of vision. The introduction of intravitreal corticosteroids or anti-VEGF drugs have shown their safety and efficacy and together with laser photocoagulation are currently the treatments of choice in the management of DME (Boyer et al. 2014; Ip et al. 2015).

The management of systemic risk factors, such as hyperglycemia and arterial hypertension, remains a task of great importance despite all modifications and increase of knowledge during recent years.

The current study intends to investigate the effect of optimized glycemic control (HbA1c < 6,5% if possible without side-effects; triglycerides < 140 mg/dl; RR < 140/90 mmHg) on diabetic macular edema and the number of treatments required.

VEGF (Vascular Endothelial Growth Factor), an angiogenic stimulating factor plays an important role in neovascularization of the retina and vascular leakage leading to macular edema (Ferrara et al. 1997; Kijlstra et al. 2005). Drugs that inhibit VEGF are therefore being investigated for their therapeutic potential (Chang et al. 2007; Edelmann et al. 2005).

Ranibizumab (Lucentis®) is a recombinant humanized IgG1 κ isotype monoclonal antibody fragment that binds to human VEGF and prevents interaction with its receptors VEGFR1 and VEGFR2 on the surface of endothelial cells, thereby reducing endothelial cell proliferation, vascular leakage and the formation of new blood vessels (Chen 1999, Gaudreault 2005).

Ranibizumab is designed for intraocular use and approved in USA and Europe for the treatment of age-related macular degeneration (AMD), visual impairment due to diabetic macular edema (DME), macular edema due to retinal vein occlusion (RVO), and choroidal neovascularization in pathologic myopia (Michels et al. 2005; Rosenfeld et al. 2006). The overall safety profile of ranibizumab, both ocular and non-ocular, was demonstrated to be favorable in many studies with wet AMD, DME and RVO.

The aim of this prospective randomized study is to investigate whether a intensified diabetic control program leads to better final visual acuity and less frequent diabetic ocular complications in patients with diabetic retinopathy when compared with a normal diabetic treatment.

2. Objectives of the clinical trial

2.1. Rationale for the clinical trial

Several studies showed the significant reduction of DME after ranibizumab injections (Do et al. 2012, DRCR Network 2012). Patients could significantly increase their visual acuity under treatment and the safety profile is favourable compared to the application of intravitreal steroids. However, the treatment burden remains high, as ideally patients would receive monthly ranibizumab injections. This still provides a challenge for health care providers and patients alike.

Published studies showed that the intensive insulin treatment and diabetic control can reduce the risk of most retinopathy-related complications (Maple-Brown et al. 2012; Zhang X et al. 2014). However the most recently published meta-analysis could not confirm the reduction of prevalence of vision loss or blindness (Zhang X et al. 2014). Therefore further studies are needed to investigate the effect of intensive diabetic control on visual acuity. Our study is based on the hypothesis that an intensive insulin treatment will positively affect the visual acuity in patients with DME and reduce the need for re-treatment.

2.2. Primary objective / Hypothesis:

The trial investigates the influence of an intensified diabetes control programme on treatment of DME.

As a primary objective the change of best corrected visual acuity in ETDRS letters score at month 12 when compared with baseline (measured by the difference in ETDRS letters score between month 12 and baseline) will be evaluated.

2.3. Secondary and other objectives

The secondary objectives of the trial are:

- To evaluate the number of treatments with ranibizumab up to 6, 12, 18 and 24 months of treatment respectively
- To evaluate the mean average change in BCVA at 6, 12, 18 and 24 months after initial treatment
- To evaluate the macular thickness (as measured with OCT) at 6, 12, 18 and 24 months after initial treatment
- To evaluate the time needed to reach the target HbA_1c
- To evaluate the number of neovascular complications with need of PRP
- To evaluate the safety of the treatment of DME with ranibizumab based on ocular (e.g. retinal detachment, central retinal artery occlusion, endophthalmitis) and systemic AEs (e.g. rates of stroke, myocardial infarction, severe hypoglycemia)

3. Rates of organisational and administrative aspects of the trial

3.1. Sponsor

Sponsor: Charité, University Medicine Berlin
Charitéplatz 1
10117 Berlin
Germany

Represented by: Prof. Dr. med. Antonia M. Joussen
(Principal Coordinating Investigator [PCI])
Department of Ophthalmology, CBF
Hindenburgdamm 30
12200 Berlin, Germany

3.2. Principal Coordinating Investigator

Principal Coordinating Investigator (PCI): Prof. Dr. med. Antonia M. Joussen
Charité University Medicine Berlin
Department of Ophthalmology, CBF
Hindenburgdamm 30
12200 Berlin, Germany

3.3. Statistics

Statistician: [redacted]

3.4. Data Monitoring Committee

There will be no Data Monitoring Committee set up in this clinical trial.

3.5. Further committees

3.5.1. Steering Committee

There will be no Steering Committee set up in this clinical trial.

3.5.2. Advisory Committee

There will be no Advisory Committee set up in this clinical trial.

3.5.3. Imaging Review Board

Best corrected visual acuity (BCVA), size of areas of macular and peripheral capillary drop-out, macular thickness will be analyzed in a blinded fashion by experienced and certified image graders that are part of the study team at the Charité.

3.6. Study laboratories and other technical services

All laboaratoy assessments will be performed by the central laboratory of Charité University Medicine Berlin.

There are no other technical service tasks that will be performed by other service providers.

3.7. Central organisation units

Project management, Randomization, Clinical Monitoring, Safety Management:

CROLLL GmbH
Wörnitzstr. 115a
90449 Nürnberg
Germany
Tel.: +49 911 252688 0
Fax: +49 911 252688 40

Data management:

Charité
Department of Ophthalmology, CBF
Hindenburgdamm 30
12200 Berlin
Germany

3.8. Investigators and trial sites

This clinical trial will be carried out as a monocentric trial at the Charité department of ophthalmology (Campus Benjamin Franklin) in collaboration with the department of diabetology, endocrinology and nutritional medicine (Campus Benjamin Franklin) in Berlin, Germany.

Requirements for investigators and trial sites

The investigators and involved physicians at the department of ophthalmology should be familiar with intravitreal injection procedures as well as macular laser. The investigators and trial site staff have to proof knowledge of regulatory procedures, GCP and experience with the conduct of the clinical testing of pharmaceutical preparations. The investigators and involved physicians are required to have special experience in the indication of DME.

3.9. Financing

This investigator initiated trial is financially supported by Novartis Pharma, Nürnberg, Germany. Trial sponsorship is taken over by Charité University Medicine Berlin.

4. Trial conduct

4.1. General aspects of trial design

This is a monocentre, phase IV, two-arm, randomised, parallel-group, controlled clinical trial.

