	Document Number:	**c34591878-06**
EudraCT No. **EU Trial No.**	2020-005425-87	
BI Trial No.	1451-0001	
BI Investigational Medicinal Product(s)	BI 765128	
Title	A First in Human trial to study safety and tolerability of single rising intravitreal doses (o**P**en label, non-randomized, uncontrolled) and in **A**ddition the early biological **R**esponse of mul**T**iple intravitreal doses (double-masked, **R**andom**I**zed, sham-controlle**D**) of BI 765128 in panretinal photocoa**G**ulation (PRP) treated diabetic r**E**tinopathy (DR) patients with diabetic macular ischemia (DMI) – the PARTRIDGE Study	
Lay Title	A study of BI 765128 in patients with an eye condition called diabetic macular ischemia who have received laser treatment	
Clinical Phase	I/IIa	
Clinical Trial Leader	[redacted] Phone: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted] Fax: [redacted]	
Version and Date	Version: 5.0	Date: 16 Mar 2023

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	22 Feb 2021
Revision date	16 Mar 2023
BI trial number	1451-0001
Title of trial	A First in Human trial to study safety and tolerability of single rising intravitreal doses (o**P**en label, non-randomized, uncontrolled) and in **A**ddition the early biological **R**esponse of mul**T**iple intravitreal doses (double-masked, **R**andom**I**zed, sham-controlle**D**) of BI 765128 in panretinal photocoa**G**ulation (PRP) treated diabetic r**E**tinopathy (DR) patients with diabetic macular ischemia (DMI) – the PARTRIDGE Study
Coordinating Investigator	[redacted] Phone: [redacted] Fax: [redacted]
Trial site(s)	Multi-centre trial
Clinical phase	I/IIa
Trial rationale	Diabetic macular ischemia (DMI) is a complication of diabetic retinopathy (DR) and can lead to vision loss. Currently, there are no approved or effective treatments to prevent either onset or progression of DMI in DR patients. As a transition from preclinical investigations to clinical development in this first-in human trial, the safety, tolerability, pharmacokinetics and early biological response of BI 765128 will be investigated in volunteer subjects with DMI. This trial will include subjects affected by DMI with visual loss since intravitreal injections in subjects without the condition would not be considered ethically justifiable.
Trial objective(s)	The objective of this trial is to determine the safety and tolerability of BI 765128 in panretinal photocoagulation (PRP) treated diabetic retinopathy (DR) patients with diabetic macular ischemia (DMI), based on the primary endpoint, the occurrence of dose limiting events (DLE) (see Section 5.2.1) in the 7 days post administration (Part A) or the occurrence of drug-related AEs until EOS (Part B). The safety, tolerability and early biological response after multiple IVT injections of BI 765128 will also be investigated.

Trial endpoints	Primary endpoints: Part A: • Number of subjects with ocular dose limiting events (DLEs) from drug administration until day 8 (7 days after treatment) Part B: • Number of subjects with drug-related AEs from drug administration until EOS Secondary endpoints: Part A: • Number of subjects with drug related AEs at EOS • Number of subjects with any ocular AEs (eye disorders) at EOS Part B: • Change from baseline of the size of the FAZ in optical coherence tomography angiography (OCTA) at visit 5 • Change from baseline of the size of the FAZ in optical coherence tomography angiography (OCTA) at visit 6 • Change from baseline of the size of the FAZ in optical coherence tomography angiography (OCTA) at visit 7 • Change from baseline of BCVA at Visit 7 • Number of subjects with any ocular AEs (eye disorders) from drug administration until EOS
Trial design	This trial will consist of two parts, A and B. Part A will be non-randomized, open-label and uncontrolled. Part B will be double-masked, randomized and sham-controlled (ratio 2:1).
Total number of subjects entered	Approximately 48 subjects in total
Number of subjects on each treatment	Up to 18 subjects in Part A (depending on the dose escalation) and 30 subjects in Part B. In Part B subjects will be randomized to receive either IVT injection or sham injection.
Diagnosis	Diabetic macular ischemia (DMI) in patients previously treated with Panretinal photocoagulation (PRP) for diabetic retinopathy (DR)
Main in- and exclusion criteria	Main inclusion criteria: Part A: • Panretinal photocoagulation-treated DR patients with either no or inactive retinal neovascularization per investigator judgement in the study eye • Evidence of DMI per investigator´s judgement, defined as any degree of disruption of retinal vascularity in superficial and/or deep retinal plexus in OCTA • Best-corrected VA ≤75 letters (20/32) in the study eye

	Part B: • Panretinal photocoagulation-treated DR patients with either no or inactive retinal neovascularization per investigator judgement • Presence of significant DMI: Large foveal avascular zone (FAZ) defined as those with ≥0.5mm^2 area present on OCTA. If FAZ is <0.5mm^2 then an enlarged peri-foveal inter-capillary space in at least 1 quadrant will be sufficient. • Best-corrected VA ≤85 letters (20/20) in the study eye Main exclusion criteria: Part A: • Patients receiving IVT injections for active Diabetic Macular Edema (DME) (anti-VEGF, steroids) and macular laser in the previous 3 months to screening in the study eye • Subjects receiving anti-VEGF IVT injections for active DR in the previous 3 months to screening in the study eye Part B: • Diabetic Macular Edema (DME), defined as a CST ≥ 305µm for men and ≥ 290 µm for women (Optovue Angiovue) in the study eye • Subjects receiving IVT injections for active DME (anti-VEGF, steroids) and macular laser in the previous 3 months to screening in the study eye • History of vitrectomy in the study eye
Test product(s)	BI 765128, solution for injection
dose	Part A: [redacted] mg (single doses) Part B: The highest dose ([redacted] mg) [redacted] if established as safe and tolerable during Part A
mode of administration	Intravitreal injection
Comparator product(s)	Not applicable
dose	Not applicable
mode of administration	Not applicable
Duration of treatment	Part A: single intravitreal dose Part B: 3 intravitreal doses at [redacted]
Statistical methods	The main objectives of this trial will be assessed by calculating descriptive statistics on DLEs and drug related AEs. For the Part B these will be compared descriptively between the treatment groups.

	The dose escalation in the SRD part will be guided by a Bayesian logistic regression model (BLRM) with overdose control that will be fitted to binary toxicity outcomes. The estimates of parameters will be updated as data are accumulated using the BLRM.

FLOW CHART I (PART A)

Trial Periods	**Screening Period**	**Treat-ment Visit**	**Follow-up period**					**End of study**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Days Study Weeks	Duration 3 to 28 days	Day 1	4	8 Week 1	15 Week 2	29 Week 4	57 Week 8	99 Week 14
Time window for visits (days)		none	±1	±2	±2	±3	±7	±7
Informed consent	X							
Demographics	X							
Medical history	X							
Physical examination (including weight)	X	X[1]				X	X	X
Vital signs	X	X	X	X	X	X	X	X
Laboratory tests	X	X		X	X	X	X	X
12-leadECG[2]	X	X	X			X	X	X
Review of in-/exclusion criteria	X	X						
Dose Assignment		X						
IVT drug administration		X						
Pregnancy test[3]	X_S	X_s		X_U	X_U	X_U	X_U	X_U
PK [redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted] sampling[4]		X			X	X	X	X
BCVA testing	X	X	X	X	X	X	X	X
SD-OCT	X	X	X	X	X	X	X	X
OCT Angiography	X	X	X	X	X	X	X	X
Fundus Photo	X	X		X	X	X	X	X
Slit lamp and intra-ocular pressure (IOP)	X	X	X	X	X	X	X	X
All AEs/SAEs/AESIs	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X
Completion of subject participation [5]								X

([1]) Could be repeated as deemed necessary at investigator´s discretion.

([2]) Single ECGs are to be recorded shortly before the PK sampling at the respective time points, (Section 5.2.5. and Appendix 10.1).

([3]) Pregnancy testing: serum pregnancy test (X_S) is done at screening and on day 1 if more than a week elapsed between screening and day 1, and at the other visits as a reflex when urine testing (X_U) is positive.

([4]) [redacted]

([5]) Completion of subject participation also needs to be completed in the eCRF if the subject withdraws prematurely following assignment to dose level (Section 3.3.4)

FLOW CHART II (PART B)

Trial Periods	**Screening Period**	**Treatment Period**			**Follow-up Period**		**End of Study**
Visit	**1**[1]	**2**	**3**	**4**	**5**	**6**	**7**
Study Day/ Week	Duration 3 to 28 days	1	[redacted]		85 Week 12	113 Week 16	141 Week 20
Time window for visits (days)		none	±3	±3	±7	±7	±7
Informed consent	X						
Informed consent Aqueous sampling (optional)	X						
Demographics	X						
Medical history	X						
Physical examination (including weight)	X				X		
Vital signs	X	X	X	X	X	X	X
Laboratory tests	X	X	X	X	X	X	X
12-lead ECG[2]	X	X	X	X	X		
Review of in-/exclusion criteria	X	X					
Dose Assignment		X					
Randomization		X					
[redacted]		[redacted]	[redacted]	[redacted]			
Pregnancy test[3]	X_S	X_S	X_U	X_U	X_U	X_U	X_U
[redacted] [4]		X	X	X	X	X	X
PK [redacted]		[redacted]	[redacted]	[redacted]	[redacted]	[redacted]	[redacted]
[redacted]		X		X		X	X
BCVA testing	X	X	X	X	X	X	X
SD-OCT	X	X	X	X	X	X	X
OCT Angiography	X	X	X	X	X	X	X
Fundus Photo	X	X	X	X	X	X	X
Slit lamp and intra-ocular pressure (IOP)	X	X	X	X	X	X	X
[redacted]		X	X	X	X	X	X
All AEs/SAEs/AESIs	X	X	X	X	X	X	X

Trial Periods	Screening Period	Treatment Period			Follow-up Period		End of Study
Concomitant therapy	X	X	X	X	X	X	X
Completion of subject participation ([6])							X

([1]) Screening visit should be performed in two visits. After Informed consent is obtained, visual acuity testing, SD-OCT, OCT Angiography and fundus photography should be performed and sent to central reading service. If subject is eligible based on the results from the reading centre, the subject should return to complete the rest of the screening. In case of scheduling difficulty for certain subjects, screening can be performed in one visit.

([2]) Single ECGs are to be recorded shortly before the PK sampling at the respective time points: (Section 5.2.5 and Appendinx 10.1).

([3]) Pregnancy testing: serum pregnancy test (Xs) is done at screening and on day 1 if more than a week elapsed between screening and day 1, and at the other visits as a reflex when urine testing (Xu) is positive.

([4]) [redacted]

([5]) See separate flow chart for Aqueous sampling (Table 10.1: 3). Aqueous samples are collected immediately before drug administration at Visits 2 and 4. At visits 6 and 7, when no drug is administered, the aqueous samples can be collected at any time during the visit (Section 4.1.5)

([6]) Completion of subject participation also needs to be completed in the eCRF if the subject withdraws prematurely following assignment to dose level (Section 3.3.4).

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[redacted]

ABBREVIATIONS

AE	Adverse Event
[redacted]	[redacted]
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate
ALT	Alanine Aminotransferase
AST	Aspartate Aminotransferase
AUC	Area under the Curve
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]
BA	Bioavailability
BCVA	Best corrected visual acuity
BI	Boehringer Ingelheim
BLRM	Bayesian logistic regression model
CA	Competent Authority
CDC	Centers for Disease Control and prevention
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence Interval
CL/F	Apparent clearance of the analyte in plasma after extravascular administration
[redacted]	[redacted]
[redacted]	[redacted]
CRA	Clinical Research Associate
CRC	Central Reading Center
CRF	Case Report Form, paper or electronic (sometimes referred to as "eCRF")
CST	Central Subfield Thickness
CRO	Contract Research Organisation
CT	Clinical Trial
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager

CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug Induced Liver Injury
DLE	Dose limiting event
DME	Diabetic macular edema
DMI	Diabetic macular ischemia
DMC	Data Monitoring Committee
DR	Diabetic Retinopathy
DRIL	Disorganisation of retinal inner layer
EC	Ethics Committee
ECG	Electrocardiogram
eCRF	Electronic Case Report Form
eDC	Electronic Data Capture
EMA	European Medicines Agency
EOS	End of study
EoT	End of Treatment
EoTrial	End of Trial
EWOC	Escalation with overdose control
ETDRS	Early treatment diabetic retinopathy study
EudraCT	European Clinical Trials Database
FA	Fluorescein angiography
FAZ	Foveal avascular zone
FSH	Follicle stimulating hormone
FC	Flow Chart
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
GRT	Global Randomization Team
HCG	Human chorionic gonadotropin
HR	Heart rate
IB	Investigator’s Brochure
ICF	Informed Consent Form
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee

IMP	Investigational Medicinal Product
IOP	Intra-ocular pressure
IPD	Important protocol deviation
IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IUD	Intrauterine Device
IUS	Intrauterine Hormone-Releasing System
IVT	Intravitreal
λ_z	Terminal rate constant of the analyte in plasma
[redacted]	[redacted]
LPLT	Last Patient Last Treatment
LOCF	Last observation carried forward
MCH	Mean corpuscular hemoglobin
MCHC	Mean corpuscular hemoglobin concentration
MCV	Mean corpuscular volume
MFD	Maximum feasible dose
MedDRA	Medical Dictionary for Drug Regulatory Activities
MoA	Mode of Action
MD	Multiple dosing
MRT	Mean residence time of the analyte in the body
[redacted]	[redacted]
NPDR	Non-proliferative diabetic retinopathy
NOAEL	No observed adverse effect level
Nrp1	Neuropilin 1
OCT	Optical coherent tomography
OCTA	Optical coherent tomography angiography
OPU	Operative Unit
PD	Pharmacodynamic(s)
PDR	Proliferative diabetic retinopathy
[redacted]	[redacted]
[redacted]	[redacted]
PR	Pulse rate

PRP	Panretinal photocoagulation
PV	Pharmacovigilance
QT	Time between start of the Q-wave and the end of the T-wave in an electrocardiogram
QTc	QT interval corrected for heart rate using the method of Fridericia (QTcF) or Bazett (QTcB)
RA	Regulatory Authority
RDW	Red cell distribution width
REP	Residual Effect Period
RR	Respiratory rate
SAE	Serious Adverse Event
SD-OCT	Spectral domain optical coherence tomography
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SRD	Single-rising dose
SUN	Standardization of Uveitis Nomenclature
SUSAR	Suspected Unexpected Serious Adverse Reactions
[redacted]	[redacted]
[redacted]	[redacted]
TS	Treated set
TSAP	Trial statistical analysis plan
[redacted]	[redacted]
ULN	Upper Level of Normal
[redacted]	[redacted]
[redacted]	[redacted]
VA	Visual Acuity
VEGF	Vascular endothelial growth factor
WG	Working group
WHO	World Health Organisation
WOCBP	Woman of childbearing potential
YAG	Yttrium aluminum garnet

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Diabetic retinopathy (DR) can cause visual loss in a number of ways. Microvascular changes due to hyperglycemia lead to increases in permeability, and thus extravascular exudation and fluid accumulation in the macula (diabetic macular edema, DME). Similarly, alterations of micro-vessels can lead to retinal non-perfusion and ischemia. Consequently, a dramatic increase of vascular endothelial growth factor (VEGF) drives the formation of retinal new vessels (proliferative diabetic retinopathy, PDR), which eventually bleed, and cause a sudden decrease in vision (vitreous hemorrhage). In both conditions, VEGF plays a fundamental role, and anti-VEGF agents are effective in improving both DME and DR. For patients with PDR, panretinal photocoagulation (PRP) is the current standard of care. Patients with severe non-proliferative diabetic retinopathy (NPDR) and a high risk of developing PDR can also benefit from PRP to prevent progression of retinopathy. PRP destroys the ischemic retina, (the major source of VEGF), and thus prevents the formation of new vessels, or promotes their regression.

In some patients, however, in the absence of DME, after successful treatment with PRP, with no evidence of active new vessels, the visual acuity continues to decrease.

