Boehringer Ingelheim

Clinical Trial Protocol

	Document Number:	**c29487972-06**
EudraCT No. **EU Trial No.**	2019-004432-28	
BI Trial No.	1436-0001	
BI Investigational Medicinal Product	BI 764524	
Title	A First-in **H**uman trial to study safety and tolerability of single rising intravitreal d**O**ses (open label, non-randomized, uncontrolled) and in addition the early biological response of multiple intravit**R**eal dosing (single-masked, ra**N**domized, sham-controlled) of **BI** 764524 in panretina**L** photocoagulation (PRP) treated pro**L**iferative diabetic retinopathy (PDR) patients with diabetic macular ischemia (DMI) – the **HORNBILL** Study	
Lay Title	HORNBILL: A study to test different doses of BI 764524 in patients who have had laser treatment for a type of diabetic eye disease called diabetic retinopathy with diabetic macular ischemia	
Clinical Phase	I/IIa	
Trial Clinical Monitor	[redacted] Phone [redacted]	
Co-ordinating Investigator	[redacted] Phone: [redacted] Fax: [redacted]	
Status	Final Protocol	
Version and Date	Version: 6.0	Date: 07 Oct 2022

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Protocol date	16 Jan 2020
Revision date	07 Oct 2022
BI trial number	1436-0001
Title of trial	A First-in **H**uman trial to study safety and tolerability of single rising intravitreal d**O**ses (open label, non-randomized, uncontrolled) and in addition the early biological response of multiple intravit**R**eal dosing (single-masked, ra**N**domized, sham-controlled) of **BI** 764524 in panretina**L** photocoagulation (PRP) treated pro**L**iferative diabetic retinopathy (PDR) patients with diabetic macular ischemia (DMI) – the **HORNBILL** Study
Co-ordinating Investigator	[redacted] Phone: [redacted] Fax: [redacted]
Trial sites	Multi-centre trial
Clinical phase	I/IIa
Trial rationale	Diabetic macular ischemia (DMI) is a chronic complication of diabetic retinopathy (DR), and can potentially lead to visual functional loss. Currently, there are no approved or effective treatments to prevent either onset or progression of DMI in laser-treated PDR patients. As a transition from preclinical investigations to clinical development in this first-in human trial, the maximum feasible dose (MFD) of BI 764524 will be determined and safety, tolerability and early biological response will be investigated in DMI volunteer patients. This trial will include patients affected by DMI with significant visual loss since intravitreal (IVT) injections in patients without the condition would not be considered ethically justifiable.

Trial objectives	The objective of this trial is to determine the maximum feasible dose (MFD) for further development of BI 764524 in patients with pan-retinal coagulation treated proliferative diabetic retinopathy (PDR) patients with diabetic macular ischemia (DMI) based on the primary endpoint occurrence of dose limiting events (DLE) during MFD evaluation period of 7 days (single rising dose (SRD)) or 28 days after last administration (multiple dosing (MD)) and to investigate the safety, tolerability and early biological response after IVT injections of BI 764524.

Trial endpoints	Primary endpoint SRD part: • number of patients with dose limiting events (DLEs) from drug administration till day 8 (7 days after treatment). MD part: • number of patients with drug related adverse events (AEs) from drug administration till end of study (EOS) Secondary endpoints: SRD part: • number of patients with drug related AEs at EOS • number of patients with ocular AEs (eye disorders) at EOS MD part: • change from baseline of the size of the foveal avascular zone (FAZ) in optical coherence tomography angiography (OCTA) in superficial and combined vascular complex at Visit 5 • change from baseline of the size of the FAZ in optical coherence tomography angiography (OCTA) in superficial and combined vascular complex at Visit 7 • change from baseline of BCVA (best corrected visual acuity) at Visit 3 • change from baseline of BCVA at Visit 4 • change from baseline of BCVA at Visit 5 • change from baseline of BCVA at Visit 6 • change from baseline of BCVA at Visit 7 • change from baseline of Central retinal thickness (SD-OCT) at Visit 3 • change from baseline of Central retinal thickness (SD-OCT) at Visit 4 • change from baseline of Central retinal thickness (SD-OCT) at Visit 5 • change from baseline of Central retinal thickness (SD-OCT) at Visit 6 • change from baseline of Central retinal thickness (SD-OCT) at Visit 7 • number of patients with ocular AEs (eye disorders) at EOS
Trial design	This trial will consist of an SRD part followed by an MD part. SRD part will be non-randomized, open-label, and uncontrolled. MD part will be single-masked, randomized and sham-controlled (ratio 2:1).

Number of patients	Approximately 45 patients in total
total entered each treatment	Up to 15 patients in the SRD part (depending on the dose escalation) and 30 patients in the MD part.
Diagnosis	Pan-retinal photocoagulation (PRP) treated proliferative diabetic retinopathy (PDR) in patients with diabetic macular ischemia (DMI)
Main criteria for inclusion	Patients to be included are pan-retinal photo coagulation (PRP) treated proliferative diabetic retinopathy (PDR) patients with diabetic macular ischemia (DMI)
Test product	BI 764524, powder for solution for injection
dose	SRD part: [redacted], [redacted] and [redacted] (single doses) MD part: The highest dose (e.g. [redacted]) (q4w) established as safe and tolerable during the SRD part
mode of admin.	Intravitreal
Comparator product	Not applicable
dose	Not applicable
mode of admin.	Not applicable
Duration of treatment	SRD part: single intravitreal dose MD part: 3 intravitreal doses in 4-weekly intervals (q4w)
Statistical methods	Descriptive statistics will be provided for all endpoints.

FLOW CHART I (SINGLE RISING DOSE PART)

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 lead-ECG(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 Sampling(4)		X	X	X	X	X	X	X
[redacted]		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 patient participation (5)								X

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

([2]) See Section 5.2.5; the ECGs are to be recorded shortly before the PK sampling at the respective time points, see 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]) See separate flow chart for PK and [redacted] sampling (Appendix 10.1).

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

FLOW CHART II (MULTIPLE DOSING PART)

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	29 Week 4	57 Week 8	85 Week 12	113 Week 16	155 Week 22
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					
IVT drug administration/Sham injection		X	X	X			
Pregnancy test([3])	X_S	X_S	X_U	X_U	X_U	X_U	X_U
[redacted]		X	X		X		
PK Sampling([4])		X	X	X	X	X	X
Optional Aqueous sampling([4])		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
Concomitant therapy	X	X	X	X	X	X	X
Completion of patient participation ([5])							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 patient is eligible based on the results from the reading centre, the patient should return to complete the rest of the screening. In case of scheduling difficulty for certain patients, screening can be performed in one visit. If screening is done as one visit, fundus photography should be performed in line with other ophthalmological examinations.

([2]) See Section 5.2.5; the ECGs are to be recorded shortly before the PK sampling at the respective time points: 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]) See separate flow chart for PK, [redacted] and aqueous sampling (Appendix 10.1)

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

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ABBREVIATIONS

[redacted]	[redacted]
ADCC	Antibody-dependent cellular cytotoxicity
AE	Adverse event
AESI	Adverse events of special interest
ALCOA	Attributable, legible, contemporaneous, original and accurate
AUC	Area under the curve
$AUC_{0-\infty}$	Area under the concentration-time curve of the analyte in serum over the time interval from 0 extrapolated to infinity
$\%AUC_{tz-\infty}$	Percentage of $AUC_{0-\infty}$ obtained by extrapolation
AUC_{t1-t2}	Area under the concentration-time curve of the analyte in serum over the time interval t_1 to t_2
AUC_{0-tz}	Area under the concentration-time curve of the analyte in serum over the time interval from 0 to the last quantifiable data point
BA	Bioavailability
BCVA	Best corrected visual acuity
BI	Boehringer Ingelheim
BIPI	Boehringer Ingelheim Pharmaceuticals Inc.
BLRM	Bayesian logistic regression model
BP	Blood pressure
CA	Competent authority
CDC	Copper diethyldithiocabamate
CDISC	Clinical Data Interchange Standards Consortium
CI	Confidence interval
CL/F	Apparent clearance of the analyte in serum after extravascular administration
C_{max}	Maximum measured concentration of the analyte in serum
CTM	Clinical Trial Manager
CRA	Clinical Research Associate
CRC	Central Reading Center
CRF	Case Report Form, paper or electronic (sometimes referred to as ‘eCRF’)
CRO	Contract Research Organisation
CST	Central subfield thickness
CT	Clinical trial
CTCAE	Common Terminology Criteria for Adverse Events
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
DNA	Deoxyribonucleic acid
DR	Diabetic retinopathy
DRIL	Disorganisation of retinal inner layer
ECG	Electrocardiogram
EMA	European Medicines Agency
eCRF	Electronic case report form
eDC	Electronic data capture
EOS	End of study
ETDRS	Early treatment diabetic retinopathy study
EudraCT	European Clinical Trials Database
EWOC	Escalation with overdose control
F	Absolute bioavailability factor
FA	Fluorescein angiography
FAZ	Foveal avascular zone
FSH	Follicle stimulating hormone
GCP	Good Clinical Practice
gMean	Geometric mean
GMP	Good Manufacturing Practice
HCG	Human chorionic gonadotropin
HR	Heart rate
IB	Investigator’s brochure
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IEC	Independent Ethics Committee
IMP	Investigational Medicinal Product
IOP	Intra-ocular pressure
IPD	Important protocol deviation
IQRMP	Integrated Quality and Risk Management Plan
IRB	Institutional Review Board
IRT	Interactive response technology
ISF	Investigator site file
IUD	Intrauterine device
IUS	Intrauterine hormone-releasing system
IV	Intravenous
IVT	Intravitreal

λ_z	Terminal rate constant of the analyte in serum
[redacted]	[redacted]
LPLT	Last patient last treatment
MedDRA	Medical Dictionary for Regulatory Activities
MoA	Mode of Action
MD	Multiple dosing
$MRT_{,ex}$	Mean residence time of the analyte in the body, extravascular
MFD	Maximum feasible dose
NOAEL	No observed adverse effect level
OCT	Optical coherent tomography
OCTA	Optical coherent tomography angiography
OIR	Oxygen induced retinopathy
OPU	Operative unit
PD	Pharmacodynamic(s)
PDR	Proliferative diabetic retinopathy
PE	Polyethylene
PfOS	Powder for reconstitution of an oral solution
PIB	Powder in the bottle
PK	Pharmacokinetic(s)
PKS	Pharmacokinetic set
PP	Polypropylene
PR	Pulse rate
PRP	Panretinal photocoagulation
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)
R	Reference treatment
REP	Residual effect period
RR	Respiratory rate
SAE	Serious adverse event
SCR	Screening
SD-OCT	Spectral domain optical coherence tomography
SMC	Safety monitoring committee
SOP	Standard operating procedure
SRD	Single-rising dose
ss	(at) steady state
SUN	Standardization of Uveitis Nomenclature

SUSAR	Suspected unexpected serious adverse reaction
SVC	Superficial vascular complex
T	Test product or treatment
$t_{\lambda z,start(end)}$	Lower (upper) limit on time for values to be included in the calculation of λ_z
TMF	Trial master file
$t_{1/2}$	Terminal half-life of the analyte in serum
t_{max}	Time from (last) dosing to the maximum measured concentration of the analyte in serum
$t_{max(,N)}$	Time from (last) dosing to the maximum measured concentration of the analyte in serum (after administration of N doses)
TS	Treated set
TSAP	Trial statistical analysis plan
t_z	Time of last measurable concentration of the analyte in serum
ULN	Upper limit of normal
V_z/F	Apparent volume of distribution during the terminal phase after extravascular administration
VA	Visual Acuity
VEGF	Vascular endothelial growth factor
WG	Working group
WOCBP	Women of childbearing potential
YAG	Yttrium aluminum garnet

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

Diabetic retinopathy can cause visual loss in a number of ways. Microvascular changes due to hyperglycemia lead to increases in permeability, 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. The consequent dramatic increase of vascular endothelial growth factor (VEGF) drives the formation of retinal new vessels (proliferative diabetic retinopathy, PDR), that can eventually bleed, with a sudden decrease in vision (vitreous hemorrhage). In both conditions, VEGF plays a fundamental role, and in fact anti-VEGF agents are effective in improving both DME and PDR. In PDR, pan-retinal photocoagulation (PRP) is the current standard of care. PRP aims to destroy the ischemic retina, which is the major source of VEGF, thus it is effective in prevention and / or regression of the formation of new vessels.