4.1.1. Time plan

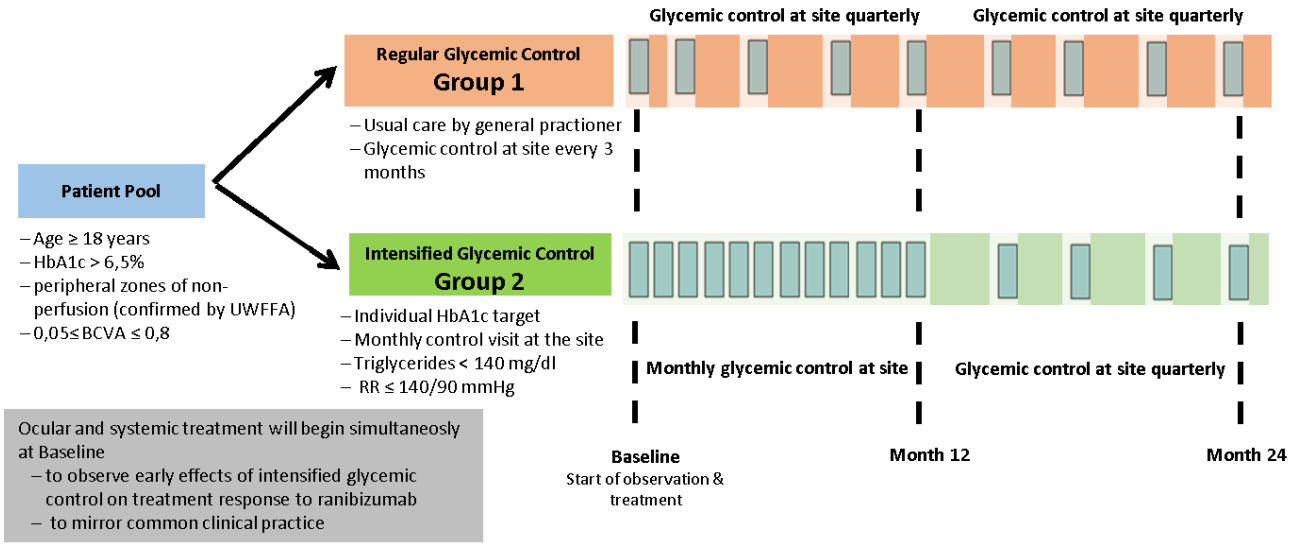
Table 1: Time plan of the trial

First patient first visit (FPFV):	01 August 2015
Last patient first visit (LPFV):	31 May 2018
Last patient last visit (LPLV):	31 May 2020
Final study report:	31 April 2021

End of the clinical trial

The end of the trial is defined as the last visit of the last patient included (LPLV).

Figure 1: Trial flowchart



4.2. Discussion of trial design, randomization and study arms

Selection bias is minimised by concealed random assignment of trial arms. Observer-masking (assessment of BCVA, macular thickness, capillary drop-out) is done to guard against *detection bias*. *Performance bias* is to be reduced by strict standardisation of trial procedures. *Attrition bias*

will be minimised by active follow-up of trial patients by a dedicated study nurse / physician (telephone, mail and in-person contact).

Randomisation of patients into two treatment arms will be performed centrally by CROLLL GmbH and will be computer-assisted, based on block-randomization lists. A randomization ratio of 1:1 will be used. No stratification is planned.
Patients will be randomized to one of the two study arms:

1. *Regular Glycemic Control (Group 1):* patients randomized into this group will be controlled by their general practitioner or private diabetologist (usual care). The glycemic control (blood measurements of HbA1c) will be performed at trial site (Department of diabetology, endocrinology and nutritional medicine) every 3 months. The site will not influence or change the diabetes medication given by general physician and serves as an observer only to monitor the diabetic control.
2. *Intensified Glycemic Control (Group 2):* patients randomized into this group will be controlled at the trial site (Department of diabetology, endocrinology and nutritional medicine) during first year monthly, in the second study year every 3 months. The individual HbA1c will be targeted according to the general status reflecting other risk factors for the vasculopathy (e.g. BMI, smoking, blood pressure, lipid status). All effort will be done to reach the target blood pressure ≤ 140/90 mmHg and blood triglyceride level < 140 mg/dl: Further the patients will be educated to improve their eating habits in regard to reduce the carbohydrate intake.

4.3. Selection of trial population

Reasons for gender distribution

We expect a homogenous (1:1) gender distribution. There is no evidence of difference by gender in the incidence of DME or in the response to anti-VEGF agents.

4.3.1. Inclusion criteria

1. Patients with diabetic macular edema relevant to visual acuity
2. OCT central retinal thickness ≥ 250µm
3. HbA1c > 6,5% at initial visit
4. BCVA ≤ 0.8 and ≥ 0,05
5. Age ≥18 years
6. Written informed consent given

4.3.2. Exclusion criteria

1. Participation in other interventional trials
2. Previous treatment with intravitreal drugs in last 6 months
3. Vitreous hemorrhage as a consequence of proliferative retinopathy which would hamper adequate diagnosis and imaging
4. Blood pressures of ≥ 180/100 (or uncontrolled pressures under pharmacological therapy)
5. Chronic systemic or ocular inflammatory/autoimmune diseases (e.g. inflammatory bowel disease, Addison's diseaes, Cushing Syndrome, Uveitis) which would influence the trial's outcome (at the physician´s discretion)
6. Systemic cortisone or anti-VEGF therapy
7. Acute systemic or ocular infectious diseases
8. Prior laser photocoagulation treatment within 3 months (focal / grid laser or panretinal) prior to study entry
9. Contraindications as stated in summary of medicinal product characteristics or Investigator's Brochure of Ranibizumab
10. Current treatment with pharmaceutical preparations with which interactions can be expected
11. Diseases or findings that may have a significant effect on the target variables and which may therefore mask or inhibit the therapeutic effect under investigation at the investigator's discretion
12. Persons who have a fluorescein allergy
13. Women who are pregnant or breast feeding (pregnancy defined as the state of a female after conception and until the termination of gestation), confirmed by a positive hCG urine test at screening
14. Women who are menstruating and capable of becoming pregnant* and not practicing a medically approved method of contraception (Pearl Index <1**) during and up to at least 12 weeks after the end of treatment. A negative pregnancy test (urine) for all women is required with sufficient lead time before inclusion

    *definition of post-menopausal: 12 months of natural (spontaneous), amenorrhea or 6 months of spontaneous amenorrhea with serum FSH levels >40 mIU/m or 6 weeks post surgical bilateral oophorectomy with or without hysterectomy

    **examples of particularly reliable methods with Pearl Index (PI) <1, according to guidelines of Deutsche Gesellschaft für Gynäkologie und Geburtshilfe:
    - Combination pill with estrogen and gestagen (no mini-pill, PI=0.1-0.9)
    - Vaginal ring (NuvaRing®, PI=0.65 uncorr.; 0.4 corr.)
    - Contraceptive patch (EVRA®, PI= 0.72 uncorr.; 0.9 corr.)
    - Estrogen-free ovulation inhibitors (Cerazette®, PI=0.14)
    - Progestin-containing contraceptives (Implanon®, PI=0-0.08)
    - Injectable 3-month depot progestins (PI=0.3-1.4; 0.88 corr.)
    - Intra-uterine progestine device (Mirena®, PI=0.16)

15. Persons with any kind of dependency on the investigator or employed by the sponsor or investigator
16. Persons held in an institution by legal or official order or legally incapacitated

4.4. Withdrawal of trial subjects after trial start

Study subjects will be early discontinued from participation in the study if

- they withdraw consent from participating in the study
- no response to the ranibizumab treatment is observed, defined as persisting macular edema without any reduction of central retinal thickness after 3 consecutitive monthly injections
- they present visual lost defined as ≥30 ETDRS Letters when compared with the baseline
- they develop vitreous bleeding due to active neovascularisation of the retina or optic disc confirmed by fluorescein angiography with need of surgical treatment (vitrectomy)
- any other clinical adverse event (AE), laboratory abnormality, illness or other medical condition or situation occurs that would not go along with the best interest of the patient in case of continuing the participation.

Note: Each patient should be followed-up even if the study treatment is discontinued.

4.4.1. Procedures for premature withdrawal from treatment during the trial

In case of patient withdrawal during the study period all data collected until this point of time will be stored according to AMG §40, 2a, 3. The patient must not be replaced.

4.5. Closure of trial sites/Premature termination of the clinical trial

4.5.1. Closure of trial sites

Not applicable, this is a monocentric trial.

4.5.2. Premature termination of trial

The sponsor has the right to terminate the trial prematurely if there are any relevant medical or ethical concerns or if completing the trial is no longer practicable. If such action is taken, the reasons for terminating the trial must be documented in detail. All trial subjects still under treatment at the time of termination must undergo a final examination which must be documented. The PCI must be informed without delay if any investigator has ethical concerns about continuation of the trial.

The trial must be terminated if:

- The risk-benefit balance for the trial subject changes markedly
- It is no longer ethical to continue treatment with the IMP
- The sponsor considers that the trial must be discontinued for safety reasons
- It is no longer practicable to complete the trial, e.g. due to scientific reasons

PCI decides on whether to discontinue the trial based on medical data and/or in consultation with the statistician.

4.6. Treatment

Patients are treated with ranibizumab for their underlying disease diabetic macular edema according to the current summary of product characteristics Lucentis®. Treatment will take place at trial site.

4.6.1. Treatments to be given

In all patients (in both study arms) the diabetic macular edema will be treated with intravitreally given ranibizumab.

Dosage and administration of Ranibizumab

Injections are administered according to the current summary of product characteristics Lucentis®, i.e. monthly until maximum BCVA can be observed:

Starting at visit 1, ranibizumab will be administered intravitreally in a multiple-dose regimen of 0.5 mg of ranibizumab every month for a total of 3 injections and as a PRN treatment thereafter (subsequent injections until maximum BCVA is observed).

Injection is discontinued when

- no BCVA improvement in spite of treatment is seen after the first three injections (i.e. after three consecutive monthly visits)

BCVA assessments will take place monthly. Monthly injections are resumed when

- decrease in BCVA due to worsening of DME in the opinion of the investigator is observed

Injections are continued until BCVA improvement is seen after three consecutive monthly visits.

If a subject is unable to receive study drug because of medical or personal reasons, treatment should be resumed within 2 weeks of the scheduled treatment. If a subject is unable to receive study drug within 2 weeks of the scheduled treatment, the subject will be allowed to miss the scheduled dose and resume treatment at the next regularly scheduled time. Dosing should not occur more frequently than every 4 weeks. Missed doses will not be replaced.

Ranibizumab Injection

Procedures will be implemented to minimise the risk of potential adverse events associated with serial intraocular injections (e.g., endophthalmitis). Aseptic technique must be observed by clinic staff involved in the injection tray assembly, anesthetic preparation and administration, and study drug preparation and administration. In addition to the procedures outlined in the protocol, added safety measures in adherence to specific institutional policies associated with intraocular injections should be observed.

4.6.2. Description of investigational medicinal product

The investigational drug is ranibizumab (Lucentis®) and will be prescribed by the investigator for treatment of diabetic macular edema. Ranibizumab is approved for intravitreal injection in wet age related macula degeneration, diabetic macular edema, retinal vein occlusions and choroidal neovascularization in pathologic myopia.

Ranibizumab (Lucentis®) binds to the receptor binding site of active forms of VEGF-A, including the biologically active, cleaved form of this molecule, $VEGF_{110}$. VEGF-A has been shown to cause neovascularization and leakage in models of ocular angiogenesis. The binding of ranibizumab to VEGF-A prevents the interaction of VEGF-A with its receptors (VEGFR1 and VEGFR2) on the surface of endothelial cells, reducing endothelial cell proliferation, vascular leakage, and new blood vessel formation. The most common adverse events following intra-ocular injection are conjunctival hyperemia and subconjunctival hemorrhage. Serious adverse events related to the injection procedure have occurred in < 0.1% of intravitreal injections, including endophthalmitis, rhegmatogenous retinal detachments, and iatrogenic traumatic cataracts (Heier 2006).

4.6.2.1. Manufacture of the investigational medicinal product

The drug supplied for this study will be manufactured by Novartis.

4.6.2.2. Supply and labelling of investigational medicinal product

Drug will be supplied to the investigator as commercially available Lucentis® by the site's pharmacy after prescription. No trial specific labelling will take place.

4.6.2.3. Storage of investigational medicinal product

The trial medication will be kept at the respective hospital pharmacies that are responsible for storage of the medication in accordance to applicable laws and local standards. The IMP should be stored in a secure, limited-access location according to the summary of product characteristics (2°-8°C, protected from light, freezing must be avoided). IMP will be delivered to the site on demand according to local practice.

4.6.3. Dispensing of investigational medicinal product

The local investigator or his/her designee will document dispensed IMP for each subject. Destruction of IMPs will be performed by the trial sites/pharmacies and will be documented according to local practice.

4.6.4. Assignment of trial subjects to treatment groups

Randomization will be done by using a randomly computer generated list allocating a patient number to each of the two investigational arms in a 1:1 ratio.

4.6.5. Selection of dosage of investigational medicinal product

See 4.6.1

4.6.6. Time of administration and adjustments to dosage of the investigational medicinal product in the individual trial subject

No dosage adjustments are planned in this clinical trial. See 4.6.1 for administration details.

4.6.7. Blinding, Unblinding

Observer-masking (assessment of BCVA, macular thickness, capillary drop-out) is done to guard against detection bias. Unblinding procedures are not applicable (treatment is not blinded).

4.6.8. Previous and concomitant medication

Permitted concomitant therapies include cataract surgery. Other surgical therapies, e.g. vitrectomy, are not permitted during the study and will be considered treatment failure.

Similarly, other pharmacological treatments for macular edema, e.g. triamcinolone or other steroids or other anti-VEGF drugs (local or systemic) are not permitted during the study period.

Any therapy (except medications which are excluded by the trial's exclusion criteria) is allowed for treatment of the underlying disease diabetes mellitus.

Concomitant therapy will be documented on the appropriate trial database/CRF pages.

4.6.8.1. Rescue therapy for emergencies

Rescue medication allowed in this study is panretinal and/or focal laser treatment (after 3 consecutive monthly injections) and only if a significant progression of neovascularization with associated threat of visual loss is seen. Laser treatment will be documented on the appropriate trial database/CRF pages.

The ranibizumab injection can be performed at the same day as a laser therapy, but not earlier than 30 minutes after laser treatment.

If the therapeutic effect will be considered insufficient by either the patient or the treating physician the patient may be withdrawn from the study and is able to receive whatever treatment is considered to be necessary.

4.6.9. Continuation of treatment after the end of the clinical trial

The investigator must provide follow-up medical care for all patients who are prematurely withdrawn from the study, or must refer them for appropriate ongoing care.

4.7. Efficacy and safety variables

4.7.1. Measurement of efficacy and safety variables

4.7.1.1. Primary target variable

- Change of best corrected visual acuity in ETDRS letters score at month 12 when compared with baseline (measured by the difference in ETDRS letters score between month 12 and baseline according to internal guideline of Charité Department of Ophthalmology)

4.7.1.2. Secondary target variables

- Number of treatments with Ranibizumab up to 6, 12, 18 and 24 months of treatment respectively
- Mean average change in BCVA at 6, 12, 18 and 24 months after initial treatment
- Macular thickness (as measured with OCT) at 6, 12, 18, and 24 months after initial treatment
- Time to reach target HbA1c
- Number of neovascular complications: need for panretinal laser photocoagulation (PRP)
- Rates of ocular and of systemic AEs (retinal detachment, Central retinal artery occlusion, endophthalmitis; and rates of stroke, myocardial infarction, severe hypoglycemia)

4.7.2. Fundus photography

At the initial time point (screening visit) and months 12 and 24, digital colour fundus photos should be made of the central area and every quadrant; central, nasal, nasal-superior, superior, temporal-superior, temporal, temporal-inferior, inferior, nasal-inferior (a total of nine photos, with an optional overview photo (compilation of the nine photos). At the other visits that require fundus photographs as indicated in the visit schedule, digital fundus photos of the central area and the optic nerve head alone will be acquired.

4.7.3. Optical Coherence Tomography (OCT)

A Spectral Domain OCT of Heidelberg Engineering (Spectralis, Heidelberg Engineering, Heidelberg, Germany) should be used to perform the measurements at every time point indicated in the visit schedule. OCT macular volume scans of both eyes should be performed.

4.7.4. Fluorescein Angiography

Standardized angiography is performed by fluorescein angiography using a confocal scanning laser ophthalmoscope (Spectralis, Heidelberg Engineering). Besides central images of the macula, the periphery will be covered with ultra-wide lens using 9 separate images. The angiograms follow a standardised protocol.

Fluorescein angiograms will include pre-injection reflectance images using the green illumination (514 nm) and autofluorescence images using the blue (488 nm) illumination. Angiographic images will be taken within the first second after dye inflow, and thereafter in 1 second intervals for 15 seconds, then at 30 seconds, 60 seconds, 120 seconds, 300 seconds, and 600 seconds, after injection. For all central images, the 30° mode and the 512x512 resolution will be used. Subsequently, peripheral images are taken with 102° lens in total 9 fields.

4.7.4.1. Description of visits

Screening assessments should be performed 1 to 7 days before treatment start (Visit 1).

Table 2: Investigations during the clinical trial (until month 12)

Visits	**Screenig**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Month	**-1 to -7 days**	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**
Procedure	a time frame of ±1 week is allowed until visit 12												
Inclusion/exclusion criteria	**x**												
Demographic data & med. history	**x**												
Informed consent[1]	**x**												
Pregnancy status[2]	**x**												
Randomization	**x**												
Study treatment		**x**	**x**	**x**	**x**[5]	**x**[5]	**x**[5]	**x**[5]	**x**[5]	**x**[5]	**x**[5]	**x**[5]	**x**[5]
Clinical lab tests[3]	**x**			**x**			**x**			**x**			**x**
Blood glucose and blood pressure measurement (**group 1**) (regular diabetic control)[4]	**x**			**x**			**x**			**x**			**x**
Blood glucose and blood pressure measurement (**group 2**) (intensive diabetic control)	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Funduscopy	**x**			**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
BCVA (ETDRS)	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Slitlamp	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Fluorescein angiography	**x**						**x**						**x**
Fundus photography	**x**			**x**			**x**			**x**			**x**
OCT	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Concomitant medication	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
AE/SAE (documentation & report)		**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**

SCR = Screening, to be performed within one week before study treatment start

[1] written informed consent has to be obtained before any study related investigations are performed

[2] for women of child-bearing potential a test will be performed at screening; all other women will be asked for pregnancy status. In the course of the trial women of child-bearing potential will be asked for pregnancy status before Ranibizumab treatment or fluorescein angiography

[3] triglycerides, HbA1c

[4] group 1 patients will be cared for diabetes by their general practitioner and will visit the site additionally every three months as indicated

[5] checkup visit according to local practice & possible PRN therapy

Table 3: Investigations during the clinical trial (months 12-24: follow-up time)

Visits/Months	**13**	**14**	**15**	**16**	**17**	**18**	**19**	**20**	**21**	**22**	**23**	**24**
Procedure	a time frame of ±4 weeks is allowed until visit 24											
Ranibizumab treatment [1]	according to local practice & possible PRN therapy											
Clinical lab tests			**x**			**x**			**x**			**x**
Blood glucose and blood pressure measurement (**group 1**) (regular diabetic control)			**x**			**x**			**x**			**x**
Blood glucose and blood pressure measurement (**group 2**) (intensive diabetic control)			**x**			**x**			**x**			**x**
Funduscopy			**x**			**x**			**x**			**x**
BCVA (ETDRS)	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Slitlamp	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Fluorescein angiography [1]						**x**						**x**
Fundus photography			**x**			**x**			**x**			**x**
OCT	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
Concomitant medication	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**
AE/SAE documentation/reporting [2]	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**	**x**

[1] women of child-bearing potential will be asked for pregnancy status before each ranibizumab treatment or fluorescein angiography

[2] until 30 days after the patient has stopped the ranibizumab treatment

4.7.5. Rationale for assessment procedures

Macular edema is assessed both anatomically (OCT and fluorescein angiography) and functionally (BCVA). For assessment of the glycemic status of the patients, blood glucose measurements and other laboratory tests are required.

The intervals for clinical assessment in the current trial were set to 4 weeks based on the Lucentis® SmPC's recommendations for visual acuity assessements.

4.7.6. Pharmacokinetics/Determination of drug levels

Not applicable.

4.8. Data quality assurance

4.8.1. Monitoring

The trial sites will be monitored to ensure the quality of the data collected. The objectives of the monitoring procedures are to ensure that the trial subject's safety and rights as a study participant are respected, that accurate, valid and complete data are collected, and that the trial is conducted in accordance with the trial protocol, the principles of GCP and local legislation.

All investigators agree that the monitor regularly visits the trial site and assure that the monitors will receive appropriate support in their activities at the trial site. The declaration of informed consent (see Section 5.4) includes a statement to the effect that the monitor has the right – while observing the provisions of data protection legislation – to compare the data entered in the trial database, respectively with the trial subject's medical records (doctor's notes, laboratory printouts etc.). The investigator will secure access for the monitor to all necessary documentation for trial-related monitoring. The aims of the monitoring visits are as follows:

- To check the declarations of informed consent
- To monitor trial subject safety (occurrence and documentation/reporting of AEs and SAEs)
- To check the completeness and accuracy of entries in the trial database
- To validate the entries in the trial database against those in the source documents (source data verification, SDV),
- To perform drug accountability checks
- To evaluate the progress of the trial
- To evaluate compliance with the trial protocol
- To assess whether the trial is being performed according to GCP at the trial site
- To discuss with the investigator aspects of trial conduct and any deficiencies found

A monitoring visit report is prepared for each visit describing the progress of the clinical trial and any problems.

The exact extent of the monitoring procedures is described in a separate monitoring plan.

4.8.2. Audits/Inspections

As part of quality assurance, the sponsor has the right to audit the trial sites and any other institutions involved in the trial. The aim of an audit is to verify the validity, accuracy and completeness of data, to establish the credibility of the clinical trial, and to check whether the trial subject's rights and trial subject safety are being maintained. The sponsor may assign these activities to persons otherwise not involved in the trial (auditors). These persons are allowed access to all trial documentation (especially the trial protocol, case report forms/trial database, trial subjects' medical records, drug accountability documentation, and trial-related correspondence).

The sponsor and all trial sites involved undertake to support auditors and inspections by the competent authorities at all times and to allow the persons charged with these duties access to the necessary original documentation.

All persons conducting audits and inspections undertake to keep all trial subject data and other trial data confidential.

4.9. Documentation

All data relevant to the trial are documented soon after measurement by the investigator in the trial database supplied. Entering data may be delegated to members of the local trial team. All changes made to the data are documented in an audit trail. The trial software has a user and role concept that can be adjusted on a trial-specific basis.

4.9.1. Data management

The IT infrastructure and data management staff will be supplied by Charité, department of Ophthalmology, CBF. The trial database will be developed and validated before data entry based on standard operating procedures. The data management system is based on commercial trial software and stores the data in a database. All changes made to the data are documented in an audit trail. The trial software has a user and role concept that can be adjusted on a trial-specific basis. The database is integrated into a general IT infrastructure and safety concept with a firewall and backup system. The data are backed up daily. After completion and cleaning of data, the database is locked and the data exported for statistical analysis.

The data will be entered online at the trial sites via the Internet. Plausibility checks are run during data entry, thereby detecting many discrepancies immediately. The Data Management will conduct further checks for completeness and plausibility and will clarify any questions with the trial sites electronically via the trial software. These electronic queries have to be answered by the trial site without unreasonable delay. Further details will be specified in the data management manual.

4.9.2. Archiving

All data in the database, informed consent forms and other important trial materials will be archived for at least 10 years in accordance with §13 (10) of the GCP-Verordnung.

5. Ethical and regulatory aspects

5.1. Independent ethics committee

The clinical trial will not be started before approval of the competent ethics committee concerning the suitability of the trial site and the qualifications of the investigators and trial team.

5.2. Ethical basis for the clinical trial

The present trial protocol and any amendments were and will be prepared in accordance with the Declaration of Helsinki of October 1996.

5.2.1. Legislation and guidelines used for preparation

The present clinical trial will be conducted in accordance with the published principles of the guidelines for Good Clinical Practice (ICH-GCP) and applicable legislation (especially the Federal Drug Law [AMG] and the GCP-Verordnung). These principles cover, amongst other aspects, ethics committee procedures, the obtaining of informed consent from trial subjects, adherence to the trial protocol, administrative documentation, documentation regarding the IMP, data collection, trial subjects' medical records (source documents), documentation and reporting of adverse events (AEs), preparation for inspections and audits, and the archiving of trial documentation. All investigators and other staff directly concerned with the study will be informed that domestic and foreign supervisory bodies, the competent federal authorities and authorised representatives of the sponsor have the right to review trial documentation and the trial subjects' medical records at any time.

5.3. Notification of the authorities, approval and registration

Before the start of the clinical trial, all necessary documentation will be submitted to the competent supreme federal authority for approval (Paul-Ehrlich-Institut [PEI]). The local authority will be informed about the trial according to German drug law.

Before the trial is started, it will be registered under www.clinicaltrials.gov a trial register approved by the World Health Organisation (WHO) (http://www.who.int/ictrp/en/).

5.4. Obtaining informed consent from trial subjects

Trial subjects may not be enrolled into the present trial unless they have consented to take part in the trial after having been informed verbally and in writing in comprehensible language of the nature, scope and possible consequences by a trial investigator or physician who is member of the trial team. Together with the consent to take part in the trial, the trial subject must also agree to representatives of the sponsor (e.g. monitors or auditors) or the competent supervisory or federal

authorities having access to the data recorded within the framework of the clinical trial. The trial subject will be informed of the potential benefit and possible side effects of the IMP. It must be clear to trial subjects that he or she can withdraw his or her consent at any time without giving reasons and without jeopardizing his / her further course of treatment.

The originally signed consent form and information sheet is archived in the investigator site file. Trial subjects receive copies of the written information sheet, confirmation of insurance with conditions, and the signed informed consent form. A copy of the written information sheet and the signed informed consent form will be filed in the patient's record.

The patient information sheet, informed consent form, all other documents handed out to the trial subject and any recruitment advertisements must be submitted for approval before use to the ethics committee. Part of the monitoring activities are to check that the most recent informed consent form was used before the trial subject was enrolled and that it was dated and signed by the trial subject himself or herself and signed and dated by the investigator or authorised physician.

5.5. Insurance of trial subjects

All trial subjects enrolled are insured in accordance with § 40 AMG under the group insurance contract of Charité University Medicine with HDI Gerling Versicherung (insurance company). The headquarters, policy number and telephone and fax number will be included in the patient information sheet.

5.6. Data protection

The provisions of data protection legislation will be observed. It is assured by the sponsor that all investigational materials and data will be pseudonymised in accordance with data protection legislation before scientific processing.

Trial subjects will be informed that their pseudonymised data will be passed on in accordance with provisions for documentation and notification pursuant to § 12 and § 13 of the GCP Regulations to the recipients described there. Subjects who do not agree that the information may be passed on in this way will not be enrolled into the trial.

6. Statistical methods and sample size calculation

6.1. Statistical and analytical plan

This is a two-arm, monocentre, therapeutic-exploratory clinical trial with 120 patients randomly assigned to treatment arms. Though the primary analysis is done at 5% significance level (two-sided). The essentials of the statistical analysis are outlined below. Further details will be layed down in the statistical analysis plan.

6.1.1. Trial populations

The first dataset for analysis is derived from the intention-to-treat (ITT) population. This dataset includes all trial subjects enrolled into the trial, randomised to treatment groups and received at least one injection of ranibizumab- no exclusions.

The second dataset for analysis is derived from the per-protocol (PP) population. This dataset includes all trial subjects who were treated according to protocol (i.e. they received at least 3 injections of ranibizumab and do not meet any exclusion criteria) and reached/provided at least one endpoint of main interest (i.e. after 6 months of follow-up).

The third dataset for analysis is the safety population. This population includes all trial subjects who received any ranibizumab treatment.

6.1.2. Description of trial subject groups

Demographic variables and baseline values of study objectives will be summarised by treatment groups. Descriptive statistics in terms of mean, standard deviation and 95% confidence interval for continuous variables and frequency tables for discrete variables will be presented.

6.1.3. Primary target variable

The primary endpoint will be the change of best corrected visual acuity in ETDRS Letters score at month 12 when compared with baseline. This endpoint will be analysed by analysis of covariance (ANCOVA) with the baseline value as covariate (type II SS will be used since no interaction terms are included in the model).

The null hypothesis is:

H_0: $\mu_{iDC} = \mu_{rDC}$

and the alternative hypothesis is:

H_1: $\mu_{iDC} \neq \mu_{rDC}$

where μ_{iDC} is the mean of the differences in ETDRS Letters score between month 12 and baseline for the investigational arm (intensified diabetic control) and μ_{rDC} is the mean of the differences in ETDRS Letters score between month 12 and baseline for the control arm (regular diabetic control).

ITT population is used for the primary efficacy analysis. If no ETDRS Letter score is available at month 12 the closest measurement (could be before or after 12 month) which was at least after 3 months will be used for the analysis.

6.1.4. Secondary efficacy variables

Different statistical methods will be applied for analysis of secondary endpoints.

For the number of treatments at 6, 12, 18 and 24 months, an ANOVA without any covariates will be applied at each endpoint 6, 12, 18 and 24 months.

The data of change in BCVA and macular thickness at 6, 12, 18 and 24 months are analysed by repeated measures analysis of variance (assuming missing at random, MAR). The missing values for BCVA and macular thickness are imputed by the last observation carried forward (LOCF). The treatment by time interaction will be included in both statistical models but the baseline value will only be included in the change in BCVA analysis since the macular thickness will not be adjusted by the baseline value in this analysis.

The change in BCVA and macular thickness with respect to baseline values is calculated at 6, 12, 18 and 24 months. For each time point, the change values are described statistically by mean, standard deviation, and 95% confidence interval.

Time to reach target HbA1c is evaluated by log-rank test and hazard ratio in terms of a Cox proportional hazard model. The results are visualised by Kaplan-Meier curves. No covariates are included in the model.

The number of neovascular complications in two treatment arms is compared by frequencies and a chi-square test if applicable (the chi-squared test will not be used when the absolute frequency in any of the cells of the contingency table is below 5), otherwise the Fishers exact test will be performed.

ITT population is used for all secondary efficacy analyses.

6.1.5. Safety variable

Safety data, concomitant therapies and concomitant medications are listed and summarized by contingency tables. Safety population is used for this analysis.

6.1.6. Sensitivity and Subgroup analyses

A sensitivity analysis for the primary endpoint based on the PP population will be performed.

Another sensitivity analysis will assess the influence of the assumption of normality for the primary analysis by transforming the data with the natural logarithm. The ANCOVA described in section 6.1.3 will be applied in the same way on the transformed data.

The primary and secondary endpoint except number of neovascular complications and rates of ocular and of systemic AEs will be analysed by descriptive statistics and statistical methods mentioned above within the following subgroups defined by the following potentially prognostic baseline variables:

- HbA1c: >= 9%
- HbA1c: >= 7,5%, < 9%

- HbA1c: >= 6,5%, < 7,5%
- Intravitreal treatment with ranibizumab before trial entry (yes vs no)
- Size of macula edema >400µm
- BCVA (>65 vs <=65)

For the sake of subgroup analysis, the ITT population will be used.

6.1.7. Interim analysis

No interim analysis is planned.

6.1.8. Handling of missing data

If not stated otherwise no imputations of missing values will be performed.

6.2. Sample size calculation

The calculation of the sample size is based on the primary endpoint. It is of interest to discover the difference between two treatment groups, and we assume that the average difference between treatments in the primary endpoint is 2.0 (δ=2.0). Assuming the standard deviation of the change of best corrected visual acuity in ETDRS letters score over 12 months be σ =3.5. Then, the study is designed to detect a decrease of 0.571 times of standard deviation in the primary endpoint for the treatment arm with intensified diabetic control program (δ/σ≈0.571). With a two-sided alpha of 5% and a power of 85%, a sample size of 112 patients is required to detect this difference. Given the allocation ratio of 1:1 between two treatment arms, 56 patients per arm are required. In order to take drop-outs into account, approx 7% increase in sample size is anticipated which leads to the randomisation of 60 patients per treatment arm (56*1.07=60). Thus, altogether, 120 patients will be included in the trial. Sample size calculation was performed with SAS 9.4.

7. Safety

7.1. Definitions of adverse events and adverse drug reactions

7.1.1. Adverse event

An adverse event (AE) is any untoward medical occurrence in a trial subject administered an IMP. There does not necessarily have to be a causal relationship with this treatment.

All events occurring after the first administration of the IMP until 30 days after the patient has stopped the treatment must be documented by the investigator or designee.

The deterioration of a preexisting illness is also an AE in the context of a clinical trial, i.e. medical conditions/diseases present before study treatment are only considered adverse events if they worsen after start of study treatment. Abnormal laboratory values or test results constitute adverse

events only if they induce clinical signs or symptoms, require study treatment discontinuation or require therapy.

Pregnancy

For reasons of drug safety, the occurrence of a pregnancy during the conduct of this trial is to be regarded as an AE.

The investigator or a member of the local trial team will inform the sponsor or designee without delay about any pregnancy that occurs during the trial at latest within 24 hours of being made aware of it. This will be documented on a separate report form ("Clinical trial pregnancy form"). If additional informations are known these must also be sent by the investigator within 24 hours of awareness. The pregnant women will be asked to give separate informed consent for pregnancy follow up. For tracing health of the newborn baby after delivery both parents have to give an informed consent.

In case of pregnancy study medication has to be stopped immediately.

7.1.2. Adverse drug reaction

An adverse drug reaction (ADR) is any noxious and unintended response to an investigational medicinal product (IMP) related to any dose with at least a reasonably possible causal relationship with the IMP.

7.1.3. Serious adverse events and serious adverse reactions

A serious AE (SAE) or serious ADR (SADR) is any untoward medical occurrence that

1. Results in death,
2. Is life-threatening at the time of the event
3. Requires inpatient hospitalisation or prolongation of existing hospitalisation, except:
   - Routine treatment or monitoring of the studied indication, not associated with any deterioration in condition (e.g. Cataract formation)
   - Elective or pre-planned treatment for a pre-existing condition that is unrelated to the indication under study and has not worsened since the start of study drug
   - Treatment on an emergency outpatient basis for an event not fulfilling any of the definitions of a 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
4. Results in persistent or significant disability/incapacity
5. Is a congenital anomaly or birth defect

6. 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

Inpatient hospitalisation is defined as any stay in hospital on the part of a trial subject that includes at least one night (midnight to 06:00).

If an AE is classified as an SAE, this is documented on a separate SAE sheet (Serious Adverse Event Report Form) in addition to the standard AE documentation.

SAE, regardless of suspected causality, occurring after the patient has provided informed consent and until 4 weeks after the patient has stopped study participation must be reported to the sponsor or designee within 24 hours of learning of its occurrence.

Any SAEs experienced after this 4-week period should only be reported if the investigator suspects a causal relationship to the respective study treatment.

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. An SAE that is considered completely unrelated to a previously reported one should be reported separately as a new event.

7.1.4. Unexpected adverse drug reaction

An unexpected ADR is an ADR the nature or severity of which is not consistent with the applicable product information available for the IMP. Expected ADRs are listed in the appropriate reference documents (for Ranibizumab/Lucentis®: Summary of product characteristics).

7.1.5. Suspected unexpected serious adverse reactions

A suspected unexpected serious adverse reaction (SUSAR) is an adverse event the nature or severity of which is not consistent with the product information available for the IMP, is regarded as serious, and has at least a possible causal relationship with the IMP.

7.2. Documentation and follow-up of adverse events

The sponsor ensures that all persons involved in the treatment of trial subjects are adequately informed of the responsibilities and actions required when AEs occur. Trial subjects will be asked at each visit whether they have experienced AEs or SAEs. AEs will be documented in the trial subject's medical records and in the trial database/CRF.

For the procedure of SAE-reporting see section 7.3 and section 7.1.3.

7.2.1. Documentation of adverse events and adverse drug reactions

All AEs occurring during the defined reporting period will be documented in the trial database/CRF including all information listed below.

The AE is documented including the following information:

- Date and time of onset and resolution
- Severity
- Causal relationship with IMP / study treatment
- Seriousness
- Interruption or withdrawal of study treatment and other measures taken

Regardless of whether a causal relationship between the AE and the IMP is suspected, trial subjects who develop adverse events must be monitored until all symptoms have been subsided, pathological laboratory values have returned to pre-event levels, a plausible explanation is found for the AE, the trial subject has died, or the study has been terminated for the trial subject concerned.

Preexisting diseases (before administration of the IMP) are not documented as adverse events but as concomitant diseases. New diseases and preexisting diseases that worsen during the trial are documented as AEs.

7.2.2. Severity of the adverse event

The investigator will classify the severity of AEs as follows:

- Mild: clinical symptoms or signs that are well tolerated
- Moderate: clinical symptoms or signs that are enough to impair everyday activities
- Severe: clinical symptoms or signs that markedly impair the trial subject and result in inability to work or go about everyday activities

7.2.3. Causal relationship between adverse event and investigational medicinal product

The investigator will assess for every AE whether a causal relationship with the IMP can be assumed or not. The assessment includes consideration of the nature and type of reaction, the temporal relationship with the IMP, the clinical status of the trial subject, concomitant medication and other relevant clinical factors. If the event is considered due to lack of efficacy or as a symptom or sign of the underlying disorder, no causal relationship will be assumed.

The following definitions are used to assess the causal relationship between all AEs and the IMP (WHO Causality Assessment of Suspected Adverse Reactions):

- Certain: A clinical event, including laboratory test abnormality, occurring in a plausible time relationship to drug administration, and which cannot be explained by concurrent disease or other drugs or chemicals. The response to withdrawal of the drug (dechallenge) should be clinically plausible. The event must be definitive pharmacologically or phenomenologically, using a satisfactory rechallenge procedure if necessary.
- Probable/likely: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, unlikely to be attributed to concurrent disease or other drugs or chemicals, and which follows a clinically reasonable response on withdrawal (dechallenge). Rechallenge information is not required to fulfill this definition.
- Possible: A clinical event, including laboratory test abnormality, with a reasonable time sequence to administration of the drug, but which could also be explained by concurrent disease or other drugs or chemicals. Information on drug withdrawal may be lacking or unclear.
- Unlikely: A clinical event, including laboratory test abnormality, with a temporal relationship to drug administration which makes a causal relationship improbable, and in which other drugs, chemicals or underlying disease provide plausible explanations.
- Conditional/unclassified: A clinical event, including laboratory test abnormality, reported as an adverse reaction, about which more data is essential for a proper assessment or the additional data are under examination.
- Unassessable/unclassifiable: A report suggesting an adverse reaction which cannot be judged because information is insufficient or contradictory, and which cannot be supplemented or verified.

An ADR is suspected if the causal relationship is at least ‘possible’ or ‘conditional/unclassified’ or ‘unassessable/unclassifiable’. Events assessed as ‘unlikely’ are not suspected ADRs.

If an ADR is considered a SUSAR it has to be reported as described in sections 7.3.3 - 7.3.7.

7.3. Reporting of serious adverse events, pregnancy, SUSARs and changes in risk-benefit assessment

7.3.1. SAE and pregnancy reporting (investigator to the sponsor)

Regardless of the assumed causal relationship, every SAE that occurs during a trial must be documented in the appropriate part of the trial database/CRF and on an SAE sheet which has to be sent to the sponsor or designee.

Information about all SAEs is collected and recorded on a Serious Adverse Event Report Form which will be provided in the investigator site file. The investigator or a physician who is a member of the local trial team must assess the relationship to study treatment, complete the SAE Report Form in English, and send the completed, signed form by fax within 24 hours to the sponsor or designee. The original copy of the SAE Report Form and the fax confirmation sheet must be kept at the study site. Follow-up information is 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.

SAE reporting is based on regulatory requirements of AMG.

Pregnancies must also be documented on separate pregnancy forms and reported to the sponsor within within 24 hours of being made aware of such (see section 7.1.1).

7.3.2. SUSAR reporting

All SAEs are assessed by the sponsor or PCI with regard to seriousness (see Section 7.1.3), causality (see Section 7.2.3) and expectedness (see Section 7.1.4), regardless of the investigator's assessments.

Every SUSAR that becomes known to the sponsor and which was assessed to be likely caused by the use of the trial's IMP in this trial or in another trial that is conducted by the sponsor with the similar IMP (Ranibizumab) will be reported by the sponsor or PCI to the competent supreme federal authority (PEI), the responsible ethics committee and all investigators involved in the study.

A CIOMS-1 format shall be used for submitting expedited reports to the above mentioned partners.

<u>Fatal and life-threatening SUSARs</u>

If a SUSAR is fatal or life-threatening the competent supreme federal authority, the ethics committee responsible and the investigators must be informed by the sponsor or PCI without delay,

at the latest 7 calendar days after becoming aware of the minimum criteria for reporting. In all cases, attempts must be made to obtain further relevant information which must be supplied to the competent supreme federal authority and the ethics committee within a further 8 days.

SUSARs that are not fatal or life-threatening

The investigators and authorities mentioned above will be informed without delay by the sponsor or PCI of all SUSARs, at the latest within 15 calendar days of becoming aware of the minimum criteria for reporting. Further relevant details will be passed on as soon as possible.

If the information at the time of reporting is incomplete, further information to enable adequate assessment of the case will be requested from the reporter or other available sources.

7.3.3. Informing the marketing authorisation holder

Novartis Pharma as the marketing authorization holder of the IMP will be notified for SAEs. The sponsor or PCI will also inform the marketing authorization holder about all SUSARs including information reported to the competent supreme authority and ethics committee in accordance with contractual agreements.

7.3.4. Review and reporting of changes in the risk-benefit ratio

Without delay, and at the latest within 15 days of the decision for the need to do so, the sponsor or PCI will inform the competent supreme federal authority, the ethics committee responsible of any events or factors that mean that the risk-benefit ratio of the IMP has to be reviewed. These consist of especially:

- Individual reports of expected serious ADRs with an unexpected outcome
- A clinically relevant increase in the rate of occurrence of expected SADRs
- SUSARs in trial subjects who have already completed the follow-up period of the clinical trial (”end-of-trial visit”)
- Factors emerging in connection with trial conduct or the development of the IMP that may affect the safety of persons concerned.

7.3.5. Informing the Data Monitoring Committee

Not applicable

7.4. Annual safety report of trial subjects

Once per year, the sponsor or PCI will supply a report on the safety of trial subjects with all available relevant information concerning patient safety during the reference period to the competent supreme federal authority and to the responsible ethics committee.

The annual safety report will be compiled according to the corresponding ICH guideline E2F „Development Safety Update Report – DSUR“.

The data lock point for the first patient data set to be included and analyzed is determined by the date of the competent’s authority’s approval to conduct the trial.

The sponsor or PCI will supply the report within 60 days of one year after the reference date (data-lock point). Following reports will be supplied annually.

8. Use of trial findings and publication

8.1. Reports

8.1.1. Interim reports

Section 7.4 describes the requirements for annual reports on the safety of trial subjects.

8.1.2. Final report

The competent authority and ethics committee will be informed within 90 days that the trial has officially ended.

Within one year of the completion of the trial, the competent federal authority and the ethics committee will be supplied with a summary of the final report on the clinical trial containing the principle results.

8.2. Publication

It is planned to publish the trial results, in mutual agreement with the PCI, in a scientific journal and at German or international congresses. Publication of the results of the trial as a whole is intended. Any publication will take account of the 'Uniform requirements for manuscripts submitted to biomedical journals (International Committee of Medical Journal Editors' (ICMJE) [JAMA 1997;277:927-34]).

The trial will also be registered in a public register in accordance with the recommendations of the ICMJE (see also Section 5.3).

Any published data will observe data protection legislation covering the trial subject and investigators. Success rates or individual findings at individual trial sites are known only to the sponsor.

Publications or lectures on the findings of the present clinical trial either as a whole or at individual investigation sites must be approved by the sponsor in advance, and the sponsor reserves the right to review and comment on such documentation before publication.

9. Amendments to the trial protocol

To ensure that comparable conditions are achieved as far as possible at individual trial sites and in the interests of a consistent and valid data analysis, changes to the provisions of this trial protocol are not planned. In exceptional cases, however, changes may be made to the trial protocol. Such changes can only be made if agreed by the sponsor, sponsor's representative, the PCI and biometrician, and all authors of this trial protocol. Any changes to the trial procedures must be made

in writing and must be documented with reasons and signed by all authors of the original trial protocol.

Amendments made in accordance with § 10 Secs. 1 and 4 GCP-Verordnung that require approval are submitted to the ethics committee and the supreme federal authority and will not be implemented until approved. Exceptions to this are amendments made to avoid immediate dangers.

10. References

1. The European Agency for the Evaluation of Medicinal Product. Note for Guidance on Good Clinical Practice (CPMP/ICH/135/95).
2. The European Agency for the Evaluation of Medicinal Product. Note for Guidance Structure and Content of Clinical Study Reports (CPMP/ICH/137/95).
3. EMEA-Guideline On Data Monitoring Committees: EMEA/CHMP/EWP/5872/03 Corr
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