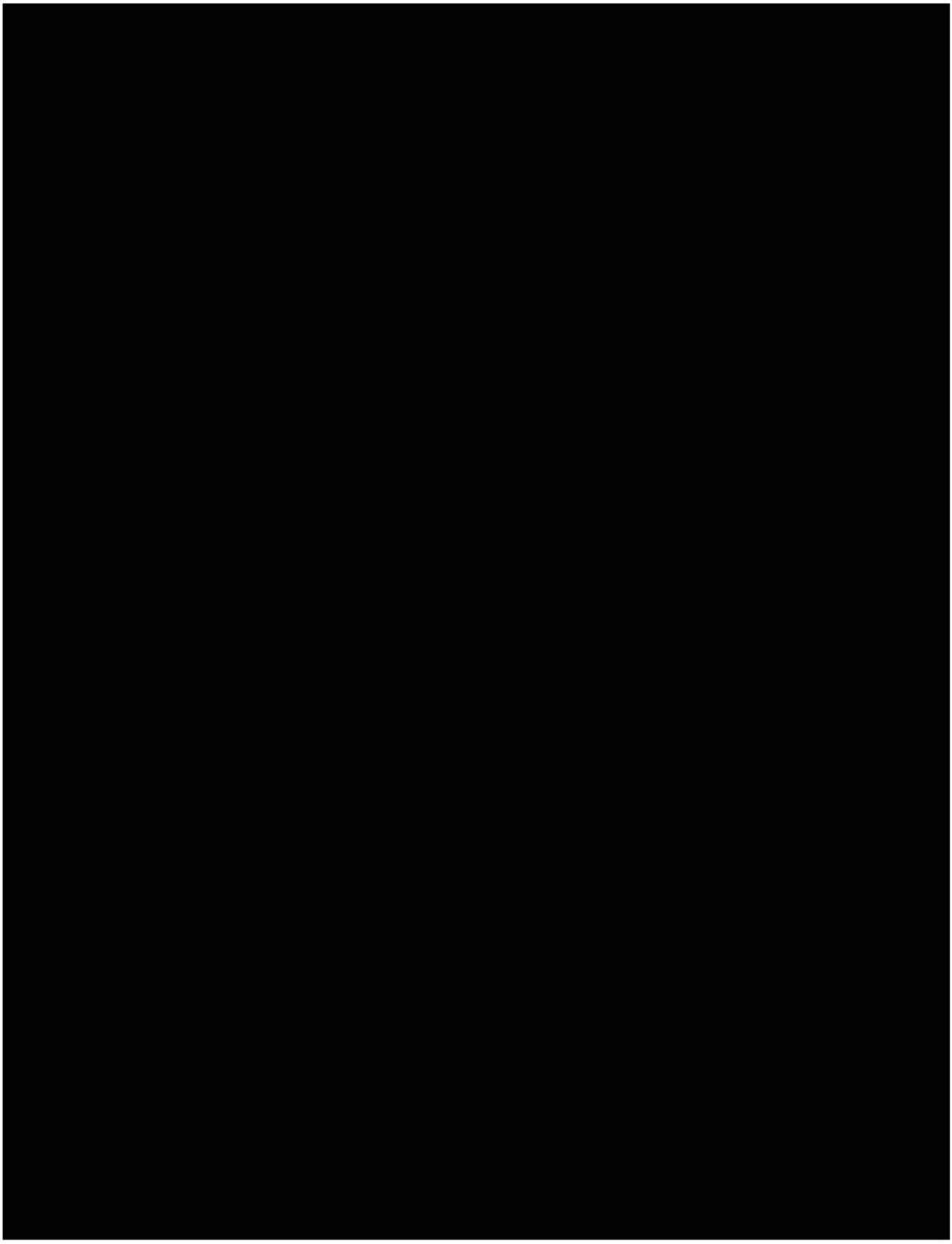
Some reports have suggested increasing ischemia in the central part of the retina, the macula, as a possible explanation. In this condition, called diabetic macular ischemia (DMI), the retinal tissue may not receive enough nutrients leading to retinal tissue loss and permanent and irreversible vision loss. In DMI, anti-VEGF therapy is not effective, and destructive laser photocoagulation cannot be applied.

Previously, DMI was observed and diagnosed by means of fluorescein angiography (FA) using an intravenous dye. It was defined as an abnormal enlargement of the foveal avascular zone (FAZ). In patients with diabetic retinopathy, FA may show an abnormal enlargement of the FAZ, which is the most common definition of DMI. Recently, optical coherence tomography angiography (OCTA) has emerged which can visualize the retinal blood vessels and hence ischemia in greater detail. OCTA is non-invasive and multiple levels of the capillary plexus can be visualised. OCTA can measure the area of the FAZ. Moreover, the FAZ measured by FA corresponds well with the FAZ measured by OCTA (R17-3317). For these reasons OCTA is likely to become the gold standard in the diagnosis and monitoring of DMI.

There are many unknowns related to DMI. Since this condition is associated with a progressive loss of neural tissue, it can be hypothesized that restoration of the macular vasculature before retinal degeneration occurs could be a key objective for these patients and prevent permanent vision loss. There are currently no treatments available for DMI making it an urgent unmet need.

1.2 DRUG PROFILE

Mode of action



Safety Pharmacology

The core safety pharmacology function (central nervous, cardiovascular, respiratory systems) were evaluated as part of the 4-week GLP repeat toxicity study in rats, the 13-week GLP intravenous and intravitreal repeat toxicity studies in cynomolgus monkeys, in accordance with the ICH S6 guidelines (R12-0027).

Overall, BI 765128 did not demonstrate any effects on neurological, cardiovascular, and respiratory function, implicating an acceptable safety profile for Phase 1 clinical trials.

Data from clinical studies

Seven subjects have been treated in part A intravitreally with BI 765128 at the time of finalization of CTP version 4.0. No DLEs, drug-related SAEs or Drug-related AEs were reported.

For a more detailed description of the BI 765128, please refer to the current Investigator's Brochure (c31489419-01).

1.3 RATIONALE FOR PERFORMING THE TRIAL

Diabetic Macular Ischemia (DMI) is a complication of diabetic retinopathy (DR) and can lead to vision loss. Currently, there are no approved or effective treatments to prevent either onset or progression of DMI in DR patients.

As a transition from preclinical investigations to clinical development in this first-in human trial, the safety, tolerability, pharmacokinetics and early biological response of BI 765128 will be investigated in volunteer subjects with DMI.

This trial will include subjects affected by DMI with significant visual loss since intravitreal injections in subjects without the condition would not be considered ethically justifiable.

This trial will consist of two parts, Part A and Part B.

In Part A of the trial, 3 rising doses (at least 3 evaluable subjects per dose cohort) are planned to be administered intravitreally. Within each dose cohort, all subjects will receive a single dose of BI 765128. The next higher dose will only be administered if the treatment in the preceeding dose cohort was safe and showed acceptable tolerability (see section 3.1).

In Part B, subjects will be randomized into a single dose cohort to receive either active IVT injection (n=20) or sham injection (n=10) and assessed over a 20-week period. After an initial active treatment period of 8 weeks [redacted] subjects will be followed up for an additional 12 weeks without further injections to study the treatment effect. This may help guide injection frequency intervals in later studies.

Part B will provide information about the early biological response of BI 765128 by comparing the treated group to the sham group.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

DMI is a progressive disease. Patients with DMI may have irreversible retinal damage if DMI is present for a long time. Degeneration of retinal tissue in the macula leads to permanent visual impairment. There is no approved treatment for this disease.

Even though pre-clinical data shows that BI 765128 can improve vascularisation of ischemic areas of the retina, because of the long duration of the pathology of DMI, long-term benefits for subjects entering this trial are unlikely. Their participation in this trial, however, is of major importance to the development of BI 765128, to determine a safe dose selection for further clinical trials in this pre-selected patient population.

1.4.2 Risks

Subjects in this trial are exposed to risks of trial procedures and risks related to ophthalmic and systemic exposure to the trial medication.

1.4.2.1 Risks related to the Mode of Action (MoA)

Because this is the First-in-human trial with BI 765128, special attention will be paid to ensure the highest level of safety for subjects when selecting the starting dose, the dose escalation steps and the highest dose applied. Based on pre-clinical toxicology studies, no specific adverse events are expected. One eye will be selected, according to inclusion /exclusion criteria, as the study eye to be treated.

Similar to other intravitreal biologic therapies, there is a risk of ocular inflammation, however, this is usually mild and reversible. Subjects will be monitored for ocular inflammation and treated if deemed appropriate by the investigator. Because of the low dosage used in intravitreal BI 765128, the systemic exposure is expected to be very low and hence unlikely to have significant effect.

1.4.2.2 Available data from pre-clinical toxicity studies

Toxicology

1.4.2.3 Risks related to intravitreal injection

Intravitreal injections have potentially serious adverse events, but these are considered rare: clinical trials assessing efficacy and safety of EYLEA® intravitreal injections showed serious adverse events related to the injection procedure, including endophthalmitis (in between 0.01 and less than 0.1% of cases) and ocular inflammation (in between 0.1 and less than 1% of cases) (R20-0435). Because the procedure of intravitreal injection of BI 765128 is the same (use of a filter needle to extract product from the vial and same needle size for injection, 30 gauge), the expected adverse events related to the procedure are considered equal to those observed with marketed drugs (e.g. EYLEA®).

BI recommends the use of material for intraocular drug delivery, which is according to standard medical practice. This material is not officially approved for intraocular drug delivery, with associated potential risks. Long-term experience as standard of medical care suggests a favourable risk-benefit profile. To the best of the sponsor´s knowledge there is currently no product on the market, which is officially approved for intravitreal drug delivery.

The needles for preparation of the drug and intravitreal injection are usually silicone oil coated to ease the injection of the needle through the tissue. This carries the potential risk for a silicone oil transfer into the vitreous with the potential risks for occurrence of side effects like vitreous floaters or intraocular inflammation. The overall risk for such events is based on long-term experience with comparable material and is considered low. However, patients should be made aware of this risk, as reflected in the Informed Consent Form (ICF). To the best of the sponsor´s knowledge there is currently no product on the market, which is silicone-free. The recommended syringes are silicone oil free and not considered to carry this risk.

The IMP handling instructions do not mandate the use of materials from certain manufacturers and leaves the decision to the treating investigators/sites on which materials to use if it meets the specifications as described in the IMP handling instructions for BI 765128.

1.4.2.4 Risks related to blood sampling

Blood sampling may be accompanied by mild bruising and in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period.

The total volume of blood withdrawn during the entire study persubject will not exceed appr. 500 mL. No health-related risk is expected from this blood withdrawal.

1.4.2.5 Planned measures for monitoring the risks

Subjects will be evaluated with functional, imaging and systemic tests to identify any possible adverse event. Specifically, signs of intraocular inflammation will be assessed by slitlamp examination of the anterior chamber, vitreous and posterior segment of the eye. This will identify flare or cells in the anterior chamber, deposits of material in the corneal endothelium, deposits on the anterior capsule of the crystalline lens, signs of vitreous haze,

vitreous cells, vitreous snowbanks/snowballs, signs of intraretinal edema or retinal thickening and signs of perivascular inflammation e.g. vessel walls sheathing, signs of incipient retinitis or intraretinal haemorrhages.

Spectral domain optical coherence tomography (SD-OCT) will identify possible intraretinal cystic edema and will be used to detect early signs of cell toxicity (e.g. increased ellipsoid zone disruption, granular appearance of outer retinal layers, increase in intraretinal foci predominantly located in the outer nuclear layers). Clinical examination or Color Fundus Photoraphy will be used to identify possible perivascular reactions.

Additionally, a systemic evaluation will be performed at the timepoints specified in the flow charts, to assess possible systemic reactions. This will include body weight, blood pressure, heart rate with ECG, full safety lab. The results of these examinations will be reported immediately to detect possible safety issues related to the drug or to an inflammatory response.

In the first dose cohort ([redacted] mg) the first subject will be dosed and observed until Visit 6 (day 29) to evaluate acute AEs, before dosing the second subject of the same cohort. The second subject will be observed until Visit 6 (day 29) before dosing the third subject of the same cohort. The third subject will be observed until Visit 5 (day 15) before the second dose cohort starts. Details of cohort 2 and cohort 3, see Section 3.1. Moreover, the duration of the observation will reflect the expected human pharmacokinetics (PK) of BI 765128, with a followup for all subjects of up to 98 days, with appropriate ophthalmologic and systemic evaluations (see Section 3.1).

In addition, a Safety Monitoring Committee (SMC) will be established to review individual and aggregated safety data at regular intervals to determine the safety profile and risk/benefit ratio (further details in the SMC charter).

1.4.2.6 Drug induced liver injury

Although rare, the potential for drug-induced liver injury (DILI) is under constant surveillance by sponsors and regulators. Therefore, this trial requires timely detection, evaluation, and follow-up of laboratory investigations of selected liver laboratory parameters to ensure subjects´ safety.

Table 1.4.2.6: 1 Overview over trial related risks

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product BI 765128		
Intraocular inflammation	IVT administration of BI 765128 in cynomolgus monkeys showed signs of intraocular inflammation (See IB chapter 5.3) in some animals. These findings in general had no impact on ophthalmic function (i.e. ERG). These are considered ADA responses due to the administration of humanized protein in monkeys and do not predict such reactions in humans.	At each visit a complete ophthalmic examination will be performed to detect early signs of intraocular inflammation (see chapter 1.4.1.4)
Immunogenic response	18 of 22 cyno monkeys showed ADA responses in the 13-week IVT toxicology study of BI765128. The immunogenicity of biotherapeutic products doesn't predict the immunogenicity in human. Therefore, potential immunogenic response may or may not occur in human	[redacted] in plasma will be evaluated at day 1,15,29, 57 and 99 in Part A, and at day 1, 29, 57, 85 and 141 in Part B
Drug-induced liver injury (DILI)	This trial is FIH application of BI 765128, and even if the expected systemic exposure is anticipated to be low, any possible effect on liver function needs to be addressed	Lab tests will be performed at each visit (except day 4 in Part A)

Possible or known risks of clinical relevance for this trial	Summary of data, rationale for the risk	Mitigation strategy
Investigational Medicinal Product BI 765128		
Trial procedures		
Risks related to IVT injection	Clinical trials assessing efficacy and safety in marketed drugs administered via IVT injection showed a low rate of complications associated with IVT injection procedure Because the procedure of intravitreal injection of BI 765128 is the same (use of a filter needle to extract product from the vial and same needle size for injection, 30 gauge), the expected adverse events related to the procedure are considered equal to what was observed with marketed drugs	At each visit a complete ophthalmic examination will be performed to detect early signs of complications. Intra-ocular pressure (IOP) will be measured at each visit.
Risks related to blood sampling	Blood sampling may be accompanied by mild bruising and also in rare cases, by transient inflammation of the wall of the vein. In addition, in rare cases a nerve might be injured while inserting the venous catheter, potentially resulting in paraesthesia, reduced sensibility, and/or pain for an indefinite period.	The total volume of blood withdrawn during the entire study per subject will not exceed the volume of appr. 500 mL.
Risks related to Anterior Chamber tap	Corneal abrasion, cataract formation, infection, iris and lens trauma	Only experienced physicians will undertake the procedure

1.4.3 Discussion

As this is a first in human trial, ophthalmic and systemic examinations are planned at all visits of the trial, despite no safety concerns being identified from pre-clinical studies

Blood tests and physical examinations will evaluate potential changes in blood cell count and in any safety lab parameters, as well as in body weight and blood pressure. Ophthalmic physical examinations will focus on the risks related to the procedure (e.g. endophthalmitis) and the risks related to a potential immunologic response. Imaging and functional tests will further assess any possible signs of neurotoxicity after the administration of the drug.

DMI is a potentially blinding disease, with no treatment available. Given the urgent need to address this unmet medical need and considering the expected safety profile of BI 765128 based on pre-clinical evaluations, it is considered acceptable to expose the subjects to the trial risks.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The objective of this trial is to determine the safety and tolerability of BI 765128 in panretinal photocoagulation (PRP) treated diabetic retinopathy (DR) patients with diabetic macular ischemia (DMI), based on the primary endpoint, the occurrence of dose limiting events (DLE) (see Section 5.2.1) in the 7 days post administration (Part A) or the occurrence of drug-related AEs until EOS (Part B) and to investigate the safety, tolerability and early biological response after multiple IVT injections of BI 765128.

2.1.2 Primary endpoint(s)

Part A:

- Number of subjects with ocular dose limiting events (DLEs) from drug administration until day 8 (7 days after treatment)

Part B:

- Number of subjects with drug related AEs from drug administration until EOS

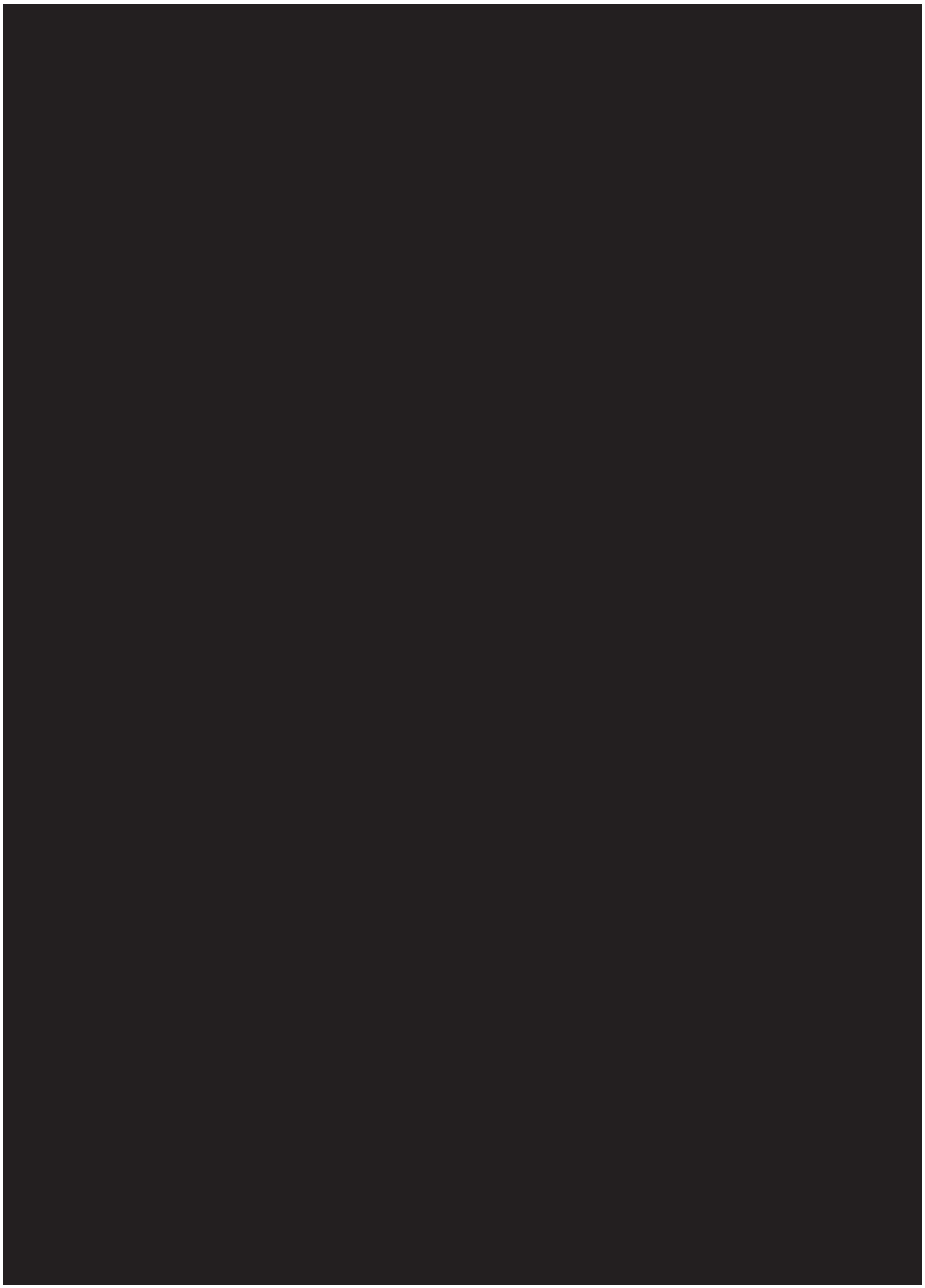
2.1.3 Secondary endpoint(s)

Part A:

- Number of subjects with drug related AEs at EOS
- Number of subjects with any ocular AEs (eye disorders) at EOS

Part B:

- Change from baseline of the size of the FAZ in optical coherence tomography angiography (OCTA) at visit 5
- Change from baseline of the size of the FAZ in optical coherence tomography angiography (OCTA) at visit 6
- Change from baseline of the size of the FAZ in optical coherence tomography angiography (OCTA) at visit 7
- Change from baseline of BCVA at Visit 7
- Number of subjects with any ocular AEs (eye disorders) from drug administation until EOS



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN

This trial will consist of two parts, A and B. Part A will be non-randomized, open-label and uncontrolled. Part B will be double-masked, randomized and sham-controlled. One eye will be selected, according to inclusion /exclusion criteria, as the study eye to be treated.

Part A:
Cohorts of subjects will receive escalating doses of BI 765128, [redacted]

For any dose-escalation cohort, at least 3 evaluable subjects will be required. Each cohort will consist of newly enrolled subjects.

Dosing of subjects will be done in the following order:

Cohort 1, [redacted] (number=3):

- 28 days after subject 1 of the first dose group is dosed, subject 2 of the first dose group can be dosed, if there is no ocular inflammation in the study eye requiring treatment
- 28 days after subject 2 of the first dose group is dosed, subject 3 of the first dose group can be dosed if there is no ocular inflammation in the study eye requiring treatment
- 14 days after subject 3 of the first dose group is dosed, the first subject of the next dose group can be dosed (If no there is no ocular inflammation in the study eye requiring treatment, and if the SMC decides it is safe to go to the next dose group)

Cohort 2, [redacted] (number=3):

- 14 days after subject 1 of the second dose group is dosed, subjects 2 and 3 of the second dose group can be dosed (if there is no ocular inflammation in the study eye requiring treatment)
- 14 days after the third subject is dosed, the first subject of the next dose group can be dosed, if there is no ocular inflammation in a study eye requiring treatment, and if the SMC decides it is safe to go to the next dose cohort

Cohort 3, [redacted] (number=6):

- 14 days after subject 1 of the third dose group is dosed, subjects 2,3,4,5 and 6 of the third dose group can be dosed, if there is no ocular inflammation in a study eye requiring treatment
- 14 days after the final subject has been dosed, Part B of the trial can start, if there is no inflammation in a study eye requiring treatment, and if the SMC decides it is safe to do so.

A Safety Monitoring Committee (SMC) will be established to regularly review the data and to provide recommendation for the further conduct of the trial.

After each subject has completed visit 4 follow-up assessments (7 days after drug administration), the dosing investigator will complete the 'DLE Safety Review Form' to summarise the key safety findings for the subject. Once completed, the site will send the form to the CTM and CTL.

First 2 subjects in cohort 1 ([redacted])
Once the first two subjects have attended visit 6 (day 29), each dosing investigator will complete the 'Ocular Inflammation Review forms'.

Subsequent subjects in part A
Once the following subjects have attended visit 5 (day 15), each dosing investigator will complete an 'Ocular Inflammation Review form' to identify any ocular inflammation. Once completed, the site will send the form to the CTM and CTL. Once the last subjectin each cohort has attended visit 5 (day 15), the CTL will forward the 'DLE Safety Review Forms' and the 'Ocular Inflammation Review Forms' for that cohort to other members of the SMC to carefully evaluate all available systemic (i.e. physical examinations, safety lab parameters, ECG and AEs) and ophthalmological (i.e. as defined in section 5.2.1 of the CTP (DLEs)) safety data. The SMC will meet after the last subject of each dose cohort has attended visit 5.

A Bayesian logistic regression model (BLRM), based on a weakly informative prior distribution, and employing the escalation with overdose control (EWOC) principle (see Section 7) will be used for guiding the dose escalation [R13-4803]. After all subjects in a cohort have either experienced a DLE or have been observed for at least the 7 days evaluation period without experiencing a DLE (i.e. 7 days after drug administration, until visit 4, will be evaluated per subject), the BLRM will be updated with the newly accumulated data. The overdose risk will then be calculated for each dose, and escalation will be permitted to all planned doses which fulfil the EWOC criterion and the respective escalation rule.

The BLRM provides estimates for the probability of observing a DLE for each planned dose. Dose escalation will be permitted to the next planned dose which fulfils the EWOC criterion. Note that this may also result in repeating the current dose level, or in going down to a lower dose level again.

If DLEs are observed in the first two consecutive subjects of a previously untested dose level, subsequent enrolment to that cohort will be stopped.

The MFD may be considered reached if all of the following criteria are fulfilled:

- Next recommended dose by the BLRM = current dose
- At least 12 subjects have been treated in the trial
- At least 6 subjects have been treated at the MFD

Part B of the study will only start if the highest dose is tolerated. Once the last subject in the highest dose cohort of Part A has attended visit 5 (day15) the SMC will meet and evaluate all

DLE data as well as available systemic and ophthalmological safety data. The decision on whether to proceed to Part B will be taken based on the occurrence of DLEs.

[redacted]

Part B:
In Part B, the highest dose will be used ([redacted]). Thirty subjects will be recruited, 2:1 ratio of active treatment versus sham. Subjects dosed in Part A of the trial will not be included.

Subjects will be randomized to receive either active treatment or sham injection.
In Part B, subjects will receive three consecutive doses/sham injections over a 3-month period ([redacted]). All subjects included in the part B of the trial, will be observed for safety and efficacy for 12 weeks after the last injection.

[redacted]

3.2 DISCUSSION OF TRIAL DESIGN, INCLUDING THE CHOICE OF CONTROL GROUP(S)

This trial is designed to confirm that the highest dose of BI765128 can be used for further testing in phase IIb trials. The trial consists of separate parts, A and B. The SRD dose escalation part is included and was designed with the goal to minimize the number of subjects exposed to subtherapeutic doses while on the other hand preserving safety and rapid dose finding. This part of the trial will enrol subjects with DMI as IVT injections in healthy subjects would not be considered ethical. Dose escalation and cohort size will be decided by the SMC, guided by a BLRM with overdose control. An EWOC design will increase the chance of treating subjects at efficacious doses while reducing the risk of overdosing. The use of BLRM for Phase I studies has also been advocated by the European Medicines Agency (EMA) guideline on small populations [R07-4856] and by the Food and Drug Administration (FDA) [R13-4881].

Part B will consist of a MD cohort [redacted] and will start after Part A. Subjects will either be randomized to the active treatment group or to a sham control group (ratio 2:1). This part of the trial will generate additional safety data after multiple dosing and allow for exploration of the time course and durability of treatment effects. This data will further inform the injection frequency and intervals in later studies.

An extended SMC will be established for both part A and part B. The SMC shall operate under the principles specified in the SMC charter. The primary objective of the SMC is to ensure and protect the safety and well-being of the trial subjects and to regularly review the trial data and provide recommendation for the further conduct of the trial (see section 8.7).

3.3 SELECTION OF TRIAL POPULATION

This trial will recruit up to 48 subjects in total; up to 18 subjects in Part A (depending on the dose escalation) and 30 subjects in Part B. In Part B subjects will be randomized to receive either active IVT injection or sham injection.

Screening of subjects for this trial is competitive, i.e. screening for the trial will stop at all sites at the same time once a sufficient number of subjects have been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional subjects for this trial.

A log of all subjects enrolled into the trial (i.e. who have signed informed consent) will be maintained in the Investigator Site File (ISF) at the investigational site irrespective of whether they have been treated with the investigational drug or not.

Subjects who do not fulfil all eligibility criteria for a reason that later resolves allowing eligibility criteria to be met after the initial screening visit, can be re-screened up to one time.

If a subject is entered in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor has to be contacted immediately.
It is planned to conduct the trial in up to 3-6 countries and at approximately 50 sites.

3.3.1 Main diagnosis for trial entry

Diabetic macular ischemia (DMI) in patients previously treated with Panretinal photocoagulation (PRP) for diabetic retinopathy (DR)

Please refer to section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.3.2 Inclusion criteria

Part A

1. Panretinal photocoagulation-treated DR patients with either no or inactive retinal neovascularization per investigator judgement in the study eye
2. Male or female subjects of age ≥ 18 years
3. Evidence of DMI per investigator´s judgement, defined as any degree of disruption of retinal vascularity in OCTA
4. HbA1c of ≤ 12.0%
5. Best-corrected VA ≤75 letters (20/32) in the study eye
6. Best corrected VA in the non-study eye must be equal to or better than best corrected VA in the study eye. If both eyes are eligible (per inclusion #5) and have identical best corrected VA the investigator may select the study eye.
7. Women of childbearing potential (WOCBP) and men able to father a child must be ready and able to use two methods of contraception with at least one of them being a highly effective method of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of

contraception methods meeting these criteria is provided in the patient information in Section 4.2.2.3.

8. Signed and dated written informed consent in accordance with ICH GCP Harmonized Guideline for Good Clinical Practice and local legislation prior to admission to the trial

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tubal ligation is NOT a method of permanent sterilisation. A postmenopausal state is defined as no menses for 2 years without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 2 years of amenorrhea, a single FSH measurement is insufficient.

Part B

1. Panretinal photocoagulation-treated DR patients with either no or inactive retinal neovascularization per investigator judgement
2. Male or female subjects of age ≥ 18 years
3. Presence of significant DMI: Large foveal avascular zone (FAZ) defined as those with ≥0.5mm^2 area present on OCTA. If FAZ is <0.5mm^2 then an enlarged peri-foveal inter-capillary space in at least 1 quadrant will be sufficient.
4. HbA1c of ≤ 12.0%
5. Best-corrected VA ≤85 letters (20/20) in the study eye
6. If both eyes are eligible, the investigator may select either eye to be the study eye.
7. Women of childbearing potential (WOCBP) and men able to father a child must be ready and able to use two methods of contraception with at least one of them being a highly effective method of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information in Section 4.2.2.3.
8. Signed and dated written informed consent in accordance with ICH GCP Harmonized Guideline for Good Clinical Practice and local legislation prior to admission to the trial

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile. Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy. Tubal ligation is NOT a method of permanent sterilisation. A postmenopausal state is defined as no menses for 2 years without an alternative medical cause. A high follicle stimulating hormone (FSH) level in the postmenopausal range may be used to confirm a post-menopausal state in women not using hormonal contraception or hormonal replacement therapy. However, in the absence of 2 years of amenorrhea, a single FSH measurement is insufficient.

3.3.3 Exclusion criteria

Part A:

1. Subjects receiving IVT injections for active Diabetic Macular Edema (DME) (anti-VEGF, steroids) and macular laser in the previous 3 months to screening in the study eye
2. Subjects receiving anti-VEGF IVT injections for active DR in the previous 3 months to screening in the study eye
3. Current or planned use of medications known to be toxic to the retina, lens or optic nerve (e.g. desferoxamine, chloroquine/hydrochloroquine, chlorpromazine, phenothiazines, tamoxifen, nicotinic acid, and ethambutol)
4. Additional progressive eye disease in the study eye that could compromise best corrected VA (BCVA), uncontrolled glaucoma (IOP>24), history of high myopia > 8 diopters in the study eye. Anterior segment and vitreous abnormalities in the study eye that would preclude adequate observation with SD-OCT and OCTA.
5. Any intraocular surgery in the study eye within 3 months prior to screening
6. Glaucoma tube shunts
7. Aphakia or total absence of the posterior capsule. Yttrium aluminum garnet (YAG) laser capsulotomy permitted, if completed more than 3 months prior to screening, in the study eye
8. Subjects not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (e.g. chronic alcohol or drug abuse or any other condition that, in the investigator´s opinion, makes the subject an unreliable trial subject)
9. Previous participation in this trial or in other trials with IVT injections administered within 3 months of screening. Subjects enrolled in trial 1436-0001 SRD part (after five half-lives since the last trial dose, if the participants were not discontinued from study due to safety reasons, and if no toxicity, adverse events or safety concerns related to the previous participation are present at the time of screening) and sham arm in the MD part may be enrolled into Part A of this trial.
10. Significant disease or other medical conditions* (as determined by medical history, examination and clinical investigations at screening) that may, in the opinion of the investigator result in any of the following:
    a) Putting the subject at risk because of participation in this study
    b) Influence the results of this study
    c) Cause concern regarding the subject's ability to participate in the study
11. Known hypersensitivity to any of the ingredients used in the investigational medicinal product (IMP) formulation
12. Active intraocular inflammation in the study eye
13. Active infectious conjunctivitis in either eye
14. Women who are pregnant, nursing, or who plan to become pregnant while in the trial

*e.g. cardiac (including tachycardia), gastro-intestinal, hepatic, renal, metabolic, dermatologic, neurological, haematological, oncological and psychiatric. Subjects with malignancy for which the subject has undergone resection, radiation or chemotherapy within past 5 years. Subjects with treated basal cell carcinoma or fully cured squamous cell carcinoma are allowed.

Part B:

1. Diabetic Macular Edema (DME), defined as a CST ≥ 305µm for men and ≥ 290 µm for women (Optovue Angiovue) in the study eye
2. Subjects receiving IVT injections for active DME (anti-VEGF, steroids) and macular laser in the previous 3 months to screening in the study eye
3. Subjects receiving anti-VEGF intravitreal IVT injections for active DR in the previous 3 months to screening in the study eye
4. Heavily lasered macula in the study eye per investigator judgement
5. History of vitrectomy in the study eye
6. Epiretinal membrane with extended foveal contour distortion in the study eye
7. Current or planned use of medications known to be toxic to the retina, lens or optic nerve (e.g. desferoxamine, chloroquine/hydrochloroquine, chlorpromazine, phenothiazines, tamoxifen, nicotinic acid, and ethambutol)
8. Additional eye disease in the study eye that could compromise best corrected VA (BCVA). Significant visual field loss, uncontrolled glaucoma (IOP>24), clinically significant diabetic maculopathy, history of ischemic optic neuropathy or retinal vascular occlusion, symptomatic vitreomacular traction, or genetic disorders such as retinitis pigmentosa; history of high myopia > 8 diopters in the study eye. Anterior segment and vitreous abnormalities in the study eye that would preclude adequate observation with SD-OCT and OCTA
9. Any intraocular surgery in the study eye within 3 months prior to screening
10. Glaucoma tube shunts
11. Aphakia or total absence of the posterior capsule. Yttrium aluminum garnet (YAG) laser capsulotomy permitted, if completed more than 3 months prior to screening) in the study eye
12. Subjects not expected to comply with the protocol requirements or not expected to complete the trial as scheduled (e.g. chronic alcohol or drug abuse or any other condition that, in the investigator´s opinion, makes the subject an unreliable trial subject)
13. Previous participation in this trial or in other trials with IVT injections administered within 3 months of screening. Subjects enrolled in the sham arm of the MD part of trial 1436-0001 may be enrolled into Part B of this trial.
14. Significant disease or other medical conditions* (as determined by medical history, examination and clinical investigations at screening) that may, in the opinion of the investigator result in any of the following:
    a. Put the subject at risk because of participation in the study
    b. Influence the results of the study
    c. Cause concern regarding the subject's ability to participate in the study
15. Known hypersensitivity to any of the ingredients used in the IMP formulation
16. Active intraocular inflammation in the study eye
17. Active infectious conjunctivitis in either eye
18. Women who are pregnant, nursing, or who plan to become pregnant while in the trial

*e.g. cardiac (including tachycardia), gastro-intestinal, hepatic, renal, metabolic, dermatologic, neurological, haematological, oncological and psychiatric. Subjects with malignancy for which the subject has undergone resection, radiation or chemotherapy within past 5 years. Subjects with treated basal cell carcinoma or fully cured squamous cell carcinoma are allowed.