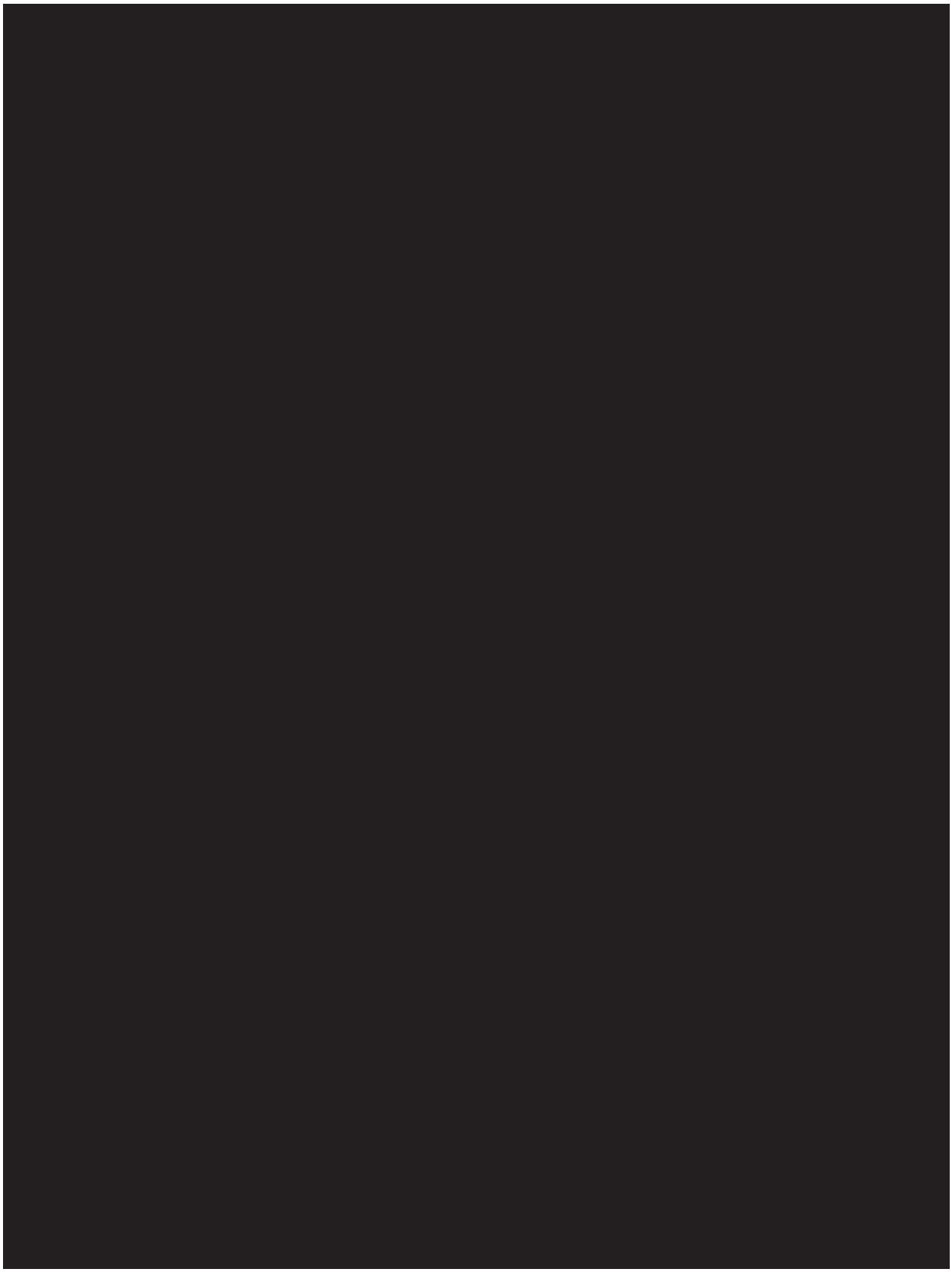
In some patients, however, even in the absence of DME, after successful treatment with PRP with no evidence of active new vessels, the visual acuity continues to decrease.

Some reports have suggested that a possible explanation might be the spreading of ischemia in the central part of the retina, the macula. 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 physiologic foveal avascular zone (FAZ). In patients with diabetic retinopathy, FA might show an abnormal enlargement of the FAZ, which is the most common definition of DMI. Recently, optical coherent 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 is able to measure the area of the FAZ. Moreover, it was found that the FAZ measured by FA corresponds well with the superficial retinal plexus recorded by OCTA (R17-3317). For these reasons OCTA is likely to become the gold standard in the diagnosis and monitoring of DMI.

There is a large list of 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



In the retina, [redacted] is secreted by retinal ganglion cells. In the body, [redacted] is secreted [redacted]

Data from clinical studies

Twelve patients have been treated in the SRD part intravitreally with BI 764524 at the time of finalization of CTP version 3. No DLEs, drug-related SAEs or Drug-related AEs were reported.

For a more detailed description of the BI 764524, please refer to the current Investigator's Brochure (IB, C27076166-01).

1.2.1 Residual Effect Period

For BI 764524 the residual effect period (REP) after IVT administration is not known.

1.3 RATIONALE FOR PERFORMING THE TRIAL

Diabetic macular Ischemia (DMI) is a chronic complication of diabetic retinopathy (DR) and can potentially lead to visual functional loss. Currently, there are no approved or effective treatments to prevent either onset or progression of DMI in laser-treated PDR patients.

As a transition from preclinical investigations to clinical development in this first-in human trial, safety, tolerability and early biological response of BI 764524 will be assessed in DMI volunteer patients

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

This trial will consist of a single rising dose (SRD) part and a multiple dosing (MD) part.

In the SRD part of the trial, 3 rising doses (at least 3 evaluable patients per dose cohort) are planned to be intravitreally administered. Within each dose cohort, all patients will receive the same BI 764524 dose. The next higher dose will only be administered, if the treatment in the preceding dose cohort was safe and showed acceptable tolerability.

In the MD part, patients will be randomized to receive either active treatment or sham injection: 20 patients on active treatment and 10 patients on sham injection over a 22-week period. After an initial active treatment period of 12 weeks (3 injections/sham injections in 4 weekly intervals) patients will be followed up for an additional 10 weeks without further injections to study the treatment effect. This might also help to guide injection frequency intervals in later studies.

The MD part of the trial will provide information about the early biological response of BI 764524 by comparing the treated groups to the sham arm.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

DMI is a progressive disease and patients will 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 764524 can improve retinal vascularization, because of the long duration of the pathology of DMI, long-term benefit for the patients entered in this trial is unlikely. Their participation in this trial, however, is of major importance to the development of BI 764524 to determine a safe dose selection for further clinical trials in this pre-selected patient population.

Because this is the First-in-human trial with BI 764524, special attention will be applied to ensure the highest level of safety for patients selecting the starting dose, the dose escalation steps and the highest dose applied (see Section 4.1.2).

1.4.2 Risks

BI 764524 has not previously been tested in humans, but based on the pre-clinical toxicology studies, no specific adverse events are expected. Patients in this trial are exposed to risks of trial procedures and risks related to ophthalmic and systemic exposure to the trial medication. Similar to other intravitreal biologic therapies, there is a risk of ocular inflammation, however, this is usually mild and reversible. Patients will be monitored for ocular inflammation and treated if deemed appropriate by the investigator. Because of the low dosage used in intravitreal BI 764524, the systemic exposure is expected to be very low and hence unlikely to have significant effect as with intravitreal anti-VEGF therapies.
In a subset of patients, an optional sampling of the aqueous humor will be performed at baseline and at visits 4, 6 and 7 in the MD part. This is known as an ‘anterior chamber tap’ and requires insertion of a 30 gauge needle into the anterior chamber of the eye under topical anesthesia to remove a small amount (0.1ml) of aqueous fluid. An assay will measure the quantity of [redacted] in the aqueous and the results will improve our understanding of the ocular PK/PD of BI 764524.

Table 1.4.2: 1 Overview of 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 764524		
Intraocular inflammation	IVT administration of BI 764524 in cynomolgus monkeys showed signs of intraocular inflammation (See IB chapter 5.3) in some animals. These findings had no impact on ophthalmic function (i.e. ERG) and was not associated with any histopathological changes and resolved during the recovery phase.	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	No ADA response was observed in the 13-week IVT toxicity study. However, because this trial is the FIH application of BI 764524, potential immunogenic response can occur	ADA in serum will be evaluated at day 1 and 99 in SRD, and at day 1 and 85 in MD
Drug-induced liver injury (DILI)	This trial is FIH application of BI 764524, 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 SRD)
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 (<0.1%, including endophthalmitis, traumatic cataract, and increased intraocular pressure). Because the procedure of intravitreal injection of BI 764524 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 patient 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

1.4.2.1 Available data from pre-clinical toxicity studies

1.4.2.1.1 IVT administration of BI 764524

[redacted]

1.4.2.1.2 Immunogenic response in pre-clinical studies

[redacted]

1.4.2.2 Risks related to intravitreal injection

Intravitreal injections may have potentially serious adverse events, but these are considered rare: clinical trials assessing efficacy and safety of EYLEA® intravitreal injections showed serious adverse reactions related to the injection procedure in <0.1%, including endophthalmitis, traumatic cataract, and increased intraocular pressure (https://www.accessdata.fda.gov/drugsatfda_docs/label/2011/125387lbl.pdf). Because the procedure of intravitreal injection of BI 764524 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 (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 suggest 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 764524**.**

1.4.2.3 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 patient will not exceed appr. 500 mL. No health-related risk is expected from this blood withdrawal.

1.4.2.4 Planned measures for monitoring the risks

Patients will be evaluated with functional, imaging and systemic tests to identify any possible adverse event. Specifically, any signs of intraocular inflammation will be assessed by slitlamp examination of anterior chamber, vitreous and posterior segment of the eye, to identify occurrence of flare or cells in the anterior chamber, deposits of material in the corneal endothelium, deposits on the anterior capsule of the crystalline lens, any signs of vitreous haze, vitreous cells, vitreous snowbanks/snowballs, signs of intraretinal edema or retinal thickening, signs of perivascular inflammation e.g. vessel walls sheathing, signs of incipient retinitis or intraretinal haemorrhages.

Spectral domain optical coherence tomography (SD-OCT) will be used to evaluate any possible occurrence of intraretinal cystic edema or perivascular reaction. The same imaging modality will be used to evaluate 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).

Additionally, a systemic evaluation will be performed at the time-points specified in the flow charts, to assess any possible systemic reaction. This will include body weight, blood pressure, heart rate with Electrocardiogram (ECG), full safety lab. The required assessments will be adapted according to the pre-clinical trial results. All these evaluations will have to be reported immediately for evaluating any possible safety issue related to the drug or to inflammatory response.

In the trial design a sentinel approach will be used in the SRD part, according to EMA and ICH guidelines (EMA/CHMP/SWP/28367/07 Rev.1; EMA/CHMP/ICH/731268/1998): for each cohort the first patient will be dosed and monitored to exclude acute AEs, before dosing the other patients of the same cohort (see Section 3.1). Moreover, the duration of the observation will reflect the expected human pharmacokinetics (PK) of BI 764524, with a follow-up for all patients 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 and decide on the next dose level and the next cohort size, or the appropriacy of further enrolment (see section 8.7).

1.4.2.5 Drug induced liver injury

Although rare, a 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 alterations in selected liver laboratory parameters to ensure patients´ safety (see also Section 5.2.7.1.4, AEs of special interest).

1.4.3 Discussion

Considering the data available from previous trials evaluating the same mode of action (MoA), and data from pre-clinical studies on BI 764524, in this trial ophthalmic and systemic examinations are planned in all the visits.

Blood tests and physical examination 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 examination will focus on the risks related to the procedure (e.g. endophthalmitis and retinal detachment), 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 764524 based on pre-clinical evaluations, it is considered acceptable to expose the patients 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 maximum feasible dose (MFD) for further development of BI 764524 in patients with pan retinal coagulation treated proliferative diabetic retinopathy (PDR) patients with diabetic macular ischemia(DMI) based on the primary endpoint occurrence of dose limiting events (DLE) during MFD evaluation period of 7 days (SRD) or 28 days after last administration (MD) and to investigate the safety, tolerability and early biological response after multiple IVT injections of BI 764524.

2.1.2 Primary endpoint

SRD part:

- number of patients with dose limiting events (DLEs) from drug administration till day 8 (7 days after treatment)

MD part:

- number of patients with drug related adverse events (AEs) from drug administration till end of study (EOS)

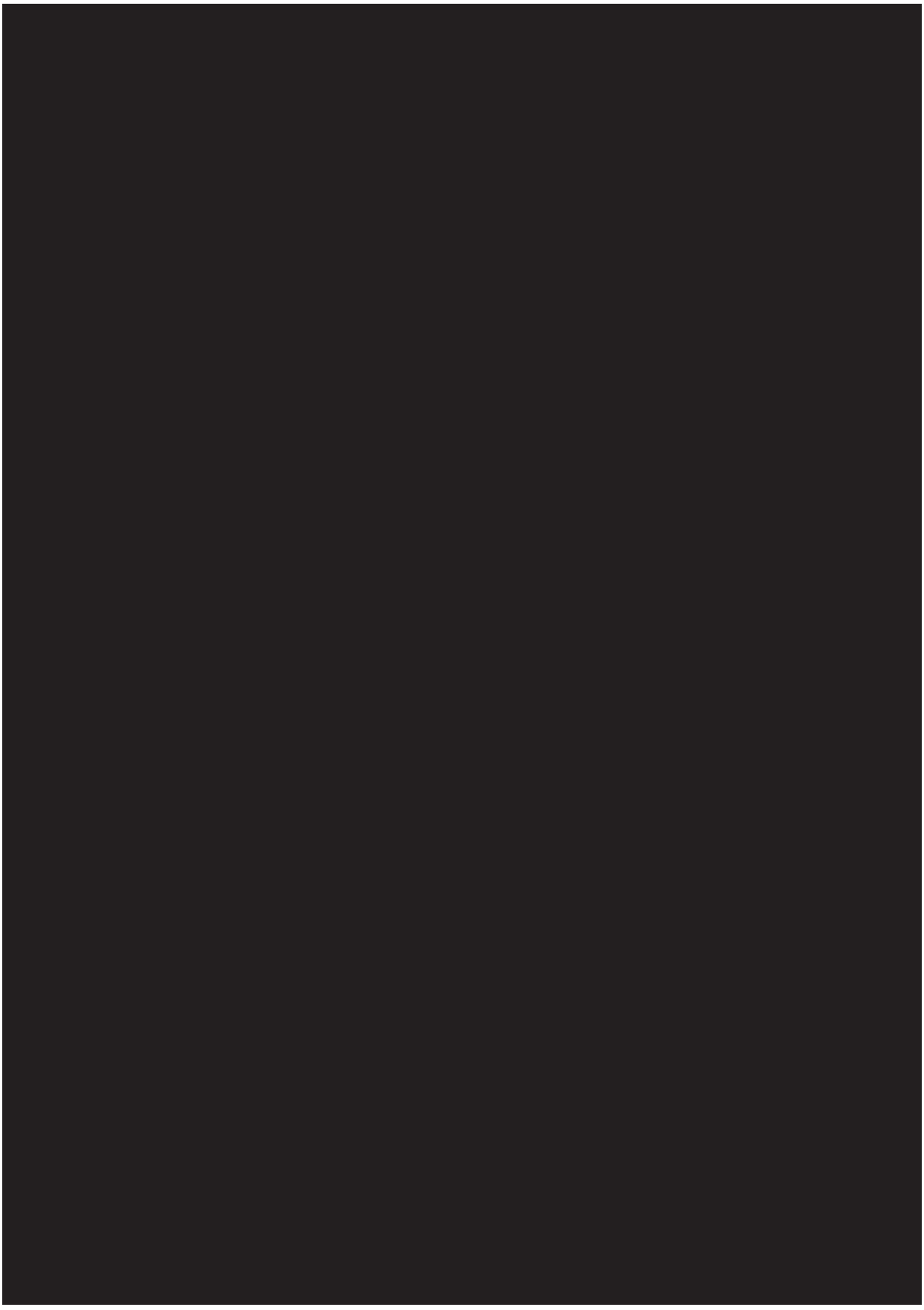
2.1.3 Secondary endpoint

SRD part:

- number of patients with drug related AEs at EOS
- number of patients with ocular AEs (eye disorders) at EOS

MD part:

- change from baseline of the size of the FAZ in optical coherence tomography angiography (OCTA) in superficial and combined vascular complex at Visit 5
- change from baseline of the size of the FAZ in optical coherence tomography angiography (OCTA) in superficial and combined vascular complex at Visit 7
- change from baseline of BCVA at Visit 3
- change from baseline of BCVA at Visit 4
- change from baseline of BCVA at Visit 5
- change from baseline of BCVA at Visit 6
- change from baseline of BCVA at Visit 7
- change from baseline of Central retinal thickness (SD-OCT) at Visit 3
- change from baseline of Central retinal thickness (SD-OCT) at Visit 4
- change from baseline of Central retinal thickness (SD-OCT) at Visit 5
- change from baseline of Central retinal thickness (SD-OCT) at Visit 6
- change from baseline of Central retinal thickness (SD-OCT) at Visit 7
- number of patients with ocular AEs (eye disorders) at EOS



3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This trial will consist of an SRD part followed by an MD part. SRD part will be non-randomized, open-label, and uncontrolled. MD part will be single-masked, randomized and sham-controlled.

SRD part:

In the SRD part, the starting dose is [redacted]. The other provisional dose level is [redacted], and the maximum planned dose is [redacted]. For each cohort, a single patient will be dosed on day 1, and the dosing investigator, coordinating investigator and 2 representatives of the sponsor who are involved in the trial will carefully evaluate all available systemic (i.e. physical examinations, safety lab parameters, ECG and AEs) and ophthalmologic (i.e. as defined in Section 5.2.1) safety data until day 4. If this patient neither has experienced an ophthalmologic nor a systemic serious adverse event, the remaining 2 patients will be dosed. Written minutes of this assessment are being distributed to all investigators participating in this trial.

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

A Safety Monitoring Committee (SMC, see Section 8.7) will decide on the next dose level to be investigated and on the size of the next cohort based on occurrence of DLEs and on additional information (systemic PK and patient profiles). Systemic PK data from preceding cohorts (not from the ongoing cohort) will be available for evaluation. First SMC meeting will take decision based on safety data only. Refer to figure 3.1:1 (SRD) and figure 3.1:2 (MD) for a schematic representation of the dose escalation.

A Bayesian logistic regression model (BLRM), based on a weekly 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 patients 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 patient), 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 patients of a previously untested dose level, subsequent enrolment to that cohort will be stopped.

The maximum feasible dose (MFD) is considered as reached if at least 6 patients have been evaluated at a dose level which is the model's recommendation for the next dose cohort. Note the MFD will likely be the highest feasible dose, [redacted], rather than the highest tolerable dose in strict sense. The MD part of the study would only start if the highest dose ([redacted]) is tolerated.

- After the DLE period (7 days after drug administration) is over for the last patient in the SRD part, all available trial data will be analyzed and a decision is made whether to proceed to the MD part or not. Before starting the MD part, regulatory authorities and institutional review boards (IRBs) / independent ethics committees (IECs) will be informed of the internal results of the SRD part.

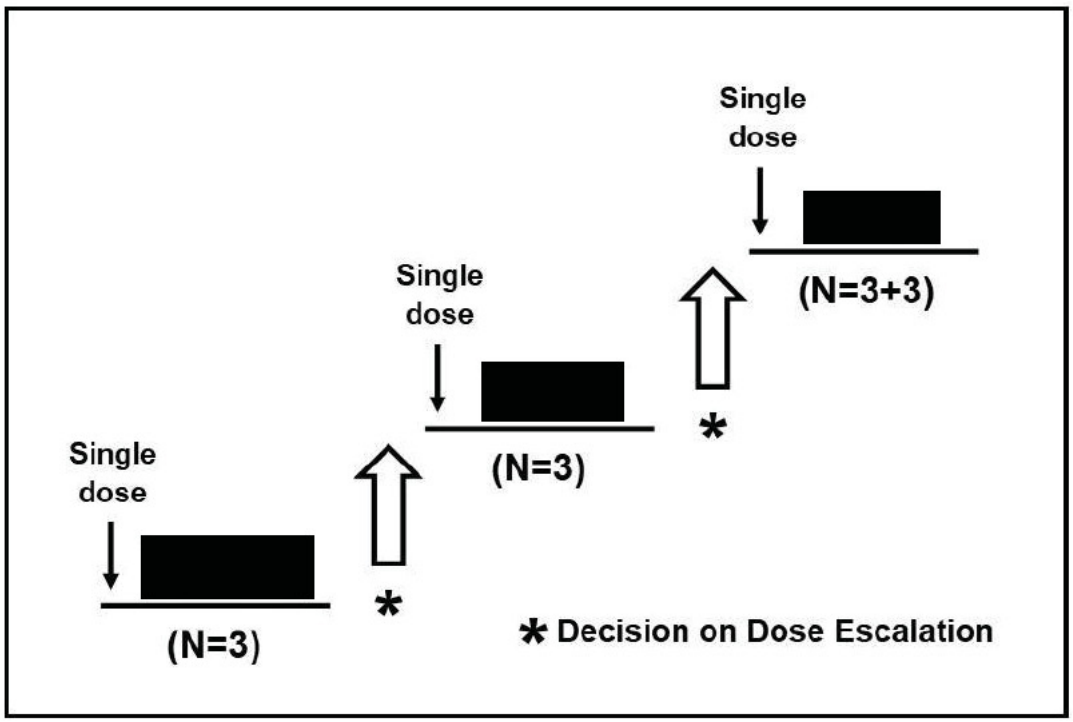


Figure 3.1: 1 Schematic representation of the dose escalation process in the SRD part of the trial

MD part:

The MD part will consist of one dose cohort (N=20 on dose + 10 sham injection). The highest dose [redacted] if established as safe and tolerable during the SRD part will be used in the MD part after the SRD part has been completed. Patients that had received a dose in the SRD part of the trial will not be included. Patients will be randomized to receive either active treatment or sham injection.

In the MD cohort, patients will receive three consecutive doses/sham injection over a 3-month period (dosing every 4 weeks). The SMC will meet regularly to review the safety data.

In all patients included in the MD part of the trial, safety and early biological response will be studied up to 98 days after the last injection.

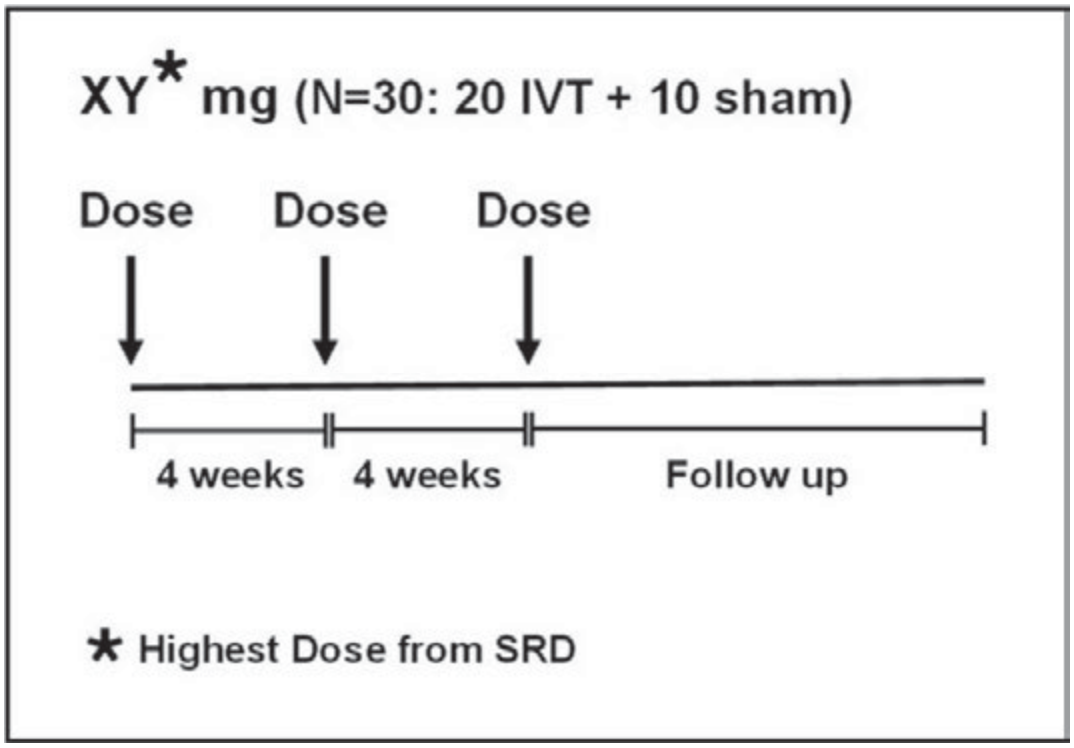


Figure 3.1: 2 Schematic representation of the dosing in the MD part of the trial

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

This trial is designed to confirm that the MFD can be used for further testing in phase IIb trials. The trial consists of separate SRD and MD parts. The SRD dose escalation part is included and was designed with the goal to minimize the number of patients exposed to sub-therapeutic doses while on the other hand preserving safety and rapid dose finding. This part of the trial will be done in patients with DMI because IVT injections in healthy volunteers would not be considered appropriate. Whilst the drug may not benefit the participant directly during the trial, DMI is a chronic and bilateral disease. Therefore, if this trial leads to the approval of a treatment for DMI, the participant's other eye as well as the eye treated in the study may benefit from the treatment in the future. The worse seeing eye of the participant will be treated. As mentioned previously, risks are low but if the eye under trial treatment comes to harm, the impact on the patient will be less as the participants' visual function is driven by the better seeing eye. 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 patients 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].

One MD cohort (3 injections in 4-weekly intervals) will be included after the SRD part. Patients will be randomized either to active treatment group or to 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. These data will further support the definition of the injection frequency and intervals in later studies.

3.3 SELECTION OF TRIAL POPULATION

This trial will recruit approximately 45 patients in total; up to 15 patients in the SRD part (depending on the dose escalation) and up to 30 patients in the MD part. In the MD part, patients will be randomized to receive either IVT injection or sham injection.

Screening of patients 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 patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this trial.

A log of all patients 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 investigational drug or not.

Patients who do not fulfil all eligibility criteria for a reason that later resolves and allows eligibility criteria to be met after the initial screening visit, can be re-screened up to one time. Please refer to Section 6.2.1 for further details.

If a patient 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 3-5 countries and at approximately 20 sites.

3.3.1 Main diagnosis for trial entry

Patients to be included are pan-retinal photo coagulation (PRP) treated proliferative diabetic retinopathy (PDR) patients with diabetic macular ischemia (DMI)

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

Patients will only be included in the trial if they meet the following criteria:

SRD part

1. Pan-retinal photo coagulation treated PDR patients with either no or inactive retinal neovascularization per investigator judgement in the study eye
2. Male or female patients of age ≥ 18 years
3. 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
4. HbA1c of ≤ 12.0%
5. Best-corrected Visual acuity (VA) in the non-study eye better or equal to the best-corrected VA in the study-eye. If both eyes are eligible and have identical VA the investigator may select the study eye.
6. Best-corrected VA ≤55 letters (20/80) or worse for SRD
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 methods 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 and in Section 4.2.2.3
8. Signed and dated written informed consent in accordance with ICH Harmonized Guideline for Good Clinical Practice (ICH GCP) 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 menorrhea, a single FSH measurement is sufficient.

MD part

1. Pan-retinal photo coagulation treated PDR patients with either no or inactive retinal neovascularization per investigator judgement in the study eye
2. Male or female patients of age ≥ 18 years
3. Presence of significant DMI: large foveal avascular zone defined as those with ≥0.5mm^2 area in superficial vascular complex (SVC) present on optical coherence tomography angiography. If FAZ is <0.5mm^2 then enlarged peri-foveal inter-capillary space in at least 1 quadrant will be sufficient.
4. HbA1c of ≤ 12.0%
5. If both eyes are eligible, the investigator may select either eye to be the study eye.
6. Best-corrected VA ≤ 85 letters (20/20) or worse for MD
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 methods 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 and local legislation prior to admission to the trial
9. Signed and dated written informed consent for aqueous sampling (optional)

[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 menorrhea, a single FSH measurement is sufficient.

3.3.3 Exclusion criteria

Patients will not be allowed to participate, if any of the following general criteria apply:

SRD part

1. Patients receiving IVT injections for active DME (anti-VEGF, steroids) and macular laser in the study eye in the previous 3 months prior to enrolment
2. Patients receiving anti-VEGF IVT injections for active PDR in the study eye in the previous 3 months prior to enrolment
3. Current or planned use of medications known to be toxic to the retina, lens or optic nerve (e.g. desferoximine, chloroquine/hydrochloroquine, chlorpromazine, phenothiazines, tamoxifen, nicotinic acid, and ethambutol)
4. Additional eye disease in the study eye that could compromise best corrected VA (BCVA) with visual field loss, uncontrolled glaucoma (IOP>24), age related macular degeneration, 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
5. Any intraocular surgery in the study eye within 3 months prior to screening
6. Aphakia or total absence of the posterior capsule. Yttrium aluminium garnet (YAG) laser capsulotomy in the study eye if performed less than 3 months prior to enrolment
7. Patients 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 patient an unreliable trial participant)
8. Previous participation in this trial or in other trials with IVT injections administered within 3 months.
9. 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 patient at risk because of participation in the study
    b. Influence the results of the study
    c. Cause concern regarding the patient’s ability to participate in the study
10. Known hypersensitivity to any of the ingredients used in the investigational medicinal product (IMP) formulation, or any of the medications used
11. Active intraocular inflammation in the study eye
12. Active infectious conjunctivitis in either eye

13. 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. Patients with malignancy for which the patient has undergone resection, radiation or chemotherapy within past 5 years. Patients with treated basal cell carcinoma or fully cured squamous cell carcinoma are allowed.

MD part

1. DME, defined as a CST ≥305µm for men and ≥290 µm women measured with Optovue OCT in the study eye
2. Patients receiving IVT injections for active DME (anti-VEGF, steroids) and macular laser in the study eye in the previous 3 months prior to enrolment
3. Patients receiving anti-VEGF IVT injections for active PDR in the study eye in the previous 3 months prior to enrolment
4. Heavily lasered macula in the study eye per investigator's judgement
5. History of vitrectomy in the study eye
6. Epiretinal membrane with extended foveal contour distortion in the study eye per investigator's judgement
7. Current or planned use of medications known to be toxic to the retina, lens or optic nerve (e.g. desferoximine, chloroquine/hydrochloroquine, chlorpromazine, phenothiazines, tamoxifen, nicotinic acid, and ethambutol)
8. Additional eye disease in the study eye that could compromise best corrected VA (BCVA) with visual field loss, uncontrolled glaucoma (IOP>24), age related macular degeneration 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
9. Any intraocular surgery in the study eye within 3 months prior to screening
10. Aphakia or total absence of the posterior capsule. Yttrium aluminium garnet (YAG) laser capsulotomy in the study eye if performed less than 3 months prior to enrolment
11. Patients 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 patient an unreliable trial participant)
12. Previous participation in this trial or in other trials with IVT injections within 3 months
13. 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 patient at risk because of participation in the study
    b. Influence the results of the study
    c. Cause concern regarding the patient's ability to participate in the study
14. Known hypersensitivity to any of the ingredients used in the IMP formulation, or any of the medications used
15. Active intraocular inflammation in the study eye
16. Active infectious conjunctivitis in either eye

17. 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. Patients with malignancy for which the patient has undergone resection, radiation or chemotherapy within past 5 years. Patients with treated basal cell carcinoma or fully cured squamous cell carcinoma are allowed.

For study restrictions, refer to Section 4.2.2.

3.3.4 Withdrawal of patients from treatment or assessments

Patients 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.

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

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

The decision to withdraw from trial treatment or from the whole trial as well as the reason must be documented in the patient files and Case Report Form (CRF).

3.3.4.1 Withdrawal from trial treatment

An individual patient will be withdrawn from trial treatment if:

1. The patient wants to withdraw from trial treatment, without the need to justify the decision
2. The patient 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 patient needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
4. The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events [AEs], other diseases or pregnancy)
5. An AE or clinically significant laboratory change or abnormality occurs that the investigator judge to warranting discontinuation of treatment.

Even if the trial treatment is discontinued (MD part), the patient remains in the trial and, given his/her agreement, will undergo the procedures 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

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

If a patient wants to withdraw consent, the investigator should be involved in the discussion with the patient 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 any of the following reasons:

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk assessment that could significantly affect the continuation of the trial
3. Deviation from GCP, the CTP, or the contract impairing the appropriate conduct of the trial.

For the following scenario further enrolment and entering into the trial 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 patients (regardless of the system organ class) confirmed by both the investigator and sponsor as having a reasonable causal relationship to the IMP administration.

The investigator / 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 patients

SRD part:

Patients withdrawn before visit 4 for another reason than DLE or patients 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 patients will be replaced if not decided otherwise by the SMC. Patients who come off study due to a DLE will not be replaced.

MD part:

If some patients 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 patients will be replaced.

A replacement patient will be assigned a unique trial patient number and will be assigned to the same treatment as the patient 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 764524

Substance:	BI 764524
Pharmaceutical form:	[redacted] for injection
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	[redacted]
Posology:	SRD part: 1 injection MD part: 3 injections, each separated by 4 weeks
Mode of administration:	Intravitreal

Table 4.1.1: 2 Diluent

Substance:	Solvent for dilution of BI 764524 solution for injection [redacted]
Pharmaceutical form:	Solvent
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	n/a
Posology:	SRD part: 1 injection
Mode of administration:	Intravitreal

4.1.2 Selection of doses in the trial and dose modification

The measurement of the avascular area in the mouse model of oxygen-induced retinopathy is an animal surrogate to evaluate the effect of Sema3A inhibition on revascularization of an ischemic retinal area supporting the therapeutic benefit in DMI patients. In an in-house study using such a model (n00262705) [redacted] BI 764524 administered intravitreally into the mouse eye resulted in a reduction of the avascular area over a period of 5 days.

A rabbit IVT PK study was performed with [redacted] BI 764524 (n00270338-01) and the rabbit vitreous half-life of 4 days is in good agreement with that previously reported for other Boehringer Ingelheim (BI) [redacted] Furthermore, the [redacted] in the rabbit vitreous was completely bound after IVT injection of BI 764524 over the whole study period of 4 weeks and no free [redacted] was present indicating that its activity would be blocked as long as the [redacted].

Human dose prediction is based on the fact that the PK of BI 764524 is similar to [redacted] in the rabbit and is thus expected to be similar to [redacted] also in humans. An IVT half-life of [redacted] days has been described for [redacted] (R18-2968). The minimum effective concentration is estimated as the upper range (about 1 nM) of the described [redacted] concentration in the vitreous for patients with DME and PDR (R17-3888, R17-3904).

Using these values, the proposed starting dose of [redacted] is predicted to maintain the minimal efficacious vitreal concentration of 1 nM for 93 days. Doses lower than [redacted] are also expected to induce PD effects in the eye. However, the duration of the effect would be shorter and might not be long enough to justify a potential sufficiently long benefit to the patients.

The proposed escalation of the doses to [redacted], and [redacted] per eye is predicted to prolong the time for [redacted] concentrations above the estimated minimally efficacious concentration to 103 days and 116 days respectively. The final dose range was chosen based on the safety margin to the no observed adverse effect level (NOAEL), of the 13-week IVT study in cynomolgus monkeys. The [redacted] dose is expected to last only 9 days longer in the vitreous than the [redacted] dose and requires an injection volume of [redacted] ml. Therefore, a decision was made to remove the [redacted] dose from the trial.

Table 4.1.2: 1 Provisional dose levels for escalation

Dose level	Proposed dose	Relative increment from previous dose
1	[redacted]	Starting dose
2	[redacted]	100%
3	[redacted]	150%

4.1.3 Method of assigning patients to treatment groups

After the assessment of all in- and exclusion criteria, patients will be enrolled into the SRD and MD part. Recruitment in the trial will start with the lowest dose group of the SRD part. The MD part will recruit patients only after the SRD part has been completed and safety of the doses has been established.

In the SRD part, 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, the clinical course for each patient in the current dose cohort 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 the SRD part will be done successively for the dose groups, i.e. if the required number of patients 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 patients for the dose groups will neither be influenced by the trial personnel nor by any characteristics of the patients, but only by temporal availability. Patients from the SRD part are not allowed to participate in the MD part.

The highest dose ([redacted]) if established as safe and tolerable during the SRD part will be used in the MD part after the SRD part has been completed. In the MD part patients will be randomized to receive either active treatment or sham injection according to a randomization plan at visit 2 via Interactive Response Technology (IRT). 20 patients on treatment and 10 on sham injection.

The randomization procedure is described in Section 7.6.

4.1.4 Drug assignment and administration of doses for each patient

BI 764524 will be administered intravitreally. "BI 764524 [redacted] for injection [redacted]" and "Solvent for dilution of BI 764524 Solution for Injection" will be provided by BI. A site pharmacist (qualified person) will prepare the ready to use drug product according to the "Instructions to Pharmacist". 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 SRD part

Dose group (mg)	Visit 2 Day 1
[redacted]	X
[redacted]	X
[redacted]	X

To determine the dose regimen for the next cohort, the available toxicity information (including DLEs and AEs that are not DLEs), PK, PD, 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 MD part

Dose group (mg)	Visit 2 Day 1	Visit 3 Day 29	Visit 4 Day 57	Visit 5 Day 85	Visit 6 Day 113
2.5	X	X	X		

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) are recommended.

The MD part is designed single-masked and personnel of the trial site are masked. Therefore, in the MD part 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 764524, patients will be monitored according to standard practice and at least for 1 hour. 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

The SRD part of the trial is open label. The MD part is designed single-masked. The treatments administered (active or sham injection) will be masked to patients and to the dedicated personnel of the trial site. For the MD part, an unmasked pharmacist (qualified

person) will prepare the active IVT injection and an unmasked injector with no other involvement in the trial will administer active/sham injections.

This single–masked design is considered acceptable because the potential bias in this type of study seems to be low and according to study procedures it is assured that the investigator's knowledge of the next treatment does not influence the decision to enter a patient.

At the sponsor site, all trial data will be handled open label. This means that trial functions of the sponsor are unmasked (including clinical monitor, data manager, statistician, bioanalyst, pharmacokineticist, pharmacometrician, drug metabolism scientist).

Within the central ECG lab, readers involved with interval measurements will be masked with respect to treatment, visit and demographic information collected.

If an interim safety analysis of ECG data is required, a part of the staff of the central ECG lab may be unmasked.

4.1.6.2 Unmasking and breaking the code

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

4.1.7 Packaging, labelling, and re-supply

The investigational products will be provided by BI or a designated Contract Research Organization (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 Interactive Response Technology (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 with min-max recordings must be maintained for documentation.

If the storage conditions are found to be outside the specified range, the Clinical Trial Manager (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 from 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 (CA)
- 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 licence 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 and/or pharmacist (qualified person) and/or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use for each patient, 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 assigned to the investigational product and trial patients. The pharmacist (qualified person) / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the CTP and reconcile all investigational products received from the sponsor. At the time of return to the sponsor and/or appointed CRO, the investigator or designee must verify 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 on 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. desferoximine, 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 participant or partner of a trial participant) must use a condom (regardless of vasectomy) if their sexual partner is a WOCBP.

WOCBP (trial participant or partner of a trial participant) 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

Patients must abstain from male-female sex if this is defined as being in line with the preferred and usual lifestyle of the patient. 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.

Patients 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 CRF 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, OCT-A) 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. OCT-A 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 images will be sent to an independent CRC for evaluation. A detailed manual for OCT 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 starting at a test distance of 4 meters. The BCVA score is the number of letters read correctly by the patient. The assessment will be performed by a trained person under specified conditions regarding examination room and equipment.

[redacted]

[redacted]

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 for Anterior Chamber Cells (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, skin and measurement of height and body weight.

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, slit lamp examination and IOPs will be obtained from both eyes by a qualified person according to the imaging manual. 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 Flow Chart I and Flow Chart II, 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 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. Patients do not have to be fasted for the blood sampling for the safety laboratory.

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. 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 AEs (please refer to Section 5.2.6).

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 electronic data capture (EDC) system. The amount of blood taken from the patient 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 laboratory at the trial site is not possible, safety laboratory analyses can be performed at a local laboratory. The results of the laboratory 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 laboratory parameters, 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 and at visit 2 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 • Hemoglobin • 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

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 patients are at complete rest.

All ECGs will be recorded for a 10 sec duration after patients 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 patient 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 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) EG standard findings list as specified in the data transmission agreement.

For masking arrangements see Section 4.1.5. ECG interval measurements from a particular patient 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 patient 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 adverse events

5.2.7.1.1 Adverse event

An adverse event (AE) is defined as any untoward medical occurrence in a patient or clinical investigation patient 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 CRF 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 pre-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
- Requires 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 upon appropriate medical judgment 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 further 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, an electronic data capture system which allows the entry of trial data at the trial site.

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 trial medication 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:

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

These lab findings constitute a hepatic injury alert and the patients 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 that 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.

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.

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 judgment 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: all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
  the investigator does not need to actively monitor the patient 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 5.2.7.1.1), 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 reporting process 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 patient'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 patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant 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 participant 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 Trials (Part B).

The ISF will contain the Pregnancy Monitoring Form for Clinical Trials (Part A and Part 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 Trials 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.

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

For the assessment of pharmacokinetics, blood samples will be collected at the time points indicated in the Flow Chart. The actual sampling times will be recorded in a CRF and used for determination of pharmacokinetic parameters. Planned time points for systemic pharmacokinetic samples are listed in Appendix 10.1.

5.3.2 Methods of sample collection

5.3.2.1 Blood sampling for pharmacokinetic analysis

For quantification of BI 764524 serum concentrations, approximately 3.0 mL of blood will be taken from a forearm vein into a serum collection tube at the time-points listed in Appendix 10.1.

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

Samples will be stored in a freezer set at the analytical laboratory until the finalization of the clinical trial report (CTR). Samples may be used for further investigations (e.g. for stability

testing), however, only data related to the analyte and mechanism of action will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years after the final study report has been signed.

5.3.4 Pharmacokinetic - pharmacodynamic relationship

No formal analysis of a pharmacokinetic (PK) /pharmacodynamics (PD) relationship is planned.

In order to characterize BI 764524's serum exposure-response relationship a pharmacometric population PKPD analysis may be performed if data allow. The pharmacometric analysis will not be part of the CTR but will be provided separately.

In addition, exploratory correlation may also be made between drug concentration and AEs.

[redacted]

5.5 BIOBANKING

Not applicable

5.6 OTHER ASSESSMENTS

Not applicable

5.6.1 Pharmacogenomic evaluation

Not applicable

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor patients' 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 OCT-A 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 serum 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, OCT-A, 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 patient in a fasted state. All patients must sign an Informed Consent consistent with ICH GCP guidelines prior to any study specific procedures, this includes the option that the patient signs the Informed Consent during an extra contact to the study site prior to the actual screening visit. The patient should be recorded on the enrolment log as a screened patient when Visit 1 is performed. Visit 1 is the beginning of the screening period. As soon as eligibility of an enrolled patient is confirmed, the treatment visit (Visit 2) may be performed. If the patient does not meet inclusion/exclusion criteria, the patient must be recorded in the eCRF as a screen failure.

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. 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

clinical 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 patients that are screened must be registered with IRT. If the patient 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

Patients 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, patient must be re-registered in IRT, which will then provide new patient number, and patient 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 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 the SRD part, masking is not required for the IVT injection preparation or administration. For the MD part, IVT injection will be prepared by the unmasked pharmacist (qualified person). For the MD part, an unmasked injector 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 SRD part and Visits 2, 3 and 4 for MD part) 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

Patients 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.

SRD part

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 CRF has to be completed.

MD part

Visit 7/End of Study:
The Visit 7/EOS will be performed 42 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 patient 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 patient is not willing to continue in the trial and wants to withdraw consent prior to the end of the study, Visit 7 (SRD part)/ Visit 6 (MD part) should be scheduled as soon as possible, and also Visit 8/EOS(SRD part)/ Visit 7/EOS(MD part) should be performed to assess for safety.

The End of Study eCRF has to be filled in even if patient 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.

Patients 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 patient'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

7.1 STATISTICAL DESIGN – MODEL

This trial will consist of an SRD part followed by an MD part. The SRD part will be conducted non-randomized, open-label, and uncontrolled. MD part will be conducted single-blind, randomized and sham-controlled. The main objectives of this trial will be assessed by calculating descriptive statistics on DLEs and drug related AEs. For the MD part these will be compared descriptively between the treatment groups.

SRD part

The dose escalation will be guided by a Bayesian 2-parameter logistic regression model with overdose control [R13-4803, R13-4806]. For a given dose, the EWOC criterion is that there should be less than 25% risk that the true ocular DLE rate is above 0.25.

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] 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 dose level with the highest posterior probability of the DLE rate falling in the target interval [0.00, 0.25) among the doses fulfilling EWOC. Thus, 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 patients are required. However, the SMC may decide to include additional number of patients 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 feasible dose of [redacted] would equal 0.10. This yields μ_1 = (-2.005 0.0516). The standard deviations were set such that large uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding $\sigma_{1,11} = 2$, $\sigma_{1,22} = 1$ 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 0.15, and the median DLE rate at [redacted] would equal 0.40. These assumptions yield μ_2 =(-0.255 -0.191) . The standard deviations and correlations were set identical to the weakly informative prior, i.e. $\sigma_{2,11} = 2$, $\sigma_{2,22} = 1$ 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 0.005, and the median DLE at [redacted] would equal 0.01. These assumptions yield μ_3 =(-4.516 -0.835) . The standard deviations and correlations were set to $\sigma_{3,11} = 5$, $\sigma_{3,22}$ = 0.01, therefore almost fixing the slope parameter to its mean. 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 large, showing the low 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 1.7 patients. A detailed evaluation of the model using hypothetical data scenarios and operating characteristics is provided in Appendix 10.2.

Table 7.1: 1 Summary of prior distribution

Prior Component	Mixture Weight	Mean Vector	SD Vector
1: Weakly inf.	0.900	-2.005 0.0516	2.00 1.00
2: High Tox.	0.050	-0.255 -0.191	2.00 1.00
3: Low Tox.	0.050	-4.516 -0.835	5.00 0.01

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]	0.883	0.117	0.091	0170	0	0.013	0.703
	0.836	0.164	0.121	0.201	0	0.025	0.775
	0.714	0.286	0.202	0.245	0.001	0.092	0.880

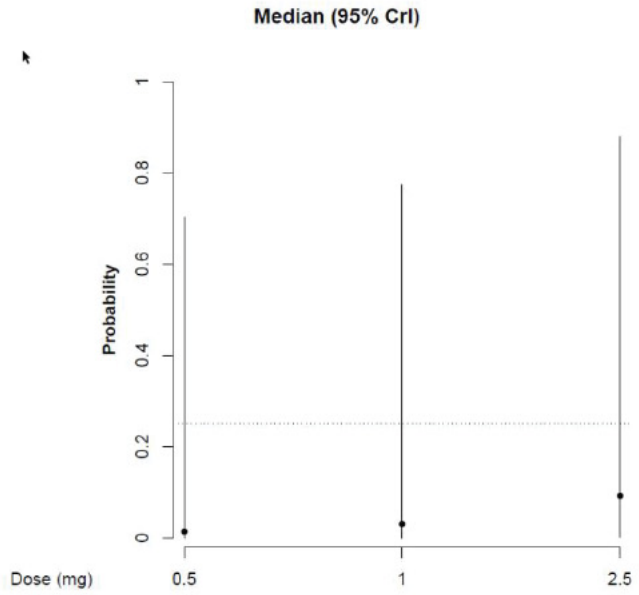


Figure 7.1: 1 Prior medians and 95% credible intervals

The prior may be updated once the trial has started in case new data that can be used will be available. Only patients 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.

MD part

The size of the FAZ of deep retinal plexus is associated with visual loss. Measuring FAZ by OCTA is highly reproducible. The assumed treatment effect of BI 764524 (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 fulfilling the EWOC criterion would be used for the MD study after completion of the SRD part.
The highest dose is usually limited by DLE in SRD or the maximum dose possible in the intravitreal injectable volume.

7.2 NULL AND ALTERNATIVE HYPOTHESES

It is not planned to test any statistical hypotheses in this study.

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.

7.3 PLANNED ANALYSES

Analysis sets

Statistical analyses will be based on the following analysis sets:

- Treated set (TS): The treated set includes all patients who were randomized and treated with at least one dose of study drug (either treatment with BI 764524 or Sham).
- Pharmacokinetic parameter analysis set (PKS): This set includes all patients in the treated set (TS) who provide at least one PK endpoint that was not excluded due to a protocol violation relevant to the evaluation of PK or due to PK non-evaluability (as specified in the following subsection ‘Pharmacokinetics’). Thus, a patient will be included in the PKS, even if he/she contributes only one PK parameter value for one period to the statistical assessment.

For the analysis the patients will be assigned to the treatment they actually received.

Adherence to the protocol will be assessed by the trial team. Important protocol deviation (IPD) categories will be suggested in the Integrated Quality and Risk Management Plan (IQRMP), IPDs will be identified no later than in the Report Planning Meeting, and the IPD categories will be updated as needed.

Pharmacokinetics

The pharmacokinetic parameters listed in Section 2.1 for drug BI 764524 and Sham-injection will be calculated according to the relevant Standard operating procedure (SOP) of the Sponsor (001-MCS-36-472).

Serum concentration data and parameters of a patient will be included in the statistical pharmacokinetic (PK) analyses if they are not flagged for exclusion due to a protocol deviation relevant to the evaluation of PK (to be decided no later than in the Report Planning Meeting) or due to PK non-evaluability (as revealed during data analysis, based on the criteria specified below). Exclusion of a patient's data will be documented in the CTR.

Relevant protocol violations may be

- Incorrect trial medication administered, i.e. the patient received at least one dose of trial medication the patient was not assigned to
- Incorrect dose of trial medication taken
- Use of restricted medications

Serum concentrations and/or parameters of a patient will be considered as non-evaluable, if for example

- Missing samples/concentration data at important phases of PK disposition curve.

Serum concentration data and parameters of a patient which is flagged for exclusion will be reported with its individual values but will not be included in the statistical analyses.

Only concentration values within the validated concentration range and actual sampling times will be used for the calculation of pharmacokinetic parameters. Concentrations used in the pharmacokinetic calculations will be in the same format provided in the bioanalytical report (that is to the same number of decimal places provided in the bioanalytical report).

7.3.1 Primary endpoint analyses

The primary endpoint as specified in Section 2.1.2 will be derived according to BI standards. The primary endpoints will be analyzed on the TS. DLEs and drug related AES will be summarized by means of frequency tables.

7.3.2 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 mm^2) of FAZ will be analysed using a generalized mixed linear model (for details refer to the TSAP).

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

In addition for the Central retinal thickness and BCVA descriptive statistics will be computed to describe the empirical distributions and descriptive p-values will be calculated with appropriate statistical tests. The endpoint Central retinal thickness will be analyzed in the same way as the endpoint FAZ. The endpoint BCVA will be analyzed using a generalized linear model.

7.3.4 Safety analyses

Safety will be assessed as defined by the endpoints listed in Section 2.1.2 and 2.2.2 based on the treated set (TS). Safety analyses will be descriptive in nature and will be based on BI standards.

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

Treatments will be compared in a descriptive way. The sham group in the safety evaluation will consist of all patients treated with sham injection, regardless of the dose group in which they were treated. The test treatment groups will be compared to the sham group in a descriptive way. Tabulations of frequencies/proportions will be used for the evaluation of categorical (qualitative) data, and tabulations of descriptive statistics will be used to analyse continuous (quantitative) data.

Measurements (such as ECGs, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment-emergent AEs). Therefore, measurements planned, or AEs recorded prior to first intake of trial medication will be assigned to the screening period. For BI 764524 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 on-treatment period for evaluation. These assignments including the corresponding time intervals will be defined in detail in the TSAP. 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.

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).

Adverse events will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Frequency, severity, and causal relationship of AEs will be tabulated by treatment, system organ class and preferred term. SAEs, AESIs (see Section 5.2.7.1) and other significant AEs (according to ICH E3) will be listed separately.

Previous and concomitant therapies will be presented per treatment group without consideration of time intervals and treatment periods.

Laboratory data will be compared to their reference ranges and frequency tables will be provided for the number of patients within and outside the reference range. Values outside the reference range as well as possibly clinically significant values will be highlighted in the listings. Additionally, differences from baseline will be evaluated.

Vital signs or other safety-relevant data will be assessed with regard to possible on-treatment changes from baseline.

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.

7.3.5 Pharmacokinetic - pharmacodynamic analysis

In order to characterize BI 764524's exposure-response relationship, a pharmacometric population PKPD analysis may be performed. The pharmacometric analysis will not be part of the CTR but will be provided separately.

7.4 INTERIM ANALYSES

For this trial, a "Fast track" analysis of the MD part is planned at Visit 6 (Week 16). After all data of the above-mentioned timepoint are available, a snapshot of the database will be taken. This snapshot will be used for performing the Fast track analysis. Details regarding statistical analysis will be outlined in the TSAP.

[redacted]

[redacted]

A final analysis (including all endpoints) will be performed when all trial data are available. In this analysis, all analyses performed for the Fast track analysis will be repeated with the (partially) updated data, in particular with respect to safety collected at EOS and efficacy endpoints collected at EOS. The results of the final analysis will be summarized in a CTR.

7.5 HANDLING OF MISSING DATA

7.5.1 Safety

It is not planned to impute missing values for safety parameters.

7.5.2 Pharmacokinetics

[redacted]

[redacted]

7.5.3 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.

7.6 RANDOMISATION

SRD part

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

MD part

Patients will be randomized in a 2:1 ratio (BI 764524: Sham injection).

The sponsor will arrange for the randomization as well as packaging and labelling of trial medication. The randomization list will be generated using a validated system that uses a pseudo-random number generator and a supplied seed number so that the resulting allocation is both reproducible and non-predictable.

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

7.7 DETERMINATION OF SAMPLE SIZE

SRD part

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 patients and a maximum of 15 patients 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 10.2). Fewer patients might be needed based on the recommendation of the SMC. However, the actual number of patients will depend on the number of dose cohorts tested. Based on the simulation study to evaluate operating characteristics of the BLRM, about 15 evaluable patients are expected to be treated in the dose escalation part for the model to have reasonable operating characteristics relating to its MFD recommendation.

MD part

In the publication Samara et al. [R17-3318] estimates for FAZ means and standard deviations (SD) were derived. The worst case was for PDR patients 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 [redacted] seems to be reasonable to be used in calculation of risk probabilities

With 20 patients in the BI 764524 2.5 mg arm and 10 patients in the sham arm, there is a likelihood of [redacted] of observing a treatment effect larger than [redacted] (a reduction of [redacted]

mm^2) and a likelihood of [redacted] of observing a treatment effect smaller than [redacted] (a reduction of [redacted]) when the assumed mean treatment difference is [redacted]. Assuming a mean treatment difference of [redacted] there is a likelihood of [redacted] observing a treatment effect larger than [redacted] and a likelihood of [redacted] of observing a treatment effect smaller than [redacted].

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 SOPs, the EU regulation 536/2014, and other relevant regulations. Investigators and site staff must adhere to these principles.

Standard medical care (prophylactic, diagnostic, and therapeutic procedures) remains the responsibility of the patient's treating physician.

The investigator will inform the sponsor immediately of any urgent safety measures taken to protect the trial patients 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 general rule, no trial results should be published prior to archiving of the CTR.

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 responsible IRB / IEC and CA according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

Prior to a patient's participation in the trial, written informed consent must be obtained from each patient (or the patient'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 patient information must be given to each patient or the patient's legally accepted representative.

The patient must be given sufficient time to consider participation in the trial. The investigator or delegate obtains written consent of the patient's own free will with the informed consent form after confirming that the patient 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 patient 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 patients 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 for each trial patient that include all observations and other data pertinent to the investigation. Source data as well as reported data should follow the 'ALCOA principles' and be attributable, legible, contemporaneous, original, and accurate. 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 patient 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 patient, documented in their medical records, would be acceptable.

Before providing any copy of patients' source documents to the sponsor, the investigator must ensure that all patient identifiers (e.g., patient's name, initials, address, phone number,

and social security number) have properly been removed or redacted to ensure patient confidentiality.

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

For the CRF, data must be derived from source documents, (some of the data will be reported in IRT and transferred to the CRF) for example:

- Patient identification: sex, year of birth (in accordance with local laws and regulations)
- Patient participation in the trial (substance, trial number, patient number, date patient was informed)
- Dates of patient's visits, including dispensing of trial medication
- Medical history (including trial indication and concomitant diseases, if applicable)
- Medication history
- AEs and outcome events (onset date [mandatory], and end date [if available])
- SAEs (onset date [mandatory], and end date [if available])
- Concomitant therapy (start date, changes)
- Completion of patient's participation in the trial (end date; in case of premature discontinuation, document the reason for it, if known)
- Prior to allocation of a patient to a treatment into a clinical trial, there must be documented evidence in the source data (e.g. medical records) that the trial participant meets all inclusion criteria and does not meet any exclusion criteria. The absence of records (either medical records, verbal documented feedback of the patient or testing conducted specific for a protocol) to support inclusion/exclusion criteria does not make the patient 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 Clinical Research Associate, 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:
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 patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

Individual patient 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 patient's personal physician or to other appropriate medical personnel responsible for the patient'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.

8.6 TRIAL MILESTONES

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

The end of the trial is defined as the date of the last visit of the last patient in the whole trial ("Last Patient Completed").
The "**Last Patient Last Treatment"** (LPLT) date is defined as the date on which the last patient in the whole trial is administered the last dose of trial treatment (as scheduled per protocol or prematurely). Individual investigators will be notified of suspected unexpected serious adverse reactions (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 patients 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 patient (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 SRD and MD parts. The SMC shall operate under the principles specified in the SMC charter. The primary responsibility of the SMC is to ensure and protect the safety and well-being of the patients participating in the trial. The primary objectives of the SMC are to make a joint decision on dose escalation in the SRD part and on the transfer to the MD part after the SRD part has been completed.
The SMC will decide on the next dose level to be investigated based on occurrence of DLEs (see section 5.2.1) and on additional information (systemic pharmacokinetics [PK] and patient profiles).

During the trial the SMC will monitor the trial for possible harmful effects of the test treatment, make an assessment as to the conduct of the trial, evaluate the accrued data in order to recommend whether the trial should continue as planned, continue with modification or stop the trial (e.g. for safety concerns or ethical reasons).
In its assessment and recommendations the SMC should always consider trial integrity/conduct issues (e.g. accrual, withdrawal rates, important protocol violations, relevant quality findings and non-compliances, missing data and censoring) and also consider factors external to the trial when relevant new information becomes available, such as scientific or therapeutic developments that may have an impact on the safety and well-being of the patients or on the ethics of the trial.

The SMC is a multidisciplinary group composed of the co-ordinating investigator, participating investigators (as deemed necessary) with treated patients in the cohort that will

be evaluated in the meeting (SRD part 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 patients 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 facilitate document exchange and maintain electronic ISF.

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 (CTMs), 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 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 764524 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

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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

9.2 UNPUBLISHED REFERENCES

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

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10. APPENDICES

10.1 TIME SCHEDULE FOR PHARMACOKINETIC (PK) AND ADA BLOOD SAMPLING AND AQUEOUS SAMPLING

Table 10.1: 1 Time schedule for PK and [redacted] sampling (SRD part)

Course	Visit	Day/ Week	Planned Time	Planned Time [h]	PK BI 764524	[redacted]
1	V2	1	Before drug administration of BI 764524*	-0:30	X	X
	V2	1	Drug administration	0:00		
	V2	1	30 min after drug administration*	00:30	X	
	V3	4 (+/- 1 day)	3 days after drug administration	72:00	X	
	V4	8 (+/- 2 day)/ Week 1	1 week after drug administration	168:00	X	
	V5	15 (+/- 2 day)/ Week 2	2 weeks after drug administration	336:00	X	X
	V6	29 (+/- 3 day)/ Week 4	4 weeks after drug administration	672:00	X	X
	V7	57 (+/- 7 day)/ Week 8	8 weeks after drug administration	1344:00	X	
EOS	V8	99 (+/- 7 day)/ Week 14	12 weeks after drug administration	2016:00	X	X**

* A time window of +/-15 min for sample drawing is allowed.
**If there is [redacted] occurrence a further follow-up will be conducted.

Table 10.1: 2 Time schedule for PK and [redacted] blood sampling (MD part)

Course	Visit	Day/ Week	Planned Time	Planned Time [h]	PK BI 764524	[redacted]
1	V2	1*	Before drug administration of BI 764524	-0:30	X	X
	V2	1	First Drug administration	0:00		
	V3	29 (+/- 3 day)*/ Week 4	4 weeks after first drug administration; predose to 2nd drug administration	671:30	X	X
	V3	29(+/- 3 day)/ Week 4	Second Drug administration	672:00		
	V4	57 (+/- 3 day)*/ Week 8	8 weeks after first drug administration; predose to 3rd drug administration	1343:30	X	
	V4	57 (+/- 3 day)/ Week 8	Third Drug administration	1344:00		
Follow Up Period	V5	85 (+/- 7 day)/ Week 12	12 weeks after first drug administration	2016:00	X	X**
Follow Up Period	V6	113 (+/- 7 day)/ Week 16	16 weeks after first drug administration	2688:00	X	
Follow Up Period	V7	155 (+/- 7 day)/ Week 22	22 weeks after first drug administration	3360:00	X	

*A time window of 30 mins to 2 hrs before dosing is allowed for sample drawing. PK and [redacted] samples must be taken before next drug administration; no window afterwards.
**If there is [redacted] occurrence a further follow-up will be conducted.

Table 10.1: 3 Time schedule for optional Aqueous sampling (MD part)

Trial Periods	Visit	Day	Time Point	Optional Aqueous sampling
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	155 (±7)	Any time during the visit	X*

* Optional 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.

10.2 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 patients in each cohort have completed the evaluation period of 7 days, 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 10.2: 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 10.2: 1). For simplicity reasons, a cohort size of 3 patients who are all evaluable is assumed.

Hypothetical data scenarios

Hypothetical data scenarios are shown in Table 10.2: 1. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model and the planned dose groups. It is assumed that each cohort has exactly three patients who are all evaluable. 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 patients at the starting dose of [redacted]. In this case, the next planned dose permitted by the model and the 200% escalation rule is [redacted]. In contrast, scenario 2 assumes that there is one DLE observed in the first dose group. This would mean over toxicity from the beginning, and the recommendation would be to stop the trial.

In scenario 3, 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 6c), dose escalation would proceed to the [redacted] dose, with an additional cohort at that dose level at the end, i.e. overall 12 patients.

In scenario 4, the first DLE occurs in dose group [redacted]. Then the recommendation would be to treat an additional cohort of 3 patients at the same dose level. If no new DLE occurs then, scenario 4b shows that the next recommended dose level would be [redacted]. Thus, the [redacted] dose would be declared as MFD and the trial would stop (after 9 patients).

However, if (after repeating dose group [redacted] according to the recommendation from scenario 4) there was another DLE in the second cohort for dose group [redacted] (as in scenario 5), then the recommendation would be to go back to dose [redacted]. If there was no further DLE then (scenario 5b), the recommendation would be to go to next dose [redacted]. If there was no DLE in the third cohort of [redacted] (scenario 5c), then the trial would stop after 15 patients and declaring [redacted] as the MFD.

Scenario 6b shows the case where the first DLE occurs in the [redacted] dose group. Then an additional cohort of 3 patients would have to be treated at [redacted] dose group. If these 3 patients have no further DLE, the next recommended dose would be [redacted]. If this second cohort of 3 patients in the [redacted] group have no DLE (scenario 6c) the next recommended dose would be [redacted]. If this second cohort of 3 patients in the [redacted] group have no DLE (scenario 6c) the next recommended dose would be [redacted]. Thus, the [redacted] dose would be declared as MFD and the trial would stop (after 15 patients)

Table 10.2: 1 Hypothetical data scenarios

Scenario	Dose (mg)	# Pat.	# DLE	Current Dose: P(OD)	Next recomm. dose	Next dose:	
						P(TD)	P(OD)
1	[redacted]	3	0	0.025	1	0.945	0.055
2		3	1	0.345	N/A	N/A	N/A
3		3 3	0 0	0.016	2.5	0.874	0.126
4		3 3	0 1	0.209	1	0.791	0.209
4b		3 6	0 1	0.091	1	0.909	0.091

Table 10.2: 1 Hypothetical data scenarios (continued)

Scenario	Dose (mg)	# Pat.	# DLE	Current Dose: P(OD)	Next recomm. dose	Next dose:	
						P(TD)	P(OD)
5	[redacted]	3 6	0 2	0.329	0.5	0.867	0.133
5b		6 6	0 2	0.022	1	0.884	0.116
5c		6 9	0 2	0.884	1	0.884	0.116
6		3 3 3	0 0 0	0.036	2.5	0.964	0.036
6a		3 3 6	0 0 0	0.013	2.5	0.987	0.013
6b		3 3 3	0 0 1	0.285	1.0	0.969	0.031
6c		3 6 3	0 0 1	0.015	2.5	0.772	0.228
6d		3 6 6	0 0 1	0.103	2.5	0.897	0.103
6e		3 6 3	0 1 1	0.098	1	0.902	0.098

Operating characteristics

Operating characteristics are a way to assess the long-run behavior 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 10.2: 2 describes 6 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 medians
- Scenario 2: aligned with prior means
- Scenario 3: high-toxicity scenario

- Scenario 4: low-toxicity scenario
- Scenario 5: non-logistic dose-toxicity scenario
- Scenario 6: low-toxicity followed by high-toxicity

Table 10.2: 2 Assumed true dose-toxicity scenarios

Scenario		**Dose (mg)**			
		[redacted]	[redacted]	[redacted]	[redacted]
1: Prior Med	P(DLE)	0.014	0.024	0.054	0.112
2: Prior Mean		0.086	0.106	0.153	0.224
3: High Tox		0.150	0.200	0.280	0.350
4: Low Tox		0.001	0.005	0.010	0.100
5: Non-Logistic		0.050	0.010	0.200	0.500
6: Low-High		0.010	0.050	0.400	0.600

For each of these scenarios, 1000 trials were simulated. Each cohort consisted of 3 patients 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 6 patients have been evaluated at a dose level which is the model's recommendation for the next dose cohort. The maximum allowed patient number for each trial was chosen as 24.

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 patients per trial and the average number of DLEs per trial are reported. Results are shown in Table 10.2: 3.

Table 10.2: 3 Simulated operating characteristics

Scenario	Max. allowed # Patients	% of trials declaring a MFD with true DLE rate in		% of stopped trials*	# Patients	# DLEs
		[ ) target dosing	[ ] overdosing		Mean (Min-Max)	Mean (Min-Max)
1	15	94.1	0.0	5.9	11.8 (3-15)	0.39 (0-3)
2	15	65.4	0.0	34.6	9.1 (3-15)	1.10 (0-4)
3	15	23.8	13.6	62.6	8.5 (3-15)	1.88 (0-6)
4	15	100	0	0	9.2 (9-15)	0.06 (0-1)
5	15	67.9	0	32.1	10.7 (3-15)	1.16 (0-4)
6	15	47.9	20.3	31.8	13.1 (3-15)	2.01 (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 patient number was reached before an MFD was found.

In scenario 1, which reflects the case that the true dose-toxicity is aligned with prior medians, 94.1% of the simulated trials declared a dose as MFD with true DLE rate in the targeted toxicity range. Note that 5.9% of the simulated trials stopped either because there was no MFD determined after 15 patients had been observed (1.4 %) or because of too high toxicity for the planned doses (4.5 %). This latter is mostly due to the cases that 1 DLE is observed out of 3 patients at the starting dose of [redacted]. In reality, this situation would rarely happen as the safety profile of starting dose is expected to be good.

In scenario 2, the assumed dose toxicities are higher than in scenario 1. This results in a higher percentage of early stopped trials (about 34.6 %). In this case, about 65.4 % of the trials would end with an estimated MFD within the targeted toxicity range, and 27.7 % in the overdosing range.

In Scenario 3 (high-toxicity scenario), only 23.8% of the trials declared a dose as MFD with true DLE rate in the targeted toxicity range. In 13.6% of the trials, the estimated MFD was in the overdosing range. Scenario 4 (low-toxicity scenario) shows the best results, i.e. the lowest number of stopped trials and a high number of trials with estimated MFD in the target range, as would be expected.

Scenarios 5 and 6 showed reasonable operating characteristics, given the quite large deviations of the assumed true dose-toxicity curve from the assumptions underlying the BLRM.

The mean patient numbers ranged from 8.5 patients (Scenario 3) to 13.1 patients (Scenario 6), and the maximum number of patients was 18. Therefore, the patient numbers are as expected and increase when moving away from the high-toxicity scenario.

Overall, by reviewing the metrics presented in table 10.2: 3, it can be seen that the model is generally conservative due to the overdose control criteria. In all scenarios, except for the

high-toxicity case (scenario 3) 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 3.5.1 was used for data scenarios and simulations.

10.3 BENEFIT-RISK ASSESSMENT IN CONTEXT OF COVID-19 PANDEMIC FOR PATIENTS PARTICIPATING IN TRIAL 1436-0001 INVESTIGATING BI 764524

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 BI764524 either may affect the immune system or increase the risk of progression of COVID-19 infection. BI 764524 is administered intravitreally using standard aseptic technique.
The low dosage of BI764524 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. Enrolment 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 patient 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 patient'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 patient.

DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

In situations where an individual patient is unable or unwilling to attend a clinic visit, the investigator must assess the risk-benefit for the individual patient and may decide to perform a visit remotely if this is in the best interest of the patient 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.

11. DESCRIPTION OF GLOBAL AMENDMENTS

11.1 GLOBAL AMENDMENT 1

Date of amendment		17 Aug 2020
EudraCT number **EU number**		2019-004432-28
BI Trial number		1436-0001
BI Investigational Medicinal Product(s)		BI 764524
Title of protocol		A First-in **H**uman trial to study safety and tolerability of single rising intravitreal d**O**ses (open label, non-randomized, uncontrolled) and in addition the early biological response of multiple intravit**R**eal dosing (single-masked, ra**N**domized, sham-controlled) of **BI** 764524 in panretina**L** photocoagulation (PRP) treated pro**L**iferative diabetic retinopathy (PDR) patients with diabetic macular ischemia (DMI) – the **HORNBILL** Study
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Synopsis, 1.2, 1.3, 1.4.2, 3.1, 3.2, 3.3, 4.1.2, 4.1.3, 4.1.2, 4.1.4, 7.1, 7.6, 7.7, 10.2
Description of change		Removal of the [redacted] dose cohort from the SRD and MD parts. Decrease of the estimated number of patients required for the SRD part. Change of the MRD part to MD design.
Rationale for change		Not much efficacy difference is expected between [redacted] and [redacted] doses. The 5mg dose is expected to last only 9 days longer in the vitreous than the [redacted] dose and requires an injection volume of [redacted]. Therefore, a decision was made to remove the 5mg dose from the trial. Furthermore, by removing the [redacted] dose cohort, the estimated number of patients required for the SRD part was decreased. As the highest dose being tested will now be [redacted], the second cohort in the MD part of the trial will no longer be required.
[redacted]		[redacted]

[redacted]		[redacted]
Section to be changed		1.2.
Description of change		Sentence was updated to indicate that no patient has been treated intravitreally or by any other route of administration with BI 764524 at the time of finalization of CTP version 2
Rationale for change		Update of the available data.
Section to be changed		1.4.2
Description of change		Update of the available data from pre-clinical toxicity studies (IVT administration of BI 764524 and Immunogenic response)
Rationale for change		Update of the available data.
Section to be changed		3.3.2, 3.3.3
Description of change		Rewording of the inclusion criteria 5 (SRD and MD parts): BCVA. Addition of inclusion criteria 9 (MD part): ICF for optional aqueous sampling. Rewording of exclusion criteria 5 (SDR part) and 10 (MD part): intraocular surgery. Addition of exclusion criteria for pregnant and lactating women (SRD and MD parts).
Rationale for change		Rewordings due to clarity. Separate ICF required for optional aqueous sampling. Authority feedback: pregnant and lactating females will be excluded from the trial.
Scetion to be changed		4.1.2
Description of change		Adding ® next to [redacted] indicating that it is a registered trademark
Rationale for change		Correction
Section to be changed		4.1.4, 4.1.6, 4.1.9, 6.2.2
Description of change		"Qualified person" added in brackets after pharmacist
Rationale for change		Clarification
Section to be changed		4.1.5, 4.1.6.1, 4.3, 6.2.2
Description of change		Clarification of the design of MD part and the role of the unmasked pharmacist and unmasked injector. Addition of the following sentence: After administration of BI 764524, patients will be monitored according to standard practice and at least for 1 hour. In this minimum post-dose

		observation period, systemic and ocular conditions will be monitored according to local practice for such procedures.
Rationale for change		Clarification
Section to be changed		4.2.2.1
Description of change		For restrictions regarding concomitant treatment the following sentence was added: For the Study eye no other treatment (IVT or otherwise) is allowed during the trial. The fellow eye can be on any on label drug. Sponsor will not provide fellow eye treatment or compensate for it.
Rationale for change		Clarification
Section to be changed		4.2.2.4
Description of change		Following sentence was added: 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.
Rationale for change		Clarification
Section to be changed		5.2.1.
Description of change		The dose-limiting event grading for sterile endophthalmitis and/or sterile inflammation of the vitreous has been reduced from Grade 4 to Grade 3. SUN Working group grading scheme for measuring anterior chamber cells was revised: `0`represents no cells
Rationale for change		Authority feedback
Section to be changed		5.2.5
Description of change		Wording of triplicate ECG was removed since ECGs will be recorded only as single ECGs.
Rationale for change		Clarification
Section to be changed		6.2.1.
Description of change		The following sentence was corrected to align with the 28 days screening period: 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.
Rationale for change		Clarification
Section to be changed		9.1.
Description of change		Update of the Published References – R17-3318 added
Rationale for change		Update
Section to be changed		Flow chart, abbreviations, 2.2, 5.1, 5.7, 6.2, 9.2

Description of change		Spelling mistakes corrected: [redacted], pregnancy test footnote (MD flowchart), BI764524
Rationale for change		Correction
Section to be changed		Appendix 10.2
Description of change		Benefit-Risk Assessment in context of COVID-19 pandemic for patients participating in trial 1436-0001 investigating BI 764524
Rationale for change		Clarification

11.2 GLOBAL AMENDMENT 2

Date of amendment		28 Sep 2021
EudraCT number **EU number**		2019-004432-28
BI Trial number		1436-0001
BI Investigational Medicinal Product(s)		BI 764524
Title of protocol		A First-in **H**uman trial to study safety and tolerability of single rising intravitreal d**O**ses (open label, non-randomized, uncontrolled) and in addition the early biological response of multiple intravit**R**eal dosing (single-masked, ra**N**domized, sham-controlled) of **BI** 764524 in panretina**L** photocoagulation (PRP) treated pro**L**iferative diabetic retinopathy (PDR) patients with diabetic macular ischemia (DMI) – the **HORNBILL** Study
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Synopsis, 2.1.3
Description of change		The following secondary endpoint was added: • change from baseline of the size of the FAZ in optical coherence tomography angiography (OCTA) in superficial and combined vascular complex at Visit 5 (week 12).
Rationale for change		This timepoint (visit 5) is used for interim analysis.
Section to be changed		Synopsis, 2.1.3, 2.2.2
Description of change		"Change from baseline of the size of the FAZ in OCTA in superficial and deep retinal plexus" was revised to "Change from baseline of the size of the FAZ in OCTA in superficial and **combined vascular complex**"

Rationale for change		Change in the terminology of the classification. No change in the actual measurements.
Section to be changed		Abbreviations
Description of change		Deletion of unnecessary abbreviations and replacement of plasma to serum in PK relevant abbreviations
Rationale for change		Correction
Section to be changed		1.2
Description of change		Information of the treated patients was added.
Rationale for change		Update: availability of new study data
Section to be changed		1.3
Description of change		The following sentence was revised as follows: "The next higher dose will only be administered ~~to the next cohort~~, if the treatment in the preceding dose cohort was safe and showed acceptable tolerability."
Rationale for change		Correction
Section to be changed		1.4.2, 1.4.2.1.2, 2.2.2, 5.3.4, 6.1, 7.3, 8.7
Description of change		Word "plasma" was replaced with "serum".
Rationale for change		Correction: serum [redacted] and PK samples will be collected and analysed.
Section to be changed		1.4.2.2
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		[redacted]
Rationale for change		
Section to be changed		
Description of change		
Rationale for change		
Section to be changed		3.1
Description of change		The following sentences were revised as follows: The MD part of the study would only start if the highest **dose** ~~2 doses (i.e.~~ [redacted] **is** ~~are~~ tolerated. The highest dose (~~e.g.~~ [redacted]) **if** established as safe and tolerable during the SRD part will be used in the MD part after the SRD part has been completed.
Rationale for change		Clarification that if the highest dose ([redacted]) is not considered safe and tolerable, MD part will not commence.
Section to be changed		Section 3.1; Figure 3.1:1
Description of change		Figure was corrected to reflect that the maximum feasible dose is considered as reached if at least 6 patients have been evaluated at a dose level which is the model´s recommendation for the next dose cohort.

Rationale for change		Correction
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 fact and corrected sentences in section 3.1 that the MD part will not commence if the highest dose (2.5mg) is not considered safe and tolerable in the SRD part.
Rationale for change		Clarification
Section to be changed		3.3.2
Description of change		Inclusion criteria #3 for the MD part was revised to reflect the endpoint change (Change from baseline of the size of the FAZ in OCTA in superficial and **combined vascular complex**)
Rationale for change		Endpoint change: change in the terminology of the classification. No change in the actual measurements.
Section to be changed		3.3.2
Description of change		Inclusion criteria # 6 for the MD part was revised as follows: Best-corrected VA ≤ ~~70~~85 letters (20/~~40~~20) or worse for MD
Rationale for change		To broaden the eligible patient population.
Section to be changed		Section 4.1.1; Table 4.1.1:2 Posology
Description of change		Reference to diluent in MD part was removed.
Rationale for change		Correction. [redacted] is not required for the reconstitution of [redacted] which is the only dose in MD part.
Section to be changed		4.1.5
Description of change		Following sentence was added: "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."
Rationale for change		Clarification
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		The sentence: "Development of sterile, endophthalmitis and/or sterile inflammation of the

		vitreous grade 3+ according to standardization of Uveitis Nomenclature (SUN) working group (WG) grading scheme for anterior chamber cells (see Table 5.2.1: 1 below) and a duration of 5 or more days between day 1 and day 8" was replaced with the sentence: 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
Rationale for change		Correction: the SUN only assesses inflammation in the anterior chamber, the NEI Grading of vitreous haze assesses inflammation in the vitreous.
Rationale for change		Clarification
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		5.3.2.1
Description of change		The following sentence was revised as follows: Samples may be used for further ~~methodological~~ investigations (e.g. for stability testing), however, only data related to the analyte **and mechanism of action** will be generated by these additional investigations. The study samples will be discarded after completion of the additional investigations but not later than 5 years ~~upon~~ **after** the final study report has been signed.
Rationale for change		Correction
Section to be changed		5.4
Description of change		The following revisions were made: **If feasible, BI 764524 levels in aqueous humor samples might also be determined.** In total, four aqueous samples collections are planned in the multiple dosing part of the trial. ~~Samples may be used for further investigations (e.g. measurements of BI 764524).~~
Rationale for change		Clarification
Section to be changed		6.2.2

Description of change		The following sentence was removed: "An additional tonometry will be performed after IVT injection to monitor IOP."
Rationale for change		Clarification: no additional tonometry required.
Section to be changed		7.1
Description of change		The following sentence was removed; "Further analyses of these endpoints comprise the power model for assessment of dose proportionality" and correction of some typos in the priors of the blrm and a typo in the table "Summary of prior distribution".
Rationale for change		Interpretation of the results of the power model for dose proportionality is challenging with maximum of 3 patients in 2 cohorts. Correction of typos.
Section to be changed		7.3.2
Description of change		Sentence was corrected: Analyses regarding safety and efficacy will be performed on the TS, ~~analysis regarding PK will be performed on the PKS.~~
Rationale for change		Correction: all PK parameters are further endpoints
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		7.4
Description of change		As an interim analysis, a "Fast track" analysis of the MD part for analyses of the efficacy endpoint was added. Clarification of the final analysis was added.
Rationale for change		Interim analysis was included for early project planning. Final analysis was defined for completeness.
Section to be changed		7.5.2
Description of change		Reference to the BI SOP (001-MCS-36-472) was deleted.
Rationale for change		Correction
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		10.1

Description of change		Separate table (10.1:3) was created for aqueous sampling.
Rationale for change		Clarification

11.3 GLOBAL AMENDMENT 3

Date of amendment		17 Jan 2022
EudraCT number **EU number**		2019-004432-28
BI Trial number		1436-0001
BI Investigational Medicinal Product(s)		BI 764524
Title of protocol		A First-in **H**uman trial to study safety and tolerability of single rising intravitreal d**O**ses (open label, non-randomized, uncontrolled) and in addition the early biological response of multiple intravit**R**eal dosing (single-masked, ra**N**domized, sham-controlled) of **BI** 764524 in panretina**L** photocoagulation (PRP) treated pro**L**iferative diabetic retinopathy (PDR) patients with diabetic macular ischemia (DMI) – the **HORNBILL** Study
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		3.3.2
Description of change		MD part: Inclusion criteria#5 was revised as follows: ~~Best-corrected VA in the non-study eye better or equal to the best-corrected VA in the study eye. If both eyes are eligible and have identical VA, the investigator may select the study eye.~~ **If both eyes are eligible, the investigator may select either eye to be the study eye.**
Rationale for change		The available data from the SRD part indicates that BI 764524 single IVT injections are well tolerated, and the benefit/risk ratio remains positive in subjects with DMI up to [redacted]. As BI764524 has proved safe in the SRD part, risks are low for the treated eye.
Section to be changed		3.3.2

Description of change		MD part: Exclusion criteria#7 removed: Clinically significant disorganisation of retinal inner layer (DRIL) in the study eye
Rationale for change		To broaden the patient population.

11.4 GLOBAL AMENDMENT 4

Date of amendment		20 Apr 2022
EudraCT number **EU number**		2019-004432-28
BI Trial number		1436-0001
BI Investigational Medicinal Product(s)		BI 764524
Title of protocol		A First-in **H**uman trial to study safety and tolerability of single rising intravitreal d**O**ses (open label, non-randomized, uncontrolled) and in addition the early biological response of multiple intravit**R**eal dosing (single-masked, ra**N**domized, sham-controlled) of **BI** 764524 in panretina**L** photocoagulation (PRP) treated pro**L**iferative diabetic retinopathy (PDR) patients with diabetic macular ischemia (DMI) – the **HORNBILL** 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		1.2
Description of change		The following sentence was revised as follows: Although no systemic adverse events were observed in the IVT pre-clinical study, at ~~each~~ **the** time-point**s specified in the flow charts**, patients will be evaluated with systemic evaluation, including body weight, blood pressure, pulse rate, and laboratory tests.
Rationale for change		Clarification
Section to be changed		1.4.2.4
Description of change		The following sentence was revised as follows: Additionally, a systemic evaluation will be performed at ~~each~~ **the** time-point**s specified in the**

		flow charts, to assess any possible systemic reaction.
Rationale for change		Clarification
Section to be changed		3.3, 6.2.1
Description of change		The following sentences were revised: Section 3.3: Patients 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: Patients 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, patient must be **re-**registered in IRT, which will then provide new patient number, and patient must sign new Informed Consent Form (ICF).
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		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 the SRD part only.
Section to be changed		Table 10.1:2
Description of changes		Footnote in the table was revised as follows: *A time window of **30 mins to 2 hrs before dosing is allowed**~~+/- 15 min~~ for sample drawing ~~is allowed here.~~ PK **and** [redacted] sample**s** must be taken before next drug administration; no window afterwards.
Rationale for change		To allow broader time window for PK and [redacted] samples before dosing.

11.5 GLOBAL AMENDMENT 5

Date of amendment		07 Oct 2022
EudraCT number **EU number**		2019-004432-28
BI Trial number		1436-0001
BI Investigational Medicinal Product(s)		BI 764524
Title of protocol		A First-in **H**uman trial to study safety and tolerability of single rising intravitreal d**O**ses (open label, non-randomized, uncontrolled) and in addition the early biological response of multiple intravit**R**eal dosing (single-masked, ra**N**domized, sham-controlled) of **BI** 764524 in panretina**L** photocoagulation (PRP) treated pro**L**iferative diabetic retinopathy (PDR) patients with diabetic macular ischemia (DMI) – the **HORNBILL** Study
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Section 7.4: Interim analyses
Description of change		Update of the Fast track analysis timepoint and removal of the language relating to interim analysis of the efficacy endpoint, change from baseline of the size of the FAZ at Visit 7 (Week 22)
Rationale for change		There has been a minor adjustment internally as to when we take the Fast track data snapshot and currently we see no benefit to conduct an interim analysis at the V7 efficacy endpoint
Section to be changed		Title page: Trial Clinical Monitor
Description of change		[redacted] Phone [redacted] [redacted] ~~Phone~~ [redacted] ~~Fax~~
Rationale for change		[redacted] has taken over the Trial Clinical Monitor (now known as Clinical Trial Leader -r) 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 dosing (single-masked, raNdomized, shamcontrolled) of BI 764524 in panretinaL photocoagulation (PRP) treated proLiferative diabetic retinopathy (PDR) patients with diabetic macular ischemia

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	07 Oct 2022 17:01 CEST
Author-Trial Statistician		07 Oct 2022 18:36 CEST
Approval		10 Oct 2022 14:57 CEST
Verification-Paper Signature Completion		10 Oct 2022 15:16 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed