Clinical Trial Protocol

Document Number:		**c25843245-07**
EudraCT No. **EU Trial No.**	2018-004125-92	
BI Trial No.	1418-0001	
BI Investigational Medicinal Product(s)	BI 754132	
Title	Safety, tolerability and pharmacokinetics of single rising intravitreal doses and multiple intravitreal dosing of BI 754132 in patients with geographic atrophy secondary to age-related macular degeneration (open label, non-randomized, uncontrolled).	
Lay Title	A study to test how well different doses of BI 754132 are tolerated in patients with an advanced form of age-related macular degeneration called geographic atrophy	
Clinical Phase	I	
Clinical Trial Leader	[redacted] Phone: [redacted] Fax: [redacted]	
Coordinating Investigator	[redacted] Phone: [redacted] Fax: [redacted]	
Status	Final Protocol (Revised Protocol (based on global amendment no. 6)	
Version and Date	**Version: 7.0**	**Date: 17 Feb 2022**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer-Ingelheim
Protocol date	19 Mar 2019
Revision date	17 Feb 2022
BI trial number	1418-0001
Title of trial	Safety, tolerability and pharmacokinetics of single rising intravitreal doses and multiple intravitreal dosing of BI 754132 in patients with geographic atrophy secondary to age-related macular degeneration (open label, non-randomized, uncontrolled).
Coordinating Investigator	[redacted]
Trial site(s)	Multi-centre trial
Clinical phase	I
Trial rationale	Currently, there are no approved or effective treatments to prevent either onset or progression of GA. Both published data as well as in-house preclinical studies showed that TrkB activation can protect photoreceptors in animal models of diabetes, retinal ischemia as well as the blue light-induced photoreceptor degeneration model. Therefore, stimulating TrkB signaling in the eyes of patients with GA might protect photoreceptors from degenerating thereby counteracting the loss of vision.
Trial objective(s)	To investigate the safety, tolerability and pharmacokinetics of single intravitreal doses and multiple intravitreal dosing of BI 754132
Trial endpoints	<u>Primary endpoints:</u> SRD Part: • Number of patients with ocular (in the study eye) and systemic dose limiting events (DLEs) from drug administration until end of trial (EOT) MD part: • Number of patients with drug-related adverse events (AEs) from drug administration until EOT <u>Secondary endpoints:</u> SRD part: • Number of patients with drug-related adverse events from drug administration until EOT • Number of patients with any ocular adverse events in the study eye from drug administration until EOT • C_{max} (maximum serum concentration of BI 754132 after a single intravitreal dose)

	• $AUC_{0-\infty}$ (area under the concentration-time curve of BI 754132 in serum over the time interval from 0 extrapolated to infinity) • t_{max} (time from dosing to maximum serum concentration of BI 754132) MD part: • Systemic exposure of BI 754132 after multiple IVT dosing by determination of $C_{min,1}$ and $C_{min,2}$ (trough levels before second and third administrations) and plasma concentrations 4, 8 and 14 weeks after the third administration
Trial design	This trial will consist of an SRD part followed by an MD part. Both parts will be open label, uncontrolled and non-randomized.
Total number of patients entered	Up to 24 in total; 18 patients (planned 15 plus 3 additional if DLEs occur) in the SRD part and 6 patients in the MD part.
Number of patients on each treatment	Planned: 3 per dose group and 6 at final dose in SRD part (actual numbers depending on the dose escalation decisions taken by the Safety Monitoring Committee (SMC)) and 6 at the dose of the MD part
Diagnosis	Patients with geographic atrophy secondary to age-related macular degeneration
Main in- and exclusion criteria	Inclusion: Men and women over the age of 50 with GA lesion at least 0.75 disk area in size and a best corrected visual acuity (BCVA) of 20/100 to 20/400 (SRD part) and 20/100 or lower (MD part) Snellen equivalent measured by the Early Treatment Diabetic Retinopathy Study protocol. Exclusion: Additional eye disease that could compromise BCVA.
Test product(s)	BI 754132
dose	SRD part: 4 dose groups, 0.3 mg, 1 mg, 3 mg, 6 mg (single doses) MD part: The highest dose (e.g. 6 mg) established as safe and tolerable dose during the SRD part
mode of administration	Intravitreal
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. The dose escalation in the SRD part will be guided by a Bayesian logistic regression model (BLRM) with overdose control that will be fitted to binary toxicity outcomes. The estimates of parameters will be updated as data are accumulated using the BLRM.

FLOW CHART I (SINGLE RISING DOSE PART)

Trial Periods	**Screening Period**	**Treatment Visit**	**Follow-up period**							**End of trial**
Visit	**1**	**2**	**3**	**4[7]**	**5**	**6**	**7**	**8**	**9**	**10**
Study Days	-3	1	4	8	15	22	29	56	84	100
Time window for visits (days)	-28[6,10]	none	±1	±1	±2	±2	±2	±4	±4	±7
Informed consent	X									
Demographics	X									
Medical history	X									
Physical examination	X						X			X
Vital signs	X	X	X	X	X	X	X	X	X	X
Laboratory tests	X	X	X	X	X		X	X	X	X
12 lead-ECG	X	X[2]	X[2]	X[2]	X[2]		X[2]			X[2]
Review of in-/exclusion criteria	X	X								
Dose Assignment		X								
IVT drug administration		X								
PK Sampling		X[3]	X	X	X		X	X	X	X
ADA Sampling		X			X		X			X
Pharmacogenomics biomarker		X[4]								
Visual Acuity Testing[8]	X	X	X	X	X	X	X	X	X	X
Fundus autofluorescence[9]	X	X	X	X	X	X	X			X
SD-OCT[9]	X	X	X	X	X	X	X	X	X	X
OCT Angiography[9]		X		X		X		X	X	X
ERG[8]		X		X	X		X			X
Color Fundus Photography[9]	X	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X[5]	X
Slit lamp and IOP[8]	X	X	X	X	X	X	X	X	X	X
Adverse events		X	X	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X
Completion of patient participation[1]										X

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

(2) Triplicate resting ECGs (see Section 5.2.6). For time points with PK sampling, the ECGs are to be recorded shortly before PK sampling (see time schedule in Appendix 10.3).

(3) PK sampling see time schedule in Appendix 10.3.

(4) One DNA sample for analysis of pre-specified genes will be collected at visit 2 (see Section 5.4.2). If not possible at Visit 2 (Day 1), this sample may also be collected at a later visit.

(5) Only to be done if considered medically necessary by the principal investigator

(6) Rescreening of eligible patients, see Section 6.2.1.1.

(7) End of observation period for DLE´s for dose escalation process (SMC).

(8) Before pupil dilation; at PI´s discretion, IOPcan be repeated after pupil dilation and after IVT injection.

(9) After pupil dilation. If fixation does not allow for acquisition of good quality images, the examination may be considered optional.

(10) If the screening visit performed earlier than 14 days before dosing visit, an additional visit for repeating of safety lab, vital signs, ECG and targeted physical examination has to be performed again, see Section 6.2.1.1.

FLOW CHART II (MULTIPLE DOSING PART)

Trial Periods	**Screening Period**	**Treatment Period**			**Follow-up period**		**End of trial**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**
Study Days/Week	Duration -3 to -28 days[5,6]	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						
Demographics	X						
Medical history	X						
Physical examination	X				X		X
Vital signs	X	X	X	X	X	X	X
Laboratory tests	X	X	X	X	X	X	X
12 lead-ECG	X	X[2,3]	X[2,3]	X[2,3]	X[2]		X[2]
Review of in-/exclusion criteria	X	X					
Dose Assignment		X					
IVT drug administration		X	X	X			
PK Sampling		X[3]	X[3]	X[3]	X	X	X
ADA Sampling		X[3]			X		X
Pharmacogenomics biomarker		X[4]					
Visual Acuity Testing[7]	X	X	X	X	X	X	X
Fundus autofluorescence[9]	X	X	X	X	X	X	X
SD-OCT[9]	X	X	X	X	X	X	X
OCT Angiography[9]		X	X	X	X	X	X
ERG[7]		X	X	X			X
Color Fundus Photography[9]	X	X	X	X	X	X	X
Slit lamp[7], IOP[7,8] and indirect ophthalmoscopy[9]	X	X	X	X	X	X	X
Post-injection assessments[10]		X	X	X			
Adverse events		X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X
Completion of patient participation[1]							X

(1) Completion of patient participation also needs to be completed if the patient withdraws prematurely following assignment to dose (see Section 3.3.4).

(2) Triplicate resting ECGs (see Section 5.2.6). For time points with PK sampling, the ECGs are to be recorded shortly before PK sampling.

(3) PK and ADA sampling as well as ECG measurement must be performed within 4 hours prior to the IVT drug administration, and each sampling and measurement timepoint has to be entered in the eCRF.

(4) One DNA sample for analysis of pre-specified genes will be collected at visit 2 (see Section 5.4.2). If not possible at Visit 2 (Day 1), this sample may also be collected at a later visit.

(5) Rescreening of eligible patients, see Section 6.2.2.1.

(6) If the screening visit performed earlier than 14 days before dosing visit, an additional visit for repeating of safety lab, vital signs, ECG and targeted physical examination has to be performed again, see Section 6.2.2.1.

(7) Before pupil dilation.

(8) IOP must be repeated 30 to 50 minutes after IVT injection at Visit 2, 3 and 4.

(9) After pupil dilation.

(10) For details of post-injection assessments, see Section 6.2.2.2.

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ABBREVIATIONS

ADA	Anti-drug antibodies
ADCC	Antibody-dependent Cell-mediated Cytotoxicity
ADME	Absorption, Distribution, Metabolism and Elimination/Excretion
AE	Adverse Event
AESI	Adverse Event of Special Interest
ALCOA	Attributable, Legible, Contemporaneous, Original, Accurate (dimensions of data integrity)
ALS	Amyotrophic Lateral Sclerosis
ALT	Alanine Aminotransferase
AMD	Age-related Macular Degeneration
AST	Aspartate Aminotransferase
AUC	Area under the Curve
BCVA	Best Corrected Visual Acuity
BDNF	Brain-derived Neurotrophic Factor
BI	Boehringer Ingelheim
BLRM	Bayesian Logistic Regression Model
CA	Competent Authority
CDC	Complement-Dependent Cytotoxicity
CFP	Color Fundus Photography
CNV	Choroidal Neovascularisation
C_{max}	Maximum Concentration
CRA	Clinical Research Associate
CRC	Central Reading Center
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organisation
CRP	C reactive Protein
CT Leader	Clinical Trial Leader
CT Manager	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug Induced Liver Injury
DLE	Dose Limiting Event

DNA	Deoxyribonucleic Acid
EC	Ethics Committee
ECD	Extracellular Domain
ECG	Electrocardiogram
EEC	European Economic Community
eCRF	Electronic Case Report Form
EMA	European Medicines Agency
EOT	End of Trial
ERG	Electroretinography
ETDRS	Early Treatment Diabetic Retinopathy Scale
EU	European Union
EudraCT	European Clinical Trials Database
EWOC	Escalation With Overdose Control
FAF	Fundus Autofluorescence
FDA	Food and Drug Administration
FSH	Follicle Stimulating Hormone
GA	Geographic Atrophy
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HA	Health Authority
HbA1c	Glycosylated haemoglobin
HCG	Chorionic Gonadotrophin
HR	Heart Rate
ICF	Informed Consent Form
IV	Intravenous
IVT	intravitreal
IB	Investigator's Brochure
ICH	International Council on Harmonisation
IEC	Independent Ethics Committee
IMP	Investigational Medical Product
IOP	Intraocular Pressure
IQRM	Integrated Quality and Risk Management
iPDs	Important Protocol Deviations

IRB	Institutional Review Board
ISF	Investigator Site File
ISO	International Organization for Standardization
IUS	Intrauterine Hormone-Releasing System
KD	Dissociation constant
LPLT	Last Patient Last Treatment
MD	Multiple Dosing
MedDRA	Medical Dictionary for Drug Regulatory Activities
MoA	Mode of Action
MTD	Maximum Tolerated Dose
µg	Microgram (10^{-6} gram)
NBE	New Biological Entity
NOAEL	No Observed Adverse Effect Level
OCT	Optical Coherence Tomography
OCT-A	OCT Angiography
OPU	Operative Unit
PD	Pharmacodynamics
PK	Pharmacokinetics
PKS	Pharmacokinetic parameter analysis set
P(OD)	Probability of over-dosing
PT	Prothrombin Time
P(TD)	Probability of target dosing
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SD-OCT	Spectral Domain Optical Coherence Tomography
SMC	Safety Monitoring Committee
SOP	Standard Operating Procedure
SRD	Single Rising Dose
STZ	Streptozotocin
SUN	Standardization of Uveitis Nomenclature
SUSAR	Suspected Unexpected Serious Adverse Reactions
$t_{1/2}$	Half Life Time
t_{max}	Timepoint of Maximum Plasma Concentration

TMF	Trial Master File
TrkA	Tropomyosin-related Kinase Receptor Type A
TrkB	Tropomyosin-related Kinase Receptor Type B
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Level of Normal
VA	Visual Acuity
VEFG	Vascular Endothelial Growth Factor
WBC	White Blood Cells
WG	Working Group
WHO	World Health Organisation
WOCBP	Woman of childbearing potential
YAG	Yttrium Aluminium Granat

1. INTRODUCTION

Boehringer Ingelheim (BI) is planning to develop BI 754132, an agonistic humanized immunoglobulin G1 (IgG1) for the TrkB (tropomyosin-related kinase receptor type B) receptor. BI 754132 binds to the extracellular domain of TrkB and causes auto-phosphorylation and induction of downstream signalling cascades, leading to increased glial cell and neuronal survival as well as potentially synaptogenesis, for treating geographic atrophy (GA) secondary to age-related macular degeneration (AMD).

1.1 MEDICAL BACKGROUND

Age-related macular degeneration (AMD) is a common cause of legal blindness in the elderly population of the developed world. Approximately 10% of individuals aged 65 to 74 years, and 30% of those aged 75 to 85 years, show signs of AMD [R13-1509]. AMD is a medical condition which may result in blurred or no vision in the center of the visual field. It preferentially affects the central vision, which is needed for reading, driving, recognizing people's faces and color vision.

Clinically, AMD is divided into dry and wet AMD. However, it is better to describe AMD as the early phase which is virtually asymptomatic, intermediate advanced phase with mild visual loss, which can then develop into geographic atrophy (GA) and / or neovascular (or wet) AMD. Highlighting the complexity of the disease, in some patients who are first diagnosed to have wet AMD and treated with anti-VEGF therapy, these patients can then develop GA even after the wet component is under control or stabilized.

The pathogenesis of AMD is not well understood, although significant progress has been made in recent years. Several theories have been put forward, including oxidative stress, mitochondrial dysfunction, choroidal perfusion dysfunction and inflammatory processes. The imbalance between production of damaged cellular components and degradation leads to the accumulation of intracellular lipofuscin and extracellular matrix material, commonly seen clinically as yellow deposits called drusen. Photoreceptor loss occurs overlying the drusen area. Incipient atrophy is demarcated by thinning or depigmentation of the retinal pigment epithelium (RPE), the supporting layer of the photoreceptors, in the macular area during early disease stages. In the advanced stages of AMD, atrophy of the RPE over a geographic area (GA) and/or development of neovascularization result in massive loss of photoreceptors and central vision loss.

In contrast to wet AMD, where loss of vision is typically acute and treatment leads to a relatively rapid reduction in retinal fluid and subsequent improvement in visual acuity (VA), disease progression and vision loss in GA is a gradual process.

While neovascular AMD is effectively treated with anti-VEGF agents, no approved therapy is available to prevent either onset or progression of GA. However, in recent years, a number of new potential therapies has been tested. Recently, results from Phase III trials of Lampalizumab (Roche), an Anti-Complement Factor D Fab, showed no efficacy. Ongoing clinical trial evaluations include e.g. APL-2 (Apellis), an Anti-Complement C3 in Phase III development.

A possible explanation for the recent failures evaluating new potential drugs for GA could be that, because this pathology includes different sub-types of diseases, trials need to better identify the target population based upon the mechanism of action of the compound [R18-3147]. Moreover, there is uncertainty on which cell type is primarily affected in GA. Some studies indicate that the first alteration is in the RPE cells, followed by photoreceptors and choriocapillaris loss [R18-3146, R18-3150]. Some other investigations suggest that photoreceptors play a fundamental role in GA onset [R18-3148]. Photoreceptor loss is already observed in early and intermediate stages of AMD before progression to the more severe form of GA [P17-03129], and accompanied by additional functional changes of the inner retina downstream of photoreceptors [R18-3153]. Therefore, neuroprotection of the retina via TrkB activation, in particular of photoreceptors, could be a promising new therapeutic concept for GA.

1.2 DRUG PROFILE

Mode of action
BI 754132 is a human IgG1 with agonistic activity for the human TrkB receptor which leads to phosphorylation and induction of downstream signaling similar to that induced by the endogenous TrkB agonist, brain-derived neurotrophic factor (BDNF), resulting in an increase in cell survival and potentially synaptogenesis.

Key pharmacokinetic characteristics
BI 754132 demonstrated similar ocular pharmacokinetics as Avastin® in the rabbit after intravitreal (IVT) administration (see Investigator`s Brochure (IB) Section 5.2 [c22785135]). Human ocular PK of BI 754132 is expected to be similar to that of Avastin® (human vitreal $t_{1/2}$ of 9.73 days). The predicted human efficacious dose of BI 754132 is 3 mg/eye administered every 3 months.

BI 754132 is a monoclonal antibody with a molecular weight of 146 KDa, which is above the renal filtration cut-off threshold (around 60 KDa). BI 754132 is not expected to have a significant renal filtration. It is expected to undergo protein catabolism therefore dedicated absorption, distribution, metabolism, and excretion studies have not been conducted for BI 754132.

Drug-Drug interactions:
BI 754132 is a therapeutic protein eliminated through protein catabolism. BI 754132 is not an immune modulator and is not expected to impact CYP450 enzymes. Therefore, pharmacokinetic drug-drug interactions between BI 754132 and co-administered drugs are not likely.

Pharmacology:
BI 754132 is an agonistic IgG1 antibody that displays high affinity for human TrkB receptor as determined by in vitro binding assessment. It binds with a binding affinity (KD) of 1.44 nM to the extracellular domain (ECD) of human TrkB receptor, which is identical to the ECD in the cynomolgus TrkB receptor [n00262761-01]. Furthermore, BI 754132 does not exhibit activity regarding the induction of human TrkA or human TrkC receptor phosphorylation [n00255513-01].

BI 754132 exhibits a pronounced species selectivity and is not active on mouse and rat TrkB receptors, precluding it from pharmaco-dynamics (PD) profiling in established rodent retinal disease models. In preclinical models, EX00077780, a TrkB agonistic antibody that is also active on rat and mouse TrkB receptors, was used as a surrogate. The in vivo efficacy of EX00077780 in rodent models of retinopathy, especially the neuroprotection and the improvement in neuronal function [n00254511-01], reflects the therapeutic potential of IVT TrkB activation for the treatment of retinal diseases, including GA.

Safety pharmacology
BI 754132 did not demonstrate any adverse effects on neurological or respiratory functions. In the 13 week IV toxicology study [n00259625-01], BI 754132 administration was associated with decreases (up to 0.6x) of mean values for blood pressure (systolic, diastolic, and mean arterial pressure) in females at ≥ 3 mg/kg on Days 22 and 85 compared to the control. Similar decreases were not noted in the males. BI 754132 did not cause changes in heart rate or electrocardiograms (ECGs) in the 13-week IV toxicology study.

Toxicology
The toxicology data suggest BI 754132 can be safely administered via IVT to humans for up to 13 weeks. Given that the tolerability and immunogenicity profiles in human may be different from those in cynomolgus monkey, the potential inflammatory and immunogenicity responses in human should be closely monitored. Escalation of doses in human should be based on the tolerability in the earlier cohorts and the maximum dose in human should not exceed 6 mg/eye. Potential systemic effects including body weight, heart rate, blood pressure and hematology should be monitored based on the findings in the cynomolgus studies (see Section 1.4.2 and IB [c22785135] Section 5.3 for further details).

BI 754132 is a human IgG1 carrying FcR-gamma receptor binding mutations for reducing ADCC and CDC. BI 754132, an agonist for the TrkB receptor, binds to the extracellular domain causing auto-phosphorylation and induction of downstream signaling cascades for increased cell survival and synaptogenesis. Based on expected pharmacology and reduced Fc effector function, the risk for cytokine release syndrome in humans is expected to be low. There were no signs of cytokine release in the monkey studies.

Data from clinical studies
The first-in human trial, 1418-0001, an open-label, multicenter, Phase I study, investigates the safety, tolerability and pharmacokinetics of BI 754132 administered intravitreally in patients with GA secondary to AMD. The study has two parts: a single rising dose (SRD) and a multiple dose (MD) part. In the SRD part, 15 patients will be included (3 patients per dose cohort and additional 3 patients in the highest tolerated dose cohort) to test an increasing exposure to BI 754132 with 4 doses (0.3, 1, 3, 6 mg). The MD part will test the highest tolerated dose from the SRD part with 6 patients. Three doses of BI 754132 will be administered 4 weeks apart.

At the time of amending this CTP, 3 patients of Cohort 1 (0.3 mg), 3 patients of Cohort 2 (1.0 mg), 3 patients of Cohort 3 (3.0 mg) and 6 patients of Cohort 4 (6 mg) had completed the SRD part of trial 1418-0001.

Pharmacokinetics:
Systemic Pharmacokinetic (PK) samples of the first-in-human single-rising dose study 1418-0001 were obtained from all patients of the SRD part. PK samples were collected before IVT injection and at 4, 72, 168, 336, 672, 1344, 2016, and 2352 h after injection. Cohort 1 (0.3 mg) had no measurable BI 754132 serum concentrations. For Cohorts 2 and 3, detectable individual patient serum concentrations of BI 754132 were 26.2 µg/L 4 h post-dose in the 1.0 mg dose and 6.38 µg/L 168 h post-dose in the 3.0 mg dose.

Patients in Cohort 4 (6.0 mg) showed systemic values ranging from 6.35 - 28.7 µg/L within 4 to 168 h post IVT administration (for further details see current version of IB [c22785135]).

Ant-drug antibodies (ADAs):
As all patients in Cohorts 1 through 4 completed the study sera collected from all visits have been analyzed for ADA responses. Thus far, one positive patient titer (1:1280) was observed at study Visit 10 (EoT) in the 3.0 mg dose group.

Safety evaluations:
The safety evaluation of the SRD part includes surveillance of dose limiting events (DLEs), physical examination, vital signs, laboratory testing, 12-lead ECG, and AEs (including ocular AEs).

At the time amending this CTP, 15 patients were enrolled in the SRD part and treated with single doses of intravitreal BI 754132 (3, 3, 3 and 6 patients in the 0.3, 1.0, 3.0 and 6.0 mg dose groups, respectively). All fifteen patients completed the study up to the final end of trial (EoT) visit 10.

Out of the15 patients treated with BI 754132, 9 patients across all dose cohorts were reported with an AE, (see Table 6.2.1: 1 in IB [c22785135]).

Two serious AEs (SAEs) were reported in which optic disc swelling was diagnosed as non-arteritic anterior optic ischaemic neuropathy (AION).

The first case occurred in the study eye of a patient in the 0.3 mg dose cohort. The patient was subjectively asymptomatic and the optic disc swelling was most likely related to an anterior ischemic optic neuropathy and diagnosed as an incidental finding during a planned study visit (visit 9, 84 days after study drug administration). The event was classified by the investigator and BI as not drug- or procedure-related. The AE was of moderate intensity, and it was reported as resolved at the last follow-up visit.

The second case occurred in the study eye of a patient in the 6.0 mg dose cohort. The patient was symptomatic and reported blurred vision and a visual field defect with an onset on day 46 after study drug administration. The diagnosis was established at an unscheduled visit on day 52. The patient had a swelling of the optic disc and hemorrhages which were diagnosed as non-arteritic AION. The event was classified by the investigator as not drug- or procedure-related and of moderate intensity. At the EoT visit the optic disc swelling had regressed and the visual field defect slightly improved. The AE was classified as ongoing.

Non-arteritic AION has an incidence of ~1:10 000/year in the general population 50 years or older.

No specific data on the non-arteritic AION incidence rate are available for patients with Geographic Atrophy. Based on the limited human exposure and the epidemiological data, the Safety Monitoring Committee (SMC) and the Sponsor concluded that the findings could be coincidental, but a causal relationship to the trial drug cannot be fully excluded. Accordingly, the second SAE was reported as a SUSAR.There were a total of 12 ocular AEs; 4 were considered study drug-related and 5 were considered procedure-related. All ocular AEs, except for the optic ischaemic neuropathies were of mild intensity. All ocular AEs related to study drug or procedure recovered, with the exception of the second AION case.

Overall, 20 systemic AEs were reported. None of these were considered study drug-related and all were of mild or moderate intensity.

No Adverse Events of Special Interest (AESIs), DLEs or deaths were reported, and there was no identifiable exposure/dose-AE relationship. There were no apparent patterns of any clinically significant abnormalities in the general (ECG, vital signs, lab safety parameters) or ophthalmological (IOP, slit lamp, BCVA, SD-OCT, FAF, CFP and OCT-A) safety assessments.

For a more detailed description of BI 754132, please refer to the current IB [c22785135].

1.3 RATIONALE FOR PERFORMING THE TRIAL

There is no available treatment for GA, and given the degenerative nature of this disease, it is likely that the visual acuity in these patients will continue to worsen up to the stage of legal blindness.

As a transition from preclinical investigations to clinical development in this first-in human trial, safety, tolerability and pharmacokinetics of BI 754132 will be assessed in GA volunteer patients using single rising intravitreal doses and a multiple intravitreal dose in order to provide the basis for an ongoing clinical development of BI 754132 in the indication GA secondary to AMD.

This trial will include patients affected by GA with significant visual loss since because intravitreal injections in healthy subjects would not be considered ethically justifiable.
This trial will consist of a single rising dose (SRD) and a multiple dosing (MD) part.

In the single rising dose parts, within each dose group, all intravitreally treated patients will receive the same BI 754132 dose. The next higher dose will only be administered to the next group, if the treatment in the preceding dose group was safe and showed acceptable tolerability. Plasma concentrations will be assessed to investigate the relationship between systemic drug exposure and potential observable systemic AEs.

In the MD part, one multiple dose cohort (6 patients) will be studies over a 22 week period. After an initial active treatment period of 12 weeks (3 injections in 4 weekly intervals)

patients will be followed up for an additional 10 weeks without further injections to study the tolerability and pharmacokinetics. This might also help to guide injection frequency intervals in later studies.

1.4 BENEFIT - RISK ASSESSMENT

1.4.1 Benefits

GA is a progressive disease that leads to an irreversible loss in central vision because of degeneration of RPE and photoreceptors. People affected by this pathology may result in blurred or no vision in the center of the visual field, needed for reading, driving, recognizing people's faces and color vision. There is no approved treatment for this disease, and usually patients can only be followed-up.

TrkB receptors are abundantly expressed by retinal neurons and glial cells. In the normal retina, TrkB signaling counteracts cell stress and promotes cell survival.

Both published data as well as in-house preclinical studies [n00254512-01, n00254511-01, n00255512-01] showed that TrkB activation can protect photoreceptors in animal models of diabetes, retinal ischemia as well as in the blue light-induced photoreceptor degeneration model. Furthermore, recent data show that levels of BDNF, the endogenous ligand of TrkB, are reduced in the eyes of AMD patients including GA [R18-3156], suggesting that reduced TrkB signaling might account for the loss of photoreceptors occurring in GA.

Therefore, stimulating TrkB signaling in the eyes of patients with GA might protect photoreceptors from degenerating, thereby counteracting the loss of vision.

1.4.2 Risks

1.4.2.1 Available clinical data on the MoA

1.4.2.1.1 Trials evaluating native ligand (BDNF)

Stimulation of TrkB receptor was previously tested in clinical trials with TrkB's native ligand, BDNF. Recombinant methionyl human BDNF was developed for the indication amyotrophic lateral sclerosis (ALS) in a Phase 1-3 development. Based on supportive data from the Phase 1-2 trials, this phase 3 controlled trial evaluated the use of recombinant methionyl human BDNF in 1135 patients affected by ALS, with daily subcutaneous administration up to 9 months (25 or 100 µg/kg/day). The safety profile was considered acceptable [R17-1162].

In 2000 a phase 1/2 trial assessed the use of the same recombinant human BDNF administered by intra-thecal infusion for 12 weeks. The major adverse events were sensory disturbances, insomnia, behavioural effects, dry mouth, increased sweating and gustatory abnormalities [R19-0073].

1.4.2.1.2 Trials evaluating agonist antibodies targeting TrkB

In 2011, Pfizer terminated a phase I trial evaluating subcutaneous administration of TAM-163, an agonist monoclonal antibody targeting TrkB, in patients affected by cachexia, due to the emergent safety concern of sensory symptoms (https://clinicaltrials.gov/ct2/show/NCT01262690?cond=TAM-163&rank=1). No data is available neither on dosages nor on the description and the severity of AEs observed in the trial. However, in a related paper on dose selection methodology employed for this trial, the authors indicated a hypothetical starting dose equal to 0.05 mg/kg, corresponding to 3 mg for a 60 kg human [R19-0077]. It should be noted that the expected systemic exposure in these clinical trials is much higher than the expected systemic exposure after intravitreal injection with the planned doses of BI 754132 (see IB [c22785135] Section 5.2).

1.4.2.2 Available data from pre-clinical toxicity studies

1.4.2.2.1 IV administration of BI 754132

BI 754132 was tested in pre-clinical studies in cynomolgus monkeys. IV administration of BI 754132 resulted in a reduction of lymphocytes in the spleen and in the thymus. The findings are not considered adverse because it was without effect on the peripheral lymphocyte count and did not result in apparent clinical effect on immune function. In IV study it was also observed an increase in body weight and a reduction of blood pressure.

Increased body weight in cyno study was not considered adverse because it did not affect the well-being of the animals under the condition of the study. Decreased blood pressure did not result in any clinically relevant finding nor affect the well-being of the animals, therefore was considered non-adverse.

1.4.2.2.2 IVT administration of BI 754132

IVT administration of BI 754132 for 13 weeks in cynomolgus monkeys was well tolerated with minimal findings (increased plasma fibrinogen and microscopic decrease of lymphocytes in the thymus).

1.4.2.2.3 Immunogenetic response in pre-clinical studies

Following IVT injection, high incidence (11/22) of plasma anti-drug antibody (ADA) after the fourth administration at day 85 was detected in treated monkeys. In two animals ADA response was associated with intraocular inflammation (perivascular sheathing, vascular leakage and optic nerve leakage, hazy media). The inflammation generally resolved after each dose (with or without topical treatment via eye drops); even severe intraocular inflammation showed resolution after dosing cessation and ophthalmic treatment. Immunogenicity to humanized protein in animal studies does not usually predict clinical immunogenicity in human. Moreover, ophthalmic inflammatory response is easily detected and monitored in patients, and usually can be addressed and resolved with topic anti-inflammatory therapy.

1.4.2.3 Risks related to intravitreal injection

Intravitreal injection has potential 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 754132 is the same, 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 suggests a favourable risk-benefit profile. To the best of the sponsor´s knowledge, there is currently no comparable material 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 considered low based on long-term experience with comparable material. 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 comparable material 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 material from certain manufacturers and leave the decision to the treating investigators/sites on which material to use if it meets the specifications as described in the IMP handling instructions for BI 754132.

1.4.2.4 Risks related to blood sampling

The use of an indwelling venous catheter for the purpose of 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 same risks apply to veinipuncture for blood sampling.

The total volume of blood withdrawn during the entire study per patient will not exceed the volume of a normal blood donation (appr. 500 mL). No health-related risk is expected from this blood withdrawal

1.4.2.5 Risks related to BI 754132 based on human clinical data

During the SRD part of this trial, two patients have experienced Non-Arteritic Anterior Ischemic Optic Neuropathy (AION) in the study eye with 0.3 and 6.0 mg BI 754132, respectively. Both events were classified as not related to study drug by the investigators, and patients had some predisposition including hypercholesterinaemia, hypertension and sleep

apnea. Non-arteritic AION is uncommon in the general population (incidence ~1:10 000/year in adults aged 50 years or older). Based on the limited human exposure and the available epidemiological data, it was concluded that the events could be coincidental, but that a causal relationship to the trial drug cannot be fully excluded. Accordingly, the second SAE was reported as a SUSAR and additional safety measures have been implemented in the MD part of the trial (see Section 1.4.2.6).

1.4.2.6 Planned measures for monitoring and minimization the risks

Taking into consideration all the clinical (during SRD) and pre-clinical findings, the AEs reported in previous trials involving the same mode of action (MoA) of BI 754132, and the risks related to the intravitreal injection, the trial will include complete ophthalmic examinations at each timepoint.

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 slit lamp 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 together with fundus autofluorescence (FAF) 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, changes in areas of focal increased autofluorescence).

Based on the safety data evaluation from the SRD part of the trial, the following measures are implemented in MD part of the trial:

- Detailed clinical assessment of optic disc morphology using indirect ophthalmoscopy Spectral Domain Optical Coherence Tomography (SD-OCT) and Color Fundus Photography (CFP)
- Implementation of a “Sentinel” strategy for the MD part
- Amendment of the inclusion and exclusion criteria to minimize the risk and impact for patients
- Update informed consent (IC) to include the potential risk for AION.

Additionally, a systemic evaluation will be performed at the timepoints specified in the flow charts under physical examination, to assess any possible systemic reaction. This will include: body weight, blood pressure, and pulse rate. At the time points specified in the Flow Chart I and Flow Chart II, full blood cell count, C-reactive protein (CRP; MD part only), Glycosylated haemoglobin (HbA1c; MD part only), prothrombin time (PT) and fibrinogen will be determined, and ECGs will be recorded. All these evaluations will have to

be reported immediately for evaluating any possible safety issue related to the drug or to inflammatory response.

1.4.2.7 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 5.2.8.1.4, AEs of special interest).

1.4.3 Discussion

Considering the data available from previous non-BI clinical trials evaluating the same MoA (see Section 1.4.2.1), and data from pre-clinical studies on BI 754132, in this trial extensive ophthalmic and systemic examinations are planned in all the visits.

Blood tests and physical examination will evaluate potential changes in blood cell count and fibrinogen plasma levels, 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.

Because of the agonistic mode of action of BI 754132, 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).

Based on the safety evaluation of the SRD part of this trial, additional assessments of the optic disc, an amendment of the inclusion and exclusion criteria as well as a sentinel recruitment strategy have been implemented in the MD part.

In the trial design a sentinel approach will be used, according to EMA and ICH guidelines (EMA/CHMP/SWP/28367/07 Rev.1; EMA/CHMP/ICH/731268/1998): In the SRD part, for each cohort the first patient will be dosed and monitored to exclude acute AEs, before dosing the other patients of the same cohort. For the MD part each patient will be dosed on a sentinel approach using the 4 weeks data to decide upon the second injection of the same patient and to start the dosing of the next patient (see Section 3.1).

Moreover, the duration of observation will reflect the expected human PK of BI 754132, with a follow-up for all patients up to 100 days (i.e. the minimum observation period per patient is 100 days), with appropriate ophthalmologic and systemic evaluations (see Section 3.1). The implications of the current Coronavirus pandemic (COVID-19) are summarized in Section 10.5.

Pre-clinical data show that BI 754132 can improve photoreceptor functionality, which holds promise to be beneficial in GA. However, because of the limited administration of BI 754132 during phase I and the long duration of the pathology of GA, long-term benefit for the

patients entered in this trial is unclear at this point of the development. Their participation in this trial, however, is of major importance to the development of BI 754132 to determine a safe dose for further clinical trials in this pre-selected patient population. Patients included in the trial will have progressed disease in the treatment eye, minimizing the effect of potential adverse events

GA is the leading cause of blindness in western countries, with no treatment available. Given the urgent need to address this unmet medical need and based on available clinical safety data analysis, SMC recommendations, as well as the added risk mitigation measures in the MD part, the benefit-risk of BI 754132 remains favorable and supports its continued use in this clinical trial.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective is to investigate ocular and systemic safety and tolerability as well as pharmacokinetics of single intravitreal and multiple intravitreal administrations of BI 754132.

2.1.2 Primary endpoint(s)

SRD part:
- Number of patients with ocular (in the study eye) and systemic dose limiting events (DLEs) from drug administration until end of trial (EOT). For definition of DLEs, refer to Section 5.2.1.

MD part:
- Number of patients with drug-related AEs from drug administration until EOT.

2.1.3 Secondary endpoint(s)

SRD part:
- Number of patients with drug-related AEs from drug administration until EOT
- Number of patients with any ocular AEs in the study eye from drug administration until EOT
- C_{max} (maximum serum concentration of BI 754132 after a single intravitreal dose)
- $AUC_{0-\infty}$ (area under the concentration-time curve of BI 754132 in serum over the time interval from 0 extrapolated to infinity)
- t_{max} (time from dosing to maximum serum concentration of BI 754132)

MD part:
- Systemic exposure of BI 754132 after multiple IVT doses by determination of $C_{min,1}$ and $C_{min,2}$ (trough levels before second and third administrations) and plasma concentrations 4, 8 and 14 weeks after the third administration

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The trial will consist of an SRD part followed by an MD part. Both parts will be conducted in a non-randomized, open-label, and uncontrolled manner.

SRD part:
Cohorts of patients will receive escalating doses of BI 754132, with the starting dose 0.3 mg. The other provisional dose levels are 1 mg, 3 mg, and the maximum planned dose 6 mg. Each cohort will consist of 3 newly enrolled patients. 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 being available systemic (i.e. physical examinations, safety lab parameters, ECG and AEs) and ophthalmological (i.e. as defined in Section 5.2.1) safety data until day 4. If this patient neither has experienced an ophthalmological nor a systemic DLE, the remaining 2 patients will be dosed. Written minutes of this assessment are being distributed to all investigators participating in this trial part.

A Safety Monitoring Committee (SMC, see Section 8.7) will decide on the next dose level to be investigated, the size of the next cohort based on occurrence of DLEs and on additional information (systemic PK and patient profiles). Refer to Figure 3.1.1 for a schematic representation of the dose escalation.

A Bayesian logistic regression model (BLRM) based on a weakly informative prior distribution, and employing the escalation with overdose control (EWOC) principle will be used for guiding the dose escalation (see Section 7.2.1.1). 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 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.

For any dose-escalation cohort, at least 3 evaluable patients will be required.

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 BLRM will be re-run to confirm that the dose level still fulfils the EWOC principle. Based on this information, the SMC will evaluate whether the next patients will be enrolled at the same dose level, or if they will be enrolled at a lower dose level.

As a sensitivity analysis, the BLRM might also be run again shortly before the SMC meeting, using all AE data available up to this time point.

The maximum tolerated dose (MTD) 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 that the MTD will likely be the highest feasible dose, 6 mg, rather than the highest tolerable dose in a strict sense. The SMC may decide on stopping the dose escalation after the criterion for MTD is fulfilled. Further patients may be included to confirm that the EWOC criterion is still fulfilled.

In Figure 3.1: 1, the dose escalation process is depicted as planned, i.e., if no DLE occurs in the trial and dose escalation may proceed up to the highest dose level.

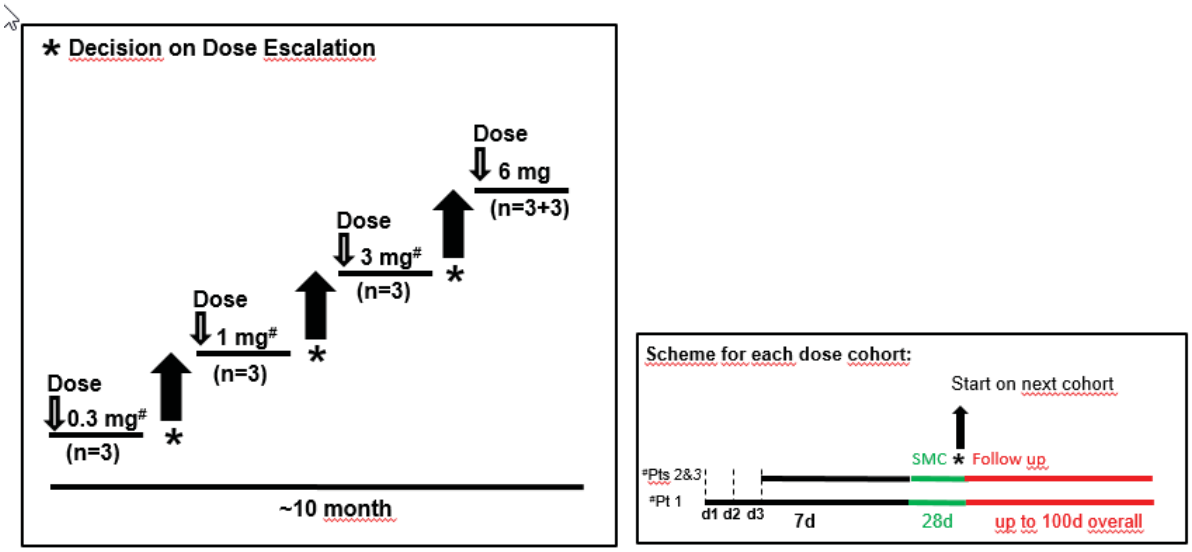

Figure 3.1: 1 Schematic representation of the dose escalation process in the SRD part

MD part:
The MD part will consist of one dose cohort (6 patients). After the SRD part has been completed, the SMC will decide on the selection of the highest dose (e.g. 6 mg) established as safe and tolerable during the SRD part to be used in the MD part. Patients that had received a dose in the SRD part of the trial (regardless of the eye) will not be included. In the MD part, patients will receive three consecutive dose injections over a 3-month period (dosing every 4 weeks).

For the MD part, the first patient will receive one dose and will be monitored after four weeks to exclude acute AEs and especially adverse changes of the optic disc. Data will be assessed by the dosing investigator and 2 representatives of the sponsor who are involved in the trial. The decision to continue will be based on pre-specified criteria and include certified gradings from the Central Reading Center (CRC). If no AEs or adverse changes of the optic disc are observed, the first patient can receive the second dose. The second patient can be dosed at least 7 days thereafter. The second to sixth patients will follow the same procedure as the first patient, with a safety review after 4 weeks. In addition, this safety review will include safety data from visit 4 of the previous patient (assessment 4 weeks after second injection) as well as all available safety data of the previous patients. Written minutes of this review are being distributed to all investigators participating in this trial part.

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

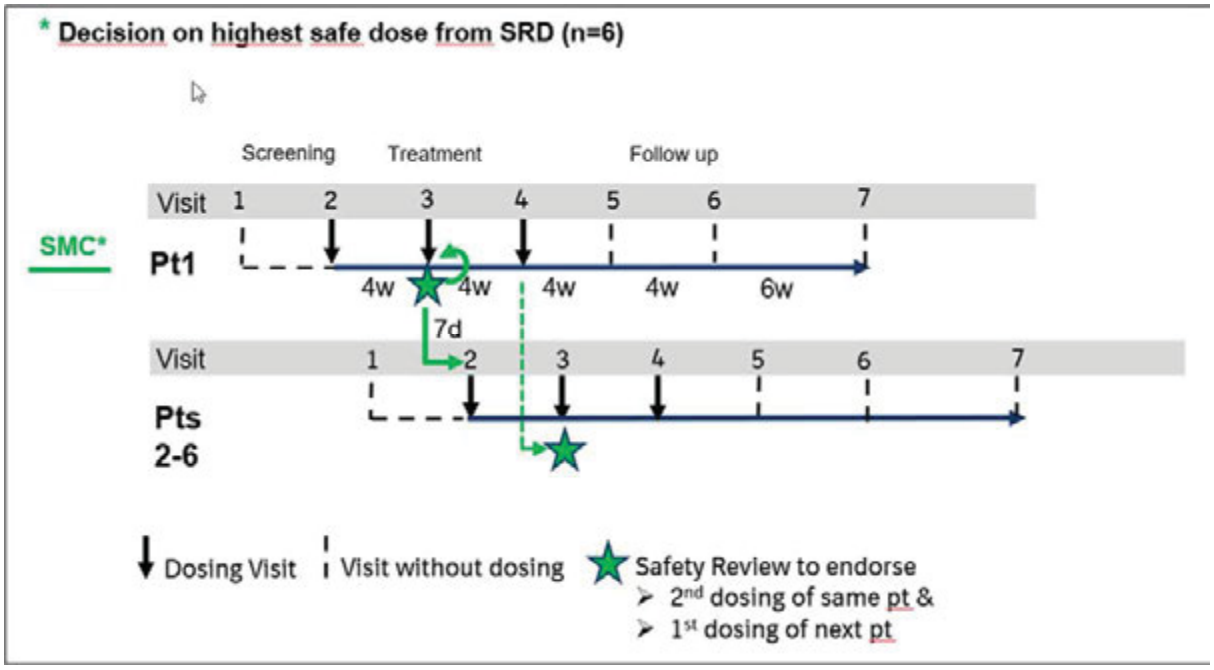

Figure 3.1: 2 Schematic representation of the sentinel dosing in the MD part

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

This trial is designed to establish a safe and tolerable dose for further testing in phase II trials. The trial consists of separate SRD and MD parts. A comparison between the untreated versus the treated eye is considered adequate to derive a safe and tolerable dose and therefore neither parts of this trial will use a comparison to sham injection.

The SRD dose escalation is designed to avoid exposure of too many patients to subtherapeutic doses while on the other hand the goal of safety and rapid dose finding is preserved.

The 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 Bayesian models 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 a 4-weekly interval) will be included after the SRD part. This part of the trial will generate additional safety data and plasma concentrations of BI 754132 after MD. These data will further support the definition of the injection frequency in later studies.

3.3 SELECTION OF TRIAL POPULATION

This trial will recruit approximately up to 24 patients in total. The SRD part is expected to enrol 18 patients; the actual number may increase depending on the occurrence of DLEs; please refer to Section 7.5 and Appendix 10.4 for details and justification. The MD part is expected to enrol 6 patients.

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) irrespective of whether they have been treated with investigational drug or not.

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.

3.3.1 Main diagnosis for trial entry

This trial enrols patients with GA secondary to AMD as diagnosed by FAF and with significant visual loss selected based on BCVA.

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

1. Men and women with GA secondary to AMD: For the SRD part, the GA lesion in the study eye must be ≥ 1.9 mm^2 disc area in size (approximately ≥ 0.75 disc area in size); for the MD part the total GA lesion size in the study eye must be ≥ 7.5 mm^2 (approximately ≥ 3 disc area in size).
2. Fellow eye is not required to have GA
3. BCVA:
   a. SRD part: BCVA of 20/100 to 20/400 Snellen (corresponding to 19 to 53 letters in the ETDRS chart) in the study eye equivalent measured by the Early Treatment Diabetic Retinopathy Study (ETDRS) protocol
   b. MD part: BCVA score of ≤53 letters (Snellen equivalent of 20/100) in the study eye
4. Age ≥ than 50 years
5. Best-corrected VA in the non-study eye must have a better best-corrected VA compared to the study-eye
6. Women of childbearing potential (WOCBP[1]) cannot be included. Men able to father a child must be ready and able to use 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

7. Signed informed consent consistent with ICH GCP guidelines and local legislation prior to participation in the trial, which includes medication washout and restrictions
8. Not under any administrative or legal supervision or under institutionalization due to regulatory or juridical order

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

3.3.3 Exclusion criteria

1. GA in either eye because of causes other than AMD
2. History of choroidal neovascularization (CNV) in the study eye and in the fellow eye
3. Previous treatment in the study eye for GA secondary to AMD within 6 months prior to screening visit (ongoing therapy with vitamin and mineral supplements is allowed)
4. Previous participation in other trials for treatment of GA receiving active drug in the study eye. For the MD part any patients that participated in SRD part of the trial (regardless of the eye).
5. Additional eye disease in the study eye that could compromise
   - best corrected VA (BCVA) with visual field loss,
   - uncontrolled glaucoma intraocular pressure (IOP>24),
   - clinically significant diabetic maculopathy,
   - history of ischemic optic neuropathy or retinal vascular occlusion,
   - symptomatic vitreomacular traction,
   - genetic disorders such as retinitis pigmentosa);
   - history of high myopia > 8 diopters in the study eye and
   - anterior segment and vitreous abnormalities in the study eye that would preclude adequate observation with SD-OCT
6. Any prior intraocular surgery in the study eye other than uneventful lens replacement for cataract within 3 months prior to screening
7. Aphakia or total absence of the posterior capsule. Yttrium aluminium granat (YAG) laser capsulotomy permitted, more than 3 months prior to enrolment in the study eye
8. 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)
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 the any of the following:
   - Put the patient at risk because of participation in the study
   - Influence the results of the study,
   - Cause concern regarding the patient's ability to participate in the study, e.g. cardiac (including tachycardia), gastro-intestinal, hepatic, renal, metabolic, dermatologic, neurological, haematological, oncological and psychiatric.

10. 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.
11. Known hypersensitivity to any of the ingredients used in the IMP formulation, or any of the medications used
12. Active intraocular inflammation in the study eye
13. Active infectious conjunctivitis in either eye
14. For the MD part: Unstable cardiovascular/metabolic disease (e.g. hypertension, diabetes mellitus, hypercholesterolemia) and/or not on stable medication for these conditions at least 3 months prior to inclusion
15. For the MD part: Any evidence for current or past giant cell arteritis

3.3.4 Withdrawal of patients from treatment or assessments

Patients may be withdrawn from trial treatment or withdraw consent to trial participation as a whole ("withdrawal of consent") with very different implications; please see Sections 3.3.4.1 and 3.3.4.2 below.

Every effort should be made to keep the 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 trial enrolment, as well as the explanation of the consequences of withdrawal.

The decision to discontinue trial treatment or withdraw consent to trial participation and the reason must be documented in the patient files and Case Report Form (CRF).

3.3.4.1 Withdrawal from trial treatment

An individual patient is to be withdrawn from trial treatment if:
- The patient wants to discontinue trial treatment, without the need to justify the decision.
- 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.
- The patient needs to take concomitant medication that interferes with the investigational medicinal product or other trial treatment
- The patient can no longer receive trial treatment for medical reasons (such as surgery, adverse events, other diseases, or pregnancy). An AE or clinically significant laboratory change or abnormality occurred that the investigator judges to warrant discontinuation of treatment.

Even if the patient is withdrawn from trial treatment, the patient remains in the trial and, given his/her agreement, will undergo the procedures for early treatment discontinuation and follow-up as outlined in the Flow Chart I and Flow Chart II and Section 6.2.

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.

This will however mean that no further information may be collected for the purpose of the trial and negative implications for the scientific value may be the consequence. Furthermore, it may mean that further patient follow up on safety cannot occur.

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 above.

3.3.4.3 Discontinuation of the trial by the sponsor

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

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

For the following scenario further enrolment and entering 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.
- For the MD part: Occurrence of AION or relevant predisposing changes of the optic disc in the study eye after administration of BI 754132.

The investigator / the trial site will be reimbursed for reasonable expenses incurred in case of trial termination (except in case of the third reason).

3.3.5 Replacement of patients

SRD part:
Patients withdrawn before visit 4 for another reason than DLE or patients who miss any visit between visits 2 and 4 are not evaluable for the occurrence of a DLE within 7 days after drug administration. These patients will be replaced until 3 evaluable patients are included.
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 subject will be assigned a unique study subject number and will be assigned to the same treatment as the subject he or she replaces.

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1:1 BI 754132

Substance:	BI 754132
Pharmaceutical form:	powder for solution for injection
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	60 mg/vial
Posology:	SRD part: One single injection MD part: 3 injections, each separated by 4 weeks
Mode of administration:	Intravitreal

Table 4.1.1:2 Diluent

Substance:	Diluent for reconstituted BI 754132 powder for solution for injection 60 mg/vial, 10 mL/vial
Pharmaceutical form:	Solution
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	n/a
Posology:	SRD part: One single injection MD part: 3 injections, each separated by 4 weeks
Mode of administration:	Intravitreal

4.1.2 Selection of doses in the trial and dose modifications

Because of the agonistic mode of action of BI 754132 and potential species differences in activation of cyno vs. human TrkB, an efficient dose selection strategy is critical to the successful clinical development of BI 754132. The selection of doses that are too high may lead to significant safety concerns, as exemplified by the case of TGN1412, an agonistic antibody against a T cell target [R19-0690]. Whereas a dose that is too low can lead to the need for clinical testing of a wide dose range and a higher number of patients exposed to the IMP.

Dose selection was driven by the invasive mode of administration and the resulting need to cover the potential dose range with a limited number of doses (in order to limit the number of patients at risk for adverse reactions related to the mode of administration). In addition, the lowest dose in the trial should provide a reasonable safety margin to the no observed adverse

effect level (NOAEL) and, on the other hand, have the potential to already result in beneficial effects to the patient to outweigh the risk of an AE caused by the IVT administration.

The observed NOAEL in the 13-week IVT study in cynomolgus monkeys was 6 mg/eye. As the vitreous volume in humans is approximately two times of that in cynomolgus monkeys [R17-3647], therefore the vitreal concentration achieved in cynomolgus is equivalent to a vitreal concentration reached after ivt injection of a 12 mg/eye dose in humans. A safety factor of 40-fold was applied; 10-fold for extrapolation from animal to human, and an additional factor of 4-fold for the potency shift observed between cyno and human in the functional assay. These combined safety factors result in a maximum recommended starting dose of 0.3 mg/eye.

The measurement of the ERG a-wave in the STZ rat model represents a reliable animal surrogate to evaluate the effect of TrkB activation on photoreceptor function supporting the therapeutic benefit in GA patients. In an-in-house study using such a model [n00254511-01] the targeted efficacious dose for BI 754132 was calculated to be a trough EC_{50} of 6.38 nM based on the pharmacological data of EX00077780 (tool TrkB antibody that cross reacts to the rat TrkB receptor). The human dose estimation of BI 754132 was performed based on scaling the PK/PD of the tool antibody from rat to human and comparison of PK between BI 754132 and Avastin [n00264883-01, R18-2968]. Taking into consideration the vitreous humor volume, the estimated human intravitreal half-life ($t_{1/2}$ = 9.73 days) and the C_{trough} value, an injection of 3 mg/eye every 90 days would maintain intravitreal concentration above the required $C_{through}$ of 6.38 nM.

The proposed starting dose of 0.3 mg/eye is predicted to maintain the predicted minimal efficacious vitreal concentration of 6.38 nM for 60 days. Doses lower than 0.3 mg are also expected to induce PD effects in the eye, however the duration of the effect would be smaller and in the light to slow down/halt GA progression with special emphasis on photoreceptor degeneration this PD effect would not be long enough to justify a potential long term benefit to the patients.

For the 1 mg and 3 mg dose, the relative increase to the next dose is 233% and 200%, respectively. These doses limit the dose steps and resulting number of trial related IVT injections. Before each subsequent dose is administered, an external safety monitoring committee will be convened to determine if it is safe to proceed to the next dose. If all previous doses are clinically well tolerated, one additional dose of 6.0 mg will be tested, as one of the development objectives is to find a dose that provides extended drug exposure and therefore longer efficacy and less injection frequency.

The provisional dose levels to be assigned to separate cohorts of patients are listed in 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.

Table 4.1.2: 1 Provisional dose levels for escalation

Dose level	Proposed dose	Relative increment from previous dose
1	0.3 mg	Starting dose
2	1 mg	233%
3	3 mg	200%
4	6 mg	100%

4.1.3 Method of assigning patients to treatment groups

Patients for this trial will be selected based on BCVA and the presence of GA as diagnosed by FAF, SD-OCT and color fundus photography.

Recruitment of the trial will be started 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 selected dose has been endorsed by SMC.

In the SRD part, the doses are planned to be escalated in cohorts at the pre-defined provisional dose levels; see Table 4.1.2: 1. 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 described 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 will be done successively for the dose groups, i.e. if the required number of patients for one dose group will be completed and the next dose is considered safe based on (the BLRM model and) the clinical course, the recruitment of the next higher dose group may be started. Therefore, the recruitment of subjects for the dose groups will neither be influenced by the trial personnel nor by any characteristics of the patients, but only by temporal availability.

The highest dose (e.g. 6 mg) established as safe and tolerable during the SRD part will be used in the MD part after the SRD part has been completed.

4.1.4 Drug assignment and administration of doses for each patient

BI 754132 solution for injection will be administered intravitreally.

The drug product “BI 754132, powder for solution for injection, 60 mg/vial” and the diluent “Diluent for reconstituted BI 754132 powder for solution for injection” will be provided by BI. A site pharmacist will prepare the BI 754132 solution for injection according to the instruction provided in the ISF and provided handling instructions of the IMP.

Table 4.1.4: 1 Planned doses and treatment schedule for the SRD part

Dose group (mg)	Visit 2 Day 1
0.3	X
1.0	X
3.0	X
6.0	X

To determine the dose regimen for the next cohort, the available toxicity information (including DLEs and AEs that are not DLEs), PK, as well as the recommendations from the BLRM will be evaluated by the SMC members at the dose escalation 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 doses and treatment schedule for the MD part

Dose group (mg)	Visit 2 Day 1	Visit 3 Day 29	Visit 4 Day 57
MD dose	X	X	X

Intravitreal Injection Technique
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. After administration of BI 754132, 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.

4.1.5 Blinding and procedures for unblinding

4.1.5.1 Blinding

In this open-label trial, treatment allocation will not be concealed throughout the trial. The CRF will contain information on treatment.

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

4.1.5.2 Unblinding and breaking the code

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

4.1.6 Packaging, labelling, and re-supply

The investigational medicinal products will be provided by BI or a designated CRO. They will be packaged and labelled in accordance with the principles of Good Manufacturing Practice (GMP).

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

4.1.7 Storage conditions

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

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

4.1.8 Drug accountability

The investigator or designee will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:
- Approval of the clinical trial protocol by the IRB / ethics committee,
- 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 CTP,
- Availability of the proof of a medical license for the Principal Investigator,
- Availability of FDA Form 1572

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

The investigator or designee must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each 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 medicinal product and trial

patients. The investigator or designee will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational medicinal products received from the sponsor. At the time of return to the sponsor and/or appointed CRO, the investigator or designee must verify that no remaining supplies are in the investigators possession or have been destroyed.

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

There is no available therapy for GA, therefore no concomitant therapy is possible. In case of CNV or occurrence of any other retinal disease/complication, as per judgment of the investigator, administration of local standard of care treatment such as Intravitreal Treatment (IVT) or peribulbar injections, or laser or other surgical treatment is allowed.

Any 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) are not allowed in the trial.

4.2.2.2 Restrictions on diet and life style

None.

4.2.2.3 Contraception requirements

WOCBP (partner of a trial participant, for the definition please refer to Section 3.3.2) and men able to father a child (trial participant) must use two medically approved methods of birth control throughout the trial (from Visit 1 until Visit 10) one barrier method, and one highly effective non-barrier method.

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

WOCBP (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 Visit 10) 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.

4.3 TREATMENT COMPLIANCE

Compliance will be assured by administration of all trial medication in the study centre under supervision of the investigating physician or a designee. The measured sample concentrations will provide additional confirmation of compliance. Subjects who are non-compliant (for instance, who do not appear for scheduled visits or violate trial restrictions) may be removed from the trial and the CRF will be completed accordingly (for further procedures, please see Section 3.3.4.1).

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

Not applicable since not expected after a single or triple (q4w) intravitreal applications and the long-term progression of the disease.

5.2 ASSESSMENT OF SAFETY

5.2.1 Dose limiting event

A dose limiting event (DLE) is defined as the occurrence of any of the following events as ocular DLE (in the study eye):

- 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 measured by slit lamp (see Table 5.2.1: 1 below) and a duration of 5 or more days
- Visual loss of more than 15 letters at any given timepoint due to treatment effect in the study eye confirmed on consecutive visits
- Persistent IOP over 30 mmHg for 3 days
- Signs of vascular occlusion in the retina, including peripheral retinal haemorrhage (haemorrhage of the macula would not be included as this is a possible sign of CNV occurrence; peripheral retinal haemorrhage may be a sign of vascular occlusion)

Table 5.2.1: 1 The SUN Working Group Grading Scheme for Anterior Chamber Cells [R18-1136]

Grade	Cells in Field[1]
0	<1
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.

or as systemic DLE:

- Drug-related AEs of moderate and severe intensity according to CTCAE [R18-1357] out of the following:
    - Self-reporting paraesthesia, dysgeusia, taste abnormality, taste disorder, hyposmia [R19-0073]
    - Diarrhea, cough [R17-1162]

Each DLE needs to be reported as AESI (see Section 5.2.8.1.4).

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 (only at Visit 1) and body weight.

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

5.2.3 Vital signs

Vital signs will be evaluated at the time points specified in 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. Prior to the blood pressure measurement, the PI should ensure that the subject has taken his or her blood pressure medications (if any) as usual at home. If the measurement results are to be doubted for example because of preceding great exertion of the subject, a new measurement should be taken after half an hour in a resting position and only this stable value has to be entered in the eCRF.

5.2.4 Ophthalmological examinations

As described in Section 1.4.2.6, the trial will include the following ophthalmologic examinations on both eyes for safety considerations at the timepoints indicated in Flow Chart I and Flow Chart II:

Ophthalmologic examination
A complete ophthalmologic examination of both eyes including slit lamp examination, IOP measurement and dilated binocular indirect ophthalmoscopy (MD part only) will be performed by qualified persons. This examination will be performed at the timepoints defined in Flow Chart I and Flow Chart II.

Color Fundus Photography (CFP)
Seven-field or modified 4-field digital fundus photographs will be obtained from both eyes by a qualified person according to the imaging manual. This examination will be performed at the timepoints defined in Flow Chart I and Flow Chart II.

SD-OCT/OCT-Angiography (OCT-A)
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 Central Reading Center (CRC) for evaluation. A detailed manual for OCT image acquisition and data transmission will be provided.

Fundus autofluorescence (FAF)
FAF is a non-invasive imaging technology for the morphological assessment of GA. The fluorescence signal predominantly originates from fluorescent material within RPE cells. In eyes with GA, distinctly dark areas are observed where the atrophy of RPE cells leaves an absence of fluorescent signal allowing for a quantification of the size of atrophic regions. The assessment is also performed by a qualified person, and only specified device(s) will be used. FAF images will be sent to an independent CRC for evaluation. A detailed manual for FAF image acquisition and data transmission will be provided.

Visual Acuity measured by ETDRS letter charts
BCVA will be determined by using the 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.

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.

Centrally collected ophthalmological data (CFP, FAF, SD-OCT/OCT-A) will be transferred from the CRC to the sponsor's database. The local measurement data will remain at the study sites as source documents. If clinically significant worsening is observed in the safety assessments during the study, it will be reported as AE in the eCRF (please also refer to Section 5.2.8).

In the MD part, special attention should be payed to relevant adverse changes of optic disc morphology (e.g. new swelling or hemorrhage, change of cup-to-disc ratio, relevant changes of thickness of the peripapillary retinal nerve fibre layer as assessed by a circular OCT scan) or function (e.g. loss of BCVA or impaired vision). Relevant changes should be reported immediately to the Sponsor.

5.2.5 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Tables 5.2.5: 1 and 5.2.5: 2. For the sampling time points please see 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, 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 adverse events (please refer to Section 5.2.8).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.8.1 and the DILI Checklist provided in the ISF 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.

Table 5.2.5: 1 Safety laboratory parameters – whole blood, serum or plasma

Hematology • Haematocrit • Haemoglobin • Glycosylated Hemoglobin (HbA1c) • MCV, MCH, RDW, MCHC • Red Blood Cells (RBC) / Erythrocytes	• WBC / Leukocytes (number of B and T-cells) • Platelet Count / Thrombocytes • Differential Automatic (relative and absolute count): Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes
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	• Creatine kinase (CK) • C-reactive protein (CRP) • CK-MB, troponin I (reflex tests if CK is elevated) • Lactate dehydrogenase (LDH) • Lipase • Magnesium • Phosphate • Potassium • Protein total • Prothrombin time • Sodium • Urea (BUN) • LDL/HDL and total cholesterol • Triglycerides • TSH • Folate • Fibrinogen

Table 5.2.5: 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) will only be performed if required by local regulations. It may also be done more frequently or in plasma instead of urine if required (please note: this trial will include no patients of child-bearing potential)

5.2.6 Electrocardiogram

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). As an optional procedure, precise electrode placement will be marked with an indelible mark on the skin to allow reproducible placement throughout the study.

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

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

ECGs will be recorded as triplicate ECGs (i.e. three single ECGs recorded within 180 sec) as indicated in Flow Chart I and Flow Chart II.

ECGs may be repeated for quality reasons for instance due to alternating current artefacts, muscle movements, or electrode dislocation. These can be done as single ECGs. For repetition within triplicate ECGs, the time window of 180 sec applies as well. 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 Flow Chart I and Flow Chart II all recorded 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.

Data transfer from the central ECG lab to the sponsor is described in the ECG data transfer agreement (see TMF).

Evaluation
Central ECG lab evaluation will be performed for all ECGs indicated in Flow Chart I and Flow Chart II. For all ECGs, this will include the intervals RR, 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 TSAP for details).

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

For blinding arrangements see Section 4.1.5. ECG interval measurements from a particular subject should be performed by a single reader. For quality assurance and control of the measurements, a random subset of all ECGs and all ECGs meeting a set of outlier parameters will undergo a second review by a Quality Control Specialist. After quality control, the fiducial point markings will be reviewed by the cardiologist assigned to the study.

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

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

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

5.2.7 Other safety parameters

Not applicable.

5.2.8 Assessment of adverse events

5.2.8.1 Definitions of AEs

5.2.8.1.1 Adverse event

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

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

The following should also be recorded as an AE in the 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 exist prior to trial inclusion, they will be considered as baseline conditions and should be collected in the eCRF only.

5.2.8.1.2 Serious adverse event

A serious adverse event (SAE) is defined as any AE, which fulfils at least one of the following criteria:
- results in death,
- is life-threatening, which refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe,
- requires inpatient hospitalisation or prolongation of existing hospitalisation
- results in persistent or significant disability or incapacity,
- is a congenital anomaly / birth defect,
- is deemed serious for any other reason if it is an important medical event when based on appropriate medical judgement which may jeopardise the patient and may require medical or surgical intervention to prevent one of the other outcomes listed in the above definitions.

Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias or convulsions that do not result in hospitalisation or development of dependency or abuse.

5.2.8.1.3 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 ISF system. A copy of the latest list of "Always Serious AEs" will be provided upon request. These events should always be reported as SAEs as described above.
Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the time since discontinuation of the drug and must be reported as described in Section 5.2.8.2, subsections "AE Collection" and "**AE reporting to sponsor and timelines".**

5.2.8.1.4 Adverse events of special interest

The term adverse event 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 5.2.8.2.2.

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 Aminotransferase) and/or ALT (Alanine Aminotransferase) ≥3 fold ULN combined with an elevation of total bilirubin ≥2 fold ULN measured in the same blood draw sample, or
- aminotransferase (ALT, and/or AST) elevations ≥10 fold ULN.

These lab findings constitute a hepatic injury alert and the patients showing these lab abnormalities need to be followed up according to the "DILI checklist" provided in the ISF.

In case of clinical symptoms of hepatic injury (icterus, unexplained encephalopathy, unexplained coagulopathy, right upper quadrant abdominal pain, etc.) without lab results (ALT, AST, total bilirubin) available, the investigator should make sure these parameters are analysed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

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.

5.2.8.1.5 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.

5.2.8.1.6 Causal relationship of AEs

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

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

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

5.2.8.2 Adverse event collection and reporting

5.2.8.2.1 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 5.2.8.1.1), but not on the CRF.

5.2.8.2.2 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 contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions, the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information. All (S)AEs, including those persisting after individual 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.

5.2.8.2.3 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.

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 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.

5.2.8.2.4 Exemptions to SAE reporting

Not applicable.

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 Flow Chart I and Flow Chart II. The actual sampling times will be recorded in the CRFs and used for determination of pharmacokinetic parameters. Sampling should be done at the timepoints listed in the flow-chart I and II and within 4 hours prior to the IVT drug administration. It is important to ensure that the exact time of the assessment of pharmacokinetics is recorded. Planned time points for systemic pharmacokinetic samples are listed in Appendix 10.3.

5.3.2 Methods of sample collection

5.3.2.1 Sampling for pharmacokinetic analysis

For quantification of BI 754132 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 10.3 under PK sampling.

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 methodological investigations, (e.g. for stability testing), however, only data related to the analyte 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 the final study report has been signed.

5.3.2.2 Sampling for ADA assessment

For the determination of anti-drug antibodies (ADA), approximately 3.0 mL of blood will be taken from a forearm vein into serum blood-drawing tube at the time points listed in Flow Chart I and Flow Chart II under ADA and in Appendix 10.3.

Samples will be stored in a freezer set at the analytical laboratory until they are analyzed. The samples may be used for further methodological investigations, e.g. for stability testing, however only data related to the anti-drug antibodies 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.

[redacted]

5.3.4 Pharmacokinetic – pharmacodynamic relationship

In order to characterize BI 754132´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 reported separately.

5.4 ASSESSMENT OF BIOMARKER(S)

5.4.1 ERG as physiological response biomarker

For assessing potential efficacy effects after single dose IVT administration, ERG b-wave implicit times will be recorded under photopic condition as exploratory physiological response biomarker. The ERG b-wave is a positive depolarizing response predominantly originating from bipolar cells, and the b-wave implicit time is defined as the time needed after a light stimulus (such as a light flash) to reach the peak of the b-wave. In principle, the b-wave implicit time is a measure for the speed of the light-induced electrical response in the retina, predominantly on the level of bipolar cells and photoreceptor-to-bipolar cell synaptic transmission.

It was shown that the b-wave implicit time can be measured robustly and conveniently in humans [e.g. R19-0308], and that patients with early or intermediate stage AMD as well as GA have significantly delayed b-wave implicit times [R19-0306; P17-03129; R18-3153; R19-0307]. Based on available preclinical data, a single IVT administration of a TrkB activating antibody can improve delayed ERG b-wave implicit times in a disease-related model of retinal dysfunction (reference to IB [c22785135], or to study report n00254511-01).

Therefore, ERG b-wave implicit times will be recorded in both eyes at baseline visit prior to IVT administration, and at follow-up visits as specified in Flow Chart I and Flow Chart II. ERGs will be evoked by brief light flashes of different intensities and flickering light stimuli of different mean light intensities. An improvement of the b-wave implicit time (together with a potential dependency of this effect on the escalating doses) will provide evidence that BI 754132 can induce a meaningful physiological response within the patients' eyes at the dose range tested.

As further exploratory biomarker, ERG a- and b-wave amplitudes, flicker b-wave amplitude and flicker b-wave implicit time will be determined.

5.4.2 Biochemical and cellular biomarkers

No biochemical or cellular biomarkers relevant to the MoA will be assessed.

5.4.3 Pharmacogenomics biomarkers

For subjects who consent in the study, one mandatory pharmacogenomics sample will be collected for DNA extraction and exploratory genotyping of genes related to the disease or the targeted pathway, such as BDNF. These data will be part of the clinical trial report.

In addition, this blood sample may also be used for exploratory analysis of variants of genes involved in Absorption, Distribution, Metabolism and Excretion (ADME) of drugs in case of unexplainable variability in pharmacokinetic parameters in patients or healthy volunteers. It is not intended to include these data in the final report. However, the data may be part of the report if necessary. All remaining samples will be destroyed no later than three years after the end of the trial.

Procedures and timing: Approximately 8.5 mL blood will be taken in a PAXgene Blood DNA tube at day 1 (Visit 2) only. If not feasible at Visit 2, the sample can also be taken at a later visit or day. Detailed instructions for sampling, handling and shipment of samples are provided in the ISF/Laboratory Manual.

5.5 BIOBANKING

Not applicable.

5.6 OTHER ASSESSMENTS

Not applicable.

5.7 APPROPRIATENESS OF MEASUREMENTS

All measurements performed during this trial are standard measurements and will be performed in order to monitor 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 systemic 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 ophthalmological examinations, colour fundus photography, SD-OCT, FAF, slit lamp, indirect ophthalmoscopy (MD part only) and IOP are considered standard, whereas OCT-A and ERG are of exploratory nature. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure. The functional and pharmacogenomics biomarkers as outlined in Section 5.4 and 5.5 are of exploratory nature only.

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 Flow Chart I and Flow Chart II. For planned individual plasma concentration sampling times, refer to Appendix 10.3.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures and assessments to be performed at each visit are listed in Flow Chart I and Flow Chart II, and in Appendix 10.3. Additional details regarding visit procedures are provided below.

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

Before pupil dilation: BCVA assessment, slit lamp examination, ERG and ocular tonometry (for determination of IOP).

After dilation: slit lamp examination, SD-OCT, OCT-A, colour fundus photography, fundus autofluorescence angiography. For the SRD part, IOP can be repeated after pupil dilation and after IVT injection on discretion of the investigator. For the MD part, IOP must be taken before pupil dilation and then repeated 30 to 50 min after IVT injection at Visit 2, 3 and 4.

6.2.1 Single Rising Dose Part

6.2.1.1 Screening and run-in period(s) of SRD part

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 enrolled patients is confirmed, the treatment visit (Visit 2) may be performed.

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 the screening visit performed earlier than 14 days before dosing visit, an additional visit for repeating of safety lab, vital signs, ECG and targeted physical examination has to be performed again.

Baseline Conditions
Any pre-existing medical conditions considered as relevant by the investigator, excluding the indication of the trial, are recorded into the eCRF in the appropriate page.

Any abnormal clinical significant findings observed during ophthalmological examinations at Visit 1 need to be documented as Baseline Conditions.

Medical History:
All relevant medical history according to the investigator judgment will be captured in the eCRF.

Re-screening:
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. For re-screening a new patient number will be assigned, and the patient must sign a new Informed Consent Form (ICF). Imaging of retina (SD-OCT, 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.

6.2.1.2 Treatment period(s) of SRD part

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 Visit 2 procedures after the ophthalmological assessments in Flow Chart I have been performed (please see Section 4.1.4 for details). After administration of BI 754132, 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. An additional tonometry could be performed after IVT injection to monitor IOP.

6.2.1.3 Follow-up period and trial completion of SRD part

Patients must continue to be followed according to the visit schedule (unless they withdraw consent for further follow-up) in order to collect data up to 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 visits 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 to administer standard treatment for ocular inflammation during the follow-up period as deemed medically appropriate.

Visit 10/End of Trial:
The Visit 10/EOT will be performed 16 days after the Visit 9 (see Flow Chart I).
The Visit 10/EOT is the final visit and the trial completion page in the eCRF has to be entered.

Withdrawal of consent
If a patient is not willing to continue in the trial and wants to withdraw consent prior to the end of the trial, Visit 9 should be scheduled as soon as possible, and also Visit 10/EOT should be performed to assess for safety and if patient agrees.

If patient refuses to participate at a Visit 9 or Visit 10, the trial completion page of the eCRF has to be filled in.

6.2.2 Multiple Dosing Part

6.2.2.1 Screening and run-in period(s) of MD part

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 enrolled patients is confirmed, the treatment visit (Visit 2) may be performed.
If the screening visit has been performed earlier than 14 days before the dosing visit, an additional visit for repeating of safety lab, vital signs, ECG and targeted physical examination has to be performed again.

Baseline Conditions
Any pre-existing medical conditions considered as relevant by the investigator, excluding the indication of the trial, are recorded into the eCRF in the appropriate page.

Any abnormal clinically significant findings observed during ophthalmological examinations at Visit 1 need to be documented as Baseline Conditions.

Medical History:
All relevant medical history according to the investigator judgment will be captured in the eCRF.

Re-screening:
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. For re-screening, a new patient number will be assigned, and the patient must sign a new ICF. Imaging of retina (SD-OCT, 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.

6.2.2.2 Treatment period(s) of MD part

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 Visit 2, Visit 3 and Visit 4 procedures after the ophthalmological assessments in Flow Chart II have been performed (please see Section 4.1.4 for details).

Post-injection assessments:
After study drug administration a gross visual function test (e.g. finger counting/hand motion) will be performed within 15 minutes. IOP will be measured between 30-50 minutes after the injection. 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 and treated according to local practice for such procedures.

6.2.2.3 Follow-up period and trial completion of MD part

Patients must continue to be followed according to the visit schedule (unless they withdraw consent for further follow-up) in order to collect data up to 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 visits 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 to administer standard treatment for ocular inflammation during the follow-up period as deemed medically appropriate.

Visit 7/End of Trial:
The Visit 7/EOT will be performed 42 days after the Visit 6 (see Flow Chart II).

The Visit 7/EOT is the final visit and the trial completion page in the eCRF has to be entered.

Withdrawal of consent
If a patient is not willing to continue in the trial and wants to withdraw consent prior to the end of the trial, the investigator should offer the possibility to continue the trial without further treatment until Visit7/EOT. If patient disagrees to continue under these circumstances, Visit 6 should be scheduled as soon as possible, and also Visit 7/EOT should be performed to assess for safety.

If patient refuses to participate at a Visit 6 or Visit 7, the trial completion page of the eCRF has to be filled in.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

The main objective of this trial is to investigate ocular and systemic safety and tolerability as well as pharmacokinetics of single intravitreal and multiple intravitreal administrations of BI 754132. This will be assessed by calculating descriptive statistics for safety and PK parameters, which will be compared between the treatment groups.

7.1 NULL AND ALTERNATIVE HYPOTHESES

No confirmatory testing is performed and hence no null and alternative hypotheses are defined. A discussion of the sample size is provided in Section 7.5.

7.2 PLANNED ANALYSES

7.2.1 General considerations

7.2.1.1 Dose escalation in the 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 and systemic DLE rate is above 0.25. The BLRM will not be used for the analysis of the primary endpoint.

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, $d^* = 6$ mg is the reference dose, allowing for the interpretation of α as the odds of a DLE at dose d*, and $\theta = (\log(\alpha), \log(\beta))$ with $\alpha, \beta > 0$ is the parameter vector of the model.

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

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

The BLRM-recommended dose for the next cohort is the 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 maximum allowable dose increment for the subsequent cohort will be no more than 233% from the previous dose up to doses of 3 mg, and to a maximum of 100% from the previous dose from dose 3 mg onwards. Dose escalation will continue up to the 6 mg 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 an 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 was 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 0.3 mg would equal 0.01, and the median DLE rate at the maximum feasible dose of 6 mg would equal 0.10. This yields μ_1 = (-2.197, -0.223). 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. 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 0.3 mg would equal 0.10, and the median DLE rate at 6 mg would equal 0.40. These assumptions yield μ_2 = (-0.405, -0.514). 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 0.3 mg would equal 0.001, and the median DLE at 6 mg would equal 0.01. These assumptions yield μ_3 = (-4.595, -0.259). 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 7.2.1.1: 1. Additionally, the prior probabilities of DLEs at different doses, as well as the corresponding probability of targeted and overdosing, are shown in Table 7.2.1.1: 2. Graphically, the prior medians with accompanying 95% credible intervals are shown in Figure 7.2.1.1: 1. As can be seen from both Table 7.2.1.1: 2 and Figure 7.2.1.1: 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 10.4.

Table 7.2.1.1: 1 Summary of prior distribution

Prior Component	Mixture Weight	Mean Vector	SD Vector
1: Weakly inf.	0.900	-2.197 -0.223	2.00 1.00
2: High Tox.	0.050	-0.405 -0.514	2.00 1.00
3: Low Tox.	0.050	-4.595 -0.259	5.00 0.01

Table 7.2.1.1: 2 Prior probabilities of DLEs at selected doses

Dose	Probability of true DLE rate in				Quantiles		
	[0, 0.25)	**[0.25, 1]**	**Mean**	**SD**	**2.5%**	**50%**	**97.5%**
0.3	0.917	0.083	0.067	0.151	0.000	0.007	0.599
1	0.876	0.124	0.096	0.179	0.000	0.017	0.704
3	0.799	0.201	0.147	0.214	0.000	0.048	0.810
6	0.696	0.304	0.212	0.249	0.001	0.101	0.882

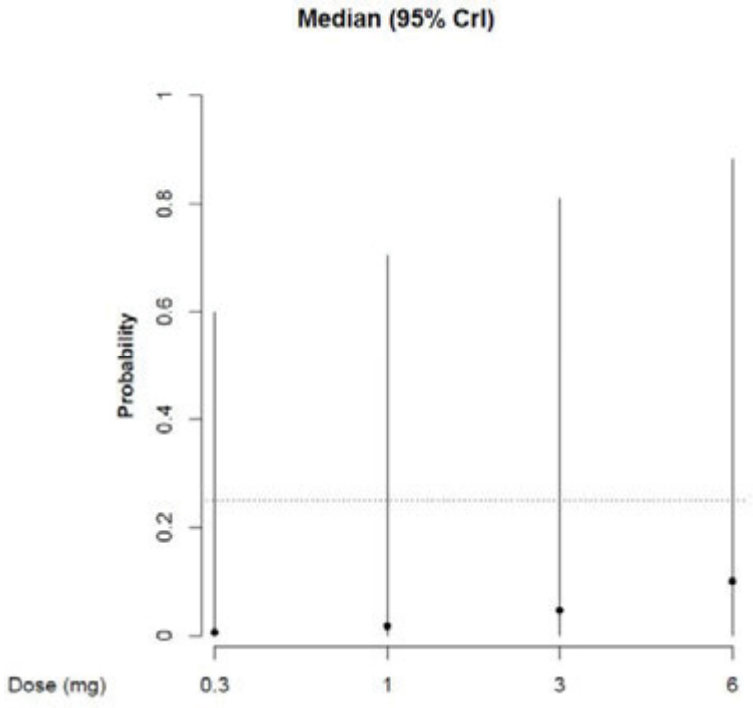

Figure 7.2.1.1: 1 Prior medians and 95% credible intervals

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.

7.2.1.2 Subject analysis sets

The main analysis populations are defined below. In the TSAP, further analysis data sets may be defined. Patients will be analysed according to the assigned treatment, unless otherwise specified. Patients who are replaced during the DLE evaluation period will be excluded from the determination of the MTD (see Section 3.1).

Important protocol deviations (iPDs) will be defined in the Integrated Quality and Risk Management (IQRM) plan. IPDs will be identified no later than in the Report Planning Meeting, and the iPD categories will be updated as needed. The handling of patients with iPDs will be described in the TSAP.

Treated Set (TS)
The TS will consist of all patients who were treated with at least one dose of BI 754132.

Pharmacokinetic parameter analysis set (PKS)
This set includes all subjects in the TS who provide at least one plasma sample for determination of PK parameters that was not excluded due to a protocol violation relevant to the evaluation of PK or due to PK non-evaluability (as specified below).

The pharmacokinetic parameters listed in Sections 2.1.3 and 2.2.2 for BI 754132 will be determined according to the relevant SOP of the Sponsor (001-MCS-36-472).

Plasma concentration data and parameters of a subject will be included in the PK analyses if they are not flagged for exclusion due to a protocol violation 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 subject's data will be documented in the CTR.

Relevant protocol violations may be

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

Plasma concentrations and/or parameters of a subject will be considered as non-evaluable, if for example, there were missing samples/concentration data at important phases of PK disposition curve.

Plasma concentration data and parameters of a subject 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 as in the bioanalytical report (that is to the same number of decimal places provided in the bioanalytical report).

7.2.2 Primary endpoint analyses

SRD part:
The primary safety endpoint "Number of patients with ocular (in the study eye) and systemic DLEs from drug administration till EOT" will be analysed descriptively, based on the TS.

For the definition of DLEs, please refer to Section 5.2.1.

MD part:
The primary safety endpoint "Number of patients with drug-related AEs from drug administration until EOT" will be analysed descriptively, based on the TS.

7.2.3 Secondary endpoint analyses

All secondary safety endpoints defined in Section 2.1.3 will be analysed descriptively, based on the TS.

SRD part:
The PK endpoints C_{max}, $AUC_{0-\infty}$, and t_{max} specified in Section 2.1.3 will be analysed descriptively, based on the PKS. Dose proportionality will be explored descriptively for the PK endpoints $AUC_{0-\infty}$ and C_{max} if feasible.

MD part:
Systemic exposure of BI 754132 after multiple IVT doses by determination of $C_{min,1}$ and $C_{min,2}$ (trough levels before second and third administrations) and plasma concentrations 4, 8 and 14 weeks after the third administration will be determined in the MD part along with descriptive statistics, based on the PKS.

[redacted]

7.2.5 Safety analyses

Adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. For BI 754132, the residual effect period (REP) after IVT administration is not known. Therefore, all AEs with

an onset between start of treatment and the respective EOT visit will be assigned to the on-treatment period for evaluation. The safety analysis will be performed by planned dose group.

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

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

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

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

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

A centralised evaluation of all 12-lead ECGs recordings (see Section 5.2.6) will be the basis for the ECG variables QT, HR, QTcF, PR, QRS, RR, and further derived ECG endpoints. The baseline value of an ECG variable is defined as the mean of the ECG measurements prior to drug administration. The derivation of the quantitative and qualitative ECG endpoints and their analyses will be described in the TSAP.

7.2.6 Other Analyses

Not applicable.

7.2.7 Interim Analyses

The sponsor will continuously monitor the safety. The dose escalation design of the SRD part foresees that the sponsor and the SMC perform regular safety evaluations. These evaluations will be unblinded to dose.

An exploratory PK analysis will be performed after each dose group of the SRD part to check the systemic exposure of BI 754132.

7.3 HANDLING OF MISSING DATA

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

7.4 RANDOMISATION

No randomisation will be performed. Patients will be assigned to escalating dose groups of the SRD part or to the MD part by order of admission into the trial.

7.5 DETERMINATION OF SAMPLE SIZE

SRD part:
If no DLE occurs, 15 DLE evaluable patients will treated in this trial part, based on the planned number of dose levels that are tested and on the requirement to have 6 DLE evaluable patients in the last dose group (see Section 3.1). However, the actual number of patients will depend on the actual number of dose cohorts tested and on the occurrence of DLEs. Based on the simulation study to evaluate operating characteristics of the BLRM (see Appendix 10.4), about 17 evaluable patients are expected to be treated in the dose escalation part for the model to have reasonable operating characteristics relating to its MTD recommendation.

MD part:
It is planned to include a total of 6 patients in this trial part. The planned sample size is not based on a power calculation but is in general considered as sufficient for the evaluation of multiple dose safety and pharmacokinetics of drugs with intravitreal route of administration.

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

The trial will be carried out in accordance with the Medical Devices Directive (93/42/EEC) and the harmonised standards for Medical Devices (ISO 14155, current version).

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

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

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 per the project publication strategy, interim cohort data may be published as available, while full results will be published after CTR finalization. The certificate of insurance cover is made available to the investigator and the patients and is stored in the ISF.

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

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

Prior to patient 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 investigator or delegate must give a full explanation to trial patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.

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 his delegate must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent:

Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.

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

8.2 DATA QUALITY ASSURANCE

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

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

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

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor. See Section 4.1.5.2 for rules about emergency code breaks. For drug accountability, refer to Section 4.1.8.

8.3.1 Source documents

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

Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the 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.

During the site visit the sponsor's Clinical Research Associate (CRA) or auditor must be granted access to copies of source documents (please see Section 8.3.2). Before sending or uploading those copies, the investigator must ensure that all patient identifiers (e.g. patient's name, initials, address, phone number, social security number) have properly been removed or redacted from any copy of the patients' source documents.

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, for example:

- Patient identification: gender, 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
- Adverse events and outcome events (onset date (mandatory), and end date (if available))
- Serious adverse events (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)
- Originals or copies of laboratory results and other imaging or testing results, with proper documented medical evaluation (in validated electronic format, if available)
- Completion of patient's participation in the trial" (end date; in case of premature discontinuation document the reason for it).
- 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.

8.3.2 Direct access to source data and documents

The sponsor will monitor the conduct of the trial by regular on-site monitoring visits and in-house data quality review. The frequency of site monitoring will be determined by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.

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

An adaptive approach to clinical trial monitoring will be utilised. The sponsor will perform a risk assessment of the trial to determine the extent and nature of monitoring required in order to ensure the reliability and robustness of the results. Regular review of risk reports will provide sponsor oversight during trial conduct and direct monitoring activities to the areas of greatest risk which have the most potential impact to patient safety and data quality.

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 7 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 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 / competent authority 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 composed of participating investigators, members of the BI trial team and two trial independent external ophthalmological experts will be established for both SRD and MD parts. The primary responsibility of the SMC is to ensure and protect the safety and well-being of the patients participating in the trial. In the SRD part, the SMC will 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. After completion of the SRD part, the SMC will decide on the selection of the highest dose established as safe and tolerable (during SRD part) and its continuing evaluation in the MD part of the trial.

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 clinical trial 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 (CT Managers), Clinical Research Associates (CRAs), and investigators of participating countries.

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

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

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

A central laboratory service will be used in this trial. Details will be provided in Central Laboratory Manual, available in the ISF.

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10. APPENDICES

10.1 INSTRUCTIONS FOR USE

Not applicable.

10.2 PHARMACOKINETIC METHODS AND ANALYSES

Not applicable.

10.3 TIME SCHEDULE FOR PHARMACOKINETIC (PK) BLOOD SAMPLING

Table 10.3: 1 Time schedule for PK and ADA blood sampling and ECG recording during SRD part

Course	Visit	Day	Planned Time	Planned Time [h]	PK BI 754312	ADA	ECG[3]
1	V2	1	Before drug administration of BI 754132	-0:30[1, 2]	X	X	X
			Drug administration	0:00			
	V2	1	4h after drug administration	4:00[4]	X		X
	V3	4 (+/- 1 day)	3 days after drug administration	72:00	X		X
	V4	8 (+/- 1 days)	1 week after drug administration	168:00	X		X
	V5	15 (+/- 2 days)	2 weeks after drug administration	336:00	X	X	X
	V6	22 (+/- 2 days)	3 weeks after drug administration	504:00			
	V7	29 (+/- 2 days)	4 weeks after drug administration	672:00	X	X	X
	V8	56 (+/- 4 days)	8 weeks after drug administration	1344:00	X		
	V9	84 (+/- 4 days)	12 weeks after drug administration	2016:00	X		
End of trial	V10	100 (+/- 7 days)	14 weeks after drug administration	2352:00	X	X	X

(1) The -0:30 sample can be taken between 1h and 5min before drug administration.
(2) Time points are also required for sample identification.
(3) Time points with triplicate resting ECG, shortly before PK sampling.
(4) A time window of +/- 15 min for sample drawing is allowed here.

Table 10.3: 2 Time schedule for PK and ADA blood sampling and ECG recording during MD part

Course	Visit	Day	Planned Time [h]	Planned Time [h]	PK BI 754132	ADA	ECG[3]
1	V2	1	Before 1st drug administration of BI 754132	-4:00[1,2]	X	X	X
			1st drug administration	0:00			
	V3	29 (+/- 3 days)	Before 2nd drug administration of BI 754132	671:55[1,2]	X		X
			2nd drug adminstration	672:00			
	V4	57 (+/- 3 days)	Before 3rd drug administration of BI 754132	1343:55[1,2]	X		X
			3rd drug administration	1344:00			
Follow up period	V5	85 (+/- 7 days)	12 weeks after first drug administratio	2016:00[2]	X	X	X
	V6	113 (+/- 7 day)	16 weeks after first drug administration	2688:00[2]	X		
End of Trial	V7	155 (+/- 7 day)	22 weeks after first drug administration	3360:00[2]	X	X	X

(1) PK and ADA sampling as well as ECG measurement must be performed within 4 hours prior to the IVT drug administration, and each sampling and measurement timepoint has to be entered in the eCRF.

(2) Time points are also required for sample identification.

(3) Time points with triplicate resting ECG, shortly before PK sampling.

10.4 STATISTICAL APPENDIX

A BLRM with overdose control will be used to guide dose escalation in the SRD part of this study. The BLRM is introduced in Section 7.2, 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 summarised 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 MTD (see

Section 3.1) under various dose-toxicity relationships through computer simulation. These results are summarized in Table 10.4: 3. In addition, recommendations of the next dose level by the BLRM with overdose control principle are provided under various hypothetical outcome scenarios, to show how it facilitates on-study dose-escalation decisions (see Table 10.4: 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 10.4: 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 0.3 mg. In this case, the next planned dose permitted by the model and the 233% escalation rule is 1 mg. In contrast, scenario 2 assumes that there is one DLE observed in the first dose group. This would mean overtoxicity from the beginning, i.e., all planned dose levels are not considered safe.

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, dose escalation would proceed to the 6 mg dose, with an additional cohort at that dose level at the end of the SRD part, i.e. overall 15 patients (scenario 3b).

In scenario 4, the first DLE occurs in dose group 1 mg. 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 still be 1 mg. Thus, the 1 mg dose would be declared as MTD and the SRD part of the trial would stop (after 9 patients).

However, if (after repeating dose group 1 mg according to the recommendation from scenario 4) there was another DLE in the second cohort for dose group 1 mg (as in scenario 5), then the recommendation would be to go back to dose 0.3 mg. If there was no further DLE then (scenario 5b), one could go up again to dose 1 mg. If there was no further DLE then, the SRD part of the trial would stop after 15 patients, declaring 1 mg as MTD (scenario 5c).

Scenario 6 shows the case where the first DLE occurs in the 3 mg dose group. Then an additional cohort of 3 patients would have to be treated at this dose level. If these 3 patients have no further DLE, the next recommended dose would still be 3 mg. Thus, 3 mg would be declared as MTD, after 12 patients (scenario 6b).

In scenario 7, there is the first DLE in the first cohort of the 6 mg dose group. Then the dose would have to be reduced to 3 mg for the next cohort. In case of no further DLE, the SRD part of the trial could stop after 18 patients overall (scenarios 7b, 7c).

In contrast, if the first DLE occurs only in the second cohort of dose group 6 mg (scenario 8), then the SRD part of the trial could still be completed with a total of 15 patients. However, if there were 2 DLEs in the highest dose group, then the model would recommend to return to dose 3 mg (scenario 9).

Table 10.4: 1 Hypothetical data scenarios

Scenario	Dose (mg/eye)	# Pat.	# DLE	Current Dose: P(OD)	Next recomm. Dose (mg/eye)	Next dose:	
						P(TD)	P(OD)
1	0.3	3	0	0.015	1	0.960	0.040
2	0.3	3	1	0.309	N/A	N/A	N/A
3	0.3 1	3 3	0 0	0.012	3	0.963	0.064
3b	0.3 1 3 6	3 3 3 6	0 0 0 0	0.013	6	0.987	0.013
4	0.3 1	3 3	0 1	0.202	1	0.798	0.202
4b	0.3 1	3 6	0 1	0.077	1	0.923	0.077
5	0.3 1	3 6	0 2	0.313	0.3	0.894	0.106
5b	0.3 1	6 6	0 2	0.047	1	0.776	0.224
5c	0.3 1	6 9	0 2	0.109	1	0.891	0.109
6	0.3 1 3	3 3 3	0 0 1	0.218	3	0.782	0.218
6b	0.3 1 3	3 3 6	0 0 1	0.088	3	0.912	0.088
7	0.3 1 3 6	3 3 3 3	0 0 0 1	0.253	3	0.960	0.040
7b	0.3 1 3 6	3 3 6 3	0 0 0 1	0.016	6	0.806	0194

Table 10.4: 1 Hypothetical data scenarios (cont'd)

Scenario	Dose (mg/eye)	# Pat.	# DLE	Current Dose: P(OD)	Next recomm. Dose (mg/eye)	Next dose:	
						P(TD)	P(OD)
	0.3	3	0				
	1	3	0				
	3	6	0				
7c	6	6	1	0.085	6	0.915	0.085
	0.3	3	0				
	1	3	0				
	3	3	0				
8	6	6	1	0.113	6	0.887	0.113
	0.3	3	0				
	1	3	0				
	3	3	0				
9	6	6	2	0.364	3	0.944	0.056

Operating characteristics

Operating characteristics are a way to assess the long-run behaviour of a model by illustrating the precision of the design in estimating the MTD. 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 10.4: 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 10.4: 2 Assumed true dose-toxicity scenarios

Scenario		Dose (mg)			
		0.3	**1**	**3**	**6**
1: Prior Med	DLE rate, P(DLE)	0.007	0.017	0.048	0.101
2: Prior Mean		0.067	0.096	0.147	0.212
3: High Tox		0.100	0.150	0.400	0.600
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 ≤ 234% increase from the current dose.

The MTD 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 18 or 21.

It was then assessed how often a dose was declared as MTD 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 10.4: 3.

Table 10.4: 3 Simulated operating characteristics

Scenario	Max. allowed # Patients	% of trials declaring a MTD with true DLE rate in		% of stopped trials**	# Patients	# DLEs
		[0, 0.25) target dosing	[0.25,1] overdosing		Mean (Min-Max)	Mean (Min-Max)
1*	18	87.3	0.7	12.0	16.5 (3-18)	1.99 (0-6)
2*	18	67.9	0.1	32.0	12.2 (3-18)	1.79 (0-6)
3	18	60.1	9.0	30.9	11.5 (3-18)	2.17 (1-6)
4*	18	85.7	1.9	12.4	17.6 (3-18)	1.91 (0-6)
5	18	69.7	3.6	26.7	13.1 (3-18)	1.97 (0-6)
6	18	73.5	15.0	11.5	13.3 (3-18)	2.27 (1-6)
1*	21	96.8	0.5	2.8	16.7 (3-21)	2.01 (1-7)
2*	21	77.0	0.2	22.8	12.7 (3-21)	1.86 (1-7)
3	21	65.8	9.1	25.1	12.2 (3-21)	2.33 (0-7)
4*	21	97.8	1.4	0.8	17.9 (3-21)	1.95 (0-6)
5	21	76.7	4.7	18.6	13.8 (3-21)	2.06 (0-6)
6	21	77.4	14.1	8.5	13.8 (3-21)	2.40 (0-6)

* Due to technical reasons, scenarios 1,2, and 4 could only be calculated with one additional dose level with assumed true DLE rate in the overdose range. As additional dose level, a dose of 15mg was chosen with the following assumed true toxicity probabilities: scenarios 1,2: 0.7, scenario 4: 0.6.

** 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 MTD was found.

Maximum number of patients =21

The case when the maximum number of patients is chosen as 21 allows the model to appropriately perform in most cases and for finding an MTD within the target dosing range with very high probability.

In scenario 1, which reflects the case that the true dose-toxicity is aligned with prior medians, 96.8% of the simulated trials declared a dose as MTD with true DLE rate in the targeted toxicity range. Note that 2.8% of the simulated trials stopped either because there was no MTD determined after 21 patients had been observed (0.5%) or because of too high toxicity for the planned doses (2.3%). This latter is mostly due to the cases that 1 DLE is observed out of 3 patients at the starting dose of 0.3 mg. 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 23%). In this case, about 77% of the trials would end with an estimated MTD within the targeted toxicity range, and 0.2% in the overdosing range.

In Scenario 3 (high-toxicity scenario), only 65.8 % of the trials declared a dose as MTD with true DLE rate in the targeted toxicity range. In 9.1% of the trials, the estimated MTD was in

the overdosing range. Scenario 4 (low-toxicity scenario) shows the best results, i.e. the lowest number of stopped trials and the highest number of trials with estimated MTD 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 range from 12.2 patients (Scenario 3) to 17.9 patients (Scenario 4), and the maximum number of patients was 21. Therefore, the patient numbers are as expected and increase when moving away from the high-toxicity scenario.

Maximum number of patients =18
If the maximum number of patients is chosen as 18, an early stopping of the trial would be more often required than above. In most cases, this would be due to reaching the maximum number of patients before an MTD could be determined. Still, the resulting operating characteristics are reasonable.

The mean patient numbers range from 11.5 patients (Scenario 3) to 17.6 patients (Scenario 4), and the maximum number of patients was 18. Again, the patient numbers are as expected and increase when moving away from the high-toxicity scenario.

Overall, by reviewing the metrics presented in Table 10.4: 3, it can be seen that the model is generally conservative due to the overdose control criteria. In all scenarios, the probabilities of recommending a dose with true DLE rate being at least 25%, P(DLE ≥ 25%), as MTD are much smaller than the probabilities of recommending a dose with true P(DLE) < 25% as MTD.

R version 3.5.1 was used for data scenarios and simulations.

10.5 BENEFIT-RISK ASSESSMENT IN CONTEXT OF COVID-19 PANDEMIC FOR PATIENTS PARTICIPATION IN TRIAL 1418-0001 INVESTIGATING BI 754132

Study population
GA secondary to AMD is affecting elderly population. Approximately 10% of individuals aged 65 to 74 years, and 30% of those aged 75 to 85 years, show signs of AMD. Even though few studies identified examined non-ophthalmic comorbidities among patients with GA, because of the old age, and potential concomitant diseases, this population is considered fragile and potentially at higher risk for complications following COVID-19 infection.

Benefits and risks conclusions and recommendations
Currently, there is no evidence that based on the pharmacological mechanism and existing non-clinical data the compound may increase the risk of progression of COVID-19 infection. BI 754132 is administered intravitreally using standard aseptic technique.

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

The current study population is potentially at higher risk of COVID-19 infection due to background or concomitant diseases. Enrollment will re-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 the 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 AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		22 May 2019
EudraCT number **EU number**		2018-004125-92
BI Trial number		1418-0001
BI Investigational Medicinal Product(s)		BI 754132
Title of protocol		Safety, tolerability and pharmacokinetics of single rising intravitreal doses of BI 754132 in patients with geographic atrophy secondary to age-related macular degeneration (open label, non-randomized, uncontrolled).
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		3.1
Description of change		Criteria of sentinel dosing, decision-maker and way of communication have been described.
Rationale for change		Authority feedback
Section to be changed		1.4
Description of change		The minimum observation period per patient has been specified.
Rationale for change		Authority feedback
Section to be changed		3.1; 3.3.5
Description of change		Increase to 3 evaluable patients for dose-escalation.
Rationale for change		Authority feedback
Section to be changed		Synopsis; 2.1.2; 3.1; 5.2.1; 7.2.1.1; 7.2.2
Description of change		The criteria for DLEs have been expanded to also address systemic effects.
Rationale for change		Authority feedback
Section to be changed		4.2.2.3
Description of change		The duration of contraception in male participants (and their partners) has been defined and the need of condom use has been expanded to vasectomized participants. The inconsistency of contraception advice of WOCBP (not to include in trial) has been resolved by defining them as partners of trial participants.
Rationale for change		Authority feedback
Section to be changed		3.3.4.3

Description of change		A single serious adverse reaction or two severe adverse reactions (regardless of system organ class) have been specified as stop criteria for enrolment.
Rationale for change		Authority feedback

11.2 GLOBAL AMENDMENT 2

Date of amendment		04 Jun 2019
EudraCT number **EU number**		2018-004125-92
BI Trial number		1418-0001
BI Investigational Medicinal Product(s)		BI 754132
Title of protocol		Safety, tolerability and pharmacokinetics of single rising intravitreal doses of BI 754132 in patients with geographic atrophy secondary to age-related macular degeneration (open label, non-randomized, uncontrolled).
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		4.1.4 and 6.2.2
Description of change		The minimum immediate post dose observation period and the including specific assessments required for each patient have been specified.
Rationale for change		Authority feedback

11.3 GLOBAL AMENDMENT 3

Date of amendment		04 Jul 2019
EudraCT number **EU number**		2018-004125-92
BI Trial number		1418-0001
BI Investigational Medicinal Product(s)		BI 754132
Title of protocol		Safety, tolerability and pharmacokinetics of single rising intravitreal doses of BI 754132 in patients with geographic atrophy secondary to age-related macular degeneration (open label, non-randomized, uncontrolled).
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒

Section to be changed		Protocol Synopsis
Description of change		Safety Monitoring Committee has been spelled
Rationale for change		The abbreviation SMC was used in the synopsis without prior explanation
Section to be changed		Flow Chart & 10.3 (Table 10.3:1)
Description of change		ECG recording has been taken out at Visit 6 (day 22) since no PK sampling is planned at that visit
Rationale for change		For the exposure-response (PK-QT) analysis, ECG recordings are needed only at time points of PK sampling
Section to be changed		Flow Chart and Table 10.3
Description of change		Add ADA sampling Visit 7 (day 29)
Rationale for change		Authority (FDA) feedback
Section to be changed		Flow Chart
Description of change		Add "resting" before term “ECG” into footnote (2)
Rationale for change		To emphasize the need of resting conditions for the ECG recordings
Section to be changed		Flow Chart
Description of change		Deletion of Footnote 9 from table line description “slit lamp and IOP”
Rationale for change		Footnote 9 text inappropriate for both ophthalmologic examinations
Section to be changed		1.4.2.5
Rationale for change		Correction w.r.t. the timepoints of safety lab and ECG recordings
Section to be changed		3.3.3
Description of change		Exclusion criteria No.4 changed to "Previous participation in other trials for treatment of GA receiving active drug **in the study eye**"
Rationale for change		Feedback by Co-ordinating Investigator
Section to be changed		4.1.5
Description of change		Blinding and unblinding requirement added for ECG evaluations
Rationale for change		Feedback central ECG reading vendor
Section to be changed		4.2.2.3
Description of change		Rephrasing of contraception requirements of men able to father a child (trial participants)
Rationale for change		Clarification that male trial participants are not required to have vasectomy but are required to use a condom (regardless of vasectomy) if their sexual partner is WOCBP.
Section to be changed		5.2.1
Description of change		Rephrasing of DLE descriptions

Rationale for change		Integration of ocular and systemic DLEs as AESIs and of CTCAE assignment for systemic DLEs
Section to be changed		5.2.6
Description of change		Rephrasing of the description of ECG recording and evaluation
Rationale for change		Feedback central ECG reading vendor
Section to be changed		6.2
Description of change		Add ERG measurement before pupil dilation
Rationale for change		Feedback from ERG vendor

11.4 GLOBAL AMENDMENT 4

Date of amendment		13 Oct 2020
EudraCT number **EU number**		2018-004125-92
BI Trial number		1418-0001
BI Investigational Medicinal Product(s)		BI 754132
Title of protocol		Safety, tolerability and pharmacokinetics of single rising intravitreal doses of BI 754132 in patients with geographic atrophy secondary to age-related macular degeneration (open label, non-randomized, uncontrolled).
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Title page; Synopsis; Flow Chart; 1.2; 1.3; 1.4.2.5 ; 2.1.1; 2.1.2; 2.1.3; 2.2.2; 3.1; 3.2; 3.3; 3.3.2; 3.3.5, 4.1.1;4.1.3; 4.1.4; 5.1; 5.2.2; 5.2.3; 5.2.4; 5.2.5; 5.2.6; 5.3.2.1; 5.3.2.2; 5.4.1; 6.1; 6.2; 6.2.1; 6.2.2; 7; 7.2.1.1; 7.2.1.2; 7.2.2; 7.2.3; 7.2.7; 7.4; 7.5; 8.7; appendices 10.3; 10.4
Description of change		The term, content and design of the MD part including an additional flow chart and timetable for PK, ADA sampling and ECG recording has been included. Where appropriate the text has been subdivided into SRD and MD part and the citation of the respective flow charts (I and II) have been added.
Rationale for change		As the intravitreal clinical development of BI 754132 is aiming for a safe drug with a preferable long lasting effect (e.g. allowing 2- or 3-monthly treatment) only the highest dose of the SRD is expected to provide sufficient eye

		exposure and efficacy to be selected assessing the safety, tolerability and pharmacokinetics after multiple dosing. The inclusion of 6 patients (as required for the last dose group in SRD part) out of an almost identical patient population and applying the same safety assessments during treatment and extended follow-up period is considered as sufficient to justify the amendment of the SRD with a multiple dosing part using the same route of administration.
Section to be changed		Flow Chart I (SRD part) and 6.2; 6.2.1.2
Description of change		Extension of text in footnote 8 with "at PI´s discretion, IOP can be repeated after pupil dilation and after IVT injection"; addition of footnote 8 to IOP. Wording in 6.2 and 6.2.1.2 adapted accordingly.
Rationale for change		For clarity and safety reasons based on PIs feedback to allow IOP measurement after pupil dilation and after IVT injection.
Section to be changed		Flow Chart I (SRD part) and 6.2.1.1
Description of change		Addition of footnote 10 and changed wording in 6.2.1.1 to "If the screening visit performed earlier than 14 days before dosing visit, an additional visit for repeating of safety lab, vital signs, ECG and targeted physical examination has to be performed again."
Rationale for change		For clarity and insertion of footnote based on PIs feedback
Section to be changed		1.2
Description of change		Description of interim PK and safety data of dose cohort 1 and 2 of SRD part and reference to actual IB.
Rationale for change		Update of available data and for transparency
Section to be changed		1.4 and Appendix 10.5
Description of change		Benefit Risk Assessment in context of COVID-19 pandemic for patients participating in trial 1418-0001 investigating BI 754132
Rationale for change		Clarification
Section to be changed		Synopsis, 2.1.3
Description of change		Deletion of eye disorders
Rationale for change		For clarity
Section to be changed		2.2.1
Description of change		Change spelling to ophthalmological
Rationale for change		Based on PI feedback

Section to be changed		2.2.2; 3.1; 5.2.4; 5.7; 6.2.1.1; 6.2.1.2; 6.2.2.1; 6.2.2.2; 7.2.4; 8.7
Description of change		OCT-A has been spelled; GA assessment has been specified; missing ERG readouts have been added
Rationale for change		For clarity and completeness
Section to be changed		3.1
Description of change		Deletion of “and on” in first sentence of third paragraph
Rationale for change		Correction
Section to be changed		3.3.2; Inclusion criteria #3
Description of change		Separation and differentiation of BCVA inclusion criteria between SRD and MD part; addition of Snellen equivalent in ETDRS letter chart.
Rationale for change		Lower visual acuity in MD part should result in better recruitment, EDTRS letter chart based on PI feedback.
Section to be changed		3.3.3
Description of change		Exclusion of patients in the MD part that participated in the SRD part
Rationale for change		For safety reasons
Section to be changed		5.2.1
Description of change		Extension and precision of term vascular occlusion
Rationale for change		For clarity and better differentiation versus CNV
Section to be changed		5.2.2
Description of change		Measurement of height only at Visit 1
Rationale for change		For Clarity
Section to be changed		5.2.6
Description of change		Description of precise ECG electrode placement as optional procedure; specify that single ECG recordings are only allowed in case of repetitions due to quality reasons
Rationale for change		For clarity and based on PI feedback
Section to be changed		5.2.8.2.2
Description of change		Deletion to fax the SAE form
Rationale for change		According to site standards and revised sponsor process
Section to be changed		5.4.1
Description of change		Missing ERG readouts have been added
Rationale for change		For clarity and completeness
Section to be changed		5.4.3
Description of change		Deletion of randomization
Rationale for change		Correction; non-randomized trial

Section to be changed		6.2
Description of change		Insertion of "slit lamp examination" and "ocular tonometry (for determination of IOP)" under assessments before pupil dilation
Rationale for change		Correction and to correspond to footnote 8 in Flow Chart I (SRD)
Section to be changed		7.2.1.2
Description of change		Deletion of "The subject experienced emesis that occurred at or before two times median t_{max} of the respective treatment (Median t_{max} is to be determined excluding the subjects experiencing emesis)"
Rationale for change		For clarity as not considered relevant for an intravitreally administered IMP
Section to be changed		8.7
Description of change		Addition of primary responsibility of SMC within trial and specification of objectives for SRD and MD part
Rationale for change		Dose selection based on SRD outcome and decision to continue with MD part
Section to be changed		10.3
Description of change		Addition of footnote (4) to define time window for PK sampling at V2
Rationale for change		Based on PI feedback

11.5 GLOBAL AMENDMENT 5

Date of amendment		12 Oct 2021
EudraCT number **EU number**		2018-004125-92
BI Trial number		1418-0001
BI Investigational Medicinal Product(s)		BI 754132
Title of protocol		Safety, tolerability and pharmacokinetics of single rising intravitreal doses of BI 754132 in patients with geographic atrophy secondary to age-related macular degeneration (open label, non-randomized, uncontrolled).
Global Amendment due to urgent safety reasons		☒
Global Amendment		☒
Section to be changed		Flow Chart II Multiple Dosing Part
Description of change		a) Addition of "indirect ophthalmoscopy" to slit lamp and IOP assessments

		b) Deletion of footnote 5 (CFP; "only be done if considered medically necessary by the principal investigator") c) Renumbering of subsequent footnote numbers 5 to 10 d) Deletion of "at PI´s discretion, IOP can be repeated after pupil dilation and after IVT injection" in footnote 7 and addition of footnote 8: "OP must be repeated 30 to 50 minutes after IVT injection at Visit 2, 3 and 4." e) Deletion of "If fixation does not allow for acquisition of good quality images, the examination may be considered optional" in footnote 9 f) Addition of "Post-injection assessments"
Rationale for change		a) In accordance with sections 1.4.2.6 and 5.2.4. b) In accordance with sections 1.4.2.6 and 5.2.4. c) To fit with the flow chart content sequence d) In accordance with section 6.2 with the aim to better monitor IOP changes after IVT injections in MD part e) FAF, SD-OCT and CFP considered mandatory in accordance with sections 1.4.2.6, 5.2.4 and 5.7 f) In accordance with insertion of post-injection assessments in section 6.2.2.2
Section to be changed		Abbreviations
Description of change		Addition of CFP, CRP, HbA1c and OCT-A
Rationale for change		Required due to additions into sections 1.2, 1.4.2, 5.2.4 and 5.2.5
Section to be changed		1.1
Description of change		Addition of: "However, in recent years, a number of new potential therapies has been tested. Recently, results from Phase III trials of Lampalizumab (Roche), an Anti-Complement Factor D Fab, showed no efficacy. Ongoing clinical trial evaluations include e.g. APL-2 (Apellis), an Anti- Complement C3 in Phase III development"
Rationale for change		To reflect the correct status of competitor´s trial outcomes
Section to be changed		1.2; sub-headings: Data from clinical studies, Pharmacokinetics, Anti-drug antibodies and Safety evaluations

Description of change		Description of all safety & PK data and addition of ADA data of SRD part
Rationale for change		Update of all available SRD data, description of all observed ocular and systemic AEs & SAEs and to reference the actual version of IB
Section to be changed		1.4
Description of change		Rearrangement of introductory part into section 1.4.3 (Discussion)
Rationale for change		To avoid redundancy and to better discuss the newly added content of sections 1.4.2.5 and 1.4.2.6
Section to be changed		1.4.2.3
Description of change		Addition of: "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 comparable material 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 effect like vitreous floaters or intraocular inflammation. The overall risk for such events is considered low based on long-term experience with comparable material. However, patients should be made aware of this risk, as reflected in the ICF. To the best of the sponsor´s knowledge there is currently no comparable material 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 material from certain manufacturers and leaves the decision to the treating investigators/sites on which material to use if it meets the specifications as described in the IMP handling instructions for BI 754132."
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. This insertion has been requested and recently approved by MHRA on the basis of a local amendment. Implementation on the basis of a global amendment will lead to harmonization across all trial sites.
Section to be changed		1.4.2.5; addition of this section
Description of change		Description of both SAEs; PI´s & sponsor´s assessments, reporting and recommended safety measures to be implemented in the MD part
Rationale for change		For clarity and transparency
Section to be changed		1.4.2.6
Description of change		Addition of "minimizing" to section title. Description of the safety measures to be implemented in the MD part. Addition of CRP and HbA1c collection to the safety laboratory parameters in accordance with sections 3.3.3 and 5.2.5
Rationale for change		Based on SMC and sponsor internal safety assessments & recommendations
Section to be changed		1.4.3
Description of change		Additions, update and edition of discussion section reflecting the content of previously added data described in sections 1.2, 1.4.2.5 and 1.4.2.6
Rationale for change		To better include and discuss all relevant safety data of SRD part
Section to be changed		3.1, sub heading: MD part and Figure 3.1:2
Description of change		Criteria of the sentinel dosing process for the MD part, decision making and communication
Rationale for change		Based on sponsor internal safety assessment and recommendation
Section to be changed		3.3.2; inclusion criteria 1., 3. and 5.
Description of change		1. Specification of GA lesion size (in mm^2 and disc area size), reference to study eye and differentiation between SRD and MD part 3. Restatement of BCVA criteria in MD part 5. Deletion of "if both eyes are eligible and have identical VA the investigator may select the study eye"
Rationale for change		Based on sponsor internal safety assessment and recommendation
Section to be changed		3.3.3
Description of change		Addition of exclusion criteria 14 and 15 for MD part

Rationale for change		Based on SMC and sponsor internal safety assessment and recommendation
Section to be changed		5.2.4; section title and content
Description of change		a) Change of section title to "Ophthalmological Examination" b) Reorganization of section, additions (to MD part) and specification of ophthalmological examinations
Rationale for change		For clarity and to reflect content of sections 1.4.2.6 and 1.4.3
Section to be changed		5.2.5
Description of change		Addition of HbA1c and CRP into safety laboratory parameters
Rationale for change		To reflect content of sections 1.4.2.6 and 3.3.3
Section to be changed		5.7
Description of change		Reassignment of certain ophthalmology examinations (SD-OCT, FAF and indirect ophthalmology) to "standard"
Rationale for change		For safety reasons and in accordance with sections 1.4.2.6, 1.4.3 and 5.2.4 for MD part
Section to be changed		6.2
Description of change		Different procedures of IOP measurements during SRD and MD part
Rationale for change		For safety reasons and in accordance with Flow Chart I (SRD part) and II (MD part)
Section to be changed		6.2.2.2
Description of change		Addition and description of "post-injection assessments"
Rationale for change		For safety reasons and to reflect added assessment in Flow Chart II (MD part)
Section to be changed		8
Description of change		Addition of "As per the project publication strategy, interim cohort data may be published as available, while full results will be published after CTR finalization"
Rationale for change		For transparency and in harmonization with other sponsor conducted retinopathy trials

11.6 GLOBAL AMENDMENT 6

Date of amendment		17 Feb 2022
EudraCT number **EU number**		2018-004125-92
BI Trial number		1418-0001
BI Investigational Medicinal Product(s)		BI 754132

Title of protocol		Safety, tolerability and pharmacokinetics of single rising intravitreal doses of BI 754132 in patients with geographic atrophy secondary to age-related macular degeneration (open label, non-randomized, uncontrolled).
Global Amendment due to urgent safety reasons		☐
Global Amendment		☒
Section to be changed		Page 6-7: Flow chart II (multiple dosing part)
Description of change		Change of footnotes 2 and 3 in and under the table: (2)…before PK sampling (see time schedule in Appendix 10.3)…→ (2)…before PK sampling. (3) PK sampling see time schedule in Appendix 10.3 → (3) PK and ADA sampling as well as ECG measurement must be performed within 4 hours prior to the IVT drug administration, and each sampling and measurement timepoint has to be entered in the eCRF.
Rationale for change		New time-window for PK & ADA sampling and ECG measurement to improve feasibility (based on PI feedback)
Section to be changed		Page 19: 1.2 Drug profile / Pharmacokinetics:
Description of change		…collectedbefore…injection.Cohort…→ …collected before…injection. Cohort
Rationale for change		Missed space in former versions
Section to be changed		Page 19: 1.2 Drug profile / Safety evaluations:
Description of change		…non-arteric…→ …non-arteritic…
Rationale for change		Correction of a typo
Section to be changed		Page 19: 1.2 Drug profile / Safety evaluations:
Description of change		…case occured…was subjectivly…→ …case occurred…was subjectively…
Rationale for change		Correction of two typos
Section to be changed		Page 24: 1.4.2.6 Planned measures for monitoring and minimization the risks
Description of change		Amendment…patientsUpdate…→ • Amendment…patients. • Update informed consent (IC)…
Rationale for change		Insertion of missing bullet point
Section to be changed		Page 24: 1.4.2.6 Planned measures for monitoring and minimization the risks
Description of change		…monitoring and mimimization…→

		…monitoring and minimization… and …Additionally , a systemic evaluation will be performed at each timepoint, to assess…→ …Additionally, a systemic evaluation will be performed at the timepoints specified in the flow charts under physical examination, to assess…
Rationale for change		Typo and wording correction.
Section to be changed		Page 26: 1.4.3 Discussion
Description of change		…continuative use in this clinical trial…→ …continued use in this clinical trial…
Rationale for change		Grammar correction
Section to be changed		Page 27: 2.1.2 Primary endpoint(s)
Description of change		…drug releated…→ …drug-related…
Rationale for change		Correction of a typo
Section to be changed		Page 27: 2.1.2 Primary endpoint(s)
Description of change		…Cmax…→ …C_{max}…
Rationale for change		Correction of a typo
Section to be changed		Page 29: 3.1 Overall trial design and plan
Description of change		…investigated,the…→ …investigated, the…
Rationale for change		Correction of a typo
Section to be changed		Page 44: 5.2.1 Dose limiting event
Description of change		…occurance…→ …occurrence…
Rationale for change		Correction of a typo
Section to be changed		Page 45: Section 5.2.3 Vital signs
Description of change		Additional text: Prior to the blood pressure measurement, the PI should ensure that the subject has taken his or her blood pressure medications (if any) as usual at home. If the measurement results are to be doubted for example because of preceding great exertion of the subject, a new measurement should be taken after half an hour in a resting position and only this stable value has to be entered in the eCRF.
Rationale for change		Better explanation of how to improve blood pressure measurments. Addtionally, instruction for the study centers to remind their patients to take all necessary medication before their visits at home.
Section to be changed		Page 45: 5.2.4 Ophthalmological examinations

Description of change		…photographswill…→ …photographs will…
Rationale for change		Correction of a typo
Section to be changed		Page 45: 5.2.4 Ophthalmological examinations
Description of change		…documents.If…→ …documents. If…
Rationale for change		Correction of a typo
Section to be changed		Page 54: 5.3.1 Assessment of pharmacokinetics
Description of change		…determination of pharmacokinetic parameters. Planned time points for systemic pharmacokinetic samples are listed in Appendix 10.3→ …determination of pharmacokinetic parameters. Sampling should be done at the timepoints listed in the flow-chart I and II and within 4 hours prior to the IVT drug administration. It is important to ensure that the exact time of the assessment of pharmacokinetics is recorded.
Rationale for change		New time-window for PK & ADA sampling and ECG measurement to improve feasibility (based on PI feedback)
Section to be changed		Page 60: 6.2.2.3 Follow-up period and trial completion of MD part
Description of change		Empty line/empty paragraph deleted
Rationale for change		Correction of formatting error
Section to be changed		Page 79: Table 10.3: 2 Time schedule for PK and ADA blood sampling and ECG recording during MD part
Description of change		Planned time for V1 was changed to -4:00h; Footnotes changed in and under the table: (1) A time window of +/- 15 min for sample drawing is allowed here. → (1) PK and ADA sampling as well as ECG measurement must be performed within 4 hours prior to the IVT drug administration, and each sampling and measurement timepoint has to be entered in the eCRF.
Rationale for change		New time-window for PK & ADA sampling and ECG measurement to improve feasibility (based on PI feedback)
Section to be changed		Page 85: 10.5 Benefit-Risk assessment in context of covid-19 pandemic for patients participation in trial 1418-0001 investigating BI 754132
Description of change		…conclusions and and…→ …conclusions and…
Rationale for change		Correction of a typo

Section to be changed		Page 86: 10.5 Benefit-Risk assessment in context of covid-19 pandemic for patients participation in trial 1418-0001 investigating BI 754132
Description of change		…COVID-19 releated…→ …COVID-19 related…
Rationale for change		Correction of a typo
Section to be changed		Page 91 11.4 Global amendment 4
Description of change		…Synopis…→ …Synopsis…
Rationale for change		Correction of a typo
Section to be changed		Page 92: 11.4 Global amendment 4
Description of change		…visual acquity…in case of repetitons…→ …visual acuity…in case of repetitions…→
Rationale for change		Correction of two typos
Section to be changed		Page 93: 11.4 Global amendment 4
Description of change		…tmax…→ …t_{max}…
Rationale for change		Correction of a typo
Section to be changed		Page 96: 11.5 Global amendment 5
Description of change		…decribed…→ …described…
Rationale for change		Correction of a typo
Section to be changed		Page 96: 11.5 Global amendment 5
Description of change		…implanted…→ …implemented…
Rationale for change		Correction of a typo

APPROVAL / SIGNATURE PAGE

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Title: Safety, tolerability and pharmacokinetics of single rising intravitreal doses and multiple intravitreal dosing of BI 754132 in patients with geographic atrophy secondary to age-related macular degeneration (open label, non-randomized, uncontrolled).

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Trial Statistician	[redacted]	17 Feb 2022 17:21 CET
Approval		18 Feb 2022 10:22 CET
Approval-Clinical Trial Leader		21 Feb 2022 10:34 CET
Verification-Paper Signature Completion		24 Feb 2022 16:46 CET

(Continued) Signatures (obtained electronically)

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