3.3.4 Withdrawal of subjects from treatment or assessment

Subjects may discontinue trial treatment or withdraw consent to trial participation as a whole ('withdrawal of consent') with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

Every effort should be made to keep the subjects in the trial: if possible, on treatment, or at least to collect important trial data.

Measures to control the withdrawal rate include careful subject selection, appropriate explanation of the trial requirements and procedures prior to trial enrolment and first administration of trial medication, as well as the explanation of the consequences of withdrawal.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the subject files and CRF. If applicable, consider the requirements for Adverse Event collection reporting (please see sections 5.2.7.1 and 5.2.7.2).

3.3.4.1 Discontinuation of trial treatment

An individual subject will discontinue trial treatment if:

1. The subject wants to discontinue trial treatment, without the need to justify the decision.
2. The subject has repeatedly shown to be non-compliant with important trial procedures and, in the opinion of both, the investigator and sponsor representative, is not willing or able to adhere to the trial requirements in the future.
3. The subject needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment.
4. The subject can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy).An AE or clinically significant laboratory change or abnormality occurs that the investigator judge to warranting discontinuation of treatment

If new efficacy/safety information becomes available, Boehringer Ingelheim will review the benefit-risk-assessment and, if needed, pause or discontinue the trial treatment for all subjects or take any other appropriate action to guarantee the safety of the trial subjects.
Even if the trial treatment is discontinued (Part B), the subjects remain in the trial and, given their agreement, will undergo the procedures for early treatment discontinuation and follow-up as outlined in the Flow Chart II and section 6.2.3.

3.3.4.2 Withdrawal of consent to trial participation

Subjects may withdraw their consent to trial participation at any time without the need to justify the decision.

If a subject wants to withdraw consent, the investigator should be involved in the discussion with the subject and explain the difference between trial treatment discontinuation and withdrawal of consent to trial participation, as well as explain the options for continued follow-up after trial treatment discontinuation, please see section 3.3.4.1.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim reserves the right to discontinue the trial overall or at a particular trial site at any time for the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site.
2. New efficacy or safety information invalidating the earlier positive benefit-risk-assessment, please see section 3.3.4.1.
3. Deviations from GCP, the trial protocol, or the contract impairing the appropriate conduct of the trial.

For the following scenario further enrolment and entering in part A and further treatments in part B will be interrupted by the sponsor once the sponsor becomes aware (i.e. stopping rule):

- A single serious adverse reaction (i.e. a single serious adverse event) or two severe adverse reactions in two different subjects (regardless of the system organ class) confirmed by both the investigator and sponsor as having a reasonable causal relationship to the IMP administration.

If the trial stops because one of the stopping rules is triggered, then the trial re-start will only be possible after regulatory authority approval via a substantial amendment.

Further follow up of subjects affected will occur as described in section 3.3.4.1.
The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

3.3.5 Replacement of subjects

Part A:
Subjects withdrawn before visit 4 for another reason than DLE or subjects who miss any visit from Visit 2 up to and including Visit 4 are not evaluable for the occurrence of a DLE within 7 days after drug administration. These subjects will be replaced if not decided otherwise by the SMC. Subjects who come off study due to a DLE will not be replaced.

Part B:
If some subjects do not complete the trial, the Clinical Trial Leader together with the Trial Pharmacokineticist and the Trial Statistician are to decide, if and how many subjects will be replaced. A replacement subject will be assigned a unique trial subject number and will be assigned to the same treatment as the subject he or she replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 BI 765128

Substance:	BI 765128
Pharmaceutical formulation:	Solution for injection
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	[redacted]
Posology:	Part A: 1 injection Part B: 3 injections, [redacted]
Method and route of administration:	Intravitreal

Table 4.1.1: 2 Diluent

Substance:	Solvent for dilution of BI 765128 solution for injection [redacted]
Pharmaceutical formulation:	Solvent
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	NA
Posology:	Part A: 1 injection
Method and route of administration:	Intravitreal

4.1.2 Selection of doses in the trial and dose modifications

Three doses [redacted] are planned in Part A. Part B will use the highest dose [redacted].

BI 765128 was injected intravitreally in New-Zealand White rabbits. Ocular tissues as well as plasma were sampled over a 14-day period and half-lives in the different tissues were

calculated. [redacted] and is, thus, also expected to be similar to [redacted] in humans. An IVT half-life in humans of 9.7 days has been described for [redacted] (R18-2968) and was assumed for BI 765128. The parameters to calculate the minimum effective vitreal concentration were based on the following assumptions: [redacted]

Using these values, the proposed therapeutic dose of [redacted] mg/eye is predicted to maintain the minimal efficacious vitreal concentration of 1000 pM (1 nM) for three months. Doses lower than [redacted] mg are also expected to induce PD effects in the eye. However, the duration of the effect would be shorter and might not provide sufficiently long potential benefit to the subjects.

The proposed escalation of the doses [redacted] is predicted to prolong the time for IVT antibody concentrations above the estimated minimally efficacious concentration, potentially allowing for longer dosing intervals. The starting dose and dose escalation were chosen based on the safety margin to the highest tested dose level [redacted] mg/eye) that did not result in adverse effects directly attributed to BI 765128no, in the 13-week IVT toxicology study in cynomolgous monkeys.

Table 4.1.2: 1 Provisional dose levels for escalation

Dose level	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]

4.1.3 Method of assigning subjects to treatment groups

After the assessment of all in- and exclusion criteria, subjects will be enrolled into the Part A and Part B. Recruitment in the trial will start with the lowest dose group of Part A. Part B will recruit subjects only after Part A has been completed and safety of the doses has been established.

In Part A, the dose is planned to be escalated in cohorts at the pre-defined provisional dose levels; see Table 4.1.2: 1. Intermediate or lower dose levels, depending on the number of DLEs observed in the study, as long as they fulfil the EWOC criterion, may be investigated if agreed upon between Investigator and Sponsor. At the end of each treatment cohort, BI will convene a meeting with the SMC members. At the dose escalation meeting, all available systemic and ophthalmological safety data (See section 3.1 and 5.2.1) will be reviewed in

detail. Based on that and on the results of the updated BLRM, a decision on the next dose level to be tested is made.

In general, recruitment for Part A will be done successively for the dose groups, i.e. if the required number of subjects for one dose group is completed and this dose is considered safe based on (the BLRM model and the clinical course), the recruitment of the next higher dose group may be started. Therefore, the recruitment of subjects for the dose groups will neither be influenced by the trial personnel nor by any characteristics of the subjects, but only by temporal availability. Subjects from the Part A are not allowed to participate in Part B.

The highest dose ([redacted]), if established as safe and tolerable during Part A will be used in Part B after Part A has been completed. If the highest dose ([redacted]) is not considered safe and tolerable Part B will not commence. In Part B subjects will be randomized to receive either active IVT treatment or sham injection according to a randomization plan at visit 2 via Interactive Response Technology (IRT). 20 subjects will receive IVT treatment and 10 will receive sham injection.

The randomization procedure is described in Section 7.5.

4.1.4 Drug assignment and administration of doses for each subject

BI 765128 will be administered intravitreally. "BI 765128 solution for injection [redacted]" and "Solvent for dilution of BI 765128 Solution for Injection" will be provided by BI. Site personnel who are qualified to prepare IVT injections will prepare the drug product according to the 'Handling and Preparation Guidelines'. The instructions will be provided by BI and will be filed in the ISF.

Table 4.1.4: 1 Planned doses and treatment schedule for the Part A

Dose group (mg)	Visit 2 Day 1	Visit 3 Day 4	Visit 4 Day 8	Visit 5 Day 15	Visit 6 Day 29	Visit 7 Day 57
[redacted]						

To determine the dose regimen for the next cohort, the available information (including DLEs and AEs that are not DLEs) as well as the recommendations from the BLRM will be evaluated by the SMC members at the dose decision meeting. The parties must reach a consensus whether further dose escalation is appropriate, or whether de-escalation and/or expanded recruitment into particular cohorts is appropriate. Minutes from these meetings will be prepared and circulated to the trial team and each investigator for comment prior to finalization. The next dose group will only be initiated after further dose escalation is considered appropriate by the SMC (see Section 4.1.2 for details on dose rationale and escalation concept).

Table 4.1.4: 2 Planned dose and treatment schedule for the Part B

Dose group (mg)	Visit 2 Day 1	Visit 3 Day 29	Visit 4 Day 57	Visit 5 Day 85	Visit 6 Day 113
[redacted]					

4.1.5 Intravitreal Injection Technique and Sham Injection

IVT injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering IVT injections. In general, adequate anaesthesia and asepsis, including topical broad-spectrum microbicide (e.g. povidone iodine applied to the periocular skin, eyelid and ocular surface) have to be ensured. Surgical hand disinfection, sterile gloves, a sterile drape, and a sterile eyelid speculum (or equivalent) to be used in accordance with local standards and regulations.

Part B is designed double-masked and personnel of the trial site are masked. Therefore, in Part B, an unmasked injector with no other involvement in the trial will administer IVT/sham injections.

For a sham injection, all pre- and post-injection procedures are identical compared to IVT injections. For a sham injection, the hub of a syringe without a needle is pressed against the conjunctival surface to simulate the force of an actual injection. For sham aqueous sampling, all procedures are identical to aqueous sampling, the hub of a syringe without a needle is pressed gently against the corneal surface to simulate aqueous sampling.

Use of antibiotics in the pre-, peri-, or post-injection period is at investigator's discretion.

After administration of BI 765128, subjects will be monitored according to standard local practice. In this minimum post-dose observation period, systemic and ocular conditions will be monitored according to local practice for such procedures.

4.1.6 Masking and procedures for unmasking

4.1.6.1 Masking

Part A of the trial is open label. Part B is designed double-masked. The treatments administered (active or sham injection) will be masked to subjects and to the dedicated personnel of the trial site. The table below summarizes the masking level of individual functions in Part B of the trial.

Table 4.1.6.1:1 Overview about masking status of trial role and functions in Part B

Role/function	**Timing of Unmasking / receiving access to the treatment information (including rationale)**
Subjects	Masked until data ready for final analysis.
Investigator/Site staff	Masked until data ready for final analysis.
Pharmacist*	Unmasked during trial conduct.
Injector**	Unmasked during trial conduct
Sponsor (incl. clinical trial/project team) SMC and database	Unmasked descriptive analyses will be performed on the subjects in the database during the trial conduct (see Section 7.3.7). The release of the treatment information at the individual time points will be documented accordingly.
Bioanalytical Staff	Unmasked as requested for analysis of bioanalytical samples.

* Unmasked independent pharmacist (qualified person) with no other involvement in the trial will prepare the active IVT injection
** Unmasked independent injector with no other involvement in the trial will administer active/sham injections.

Within the central ECG lab, readers involved with interval measurements will be masked with respect to treatment, visit and demographic information collected. During the time a role/function is masked, the treatment information is kept restricted by the global Randomization Team (gRT) per Sponsor Standard Operating Procedure (SOP).

4.1.6.2 Unmasking and breaking the code

Emergency unmasking will be available to the investigator via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial subjects. The reason for unmasking must be documented in the source documents and/or appropriate CRF page.

Due to the requirements to report Suspected Unexpected Serious Adverse Reactions (SUSARs), it may be necessary for a representative from BI's Pharmacovigilance group to access the randomization code for individual subjects during trial conduct. The access to the code will only be given to authorised Pharmacovigilance representatives for processing in the PV database system and not be shared further.

4.1.7 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP). Re-supply to the sites will be managed via an IRT system, which will also monitor expiry dates of supplies available at the sites.

For details of packaging and the description of the label, refer to the ISF.

4.1.8 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the Clinical Research Associate CRA (as provided in the list of contacts) must be contacted immediately.

4.1.9 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol by the IRB / EC
- Availability of a signed and dated clinical trial contract between the sponsor and the investigational site,
- Approval/notification of the regulatory authority, e.g. competent authority,
- Availability of the *curriculum vitae* of the Principal Investigator,
- Availability of a signed and dated clinical trial protocol,
- Availability of the proof of a medical license for the Principal Investigator (if applicable)
- Availability of FDA Form 1572 (if applicable).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics.

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each subject, and the return to the sponsor or warehouse / drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

These records will include dates, quantities, batch / serial numbers, expiry ('use-by') dates, and the unique code numbers (part A) assigned to the investigational medicinal product and trial subjects. The investigator or designee will maintain records that document adequately that the subjects were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor and/or appointed CRO, the investigator or designee must verify that all unused or partially used drug supplies have been returned by the clinical trial subject and that no remaining supplies are in the investigator's possession.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Medications listed under the exclusion criteria (Section 3.3.3) are restricted during the trial.

For the Study eye no other treatment (IVT or otherwise) is allowed during the trial.
The fellow eye can be treated with any on-label drug. The Sponsor will not provide fellow eye treatment or compensate for it.

Any intravitreal treatment and use of medications known to be toxic to the retina, lens or optic nerve (e.g. desferoxamine, chloroquine/hydrochloroquine, chlorpromazine, phenothiazines, tamoxifen, nicotinic acid, and ethambutol) are restricted during the trial.

4.2.2.2 Restrictions on diet and lifestyle

None

4.2.2.3 Contraception requirements

WOCBP (for the definition please refer to Section 3.3.2) and men able to father a child must use two medically approved methods of birth control throughout the trial (from Visit 1 until End of Study visit) one barrier method (condom), and one highly effective non-barrier method.

Men (trial subject or partner of a trial subject) must use a condom (regardless of vasectomy) if their sexual partner is a WOCBP.

WOCBP (trial subject or partner of a trial subject) must use a highly effective method of birth control per ICH M3 (R2) throughout the trial (from Visit 1 until EOS visit) that results in a low failure rate of less than 1% per year when used consistently and correctly if their sexual partner is a man able to father a child.

- Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal).
- Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable).
- Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS).
- Bilateral tubal occlusion

Or

Subjects must abstain from male-female sex if this is defined as being in line with the preferred and usual lifestyle of the subject. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods, declaration of abstinence for the duration of exposure to study drug and withdrawal are not acceptable.

4.2.2.4 Restrictions regarding gamete donation

Gamete donation must not be performed from the time of the first dose of the investigational drug, and for at least 3 months after the last dose of the investigational drug.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study centre. This is performed by a qualified physician. In the MD part the unmasked injector with no other involvement in the trial will administer the trial medication.

Subjects who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the eCRF will be completed accordingly (for further procedures, please see Section 3.3.4.1).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

For the endpoints, baseline is defined as the value at Visit 2; if not measured at Visit 2 then baseline is the value at Visit 1. All ophthalmologic examinations will be performed on both eyes, as described below.

Centrally collected ophthalmological data (color fundus photography, SD-OCT, OCTA) will be transferred from the Central Reading Center (CRC) to the sponsor's database. The local measurement data (BCVA, Slit lamp, IOP, LLBCVA) will be transferred to the appropriate eCRFs and will remain at the study sites as source documents.

If clinically significant worsening is observed in the assessments of efficacy during the study, it will be reported as AE in the eCRF (please also refer to Section 5.2.7).

SD-OCT/OCT-Angiography

The retinal layers and their thickness can be visualized and measured by SD-OCT. The assessment will be performed by a qualified person, and only specified OCT equipment will be used. OCTA is a non-invasive imaging technique that provides high-resolution volumetric blood flow information without the use of dye. The assessment is also performed by a qualified person, and only specified device(s) will be used.

OCT and OCTA images will be sent to an independent CRC for evaluation. A detailed manual for OCTand OCTA image acquisition and data transmission will be provided.

Visual Acuity measured by ETDRS letter charts

BCVA will be measured using the early treatment diabetic retinopathy study (ETDRS) VA chart. The BCVA score is the number of letters read correctly by the subject. The assessment will be performed by a trained person under specified conditions regarding examination room and equipment.

5.2 ASSESSMENT OF SAFETY

5.2.1 Dose limiting event

A DLE is defined as the occurrence of any of the following events in the study eye within the evaluation period (7 days after drug administration):

- Development of sterile endophthalmitis and/or sterile inflammation of the vitreous of grade 3+ according to the NEI Grading of vitreous haze, and anterior chamber cells of 3+ according to the Standardization of Uveitis Nomenclature (SUN) working group (WG) grading scheme (see Table 5.2.1: 1 below) and a duration of 5 or more days between day 1 and day 8
- Visual loss of more than 15 letters at any given time-point
- Persistent IOP over 30 mmHg for 3 days
- Signs of vascular occlusion in a 1st (the main branch) or 2nd degree (the vessel after the first bifurcation of the main branch) retinal vessel, including peripheral retinal hemorrhages in the area supplied by the occluded vessel (hemorrhage of the macula would not be included as this is a symptom of the disease)

Table 5.2.1: 1 The SUN Working Group Grading Scheme (R18-1136)

Grade	Cells in Field[1]
0	0
0.5+	1-5
1+	6-15
2+	16-25
3+	26-50
4+	>50

[1] Field size is a 1 mm by 1 mm slit beam.

5.2.2 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart I and Flow Chart II. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities.

Measurement of height and body weight will be performed at the time points specified in the flowchart.

The results must be included in the source documents available at the site.

Color Fundus Photography, Slit Lamp and IOP

Seven-field or modified 4-field digital fundus photographs or ultrawide field imaging, will be obtained from both eyes by a qualified person according to the imaging manual. Slit lamp examination and IOPs will be performed by a qualified person.

This examination will be performed at the time-points defined in the Flow Chart I and Flow Chart II.

5.2.3 Vital signs

Vital signs will be evaluated at the time points specified in the flowchart, prior to blood sampling.

This includes systolic and diastolic blood pressure and pulse rate (electronically or by palpation count for 1 minute) in a seated position after 5 minutes of rest. The results must be included in the source documents available at the site.

5.2.4 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.4: 1. For the sampling time points please see the Flow Chart I and Flow Chart II.

All analyses will be performed by a central laboratory, except urine pregnancy test which will be performed by the site staff. The respective reference ranges will be provided in the ISF. Subjects do not have to be fasted for the blood sampling for the safety laboratory.

Instructions regarding sample collection, sample handling/ processing and sample shipping are provided in the Laboratory Manual in the ISF.

The central laboratory will send reports to the investigator. It is the responsibility of the investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the investigator will be reported as adverse events (please refer to section 5.2.7).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see section 5.2.7.1.4 and the DILI Checklist provided in the eDC system. The amount of blood taken from the subject concerned will be increased due to this additional sampling.

The central laboratory will transfer the results of the analysis to the sponsor.

If blood sampling for central lab at the trial site is not possible, safety lab analyses can be performed at a local lab. The results of the lab tests must be transferred to the investigator who ensures medical review and documents a clinically relevant safety issue as an adverse event. For minimum required safety lab parameters, please see Table 5.2.4: 1.

Table 5.2.4: 1 Safety laboratory parameters – whole blood, serum or plasma

Hematology

- Haematocrit
- Haemoglobin
- MCV, MCH, RDW, MCHC
- Red Blood Cells (RBC) / Erythrocytes
- WBC / Leukocytes
- Platelet Count / Thrombocytes
- Differential Automatic (relative and absolute count): Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes
- HbA1c

Clinical chemistry

- Albumin
- Alkaline phosphatase
  - γ-GT (gamma-glutamyl transferase) reflex test triggered by elevated alkaline phosphatase on two sequential measures
- ALT (alanine aminotransaminase, SGPT)
- AST (aspartate aminotransaminase, SGOT)
- Bicarbonate
- Bilirubin total, fractionated if increased
- Calcium
- Chloride
- Creatinine
- Serum Pregnancy test*
- Creatine kinase (CK)
- CK-MB, troponin I (reflex tests if CK is elevated)
- Lactate dehydrogenase (LDH)
- Lipase
- Magnesium
- Phosphate
- Potassium
- Protein total
- Sodium
- Urea (BUN)
- LDL/HDL and total cholesterol
- Triglycerides
- TSH
- Folate

*Serum pregnancy test at screening as well as confirmation of positive urine pregnancy test (only for WOCBP)

Table 5.2.4: 2 Safety laboratory parameters – urine

Urinalysis
Semi quantitative • Nitrite • Protein • Glucose • Blood • Ketone • Urine pH • Leukocyte esterase (for WBC)
Human urine chorionic gonadotropin (HCG)*

*Pregnancy testing (HCG, urine): performed on-site, see flow chart I and flow chart II (only for WOCBP)

5.2.5 Electrocardiogram

5.2.5.1 12-lead resting ECG

Recording

Single Twelve-lead resting ECGs (I, II, III, aVR, aVL, aVF, V1 - V6) will be recorded using a computerised electrocardiograph at the time points given in the Flow Chart I and Flow Chart II. Electrode placement will be performed according to the method of Wilson, Goldberger and Einthoven modified by Mason and Likar (hips and shoulders instead of ankles and wrists). Precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the study.

To achieve a stable heart rate at rest and to assure high quality recordings, the site personnel will be instructed to assure a relaxed and quiet environment, so that all subjects are at complete rest.

All ECGs will be recorded for a 10 sec duration after subjects have rested for at least 5 min in a supine position. ECG recording will always precede all other study procedures scheduled for the same time to avoid compromising ECG quality.

ECGs may be repeated for quality reasons for instance due to alternating current artefacts, muscle movements, or electrode dislocation. The repeat ECGs are assigned to the respective scheduled time point.

Additional (unscheduled) ECGs may be recorded for safety reasons.

Data transfer

For time points specified in the Flow Chart I and Flow Chart II, ECGs will be transferred electronically to the central ECG lab for evaluation.

In case of repeat ECGs due to quality reasons, only the repeated ECG recordings will be transferred to the central ECG lab, whereas the initially recorded ECGs will be discarded. Unscheduled ECGs (for safety reasons) will be transferred to the central ECG lab but will not be included into the statistical analysis of interval lengths.

The data from the central ECG will be transferred to the sponsor.

Evaluation

Central ECG lab evaluation will be performed for all ECGs indicated in the Flow Chart I and Flow Chart II. For all ECGs this will include the intervals respiratory rate (RR), pulse rate (PR), QRS and QT measured semi-automatically. The screening ECGs will be checked for abnormalities.

Heart rate (HR) and the QT interval corrected for HR (QTc e.g. QTcF and QTcB) will be determined by the sponsor (see Trial statistical analysis plan (TSAP) for details).

All semi-automatic interval measurements in one subject will be performed on the same lead as far as possible. The intervals will be measured from four cardiac cycles (beats) in lead II. If lead II shows a flat T wave or is not measurable for any reason, lead V5 will be used, or if that lead is not measurable, then lead I will be used. In case of an occurrence where an interval cannot be measured from the same lead, a different lead will be used to measure the interval. This change in the lead will be noted. The lead actually used will be reported in the CTR.

Morphological analyses of the ECGs will be performed centrally by a board-certified cardiologist or equivalent. The ECG interpretation will include an overall assessment (normal, abnormal, not evaluable) and findings with respect to e.g. rhythm, conduction, presence of myocardial infarction, ST-segment, T-wave, and presence of U-wave. Basis of the terminology used for the evaluation is the Clinical Data Interchange Standards Consortium (CDISC) ECG standard findings list as specified in the data transmission agreement.

For masking arrangements see Section 4.1.6. ECG interval measurements from a particular subject should be performed by a single reader. For quality assurance and control of the measurements, a random subset of all ECGs and all ECGs meeting a set of outlier parameters will undergo a second review by a Quality Control Specialist. After quality control, the fiducial point markings will be reviewed by the cardiologist assigned to the study.

Evaluation of ECGs will comply with the ICH E14 guidance document and supplements [R07-4722, R16-0366] as well as the FDA requirements for annotated digital ECGs [R09-4830].

Abnormal findings will be reported as AEs (during the trial) or baseline conditions (at screening) if judged clinically relevant by the investigator.

Any ECG abnormalities will be monitored carefully and, if necessary, the subject will be removed from the trial and will receive the appropriate medical treatment.

5.2.6 Other safety parameters

Not applicable.

5.2.7 Assessment of adverse events

5.2.7.1 Definitions of AEs

5.2.7.1.1 Adverse event

An AE is defined as any untoward medical occurrence in a subject or clinical investigation subject administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following should also be recorded as an AE in the eCRF and BI SAE form (if applicable):

- Worsening of the underlying disease or of other pre-existing conditions
- Changes in vital signs, ECG, physical examination and laboratory test results, if they are judged clinically relevant by the investigator.

If such abnormalities already exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.7.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE, which fulfils at least one of the following criteria:

- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions. Examples of such events are intensive treatment in an emergency

room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

5.2.7.1.3 AEs considered "Always Serious"

In accordance with the European Medicines Agency initiative on Important Medical Events, Boehringer Ingelheim has set up a list of AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.

The latest list of "Always Serious AEs" can be found in the eDC system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described in section 5.2.7.2.
Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in 5.2.7.2, subsections "AE Collection" and "AE reporting to sponsor and timelines".

5.2.7.1.4 Adverse events of special interest

The term adverse events of special interest (AESI) relates to any specific AE that has been identified at the project level as being of particular concern for prospective safety monitoring and safety assessment within this trial, e.g. the potential for AEs based on knowledge from other compounds in the same class. AESIs need to be reported to the sponsor's Pharmacovigilance Department within the same timeframe that applies to SAEs, please see section 5.2.7.2.2.

The following are considered as AESIs:

- DLE
  All AEs meeting the criteria for a dose limiting event (DLE) as defined in Section 5.2.1 are defined as AESIs for this trial.

- Hepatic injury
  A hepatic injury is defined by the following alterations of hepatic laboratory parameters:
  - an elevation of AST (Aspartate Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3-fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or
  - aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

These lab findings constitute a hepatic injury alert and the subjects showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the eDC. In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary, in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

5.2.7.1.5 Intensity (severity) of AEs

The intensity (severity) of the AE should be judged based on the following:

Mild: Awareness of sign(s) or symptom(s) that is/are easily tolerated.
Moderate: Sufficient discomfort to cause interference with usual activity.
Severe: Incapacitating or causing inability to work or to perform usual activities.

5.2.7.1.6 Causal relationship of AEs

Medical judgement should be used to determine whether there is a reasonable possibility of a causal relationship between the adverse event and the given study treatment, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

Arguments that may suggest that there is a reasonable possibility of a causal relationship could be:

- The event is consistent with the known pharmacology of the drug.
- The event is known to be caused by or attributed to the drug class.
- A plausible time to onset of the event relative to the time of drug exposure.
- Evidence that the event is reproducible when the drug is re-introduced.
- No medically sound alternative aetiologies that could explain the event (e.g. pre-existing or concomitant diseases, or co-medications).
- The event is typically drug-related and infrequent in the general population not exposed to drugs (e.g. Stevens-Johnson syndrome).
- An indication of dose-response (i.e. greater effect size if the dose is increased, smaller effect size if dose is reduced).

Arguments that may suggest that there is no reasonable possibility of a causal relationship could be:

- No plausible time to onset of the event relative to the time of drug exposure is evident (e.g. pre-treatment cases, diagnosis of cancer or chronic disease within days / weeks of drug administration; an allergic reaction weeks after discontinuation of the drug concerned).
- Continuation of the event despite the withdrawal of the medication, taking into account the pharmacological properties of the compound (e.g. after 5 half-lives). Of note, this criterion may not be applicable to events whose time course is prolonged despite removing the original trigger.
- Additional arguments amongst those stated before, like alternative explanation (e.g. situations where other drugs or underlying diseases appear to provide a more likely explanation for the observed event than the drug concerned).
- Disappearance of the event even though the trial drug treatment continues or remains unchanged.

5.2.7.2 Adverse event collection and reporting

5.2.7.2.1 AE Collection

The investigator shall maintain and keep detailed records of all AEs in the patient files.

The following must be collected and documented on the appropriate CRF(s) by the investigator:

- From signing the informed consent onwards until the individual patient's end of trial (the End of Study (EOS) visit): all AEs (serious and non-serious) and all AESIs.
- After the individual subject's end of trial:
  the investigator does not need to actively monitor the subject for new AEs but should only report any occurrence of cancer and trial treatment related SAEs and trial treatment related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should be reported on the BI SAE form (see section 5.2.7.2.2), but not on the CRF.

5.2.7.2.2 AE reporting to the sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.
With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual subject's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

5.2.7.2.3 Pregnancy

In rare cases, pregnancy might occur in a clinical trial. Once a subject has been enrolled in the clinical trial and has received trial medication, the investigator must report any drug exposure during pregnancy in a trial subject immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring Form to the sponsor's unique entry point.

Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial subject becomes pregnant. This requires written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.

The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Studies (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Studies (Part A and B).

As pregnancy itself is not to be reported as an AE, in the absence of an accompanying SAE and/or AESI, only the Pregnancy Monitoring Form for Clinical Studies and not the SAE form is to be completed. If there is an SAE and/or AESI associated with the pregnancy an SAE form must be completed in addition.

[redacted]

5.4 ASSESSMENT OF BIOMARKER(S)

To evaluate the changes in NRP-1levels in [redacted]
(separate informed consent) will be collected in a subset of subjects and levels of NRP-1 will

be assessed in the study eye at times indicated in the Flow Chart II. If feasible BI 765128 levels in [redacted] samples might be determined. In total, four [redacted] collections are planned in the multiple dosing part of the trial.

Full instructions for collection, labelling, storage and shipment of samples are provided in the Laboratory Manual.

Additionally, if feasible proteins affected by the drug's mode of action might be determined in serum samples.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor subjects' safety and to determine pharmacokinetic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an intravitreally administered drug and are widely used in clinical trials. Within the ophthalmologic examinations, colour fundus photography, slit lamp IOP and SD-OCT are considered standard, whereas OCTA is of exploratory nature. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

For visit schedule, refer to Flow Chart I and Flow Chart II. The acceptable time windows for visits are given in the Flow Charts. For planned individual plasma concentration sampling times, refer to appendix 10.1.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures and assessments to be performed at each visit are listed in the Flow Chart I, Flow Chart II, and in the appendix 10.1. Additional details regarding visit procedures are provided below.

All ophthalmic examinations will be performed in both eyes and should be performed in the specific order described below:

- Before pupil dilation: BCVA assessment and [redacted] assessment
- After dilation: slit lamp examination, SD-OCT, OCTA, colour fundus photography.
- At the end: ocular tonometry (for determination of IOP)

6.2.1 Screening and run-in period(s)

Screening Period

The screening visit does not need to be done with the subject in a fasted state. All subjects must sign an Informed Consent consistent with ICH GCP guidelines prior to any study specific procedures. This includes the option that the subject signs the Informed Consent during an extra contact to the study site prior to the actual screening visit. The subject should be recorded on the enrolment log as a screened subject when Visit 1 is performed. Visit 1 is the beginning of the screening period. As soon as eligibility of an enrolled subject is confirmed, the treatment visit (Visit 2) may be performed. If the subject does not meet inclusion/exclusion criteria, the subject must be recorded in the eCRF as a screen failure.

Applies to part A: In case of closed dose groups no further rescreening activities for a screened and eligible subject are required within 12 weeks after completed screening visit. If screening visit has been performed earlier than 28 days before randomization, an additional visit for repeating of safety lab, vital signs, ECG and targeted physical examination has to be performed.

Baseline Conditions

Any pre-existing medical conditions considered as clinically relevant by the investigator, excluding the indication of the trial, are recorded into the appropriate eCRF. Any abnormal clinically significant findings observed during ophthalmological examinations at Visit 1 need to be documented as Baseline Conditions.

Medical History

All clinically relevant medical history according to the investigator judgment will be captured in the appropriate eCRF.

IRT

All subjects that are screened must be registered with IRT. If the subject results in a screen failure, IRT should be notified as soon as possible and within the screening period. Details of IRT procedures can be found in the IRT manual located in the ISF.

Re-screening

Subjects who do not fulfil all eligibility criteria and are screen failed for a reason that later resolves and allows eligibility criteria to be met can be rescreened up to one time. For re-screening, subject must be registered in IRT, which will then provide a new subject number, and the subject must sign new Informed Consent Form (ICF). Imaging of retina (SD-OCT, OCTA, fundus photography) does not need to be repeated at the re-screening visit if the corresponding criteria for inclusion of the study eye were met at the initial screening visit and if the images are not older than 28 days at the re-screening visit; otherwise, new images have to be performed.

6.2.2 Treatment period(s)

For Part A, masking is not required for the IVT injection preparation or administration. For Part B, IVT injection will be prepared by the unmasked pharmacist/qualified person (Section 4.1.6). In addition, an unmasked injector (Section 4.1.6) with no other involvement in the trial will administer either active or sham injection according to the treatment assigned by IRT. IVT injections must be carried out according to medical standards and applicable guidelines by a qualified physician experienced in administering IVT injections and will be done as part of drug administration visit procedures (Visit 2 for Part A and Visits 2, 3 and 4 for Part B) after the other ophthalmologic assessments in the Flow Chart I and Flow Chart II have been performed (please see Section 4.1 for details).

6.2.3 Follow-up period and trial completion

Subjects must continue to be followed according to the visit schedule (unless they withdraw consent for further follow-up) in order to collect data at the end of the planned observation period. Unscheduled visits will be possible at the discretion of the investigator at any time for safety reason. The unscheduled visit may include any assessments considered necessary by the investigator. All unscheduled visits should be described and documented in the medical /source record. The investigator may decide other treatment options during the follow-up period as deemed medically appropriate.

Part A

Visit 8/End of Study:
The Visit 8/EOS will be performed 42 days after Visit 7 (see Flow Chart I).
The Visit 8/EOS is the final visit and the End of Study eCRF has to be completed.

Part B

Visit 7/End of Study:
The Visit 7/EOS will be performed 28 days after Visit 6 (see Flow Chart II).
The Visit 7/EOS is the final visit and the End of Study eCRF has to be completed.

Withdrawal of consent

Every effort should be made to keep the subject in the trial and undergoing the procedures and follow up as outlined in the Flow Charts I and II and Section 6.2.3.

If a subject is not willing to continue in the trial and wants to withdraw consent prior to the end of the study, Visit 7 (Part A)/ Visit 6 (Part B) should be scheduled as soon as possible, and also Visit 8/EOS(Part A)/ Visit 7/EOS(Part B) should be performed to assess for safety.

The End of Study eCRF has to be filled in even if subject refuses to participate to the above specified visits.

For AE assessment, laboratory tests, recording of ECG and vital signs, and physical examination during the follow-up period, see Section 5.2.

Subjects who discontinue treatment before the end of the planned treatment period should undergo the EOS Visit.

All abnormal values (including laboratory parameters) that are assessed as clinically relevant by the investigator will be monitored using the appropriate tests until a return to a medically acceptable level is achieved. (S)AEs persisting after a subject's EOS Visit must be followed until they have resolved, have been sufficiently characterised, or no further information can be obtained.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The objective of this trial is to determine the safety and tolerability of BI 765128 in panretinal photocoagulation (PRP) treated diabetic retinopathy (DR) patients with diabetic macular ischemia (DMI), based on the primary endpoint, the occurrence of dose limiting events (DLE) (see Section 5.2.1) in the 7 days post administration (Part A) or the occurrence of drug-related AEs until EOS (Part B).The safety, tolerability and early biological response after multiple IVT injections of BI 765128 will also be investigated.

7.1 STATISTICAL DESIGN – MODEL

This trial will consist of a Part A followed by a Part B. The Part A will be conducted non-randomized, open-label, and uncontrolled. Part B will be conducted double-masked randomized and sham-controlled.

Part A:

The dose escalation will be guided by a Bayesian 2-parameter logistic regression model with overdose control [R13-4803, R13-4806].

The model is given as follows:

$$\text{logit}(\pi_d) = \log(\alpha) + \beta * \log(d/d^*),$$

where $\text{logit}(\pi) = \log(\pi/(1-\pi))$, π_d represents the probability of having a DLE in the evaluation period at dose d, d* = [redacted] mg is the reference dose, allowing for the interpretation of α as the odds of a DLE at dose d*, and $\theta = (\log(\alpha), \log(\beta))$ with $\alpha, \beta > 0$ is the parameter vector of the model.

The estimated probability of a DLE at each dose level from the model will be summarized using the following intervals:

Target toxicity: [0.00, 0.25)
Over toxicity: [0.25, 1.00]

The BLRM-recommended dose for the next cohort is the highest dose level with posterior probability of the DLE rate falling in the target interval [0.00, 0.25) among the doses fulfilling EWOC. Thus, applying the EWOC criterion it should be unlikely (< 25% posterior probability) that the DLE rate at that dose will exceed 0.25. However, the allowed dose increment will always be the next higher pre-planned dose. However, the maximum allowable dose increment for the subsequent cohort will be no more than 250% from the previous dose. Dose escalation will continue up to the [redacted] dose as long as the EWOC criterion for the next dose level is fulfilled. At the final dose, at least 6 treated subjects are required. However, the SMC may decide to include additional number of subjects at this dose level.

Since a Bayesian approach is applied, a prior distribution f(θ) for the unknown parameter vector θ needs to be specified. This prior distribution will be specified as a mixture of three multivariate normal distributions, i.e.

$$f(\theta) = a_1 f_1(\theta) + a_2 f_2(\theta) + a_3 f_3(\theta)$$

with a_i, i = 1, 2, 3 the prior mixture weights ($a_1 + a_2 + a_3 = 1$), and $f_i(\theta) = MVN(\mu_i, \Sigma_i)$, the multivariate normal distribution of the i-th component with mean vector μ_i and covariance matrix Σ_i, where

$$\Sigma_i = \begin{pmatrix} \sigma^2_{i,11} & \sigma_{i,11}\sigma_{i,22}\rho_i \\ \sigma_{i,11}\sigma_{i,22}\rho_i & \sigma^2_{i,22} \end{pmatrix}.$$

Mixture prior distributions have the advantage that they allow for specification of different logistic dose-toxicity curves, therefore making the prior more robust.

For the current study, no relevant information in the form of human data is available, since no study in a comparable population has been conducted. Therefore, the three mixture components were established as follows:

1. A weakly informative prior was derived reflecting the a priori assumption that the median DLE rate at the starting dose of [redacted] would equal 0.02, and the median DLE rate at the maximum dose of [redacted] would equal 0.1. This yields $\mu_1 = (-2.197, 0.052)$. The standard deviations were set such that medium uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding $\sigma_{1,11} = 1.2$, $\sigma_{1,22} = 1.5$ and $\rho_1 = 0$, respectively. The prior weight a_1 for the first component was chosen as 0.9.
2. A high-toxicity weakly informative prior was derived reflecting the case that the compound would be much more toxic than expected. For this prior component, it was assumed that the median DLE rate at the starting dose of [redacted] would equal 0.1, and the median DLE rate at [redacted] would equal 0.3. These assumptions yield $\mu_2 = (-0.847, -0.176)$. The standard deviations and correlations were such that large uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding $\sigma_{2,11} = 2$, $\sigma_{2,22} = 1$ and $\rho_2 = 0$, respectively. The prior weight a_2 for the second component was chosen as 0.05.
3. A low-toxicity weakly informative prior was derived reflecting the case that the compound would be much less toxic than expected. For this prior component, it was assumed that the median DLE rate at the starting dose of [redacted] would equal 0.001, and the median DLE at [redacted] would equal 0.01. These assumptions yield $\mu_3 = (-4.595, 0.362)$. The standard deviations and correlations were set to $\sigma_{3,11} = 2$, $\sigma_{3,22} = 1$. The correlation was set to 0, i.e. $\rho_3 = 0$. The prior weight a_3 for the third component was chosen as 0.05.

A summary of the prior distribution is provided in Table 7.1: 1. Additionally, the prior probabilities of DLEs at different doses, as well as the corresponding probability of targeted and overdosing, are shown in Table 7.1: 2. Graphically, the prior medians with accompanying 95% credible intervals are shown in Figure 7.1: 1. As can be seen from both Table 7.1: 2 and Figure 7.1: 1, the prior medians of the DLE probabilities are in line with the prior medians derived from the weakly informative prior, and the uncertainty around the medians is realtively large, showing the medium amount of information this prior provides. This is also supported by the prior sample size, i.e. the information contained in the prior. This is approximately equal to 3.7 subjects. A detailed evaluation of the model using hypothetical data scenarios and operating characteristics is provided in Appendix 10.3.

Table 7.1: 1 Summary of prior distribution

Prior Component	Mixture Weight	Mean Vector	SD Vector	Correlation
1: Weakly inf.	0.900	-2.197, 0.052	1.2, 1.5	0
2: High Tox.	0.050	-0.847, -0.176	2, 1	0
3: Low Tox.	0.050	-4.595, 0.362	2, 1	0

Table 7.1: 2 Prior probabilities of DLEs at selected doses

Dose	Probability of true DLE rate				Quantiles		
	(0-0.25]	**[0.25-1]**	**mean**	**sd**	**2.50%**	**50%**	**97.50%**
[redacted]	0.950	0.050	0.054	0.104	0.000	0.013	0.361
[redacted]	0.927	0.073	0.073	0.120	0.000	0.027	0.428
[redacted]	0.810	0.190	0.153	0.160	0.006	0.098	0.608

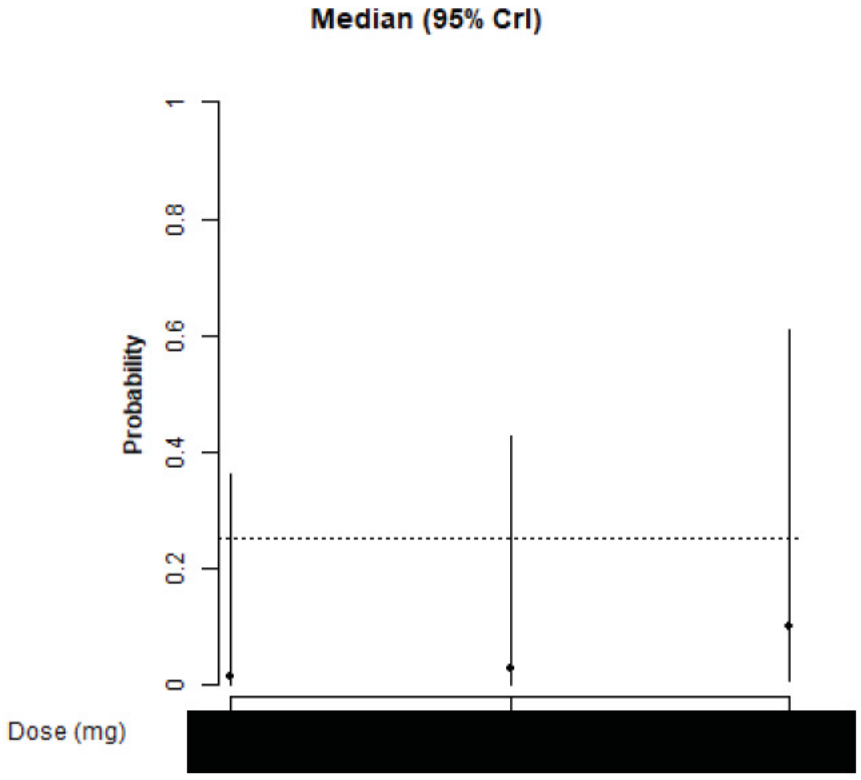


Figure 7.1: 1 Prior medians and 95% credible intervals

The prior may be updated once the trial has started in case new data that can be used will be available. Only subjects for which the occurrence of DLEs within the evaluation period can be evaluated will be considered. The prior that is used for each BLRM analysis for the SMC meetings will be documented in the SMC minutes, the prior used for the final analysis will be documented in the TSAP in case a different prior than described above will be used.

The MFD may be considered reached if all of the following criteria are fulfilled:

- Next recommended dose by the BLRM = current dose
- At least 12 subjects have been treated in the trial.
- At least 6 subjects have been treated at the MFD.

Part B:
The size of the foveal avascular zone (FAZ) is associated with visual loss. Measuring FAZ by OCTA is highly reproducible. The assumed treatment effect of BI 765128 (reduction in the area of FAZ) as compared with sham treatment after 3 months of treatment is 10%. Showing this reduction in size of FAZ is believed to be clinically relevant.

Only 1 dose, the highest dose, of Part A will be used for Part B, the MD study. The highest dose is usually limited by the maximum dose possible in the IVT injectable volume.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No confirmatory testing is performed and hence no null and alternative hypotheses are defined. Any confidence intervals computed are to be interpreted in the perspective of the exploratory character of the study; i.e., confidence intervals are considered as interval estimates for effects. A discussion of the sample size is provided in Section 7.6.

7.3 PLANNED ANALYSES

7.3.1 Subject analysis sets

The main analysis populations are defined below. In the TSAP, further analysis data sets may be defined. Subjects will be analysed according to the assigned treatment, unless otherwise specified.

Important protocol deviations (IPD) categories will be defined in the IPD specificatioin document. IPDs will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed. The handling of subjects with iPDs will be described in the TSAP.

Treated set (TS)

For part A the treated set includes all subjects who were treated with at least one dose of study drug.

For part B the treated set includes all subjects who were randomized and treated with at least one dose of study drug (either treatment with BI 765128 or Sham).

[redacted]

7.3.2 Primary endpoint analyses

Part A:
The primary safety endpoint "Number of subjects with ocular (in the study eye) DLEs from drug administration till day 7" will be analysed descriptively, based on the TS.

Part B:
The primary safety endpoint "Number of subjects with drug-related AEs from drug administration until EOS" will be analysed descriptively, based on the TS.

7.3.3 Secondary endpoint analyses

The secondary endpoints (refer to Section 2.1.3) will be summarized by means of descriptive statistics (at least n, mean, standard deviation, median, minimum and maximum) for continuous variables or frequency tables for categorical variables. The change from baseline (in mm2) of FAZ will be analysed using a generalized mixed linear model (for details refer to the TSAP). The endpoint Central retinal thickness (µm) will be analyzed in the same way as the endpoint FAZ. In addition, the BCVA will be analyzed using a generalized linear model.

Analyses regarding safety and efficacy will be performed on the TS.

7.3.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. For BI 765128, the residual effect period (REP) after IVT administration is not known. Therefore, all AEs with an onset between start of treatment and the respective EOS visit will be assigned to the ontreatment period for evaluation. The safety analysis will be performed by planned dose group.

All treated subjects will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of adverse events will concentrate on treatment-emergent adverse events, i.e. all adverse events occurring between start of treatment and end of the EOS. Adverse events that start before first drug intake and deteriorate under treatment will also be considered as ‘treatment-emergent’.

For all analyses the treatment actually administered (= treatment at onset) to the subject will be used (any deviations from the randomized treatment will be discussed in the minutes of the Report Planning Meeting).

Frequency, severity, and causal relationship of adverse events will be tabulated by system organ class and preferred term after coding according to the current version of the Medical Dictionary for Drug Regulatory Activities (MedDRA) at database lock.

Note that AEs occurring after the last per protocol contact but entered before database lock will be reported to Pharmacovigilance only and will not be captured in the trial database (See section 5.2.7.2.1).

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be summarised. Treatment groups will be compared descriptively with regard to distribution parameters as well as with regard to frequency and percentage of subjects with abnormal values or clinically relevant abnormal values.

Vital signs, physical examinations, or other safety-relevant data observed at screening, baseline, during the course of the trial and at the end-of-trial evaluation will be assessed with regard to possible changes compared to findings before start of treatment.

Additionally, further treatment intervals (called analysing treatments) may be defined in the TSAP in order to provide summary statistics for other than above periods, such as combined treatments, on-treatment totals, or periods without treatment effects (such as screening and post-study intervals).

The ECG variables QT, HR, QTcF, QTcB, PR, QRS, and RR obtained from the centralised evaluation of 12-lead ECG recordings will be the basis for the derivation of quantitative and categorical ECG endpoints. These endpoints and their analyses will be described in the TSAP.

7.3.6 Other Analyses

In order to characterize BI 765128's exposure-response relationship, a pharmacometric population PKPD analysis may be performed. Furthermore, if data allow, a pharmacometric analysis will be conducted to estimate vitreal concentrations. The pharmacometric analysis will not be part of the CTR but will be provided separately.

7.3.7 Interim Analyses

No interim analysis is planned.

The sponsor will continuously monitor the safety.

Part A

The dose escalation design of the Part A foresees that the sponsor and the SMC perform regular safety evaluations, the SMC will meet after the last subject of each dose cohort has attended Visit 5 (section 3.1) These evaluations will be unmasked to dose.

Part B

The sponsor and the SMC perform one safety evaluation, the SMC will meet after 50% of the subjects were randomized and finished Visit 5. This analysis will involve descriptive and graphical presentation of primary, secondary and further endpoints. These evaluations will be unmasked to dose.

In addition, a fast track analysis will be performed after the final subject of Part B has attended Visit 6 (i.e. approximately 8 weeks after receiving the final dose).

7.4 HANDLING OF MISSING DATA

7.4.1 Safety

Missing baseline laboratory values will be imputed by the respective values from the screening visit. No other imputations will be performed on missing data although every effort will be made to obtain complete information on all AEs, with particular emphasis on potential DLEs.

[redacted]

7.4.3 Efficacy

All data will be analyzed and presented without any form of imputation. For the statistical sensitivity analysis missing values will be imputed using LOCF.

7.5 RANDOMISATION

Part A

Subjects within a cohort receive the same trial medication, therefore no randomization for treatment assignment is performed.

Part B

Subjects will be randomized in a 2:1 ratio (BI 765128: Sham injection).

BI will arrange for the randomisation and the packaging and labelling of trial medication. The randomization list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the Clinical Trial Report. Access to the codes will be controlled and documented.

The randomization list will contain additional blocks to allow for subject replacement (refer to Section 3.3.5).

7.6 DETERMINATION OF SAMPLE SIZE

Part A:

No formal statistical power calculations to determine sample size were performed for this explorative study. A Bayesian logistic regression model (BLRM) was used for guiding the dose escalation process (see Section 3.1 for details). For the SRD part, a minimum of 3 subjects and a maximum of 18 subjects will be expected for this trial based on the number of dose levels/cohorts that are tested (for details regarding the BLRM assumptions refer to appendix 10.3). Fewer subjects might be needed based on the recommendation of the SMC. However, the actual number of subjects will depend on the number of dose cohorts tested. Based on the simulation study to evaluate operating characteristics of the BLRM, about 15 evaluable subjects are expected to be treated in the dose escalation part for the model to have reasonable operating characteristics relating to its MFD recommendation.

Part B:

In the publication Samara et al. [R17-3318] estimates for FAZ means and standard deviations (SD) were derived. The worst case was for PDR subjects with mean deep FAZ of 0.766 mm^2. The standard deviation of FAZ ranged from 0.112 mm^2 to 0.3402 mm^2 for disease categories from control to PDR. It is assumed that intra-individual variability is much lower than the inter-individual SD from Samara et al. because of the high correlation of the baseline and the FAZ values after treatment. Taking into account the high correlation, a SD of FAZ of 0.1 mm^2 seems to be reasonable to be used in calculation of risk probabilities. With 20 subjects in the BI 765128 [redacted] arm and 10 subjects in the sham arm, there is a likelihood of 81.7% of observing a treatment effect larger than 6% (a reduction of 0.0462 mm2) and a likelihood of 10.2% of observing a treatment effect smaller than 4% (a reduction of 0.0308mm^2) when the assumed mean treatment difference is10%. Assuming a mean treatment difference of 0% there is a likelihood of 12.3% observing a treatment effect larger than 6% and a likelihood of 78.7% of observing a treatment effect smaller than 4%.

8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Guideline for Good Clinical Practice (GCP), relevant BI Standard Operating Procedures (SOPs), the EU directive 2001/20/EC / EU regulation 536/2014 and other relevant regulations. Investigators and site staff must adhere to these principles. Deviation from the protocol, the principles of ICH GCP or applicable regulations as will be treated as "protocol deviation".
Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the treating physician of the subject.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial subjects against any immediate hazard, as well as of any serious breaches of the protocol or of ICH GCP.

The Boehringer Ingelheim transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalisation of the Clinical Trial Report.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This trial will be initiated only after all required legal documentation has been reviewed and approved by the respective Institutional Review Board (IRB / Independent Ethics Committee (IEC and competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to subject participation in the trial, written informed consent must be obtained from each subject (or the subject's legally accepted representative) according to ICH-GCP and to the regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional subject information must be given to each subject or the subject's legally accepted representative."

The subject must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the subject's own free will with the informed consent form after confirming that the subject understands the contents. The investigator or [redacted] delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

A risk-based approach is used for trial quality management. It is initiated by the assessment of critical data and processes for trial subject protection and reliability of the results as well as identification and assessment of associated risks. An Integrated Quality and Risk Management Plan documents the rationale and strategies for risk management during trial conduct including monitoring approaches, vendor management and other processes focusing on areas of greatest risk.

Continuous risk review and assessment may lead to adjustments in trial conduct, trial design or monitoring approaches.

A quality assurance audit/inspection of this trial may be conducted by the sponsor, sponsor's designees, or by IRB / IEC or by regulatory authorities. The quality assurance auditor will have access to all medical records, the investigator's trial-related files and correspondence, and the informed consent documentation of this clinical trial.

8.3 RECORDS

CRFs for individual subjects will be provided by the sponsor. See section 4.1.6.2 for rules about emergency code breaks. For drug accountability, refer to section 4.1.9.

8.3.1 Source documents

In accordance with regulatory requirements, the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial subject. Source data as well as reported data should follow the "ALCOA principles" and be **a**ttributable, **l**egible, **c**ontemporaneous, **o**riginal and **a**ccurate. Changes to the data should be traceable (audit trail).

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the subject may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case, the investigator must make at least one documented attempt to retrieve previous medical records. If this fails, a verbal history from the subject, documented in their medical records, would be acceptable.

Before sending or uploading those copies, the investigator must ensure that all subject identifiers (e.g. subject's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the subjects' source documents.

If the subject is not compliant with the protocol, any corrective action e.g. re-training must be documented in the subject file.

For the CRF, data must be derived from source documents, for example:

- Subject identification: gender, year of birth (in accordance with local laws and regulations)
- Subject participation in the trial (substance, trial number, subject number, date subject was informed)
- Dates of subject's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of subject's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- Prior to allocation of a subject to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial subject meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the subject or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the subject eligible for the clinical trial.

Originals or copies of laboratory results and other imaging or testing results (with proper documented medical evaluation (in validated electronic format, if available) will be electronically transferred and uploaded into the trial database.

8.3.2 Direct access to source data and documents

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the CRA, auditor and regulatory inspector (e.g. FDA). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

Trial site(s):

The trial site(s) must retain the source and essential documents (including ISF) according to contract or the local requirements valid at the time of the end of the trial (whatever is longer).

Sponsor:

The sponsor must retain the essential documents according to the sponsor's SOPs.

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of subject data in accordance with the principles 7 and 12 of the WHO GCP handbook.

Individual subject data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the following exceptions:

Personalised treatment data may be given to the subject's personal physician or to other appropriate medical personnel responsible for the subject's welfare. Data generated at the site as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

8.5.1 Collection, storage and future use of biological samples and corresponding data

Not applicable.

8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date when the first subject in the whole trial signs informed consent.

The end of the trial is defined as the date of the last visit of the last subject in the whole trial ("Last Patient Completed").

The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last subject in the whole trial is administered the last dose of trial treatment (as scheduled per

protocol or prematurely). Individual investigators will be notified of SUSARs occurring with the trial medication until 30 days after LPLT at their site.
Early termination of the trial is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.

Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / CA in each participating EU member state will be notified about the trial milestones according to the respective laws.

A final report of the clinical trial data will be written only after all subjects have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.

The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last subject (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by Boehringer Ingelheim (BI).

A Coordinating Investigator is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

An extended SMC will be established for both part A and part B. The SMC shall operate under the principles specified in the SMC charter. The primary objective of the SMC is to to ensure and protect the safety and well-being of the trial subjects and to regularly review the trial data and provide recommendation for the further conduct of the trial.

The SMC is a multidisciplinary group composed of the co-ordinating investigator, participating investigators (as deemed necessary) with treated subjects in the cohort that will be evaluated in the meeting (Part A only), members of the BI trial team and two experts independent from the BI trial / project team in the field of ophthalmology. The SMC members have been selected for their expertise in these areas, their knowledge of the management of subjects with DMI and their experience in clinical trials and SMC activities. Details of the SMC responsibilities and procedures are described in the SMC charter.

Relevant documentation on the participating (Principal) Investigators (e.g. their curricula vitae) will be filed in the ISF.

The investigators will have access to the BI web portal Clinergize to access documents provided by the sponsor.

BI has appointed a Clinical Trial Leader (CT Leader), responsible for coordinating all required activities, in order to

- manage the trial in accordance with applicable regulations and internal SOPs,
- direct the clinical trial team in the preparation, conduct, and reporting of the trial,
- ensure appropriate training and information of Clinical Trial Managers (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

The organisation of the trial in the participating countries will be performed by the respective local or regional BI-organisation (Operating Unit, OPU) in accordance with applicable regulations and BI SOPs, or by a Contract Research Organisation (CRO) with which the responsibilities and tasks will have been agreed and a written contract filed before initiation of the clinical trial.

Data Management and Statistical Evaluation will be done by BI according to BI SOPs.

Tasks and functions assigned in order to organise, manage, and evaluate the trial are defined according to BI SOPs. A list of responsible persons and relevant local information can be found in the ISF.

A central laboratory, central ECG, central ophthalmologic reading centre and an IRT vendor will be used in this trial. Details will be provided in corresponding manuals, available in the ISF.

Analyses of BI 765128 concentrations in serum will be performed at a qualified analytical laboratory or at another Contract Research Organization (CRO) with given authorisation by BI.

9. REFERENCES

9.1 PUBLISHED REFERENCES

R17-3317 Botto de Borros Garcia JM, Toledo Lima T, Noguera Louzada R, Thome Rassi A, Cruvinel Isaac DL, Avila M
Title: Diabetic macular ischemia diagnosis: comparison between optical coherence tomography angiography and fluorescein angiography. Source: J Ophthalmol 2016; 2016; 3989310

R17-2540 Committee for Medicinal Products for Human Use (CHMP): guideline on immunogenicity assessment of biotechnology-derived therapeutic proteins: draft (24 September 2015, EMEA/CHMP/BMWP/ 14327/2006 rev. 1). Source: http://www.ema.europa.eu/docs/ en_GB/document_library/Scientific_guideline/2015/1 0/ WC500194507.pdf (access date: 17 July 2017); London: European Medicines Agency (EMA); 2015.

R12-0027 European Medicines Agency (EMA). Committee for medicinal products for human use (CHMP): ICH guideline S6 (R1) - preclinical safety evaluation of biotechnology-derived pharmaceuticals: step 5 (June 2011, EMA/CHMP/ICH/731268/1998). Source: http://www.emea.europa.eu/docs/en_GB/document_library/Scientific_ guideline/2009/ 09/WC500002828.pdf (access date: 10 January 2012) ; London: European Medicines Agency (EMA); 2011.

R20-4303 Wakshull E, Quarmby V, Mahler HC, Rivers H, Jere D, Ramos M, et al
Title: Advancements in understanding immunogenicity of biotherapeutics in the intraocular space. Source: AAPS J 2017; 19(6); 1656-1668

R20-0435 Eylea (aflibercept) injection, for intravitreal use (Regeneron Pharmaceuticals) (U. S. prescribing information, revised: 5/2019). Source: https://www.accessdata.fda.gov/drugsatfda_docs/label/ 2019/125387s061lbl.pdf (access date: 10 February 2020); 2019.

R07-4856 European Medicines Agency (EMEA). Committee for Medicinal Products for Human Use (CHMP): guideline on clinical trials in small populations (London, 27 July 2006, doc. ref. CHMP/EWP/83561/2005). London: EMEA 2006

R18-2968 Hutton-Smith LA, Gaffney EA, Byrne HM, Maini PK, Schwab D, Mazer NA; A mechanistic model of the intravitreal pharmacokinetics of large molecules and the pharmacodynamic suppression of ocular vascular endothelial growth factor levels by ranibizumab in patients with neovascular age-related macular degeneration. Mol Pharm 13, 2941 – 2950 (2016)

R17-3888 Cerani A, Tetreault N, Menard C, Lapalme E, Patel C, Sitaras N, et al; Neuron-derived [redacted] is an early inducer of vascular permeability in diabetic retinopathy via neuropilin-1. Cell Metab 18, 505 - 518 (2013)

R13-4881 FDA's critical path initiative (page last updated: 12/28/2012). cm076689.htm (access date: 8 November 2013); Silver Spring: U.S. Food and Drug Administration 2012

R13-4803 Neuenschwander B, Branson M, Gsponer T. Critical aspects of the Bayesian approach to phase I cancer trials. Stat Med 2008. 27:2420-2439

R13-4806 Babb J, Rogatko A, Zacks S. Cancer phase I clinical trials: efficient dose escalation with overdose control. Stat Med 1998. 17:1103-1120

R18-1136 Trusko B, Thorne J, Jabs D, Belfort R, Dick A, Gangaputra S, et al, Standardization of Uveitis Nomenclature (SUN) Project. The Standardization of Uveitis Nomenclature (SUN) Project: development of a clinical evidence base utilizing informatics tools and techniques. Methods Inf Med 2013. 52(3):259-265

R07-4722 Guidance for industry: E14 clinical evaluation of QT/QTc intervalprolongation and proarrhythmic potential for non-antiarrhythmic drugs. Rockville: U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research (CDER), Center for Biologics Evaluation and Research (CBER) (2005)

R16-0366 E14 Implementation Working Group ICH E14 guideline: the clinical evaluation of QT/QTc interval prolongation and proarrhythmic potential for non-antiarrhythmic drugs: questions & answers (R3) (current version dated 10 December 2015). http://www.ich.org/fileadmin/Public_Web_Site/ICH_Products/Guidelines/Efficacy/E1 4/E14_Q_As_R3__Step4.pdf (access date: 29 January 2016); Geneva: International Council for Harmonisation of Technical Requirements for Pharmaceuticals for Human Use (2015)

R09-4830 Brown BD, Badilini F. HL7 aECG implementation guide (March 21, 2005).

R17-3318 Samara WA, Shahlaee A, Adam MK, Khan MA, Chiang A, Maguire JI, et al, Quantification of diabetic macular ischemia using optical coherence tomography angiography and its relationship with visual acuity. Ophthalmology. Rochester 124 (2), 235 - 244 (2017)

9.2 UNPUBLISHED REFERENCES

c31489419-01 BI 765128 Investigators's Brochure, Current Version

001-MCS-36-472 Corporate SOP: Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics. Current version

10. APPENDICES

10.1

[redacted]

Table 10.1: 3 Time schedule for optional [redacted] (Part B)

Trial Periods	Visit	Day	Time Point	Optional [redacted]
Treatment	2	1	Just before drug administration	X *
	3	29 (±3)		
	4	57 (±3)	Just before drug administration	X *
Follow-up	5	85 (±7)		
Follow-up	6	113 (±7)	Any time during the visit	X*
EOS	7	141 (±7)	Any time during the visit	X*

* Optional [redacted] samples are collected immediately before drug administration at Visits 2 and 4. At visits 6 and 7, when no drug is administered, the aqueous samples can be collected at any time during the visit.

10.2 BENEFIT-RISK ASSESSMENT IN CONTEXT OF COVID-19 PANDEMIC FOR SUBJECTS PARTICIPATING IN TRIAL 1451-0001 INVESTIGATING BI 765128

STUDY POPULATION

As per the Centers for Disease Control and prevention (CDC), people with serious chronic medical conditions, including diabetes and heart disease, might be at higher risk for severe illness from COVID-19.

BENEFITS AND RISKS CONCLUSIONS AND RECOMMENDATIONS

Currently, there is no evidence that based on the pharmacological mechanism and existing non-clinical data BI 765128 either may affect the immune system or increase the risk of progression of COVID-19 infection. BI 765128 is administered intravitreally using standard aseptic technique.

The low dosage of BI 765128 means the systemic exposure is expected to be very low.

Therefore, no change on the Benefit-Risk assessment of the compound in the context of the COVID-19 pandemic is foreseen.

The current study population is potentially at higher risk of COVID-19 infection due to background or concomitant diseases. Enrollment will start when the local situation allows, and appropriate risk mitigation measures (e.g. use of Personal Protective Equipment) will be implemented in line with local instructions and recommendations

The investigators will take the totality of information related to each single subject and the local COVID-19 situation into consideration when performing the individual benefit-risk assessment on a case-by-case basis. Considering all aspects, the investigator will decide upon each subject's (continued) participation in the trial. BI as the sponsor, where required, will support the investigator in their decision finding. It is acknowledged that the investigator may decide to implement protocol deviations where this protects the safety, wellbeing and/or is in the best interest of the subject.

DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

In situations where an individual subject is unable or unwilling to attend a clinic visit, the investigator must assess the risk-benefit for the individual subject and may decide to perform a visit remotely if this is in the best interest of the subject and if agreed with the sponsor. All COVID-19 related deviations from the original schedule of visits and procedures will be documented and the implications considered for the analysis of the trial data.

No trial specific SARS-CoV-2 testing will be performed. Testing will be performed in line with local standard procedures. In case of a confirmed infection appropriate measures e.g. for monitoring and quarantine will be implemented.

10.3 STATISTICAL APPENDIX

A BLRM with overdose control will be used to guide dose escalation in this study. The BLRM is introduced in Section 7.1, which also specifies the prior for the model. After subjects in each cohort have completed the evaluation period, the prior distribution will be updated through Gibbs sampling procedures with the accumulated DLE data from the evaluation period. Posterior probabilities for the rate of DLEs will be summarized from the BLRM. Selection of the next dose will be based on these probabilities as well as on other safety and laboratory data.

The purpose of this statistical appendix is to present performance metrics (operating characteristics) that illustrate the precision of the design in estimating the MFD (see Section 3.1) under various dose-toxicity relationships through computer simulation. These results are summarized in Table 10.3: 3. In addition, recommendations of the next dose level by the BLRM with overdose control principle are provided under various hypothetical outcome scenarios in early cohorts, to show how it facilitates on-study dose-escalation decisions (see Table 10.3: 1). For simplicity reasons, a cohort size of 3 subjects who are all evaluable is assumed.

Hypothetical data scenarios

Hypothetical data scenarios are shown in Table 10.3: 1. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model and the planned dose groups. For each scenario, the probability of overdose for the current dose, as well as the next potential dose and related probabilities of target dosing and over-dosing are shown (probability of over-dosing: P(OD), probability of target dosing: P(TD).

For example, scenario 1 represents the case that no DLE is observed in 3 subjects at the starting dose of [redacted]. In this case, the next planned dose permitted by the model is 1 mg.

In scenario 6, there is no DLE after the first 2 dose groups, which would allow the trial to continue to the next dose level. If no further DLE occurs in the trial (scenario 13), dose escalation would proceed to the [redacted] dose, with an additional cohort at that dose level at the end, i.e. overall 12 subjects.

Table 10.3: 1 Hypothetical data scenarios

Scenario	[redacted]	# Pat.	# DLE	[redacted]
1	[redacted]	3	0	[redacted]
2	[redacted]	3	1	[redacted]
3	[redacted]	3	2	[redacted]
4	[redacted]	6	1	[redacted]
5	[redacted]	6	2	[redacted]

Scenario	[redacted]	# Pat.	# DLE	[redacted]
6		3	0	
		3	0	
7		3	0	
		3	1	
7b		3	0	
		6	1	
7c		3	0	
		6	2	
8		3	0	
		3	2	
10		6	1	
		3	0	
11		6	1	
		3	1	
11b		6	1	
		6	1	
11c		6	1	
		6	2	
12		6	1	
		3	2	
13		3	0	
		3	0	
		6	0	
14		3	0	
		3	0	
		6	1	
15		3	0	
		3	0	
		6	2	
16		3	0	
		6	1	
		6	0	
17		3	0	
		6	1	
		6	1	
18		3	0	
		6	1	
		6	2	

Scenario	[redacted]	# Pat.	# DLE	[redacted]
19		6	1	
		6	1	
		6	0	
20		6	1	
		6	1	
		6	1	
21		6	1	
		6	1	
		6	2	

*Non of the pre-specified dose levels is fulfilling the EWOC criterion
No higher dose level specified

Operating characteristics

Operating characteristics are a way to assess the long-run behaviour of a model by illustrating the precision of the design in estimating the MFD. Under an assumed true dose-toxicity curve, metrics such as the probability of recommending a dose with true DLE rate in the target interval can be approximated via simulation. Table 10.3: 2 describes 5 assumed true dose-toxicity scenarios which were used to assess the operating characteristics of the model. These scenarios reflect a wide range of possible cases as follows:

- Scenario 1: aligned with prior means
- Scenario 2: high-toxicity scenario
- Scenario 3: low-toxicity scenario
- Scenario 4: very high toxicity scenario
- Scenario 5: low-toxicity followed by high-toxicity

Table 10.3: 2 Assumed true dose-toxicity scenarios

Scenario		[redacted]			
		[redacted]	[redacted]	[redacted]	[redacted]
1: Prior Mean	P(DLE)	0.054	0.073	0.153	0.364
2: High Tox		0.154	0.173	0.243	0.464
3: Low Tox		0.005	0.007	0.053	0.264
4: Very high Tox		0.245	0.353	0.564	0.689
5: Low-High		0.005	0.007	0.243	0.464

The dose level 5 was added for technical reasons, since for simulations at least one dose with assumed true DLE rate in each toxicity interval was required

For each of these scenarios, 1000 trials were simulated. Each cohort consisted of 3 subjects and dose escalation complied with the following rule:

> *Escalate to the maximum dose which satisfies the overdose criterion and is ≤ 500% increase from the current dose.*

The MFD was considered reached if at least 12 subjects have been included in the trial and if at least 6 subjects have been evaluated at a dose level which was the model's recommendation for the next dose. The maximum allowed subject number for each trial was chosen as 18.

It was then assessed how often a dose was declared as MFD with true DLE rate in the targeted or in the overdosing range. Furthermore, the average, minimum and maximum number of subjects per trial and the average number of DLEs per trial are reported. Results are shown in Table 10.3: 3.

Table 10.3: 3 Simulated operating characteristics

Scenario	% of trials declaring a MFD with true DLE rate in		% of stopped trials*	# Subjects	# DLEs
	[redacted]	[redacted] overdosing		Mean (Min-Max)	Mean (Min-Max)
1	94.1	2.0	3.9	10.99 (3 - 27)	1.21 (0 - 6)
2	76.2	0.6	23.2	11.39 (3 - 27)	2.14 (0 - 8)
3	99.0	0.8	0.2	9.32 (9 - 27)	0.33 (0 - 5)
4	15.1	18.1	66.8	10.10 (3 - 27)	3.40 (0 - 7)
5	99.9	0.0	0.1	11.84 (9 - 27)	1.37 (0 - 5)

* The stopped trials include early stopped trials (stopped due to too much toxicity), as well as trials that stopped because the maximum allowed subject number was reached before an MFD was found.

In scenario 1, which reflects the case that the true dose-toxicity is aligned with prior mean, 94.1% of the simulated trials declared a dose as MFD with true DLE rate in the targeted toxicity range. Note that 3.9% of the simulated trials stopped either because there was no MFD determined after 27 subjects had been observed or because of too high toxicity for the planned doses.

In scenario 2, the assumed dose toxicities is high. This results in a higher percentage of early stopped trials (about 23.2 %). In this case, about 76.2 % of the trials would end with an estimated MFD within the targeted range, and 0.6 % in the overdosing range.

In Scenario 3 (low-toxicity scenario), only 99.0 % of the trials declared a dose as MFD with true DLE rate in the targeted range. In 0.8 % of the trials, the estimated MFD was in the overdosing range.

Scenario 4 (very-high-toxicity scenario) shows the worst results, i.e. the highest number of stopped trials (66.8 %) and a low number of trials with estimated MFD (15.1 %) in the target range, as would be expected.

Scenarios 5 (low-high toxicity scenario) shows the best results, i.e. the lowest number of stopped trials (0.1 %) and a highest number of trials with estimated MFD (99.9 %) in the target range.

The mean subject numbers ranged from 9.3 subjects (Scenario 3) to 11.8 subjects (Scenario 5), and the maximum number of subjects was 27.

Overall, by reviewing the metrics presented in Table 10.3: 3, it can be seen that the model is generally conservative due to the overdose control criteria. In all scenarios, except for the very-high-toxicity case (scenario 4) the probabilities of recommending a dose with true DLE rate being at least 25%, P(DLE ≥ 25%), as MFD are much smaller than the probabilities of recommending a dose with true P(DLE) < 25% as MFD.

R version 4.0.2 and Jags version 4.3.0 was used for data scenarios and simulations.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		02 Jun 2021
EudraCT number **EU number**		2020-005425-87
BI Trial number		1451-0001
BI Investigational Medicinal Product(s)		BI 765128
Title of protocol		A First in Human trial to study safety and tolerability of single rising intravitreal doses (o**P**en label, non-randomized, uncontrolled) and in **A**ddition the early biological **R**esponse of mul**T**iple intravitreal doses (double-masked, **R**andom**I**zed, sham-controlle**D**) of BI 765128 in panretinal photocoa**G**ulation (PRP) treated diabetic r**E**tinopathy (DR) patients with diabetic macular ischemia (DMI) – the PARTRIDGE Study
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Abbreviations
Description of change		Nrp1 – Neuropilin 1 was added
Rationale for change		Clarification
Section to be changed		1.4.2.5, 3.1
Description of change		In part A the interval between dosing of subjects was extended.
Rationale for change		Authority feedback
Section to be changed		1.3
Description of change		Correction of the following sentence: The next higher dose will only be administered ~~to the next cohort~~ if the treatment in the preceeding dose cohort was safe and showed acceptable tolerability **(see section 3.1).**
Rationale for change		Clarification
Section to be changed		1.4.2.1
Description of change		The following sentence was deleted: There are no previous trials testing Neuropilin-1 inhibitors in humans.
Rationale for change		Correction
Section to be changed		1.4.2.3
Description of change		Risks related to IVT injection regarding the use of material for intraocular drug delivery was updated.
Rationale for change		Following release of a caution statement by Becton Dickinson (BD), who supply materials for use in

		this trial, a risk-benefit evaluation and associated mitigation steps was performed and incorporated into the trial protocol.
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		3.1, 7.1, 10.3
Description of change		The required number of subjects was corrected from 9 to 12 to the definition when the MFD may be considered reached.
Rationale for change		Correction
Section to be changed		3.3.3
Description of change		Exclusion criteria number 9 (part A) was revised to indicate that subjects enrolled in trial 1436-0001 SRD part may be enrolled into part A of this trial only after five half-lifes since the last trial dose, if the participants were not discontinued from study due to safety reasons, and if no toxicity, adverse events or safety concerns related to the previous participation are present at the time of screening
Rationale for change		Authority feedback
Section to be changed		3.3.4.3
Description of change		The following sentence was added to clarify the re-start of the trial in case one of the stopping rules is triggered: “If the trial stops because one of the stopping rules is triggered, then the trial re-start will only be possible after regulatory authority approval via a substantial amendment.”
Rationale for change		Authority feedback
Section to be changed		Section 3.1; Figure 3.1:2
Description of change		Word “safe” was removed from Figure 3.1:2 to be consistent with the statement on page 40 that Part B will not commence if the highest dose ([redacted]) is not considered safe and tolerable in Part A.

Rationale for change		Clarification
Section to be changed		Section 4.1.1; Table 4.1.1:2 Posology
Description of change		Reference to diluent in Part B was removed.
Rationale for change		Correction
Section to be changed		4.1.2
Description of change		The following sentence was revised as follows: The proposed escalation of the doses to [redacted] and [redacted] per eye is predicted to prolong the time for IVT antibody concentrations above the estimated minimally efficacious concentration, potentially allowing for longer dosing intervals. The starting dose and dose escalation were chosen based on the safety margin to the **highest tested dose level [redacted] mg/eye) that did not result in adverse effects directly attributed to BI 765128**~~no observed adverse effect level (NOAEL~~), in the 13-week IVT toxicology study in cynomolgous monkeys.
Rationale for change		Correction
Section to be changed		4.2.2.3
Description of change		Word "condom" was added in brackets to the following sentence as an acceptable barrier method: WOCBP (for the definition please refer to Section 3.3.2) and men able to father a child must use two medically approved methods of birth control throughout the trial (from Visit 1 until End of Study visit) one barrier method **(condom)**, and one highly effective non-barrier method.
Rationale for change		Clarification
Section to be changed		5.2.1
Description of change		DLE definition was revised to include the following event: Signs of vascular occlusion in a 1st (the main branch) or 2nd degree (the vessel after the first bifurcation of the main branch) retinal vessel, including peripheral retinal hemorrhages in the area supplied by the occluded vessel (hemorrhage of the macula would not be included as this is a symptom of the disease)
Rationale for change		Authority feedback
Section to be changed		5.2.4
Description of change		Option to use local lab for safety lab analysis was added if blood sampling for central lab at the trial site is not possible.
Rationale for change		Clarification
Section to be changed		5.3.2
Description of change		Correction of the following sentence: The samples may be used for further methodological

		investigations e.g. [redacted], to characterize [redacted] response or to address Health authority questions regarding the results/methodology; however, only data related to the analyte, ~~and~~ anti-drug antibodies, **and mechanism of action** will be generated by these additional investigations.
Rationale for change		Clarification
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		5.4
Description of change		The following sentences were added: "If feasible BI 765128 levels in [redacted] samples might be determined" "Additionally, if feasible proteins affected by the drug's mode of action might be determined in serum samples"
Rationale for change		Clarification of additional measurements
Section to be changed		8
Description of change		Wording applicable for Germany was deleted.
Rationale for change		Germany will not participate in the trial.
Section to be changed		8.7
Description of change		"As deemed necessary" was added in brackets after participating investigator to clarify the role of the participating investigator in the SMC meetings.
Rationale for change		Clarification
Section to be changed		10.3
Description of change		The following sentence was corrected: The maximum allowed subject number for each trial was chosen as **18**~~27~~.
Rationale for change		Correction

11.2 GLOBAL AMENDMENT 2

Date of amendment		18 Jan 2022
EudraCT number **EU number**		2020-005425-87
BI Trial number		1451-0001
BI Investigational Medicinal Product(s)		BI 765128
Title of protocol		A First in Human trial to study safety and tolerability of single rising intravitreal doses (o**P**en label, non-randomized, uncontrolled) and in **A**ddition the early biological **R**esponse of mul**T**iple

		intravitreal doses (double-masked, **R**andom**I**zed, sham-controlle**D**) of BI 765128 in panretinal photocoa**G**ulation (PRP) treated diabetic r**E**tinopathy (DR) patients with diabetic macular ischemia (DMI) – the PARTRIDGE Study
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Synopsis, 3.3.2
Description of change		Part A, inclusion criteria # 5: BCVA was revised from ≤65 to 75 letters (20/50 to 20/32) in the study eye. Part B, inclusion criteria #5: BCVA was revised from ≤80 to 85 letters (20/25 to 20/20) in the study eye.
Rationale for change		To include a broader patient population on the study.
Section to be changed		3.3.2
Description of change		Part B, inclusion criteria 6 was revised: "Best-corrected VA in the non-study eye must be equal to or better than best-corrected VA in the studyeye. If both eyes are eligible (per inclusion #5) and have identical best corrected VA, the investigator may select the study eye." was replaced with "**If both eyes are eligible, the investigator may select either eye to be the study eye**."
Rationale for change		Part B of the trial will only start if the highest dose is tolerated in part A. Once BI765128 has proved safe in part A, risks are low for the treated eye.
Section to be changed		Synopsis, 3.3.3
Description of change		Part A: Exclusion criteria#1: restriction of IVT injections for active DME (anti-VEGF, steroids) and macular laser decreased from 6 months to 3 months Exclusion criteria #2: restriction of anti-VEGF IVT injections for active DR decreased from 6 months to 3 months Part B: Exclusion criteria#2: restriction of IVT injections for active DME (anti-VEGF, steroids) and macular laser decreased from 6 months to 3 months Exclusion criteria#3: restriction of anti-VEGF IVT injections for active DR decreased from 6 months to 3 months

Rationale for change		To include a broader patient population participation on the study. Decreasing the restriction of the previous treatments from 6 months to 3 months is not expected to impact the results.

11.3 GLOBAL AMENDMENT 3

Date of amendment		15 Jun 2022
EudraCT number **EU number**		2020-005425-87
BI Trial number		1451-0001
BI Investigational Medicinal Product(s)		BI 765128
Title of protocol		A First in Human trial to study safety and tolerability of single rising intravitreal doses (o**P**en label, non-randomized, uncontrolled) and in **A**ddition the early biological **R**esponse of mul**T**iple intravitreal doses (double-masked, **R**andom**I**zed, sham-controlle**D**) of BI 765128 in panretinal photocoa**G**ulation (PRP) treated diabetic r**E**tinopathy (DR) patients with diabetic macular ischemia (DMI) – the PARTRIDGE Study
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Synopsis; Flow Chart I and II
Description of change		"including weight" included in brackets next to Physical examination
Rationale for change		Clarification in flow chart to indicate that weight is part of Physical examination.
Section to be changed		Synopsis; Flow Chart II, Tables 10.2:1 and 10.1:2
Description of change		Footnote in the Flowchart was revised as follows: See separate flow chart for [redacted], [redacted] sampling (Table 10.1: 2). PK samples during Visits 2, 3, & 4 should be taken **within** 30 min **to 2hrs** before drug administration. Tables: Time Point was revised as follows: ~~Just~~ **Within 2 hrs before** drug administration~~*.~~ Footnote was deleted: ~~* A time window of +/ 15 min for sample drawing is allowed.~~
Rationale for change		To allow broader time window for [redacted] samples before dosing.

Section to be changed		1.2.
Description of change		Data from clinical studies updated
Rationale for change		Update
Section to be changed		1.4.2.2
Description of change		The following sentence was revised as follows: Although no systemic adverse events were observed in the pre-clinical studies, at each time-point, subjects will undergo systemic evaluation **as specified in the flow charts**, including body weight, blood pressure, pulse rate, ECG and laboratory tests.
Rationale for change		Clarification
Section to be changed		1.4.2.5
Description of change		The following sentence was revised as follows: Additionally, a systemic evaluation will be performed at ~~each~~ the timepoint**s specified in the flow charts**, to assess possible systemic reactions.
Rationale for change		Clarification
Section to be changed		3.3, 6.2.1
Description of change		The following sentences were revised: Section 3.3: Subjects who do not fulfil all eligibility criteria for a reason that later resolves and allows eligibility criteria to be met ~~within a 12-week period~~ after the initial screening visit, can be re-screened up to one time. Section 6.2.1: Subjects who do not fulfil all eligibility criteria **and are screen failed** for a reason that later resolves and allows eligibility criteria to be met ~~within a 12-week period after initial screening visit~~, can be rescreened up to one time. For re-screening, subject must be registered in IRT, which will then provide a new subject number, and the subject must sign new Informed Consent Form (ICF). Imaging of retina (SD-OCT, OCTA, fundus photography) does not need to be repeated at the re-screening visit if the corresponding criteria for inclusion of the study eye were met at the initial screening visit and if the images are not older than 28 days at the re-screening visit; otherwise new images have to be performed.
Rationale for change		To remove the time restriction for rescreening of patients and allow patients beyond 12 weeks from date of initial screening to be rescreened once.
Section to be changed		3.3

Description of change		Update of the amounts of planned countries and sites
Rationale for change		Update
Section to be changed		3.3.3
Description of change		Part B: Exclusion criteria#7 removed: ~~Clinically significant disorganisation of retinal inner layer (DRIL) in the study eye~~
Rationale for change		To broaden the subject population
Section to be changed		3.3.3
Decsription of change		Part B: Exclusion criteria 13 revised as follows: Previous participation in this trial or in other trials with IVT injections **administered** within 3 months of screening. Subjects enrolled in the sham arm of the MD part of trial 1436-0001 may be enrolled into Part B of this trial.
Rationale for change		Clarification
Section to be changed		6.2.1
Description of change		Revision as follows: **Applies to the SRD part**: In case of closed dose groups no further rescreening activities for a screened and eligible patient are required within 12 weeks after completed screening visit.
Rationale for change		Clarification to indicate that closed dose groups apply to Part A only.
Section to be changed		7.3.7
Description of change		Revision as follows: A preliminary analysis of [redacted] **and** [redacted] provided as individual values and geometric means of each cohort per dose level may be performed~~, if feasible~~.
Rationale for change		Clarification that in addition to PK parameters also a preliminary analysis of [redacted] may be performed.

11.4 GLOBAL AMENDMENT 4

Date of amendment		16 Mar 2023
EudraCT number **EU number**		2020-005425-87
BI Trial number		1451-0001
BI Investigational Medicinal Product(s)		BI 765128
Title of protocol		A First in Human trial to study safety and tolerability of single rising intravitreal doses (o**P**en label, non-randomized, uncontrolled) and in

		Addition the early biological **R**esponse of mul**T**iple intravitreal doses (double-masked, **R**andom**I**zed, sham-controlle**D**) of BI 765128 in panretinal photocoa**G**ulation (PRP) treated diabetic r**E**tinopathy (DR) patients with diabetic macular ischemia (DMI) – the PARTRIDGE Study
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		7.3.7 Interim Analyses
Description of change		Changing the fast track analysis data snapshot timepoint from V5 (Week 12) to V6 (Week 16) in Part B.
Rationale for change		Update made to ensure alignment with the PoCP criteria for the trial.
Section to be changed		Title page: Clinical Trial Leader
Description of change		Insertion of contact information for [redacted] and removal of contact information for [redacted]
Rationale for change		[redacted] has taken over the Clinical Trial Leader role from [redacted].

APPROVAL / SIGNATURE PAGE

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Title: A First in Human trial to study safety and tolerability of single rising intravitreal doses (oPen label, non-randomized, uncontrolled) and in Addition the early biological Response of mulTiple intravitreal doses (double-masked, RandomIzed, sham-controlleD) of BI 765128 in panretinal photocoaGulation (PRP) treated diabetic rEtinopathy (DR) patients with diabetic macular ischemia (DMI) - the

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	17 Mar 2023 12:07 CET
Author-Trial Statistician		17 Mar 2023 12:24 CET
Approval		20 Mar 2023 13:01 CET
Verification-Paper Signature Completion		20 Mar 2023 13:17 CET

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed