Clinical Trial Protocol

	Document Number:	**c17360540-08**
EudraCT No.: **EU Trial No:**	2017-001221-40	
BI Trial No.:	1336-0007	
BI Investigational Product(s):	BI 836880	
Title:	Safety, tolerability and pharmacodynamics of single rising intravitreal and multiple rising intravitreal doses of BI 836880 in patients with wAMD (open label, non-randomized, uncontrolled).	
Lay Title:	A study to test different doses of BI 836880 in patients with an eye disease called wet age-related macular degeneration (wAMD)	
Clinical Phase:	I/IIa	
Trial Clinical Monitor:	[redacted] Phone [redacted] Fax [redacted]	
Coordinating Investigator:	[redacted] Phone [redacted], Fax [redacted]	
Status:	Final Protocol (Revised Protocol (based on global amendment No. 7))	
Version and Date:	**Version: 8.0**	**Date: 28 Sep 2022**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	NA
Active ingredient name:	BI 836880
Protocol date	05 Nov 2018
Revision date	28 Sep 2022
Trial number	1336-0007
Title of trial:	Safety, tolerability and pharmacodynamics of single rising intravitreal and multiple rising intravitreal doses of BI 836880 in patients with wAMD (open label, non-randomized, uncontrolled).
Coordinating Investigator	[redacted] Phone [redacted], Fax [redacted]
Trial site(s):	Multi-centre trial
Clinical phase:	I/IIa
Objective(s):	To investigate the safety, tolerability, and pharmacodynamics of single and multiple intravitreal doses of BI 836880
Methodology:	Open label, uncontrolled, non-randomized trial of BI 836880 administered intravitreally as single dose in the single rising dose (SRD) part and as multiple doses in the multiple rising dose (MRD) part.
Number of patients entered:	Approximately 42; 15 in the SRD part and approximately 27 in the MRD part
Number of patients on each treatment:	SRD part: 15, in different dose groups MRD part: 11 patients in dose group 1 (cohort 1); approximately 16 patients in dose group 2 (4 patients from cohort 2, 12 patients from cohort 3).
Diagnosis:	Treatment-resistant wet age-related macular degeneration (wAMD) in SRD part and MRD cohort 1; treatment-naïve wAMD for MRD cohort 2; patients within 3 years of initial wAMD diagnosis for MRD cohort 3.
Main in- and exclusion criteria	Inclusion: SRD and MRD cohort 1: Men and women over the age of 55 with active choroidal neovascularization (CNV) secondary to wAMD despite prior anti-VEGF therapies; for MRD cohort 1 only: central subfield retinal thickness (CSFT) > 300 microns. For MRD cohort 2: Men and women over the age of 55 with treatment-naïve CNV secondary to AMD.

	For MRD cohort 3: Men and women over the age of 55 with active CNV secondary to wAMD that require frequent intravitreal (IVT) treatment (28 to 56 days between treatments) with ranibizumab, aflibercept, or bevacizumab for standard of care for at least 6 months, with the last IVT administration between 4-8 weeks before the first study drug administration. Exclusion: Additional eye disease in the study eye that could compromise best corrected visual acuity. For MRD cohort 3: Active intraocular inflammation in the study eye, > 0.5+ anterior chamber cell and/or vitreous haze grading, or history of intraocular inflammation in either eye with previous IVT administration(s), history of retinal vein occlusion, previous treatment with brolucizumab or faricimab, and/or medical history of autoimmune disease that has caused ocular inflammation.
Test product(s):	BI 836880
dose:	SRD Part: 0.06 mg, 0.18 mg, 0.5 mg, 1.0 mg, 2.0 mg (single doses) MRD Part: 1 mg (cohort 1) and 2 mg (cohort 2 and 3) (q4w)
mode of administration:	Intravitreal injection
Comparator products:	Not applicable
dose	Not applicable
mode of administration:	Not applicable
Duration of treatment:	SRD part: Single intravitreal dose MRD part: 3 intravitreal doses in 4-weekly intervals (q4w)
Endpoints:	SRD part: Primary endpoint: • Number of patients with ocular dose limiting events (DLEs) Secondary endpoints: • Number of patients with drug related adverse events (AEs) • Number of patients with any ocular adverse events in the study eye MRD part: Primary endpoint: • Number of patients with drug related AEs Secondary endpoints: • Percent change from baseline in CSFT in the study eye at Week 12 (Visit 5) • Change from baseline in best corrected visual acuity (BCVA) in the study eye at Week 12 (Visit 5) • Time to recurrence after the last treatment

	• Number of patients with any ocular adverse events in the study eye
Criteria for Pharmacokinetics	Further criteria of interest: SRD part: • Systemic pharmacokinetics of BI 836880 after a single intravitreal dose • Systemic immunogenic response (pre-existing anti-drug antibody [ADA], treatment emergent ADA) MRD part: • Systemic exposure of BI 836880 after multiple intravitreal doses • Systemic immunogenic response (pre-existing ADA, treatment emergent ADA) after multiple intravitreal doses
Criteria for Pharmacodynamics:	Further criteria of interest: SRD part: • Systemic free Vascular Endothelial Growth Factor (VEGF) and free/total ANG2 levels after a single intravitreal dose MRD part: • Change from baseline in CSFT in the study eye at Week 12 (Visit 5) • Changes from baseline in selected parameters derived from color fundus photography (CFP)/optical coherence tomography (OCT)/OCT-angiography (OCT-A) in both eyes • Systemic free VEGF and free angiopoietin 2 (ANG2) after multiple intravitreal doses
Safety criteria:	Further criteria of interest: • Ocular inflammation in the study eye • Retinal haemorrhage in the study eye • BCVA reduction by more than 15 letters in the study eye • AEs including clinically relevant findings from the physical examination, safety laboratory tests, 12-lead electrocardiogram (ECG), vital signs
Statistical methods:	Descriptive statistics will be provided for all endpoints for SRD and MRD parts. No statistical testing is planned. In addition, in SRD part, the dose escalation 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**	**Treat-ment Visit**	**Follow-up Period**					**End of trial**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Days Study Week	Duration 3 to 42 days	Day 1	4	8 Week 1	15 Week 2	22 Week 3	29 Week 4	43 Week 6
Time window for visits (days)		none	±1	±2	±2	±2	±2	±2
Informed consent	X							
Demographics	X							
Medical history	X							
Physical examination [3]	X						X	X
Vital signs	X	X	X	X	X	X	X	X
Laboratory tests	X	X		X	X	X	X	X
12 lead-ECG [2]	X	X	X	X	X		X	X
Review of in-/exclusion criteria	X	X						
Dose Assignment		X						
IVT drug administration		X						
PK Sampling		X	X	X	X		X	X
Biomarker sampling		X	X	X	X		X	X
ADA sampling		X			X			X
Visual Acuity testing	X	X	X	X	X	X	X	X
SD-OCT	X	X	X	X	X	X	X	X
OCT Angiography	X	X		X	X	X	X	X
Fundus Photo	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X
Slit lamp and IOP	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
Concomitant therapy	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) See Section 5.2.6; the ECGs are to be recorded shortly before the PK sampling at the respective time points; see Appendix 10.1.

(3) Physical examinations will also include measurement of weight and height (height only at Visit 1).

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

FLOW CHART II (MULTIPLE RISING DOSE PART, COHORT 1)

Trial Periods	**Screening Period**	**Treatment Period**			**Follow-up Period**			**End of Trial[1]**
Visit	**1**	**2**	**3**	**4**	**5**	**6**	**7**	**8**
Study Day Study Week	-14	1	29 Week 4	57 Week 8	85 Week 12	113 Week 16	141 Week 20	169 Week 24
Time window for visits (days)	±10	none	±3	±3	±3	±3	±3	±3
Informed consent	X							
Demographics	X							
Medical history	X							
Physical examination [5]	X				X			
Vital signs	X	X	X	X	X	X	X	X
Laboratory tests	X	X	X	X	X	X	X	X
12 lead-ECG [2]	X	X	X	X	X			
Review of in-/exclusion crit.	X	X						
Dose Assignment		X						
IVT drug administration		X	X	X				
PK sampling		X	X	X	X	X	X	X
Biomarker sampling		X	X	X	X	X	X	X
ADA sampling		X	X	X	X			X
Biobanking		X[3]						
Visual Acuity testing	X	X	X	X	X	X	X	X
SD-OCT	X	X	X	X	X	X	X	X
OCT Angiography	X	X	X	X	X	X	X	X
Fundus Photo	X	X[4]	X[4]	X[4]	X[4]	X[4]	X[4]	X
Slit lamp	X	X	X	X	X	X	X	X
IOP	X	X	X	X	X	X	X	X
Adverse events	X	X	X	X	X	X	X	X
Concomitant therapy	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) See Section 5.2.6; the ECGs are to be recorded shortly before the PK sampling at the respective time points; see Appendix 10.1.

(3) Collection of biobanking samples is optional. Participating patients are required to give informed consent specifically for biobanking. Samples will be stored at a biobanking facility for future research. DNA biobanking requires only one blood sample to be taken, preferably at Visit 2. However, collection at later visits is permitted as long as the informed consent for biobanking remains valid.

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

(5) Physical examinations will also include measurement of weight and height (height only at Visit 1).

FLOW CHART III (MULTIPLE RISING DOSE PART, COHORT 2)

Trial Periods	**Screening Period**	**Treatment Period**						**Follow-up Period**			**End of Trial[1]**
Visit	**1**	**2**	**2a[6]**	**3**	**3a[6]**	**4**	**4a[6]**	**5**	**6**	**7**	**8**
Study Day	-14	1	2	29	30	57	58	85	113	141	169
Study Week				Week 4		Week 8		Week 12	Week 16	Week 20	Week 24
Time window for visits (days)	±10	none	+6	±3	+6	±3	+6	±3	±3	±3	±3
Informed consent	X										
Demographics	X										
Medical history	X										
Physical examination [5]	X							X			
Vital signs	X	X		X		X		X	X	X	X
Laboratory tests	X	X		X		X		X	X	X	X
12 lead-ECG [2]	X	X		X		X		X			
Review of in-/exclusion crit.	X	X									
Dose Assignment		X									
IVT drug administration		X		X		X					
PK sampling		X		X		X		X	X	X	X
Biomarker sampling		X		X		X		X	X	X	X
ADA sampling		X		X		X		X			X
Biobanking		X[3]									
Visual Acuity testing	X	X		X		X		X	X	X	X
SD-OCT	X	X		X		X		X	X	X	X
OCT Angiography	X	X		X		X		X	X	X	X
Fundus Photo	X	X[4]		X[4]		X[4]		X[4]	X[4]	X[4]	X
Slit lamp	X	X	X	X	X	X	X	X	X	X	X
IOP	X	X		X		X		X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	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) See Section 5.2.6; the ECGs are to be recorded shortly before the PK sampling at the respective time points; see Appendix 10.1.

(3) Collection of biobanking samples is optional. Participating patients are required to give informed consent specifically for biobanking. Samples will be stored at a biobanking facility for future research. DNA biobanking requires only one blood sample to be taken, preferably at Visit 2. However, collection at later visits is permitted as long as the informed consent for biobanking remains valid.

(4) Only to be done if considered medically necessary by the principal investigator.
(5) Physical examinations will also include measurement of weight and height (height only at Visit 1).
(6) Additional safety procedures may be performed according to local safety standard practice.

FLOW CHART IV (MULTIPLE RISING DOSE PART, COHORT 3)

Trial Periods	**Screening Period**	**Treatment Period**						**Follow-up Period**			**End of Trial[1]**
Visit	**1**	**2**	**2a[6]**	**3**	**3a[6]**	**4**	**4a[6]**	**5**	**6**	**7**	**8**
Study Day	-14	1	2	29	30	57	58	85	113	141	169
Study Week				Week 4		Week 8		Week 12	Week 16	Week 20	Week 24
Time window for visits (days)	±10	none	+6	±3	+6	±3	+6	±3	±3	±3	±3
Informed consent	X										
Demographics	X										
Medical history	X										
Physical examination [5]	X							X			
Vital signs	X	X		X		X		X	X	X	X
Laboratory tests	X	X		X		X		X	X	X	X
12 lead-ECG [2]	X	X		X		X		X			
Fluorescein angiography [7]	X										
Review of in-/exclusion crit.	X	X									
Dose Assignment		X									
IVT drug administration		X		X		X					
PK sampling		X		X		X		X	X	X	X
Biomarker sampling		X		X		X		X	X	X	X
ADA sampling		X		X		X		X			X
Biobanking		X[3]									
Visual Acuity testing	X	X		X		X		X	X	X	X
SD-OCT	X	X		X		X		X	X	X	X
OCT Angiography	X	X		X		X		X	X	X	X
Fundus Photo (multi-field) [4]	X	X	X	X	X	X	X	X	X	X	X
Fundus Photo (widefield)	X	X	X	X	X	X	X	X	X	X	X
Slit lamp	X	X	X	X	X	X	X	X	X	X	X
IOP	X	X		X		X		X	X	X	X
Adverse events	X	X	X	X	X	X	X	X	X	X	X
Concomitant therapy	X	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) See Section 5.2.6; the ECGs are to be recorded shortly before the PK sampling at the respective time points; see Appendix 10.1.

(3) Collection of biobanking samples is optional. Participating patients are required to give informed consent specifically for biobanking. Samples will be stored at a biobanking facility for future research. DNA biobanking requires only one blood sample to be taken, preferably at Visit 2. However, collection at later visits is permitted as long as the informed consent for biobanking remains valid.

(4) Vitreous haze assessment to be completed with every examination.

(5) Physical examinations will also include measurement of weight and height (height only at Visit 1).

(6) Additional safety procedures may be performed according to local safety standard practice.

(7) Fluorescein angiography imaging during Visits 2-8 should be performed at the discretion of the investigator, e.g. if signs of inflammation are observed.

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ABBREVIATIONS

ADA	Anti-Drug Antibody
AE	Adverse Event
AESI	Adverse Event of Special Interest
AMD	Age-related macular degeneration
ANG2	Angiopoietin 2
AUC	Area Under the Curve
AUEC	Area Under the Effect-time Curve
BCVA	Best Corrected Visual Acuity
BI	Boehringer Ingelheim
BLRM	Bayesian Logistic Regression Model
CA	Competent Authority
CFP	Color Fundus Photography
CI	Coordinating Investigator
CMC1	C-X9-C Motif Containing 1
CMC2	C-X9-C Motif Containing 2
CNV	Choroidal Neovascularisation
COVID-19	Coronavirus Disease 2019
CRA	Clinical Research Associate
CRC	Central Reading Center
CRF	Case Report Form, paper or electronic (sometimes referred to as “eCRF”)
CRO	Contract Research Organization
CSFT	Central Subfield Thickness
CTL	Clinical Trial Leader
CTM	Clinical Trial Manager
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
DILI	Drug-Induced Liver Injury
DLE	Dose Limiting Event
eDC	Electronic Data Capture
ECG	Electrocardiogram
EDTA	Ethylenediaminetetraacetic acid
EMA	European Medicines Agency
EOT	End of Trial
ERS	Evaluable Responders’ Set
ETDRS	Early Treatment Diabetic Retinopathy Study
EudraCT	European Clinical Trials Database
EWOC	Escalation with overdose control
FA	Flurescence Angiography
FAS	Full Analysis Set
FDA	Food and Drug Administration
FiH	First-in-Human
GCP	Good Clinical Practice
GFR	Glomerular Filtration Rate
GMP	Good Manufacturing Practice
HR	Heart Rate
IB	Investigator’s Brochure

ICF	Informed Consent Form
IEC	Independent Ethics Committee
IOI	Intra-Ocular Inflammation
IOP	Intra-Ocular Pressure
iPD	Important Protocol Deviation
IQRM	Integrated Quality and Risk Management
IRB	Institutional Review Board
IRT	Interactive Response Technology
IRF	Intra-Retinal Fluid
ISF	Investigator Site File
IVT	Intravitreal
LPDD	Last Patient Drug Discontinuation
LPO	Last Patient Out
MedDRA	Medical Dictionary for Drug Regulatory Activities
MRD	Multiple Rising Dose
MTD	Maximum Tolerated Dose
NEI	National Eye Institute
NOAEL	No Observed Adverse Effect Level
OCT	Optical Coherence Tomography
OCT-A	Optical Coherence Tomography - Angiography
OIR	Oxygen Induced Retinopathy
OPU	Operating Unit
PD	Pharmacodynamics
PlGF	Placental Growth Factor
PED	Pigment Epithelial Detachment
PK	Pharmacokinetics
REP	Residual Effect Period
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SD-OCT	Spectral Domain Optical Coherence Tomography
SHRM	Subretinal Hyper-Reflective Material
SMC	Safety Monitoring Committee
SoC	Standard of Care
SOP	Standard Operating Procedure
SRD	Single Rising Dose
SRF	Sub-Retinal Fluid
SUN	Standardization of Uveitis Nomenclature
SUSAR	Suspected Unexpected Serious Adverse Reactions
TMF	Trial Master File
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
VA	Visual Acuity
VEGF	Vascular Endothelial Growth Factor
wAMD	Wet Age-related Macular Degeneration
WG	Working Group
WHO	World Health Organization
WOCBP	Women of childbearing potential
YAG	Yttrium Aluminum Garnet

1. INTRODUCTION

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]. Early stage AMD is associated with the accumulation of drusen and disturbances of the retinal pigment epithelium (RPE). Morphology, number, and location of drusen relative to macula are indicative of disease progression, although over 75% of patients with early AMD never progress to either of the two forms of advanced AMD over 10 years.

Clinically, advanced AMD is classified into the nonexudative or atrophic form and the exudative "wet" or neovascular form and occurs in 15% and 10% of AMD patients respectively. Wet AMD is the more aggressive and debilitating form of AMD and is caused by the growth of abnormal choroidal neovascular membranes (CNV). New vessels sprout from the choriocapillaris, grow under the RPE or retina, and leak serum and blood. Fluid accumulation in the sub-RPE and subretinal spaces along with the neurosensory retina usually leads to measurable macular thickening. Involvement of the fovea by the CNV, edema and hemorrhage may profoundly impair visual acuity (VA) and loss of vision can be precipitous.

Intravitreally administered therapies that target vascular endothelial growth factor (VEGF) have become the standard of care, and have led to significant improvements in lesion morphology, vascular leakage, and, most importantly, improvement in VA.

Despite the availability of anti-VEGF therapies, AMD causes 50% of irreversible blindness in the developed world today. In many patients, it is difficult to continue long term treatment requiring frequent visits to the retinal specialists. Intravitreal (IVT) injections also present a risk to patients and a burden to both patients and caregivers. First, there is the potential for serious side effects associated with each IVT injection procedure, including endophthalmitis, retinal detachments, traumatic cataract, and increased intra-ocular pressure (IOP). Second, monthly treatment and monthly monitoring, which may continue for a patient's lifetime, is a substantial burden to patients, ophthalmologists, and the healthcare system. Extensive efforts have been undertaken to lower the injection frequency of anti-VEGF agents in wet Age-related Macular Degeneration (wAMD) [R13-4487]. However, unmet medical need still exists for new therapies that allow for a reduced frequency of IVT injections. The second major aspect of unmet medical need concerns further improvement in maintenance therapy and incremental VA gains over current therapies, especially in patients not sufficiently responded to the available anti-VEGF treatments.

1.2 DRUG PROFILE

BI 836880 is an anti-angiogenesis agent composed of VEGF-A and angiopoietin 2 (ANG2) binding domains with a third domain that binds to human serum albumin for improved half-life extension. BI 836880 is highly potent and showed efficacy in preclinical animal models for pathological retinal angiogenesis and neovascular leakage following IVT injection.

BI 836880 is selective for VEGF-A and ANG2, as the molecule does not bind to the related growth factors VEGF-B, -C, -D, placental growth factor (PlGF) and angiopoietin1 (ANG1). BI 836880 inhibits VEGF and Ang2- mediated intracellular signaling and functional activity.

It was found to be cross reactive to cynomolgus VEGF, as well as mouse, rat and cynomolgus ANG2 which indicates cynomolgus monkey as the most suitable species for pharmacological and toxicological studies.

In rodents, BI 836880 is not binding VEGF but ANG2 only. Nevertheless, BI 836880 is efficacious in a mouse oxygen induced retinopathy (OIR) model on pathological neoangiogenesis comparable to Eylea™, a potent inhibitor of the VEGF pathway [n00253677]. In cynomolgus monkeys BI 836880 is crossreactive to VEGF and ANG2. On laser induced CNV in cynomolgus monkeys, a disease model for neovascular wAMD, BI 836880 was superior to Lucentis™ on the reduction of clinically relevant severe lesions [n00256189] The potential for superior clinical efficacy of dual VEGF and ANG2 inhibition over VEGF inhibition is supported by these preclinical data.

After intravenous administration in the monkey, BI 836880 displayed dose-dependent pharmacokinetics (PK) (higher clearance and shorter half-life at lower doses; lower clearance and longer half-life at higher doses) [n00234399]. After IVT administration in the monkey, BI 836880 displayed a biphasic clearance in the vitreous humor, with a short initial half-life of 3 days and a long terminal half-life of 13 days. The long terminal half-life is likely due to the formation of BI 836880-albumin complex in the terminal phase [n00258450]. After IVT coadministration of BI 836880 and human albumin in rabbit eyes, human albumin extended the half-life of BI 836880 by 3-fold [n00259128]. The albumin concentration in the human vitreous humor is significantly higher than monkey vitreous humor. BI 836880 is expected to exist mostly in the BI 836880-albumin complex form in human vitreous humor and the ocular half-life of BI 836880 in human is predicted to be 21 days [n00259128].

For a more detailed description of the drug profile please refer to the current Investigator's Brochure (IB) [c21397543]. At the time of data cut-off for the current IB (25 March 2022), the SRD part of the trial described here (1336-0007) was completed: 15 patients had been treated with a single dose of intravitreal BI 836880 and followed up until the end of trial visit (EOT). In the ongoing MRD part, 14 patients had received at least one dose of BI 836880 (Table 1.2: 1). Six patients in the SRD part and 10 patients in the MRD part were reported with an adverse event (AE) after trial drug administration.

Table 1.2: 1 Summary of patient exposure to BI 836880*

Trial part/cohort	1 dose	2 doses	3 doses	Total patients exposed per cohort
SRD	15	---	---	15
MRD/cohort 1		2	8	10
MRD/cohort 2	1	2	1	4

* At the time of data cut off for the current IB (25 March 2022)

In the SRD part, all of the corresponding 6 AEs were eye disorders (conjunctival haemorrhage in the study eye, subretinal fluid in the study eye, dry eye in the study eye, 2 vitreous floaters in the study eye, neovascular AMD in the fellow eye). None of the reported AEs was judged as related to BI 836880 by investigators or fulfilled criteria for dose-limiting events. The AEs of neovascular AMD and of subretinal fluid were reported as of moderate intensity, the other AEs were rated as mild. The AE of neovascular AMD in the fellow eye was considered serious. All AEs but the neovascular AMD, the subretinal fluid and the dry

eye were recovered by the end of follow up. [redacted]

1.3 RATIONALE FOR PERFORMING THE TRIAL

IVT anti-VEGF injections are the current gold standard for treatment of patients with wet AMD. Anti-VEGF therapies are recognized to be effective and fast acting. However, the injection frequency (once every month or once every 2 months) is a burden and considered to be problematic for many patients to adhere to for a long time. Furthermore, many wet AMD patients do not have vision gain after anti-VEGF treatment and some continue to lose vision.

Treatment with a dual anti-VEGF/ANG2 antibody is anticipated to have better efficacy than current anti-VEGF treatments and also has the potential to allow for a lower injection frequency.

This trial will consist of a single rising dose (SRD) part and a multiple rising dose (MRD) part including MRD cohorts 1, 2, and 3. Since this is the First-in-Human (FiH) application with IVT route of administration, the SRD part and the MRD cohort 1 of this trial will include patients who have not sufficiently responded to anti-VEGF treatment and still have active disease with significant retinal edema after a minimum of three previous injections. After safety has been investigated in SRD and the first 3 patients of MRD cohort 1, the MRD cohort 2 will start to evaluate treatment-naïve patients. This treatment-naïve population was initially thought to be the final target population, however, an exploratory analysis of the available interim data (patients from SRD, MRD cohorts 1 & 2 of the current trial) suggests that BI 836880 may reduce CSFT, PED, SRHM, and/or PCV in an additional subset of patients (see Figure 1.3: 1). These patients included those with wAMD that was not sufficiently controlled despite receiving frequent standard of care (SoC) treatment. Therefore, it is expected that patients previously receiving frequent SoC treatment every 4-8 weeks, so called “frequent flyers” (frequently treated patients; MRD cohort 3) will highly benefit from IVT administration of BI 836880.

In the SRD part of the trial, 5 rising doses are planned to be administered intravitreously. Safety and tolerability will be established unless dose-limiting safety or tolerability issues are noted.

In the MRD part, three multiple dose cohorts will be studied over a 24 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 12 weeks without further injections to study the durability of the treatment effect and to identify the need for additional standard treatment and the time to development of recurrence of any retinal fluid. This will help to guide injection frequency intervals in later studies.

The therapeutic benefit or specific adverse events (AE) in patients cannot always be anticipated during the trial setup. Later on, there may be new scientific knowledge about biomarkers and other factors contributing to diseases or the action of a drug. In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking. If the patient agrees, banked samples may be used for future drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an AE, and thereby better match patients with therapies or to gain mechanistic understanding of drug effects and/or to identify genetic or other factors associated with response to therapy or the risk of adverse drug reactions.

1.4 BENEFIT - RISK ASSESSMENT

Based on available non-clinical data and based on clinical data from other compounds with a comparable mode of action BI 836880 is assessed to be generally safe for IVT use in humans (c21397543).

This is the first study using an IVT route of administration for this compound. However, IVT administration of an antibody that simultaneously binds to VEGF and ANG2 (faricimab, previously referred to as bispecific antibody RG7716) for treatment of wAMD has previously been tested in humans in a Phase 1 clinical trial [R18-0309], and a Phase 2 clinical trial [R21-0692]. In the Phase 1 trial, the co-adminstration of RG7716 was reported to be well tolerated and to exhibit a favourable safety profile overall [R18-0309]. In addition, there was preliminary evidence of improvements in BCVA and anatomic parameters for this mode of

action. In the Phase 2 trial, faricimab maintained vision and anatomic improvements comparable with SoC in wAMD in treatment naïve patients, resulting in the start of Phase 3 trials. These data support that the combination of anti-VEGF and anti-ANG2 can be used safely in patients with wAMD.

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 favorable risk-benefit profile. To the best of the sponsor's knowledge there is currently no product on the market, which is officially approved for intravitreal drug delivery.

The needles for preparation of the drug and intravitreal injection are usually silicone oil coated to ease the injection of the needle through the tissue. This carries the potential risk for a silicone oil transfer into the vitreous with the potential risks for occurrence of side effects like vitreous floaters or intraocular inflammation. The overall risk for such events is based on long-term experience with comparable material and is considered low. However, patients should be made aware of this risk, as reflected in the Informed Consent Form (ICF). To the best of the sponsor's knowledge, there is currently no product on the market, which is silicone-free. The recommended syringes are silicone-oil-free and not considered to carry this risk. The IMP handling instructions do not mandate the use of materials from certain manufacturers and 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 836880.

This trial will include in the SRD part and MRD cohort 1 patients with an insufficient response to the standard treatment for wAMD (IVT anti-VEGF therapy). Therefore, although this is a newly developed drug at an early stage of testing and an individual benefit cannot be guaranteed, trial treatment may result in an individual benefit to the individual patient. In addition, due to the long duration of the disease the patient may directly benefit from the drug development based on the results of this trial.

For the MRD cohort 2, treatment-naïve patients will be included based on a positive safety assessment as confirmed by the Safety Monitoring Committee (SMC), after three patients of MRD cohort 1 reach Visit 5, i.e. 4 weeks after the third injection.

For MRD cohort 3, frequently treated patients will be included (defined as patients receiving anti-VEGF every 4-8 weeks on average). These frequently treated patients are the intended final target population for BI 836880, because of the remaining unmet medical need for these patients to receive a higher potency anti-VEGF therapy. BI 836880 has shown potential efficacy signals in pretreated patients in the SRD/MRD part of the study and could therefore have a role in the treatment of patients needing frequent anti-VEGF therapy.

The following safety measures have been implemented to mitigate the risk and ensure early detection of intraocular inflammation (IOI): fluorescein angiography (FA) imaging will be required at screening and wide-angle fundus photography with a vitreous haze assessment will be required at every visit. Reports of IOI will be treated as an AE of special interest (AESI), see also Section 5.2.8.1.4.

Furthermore, 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, AESIs. The implications of the current Coronavirus Disease 2019 (COVID-19) pandemic are summarized in Section 10.4.

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 disease improvement of BI 836880 after a single IVT injection and after multiple IVT injections of several doses.

2.1.2 Primary endpoint(s)

SRD part:

- Number of patients with ocular dose limiting events (DLEs) from drug administration until end of trial (EOT). For definition of DLEs, refer to Section 5.2.1.

MRD 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
- Number of patients with any ocular AEs in the study eye

MRD part:

- Percent change from baseline in Central Subfield Thickness (CSFT) in the study eye at Week 12 (Visit 5), for each dose
- Change from baseline in BCVA in the study eye at Week 12 (Visit 5)
- Time to recurrence after the last treatment
- Number of patients with any ocular AEs in the study eye

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

This trial will consist of an SRD part followed by an MRD part. Both parts of the trial will be conducted non-randomized, open-label, and uncontrolled.

SRD part:
The starting dose is 0.06 mg. Dose-escalation will be restricted to a maximum of 200% from the previous dose up to doses of 0.5 mg, and to a maximum of 100% from the previous dose from dose 0.5 mg onwards. The maximum planned dose is 2 mg. For any dose-escalation cohort, at least 3 patients will be required. However, in the case that only 2 patients are evaluable and neither has experienced a DLE within the evaluation period (7 days after drug administration), then dose-escalation might occur based on these 2 patients if a joint decision of the Safety Monitoring Committee (SMC), see Section 8.7 is reached. Refer to Figure 3.1: 1 for a schematic representation of the dose escalation. For each dose group a single patient will be dosed on day 1 in each cohort, and only after a favorable safety and tolerability assessment on day 4 the remaining 2 patients will be dosed. A Bayesian logistic regression model (BLRM), based on a weakly informative prior distribution, and employing the escalation with overdose control (EWOC) principle (see Section 7) will be used for guiding the dose escalation [R13-4803]. Cohorts of patients will receive escalating doses of BI 836880. Each cohort will consist of newly enrolled patients.

The BLRM provides estimates for the probability of observing an ocular DLE for each dose level in the study as patient information becomes available. The corresponding methodology is described in Section 7.1 and in Appendix 10.3. At any time in the trial, it will not be permitted to escalate to a dose which does not fulfil the EWOC principle.

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 the MTD will likely be the highest feasible dose, 2 mg, rather than the highest tolerable dose in a strict sense.

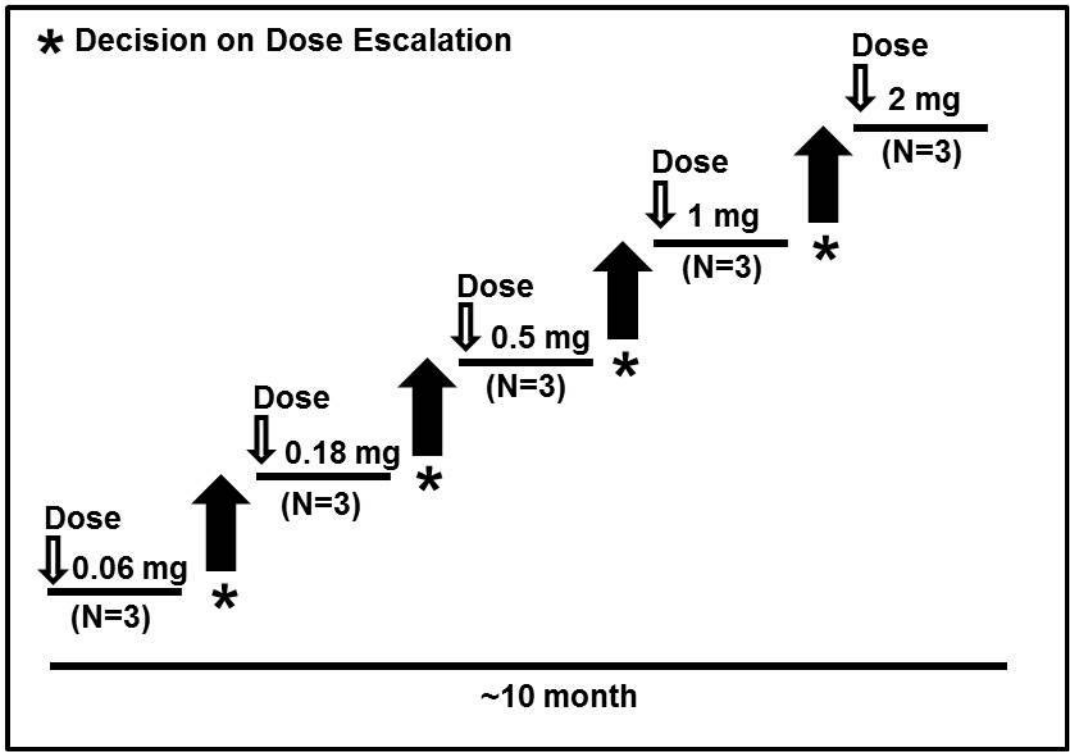

Figure 3.1: 1 Schematic representation of the dose escalation process in the SRD part of the trial

The SMC recommends the size for the next dose escalation cohort. After all patients in a cohort have either experienced an ocular DLE or have been observed for at least the 7 days evaluation period without experiencing a DLE, the Bayesian model will be updated with the newly accumulated data. The overdose risk will then be calculated for each dose, and escalation will be permitted to all planned doses which fulfil the EWOC criterion and the respective escalation rule. As a sensitivity analysis, the BLRM might also be run again shortly before the SMC meeting, using all data available up to this time point. Based on the model results and on additional information (PK, pharmacodynamics [PD], patient profiles), the members of the SMC will reach a joint decision on the next dose level to be investigated.

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.

The SMC may decide on stopping the dose escalation after the above criterion for MTD is fulfilled. Further patients may be included to confirm that the EWOC criterion is still fulfilled.

MRD part:
The MRD part will consist of a first part (1 mg) with 11 treatment-resistant patients (cohort 1), a second part (2 mg) with 4 treatment-naïve patients (cohort 2), and approximately 12 frequently treated patients (cohort 3; inclusion criteria defined in Section 3.3.2). These are the two highest doses established by the SMC as safe and tolerable during the SRD part. Patients that had received a dose in the SRD part of the trial will not be included. In the MRD

groups, patients will receive three consecutive doses over a 3-month period (once a month dosing, Figure 3.1: 2). The SMC will decide on dose escalation after 3 patients from the first MRD cohort have completed visit 5 (first follow up visit). In all patients included in the MRD parts of the trial, safety and efficacy will be studied to 12 weeks after the treatment period.

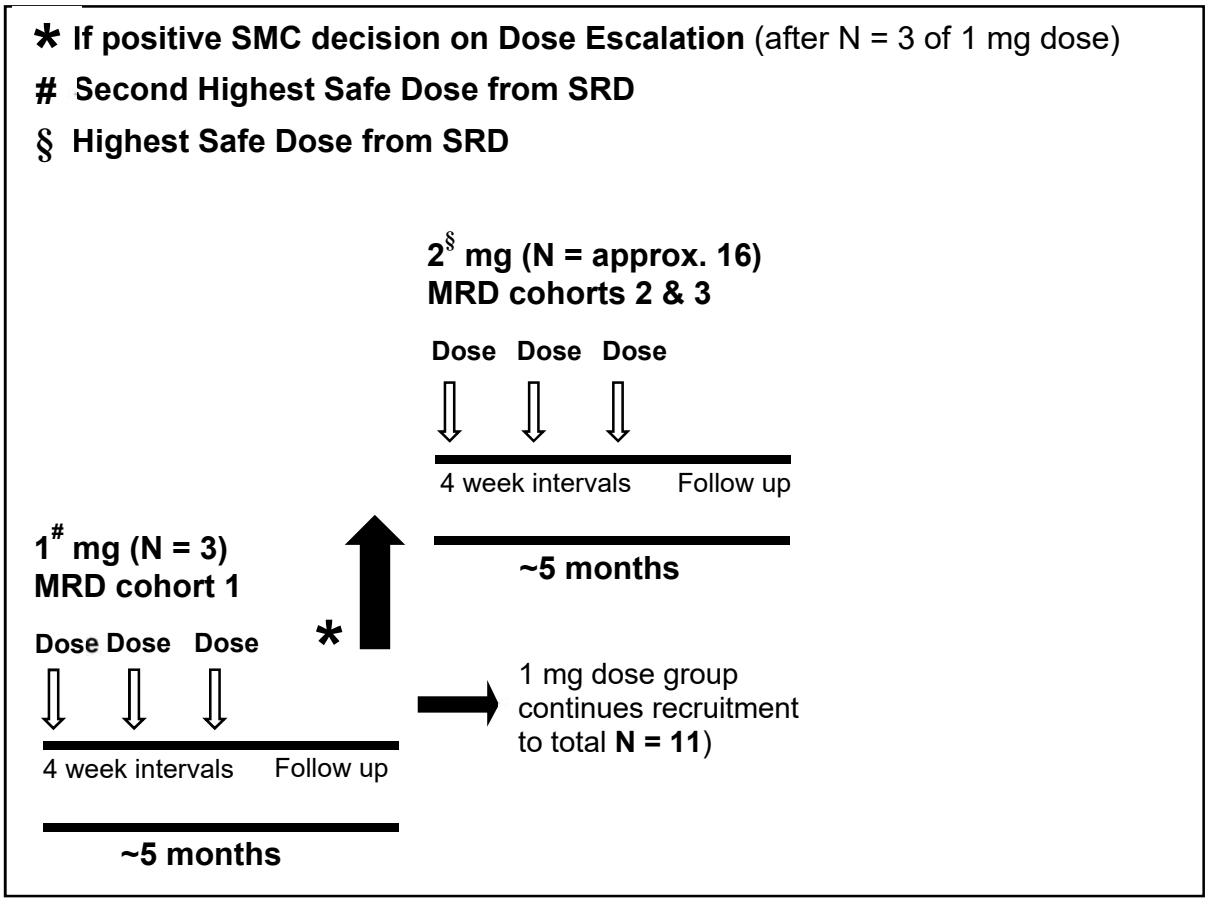

Figure 3.1: 2 Schematic representation of the dose escalation process in the MRD part of the trial

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

This trial is designed to establish a safe and effective dose for further testing in phase II trials. The trial consists of separate SRD and MRD parts. This trial will not use a placebo comparison because inclusion of a placebo arm would withhold patients with wAMD from an effective treatment for several weeks. The objectives to establish a safe and effective dose can be met without a placebo comparison.

The SRD dose escalation part is included and 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. This part of the trial will already be done in patients because IVT injections in healthy subjects would not be considered appropriate. 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].

It is expected that, in the study population of patients not sufficiently responding to anti-VEGF treatment, a reduction of fluid in the retina should be observed only after multiple treatments. Therefore, two MRD cohorts (3 injections in a monthly interval) will be included after the SRD part. This part of the trial will generate additional safety data after multiple dosing and allow for exploration of the time course and durability of treatment effects. These data will further support the definition of the injection frequency and intervals in later studies.

3.3 SELECTION OF TRIAL POPULATION

This trial will recruit up to 18 patients in the SRD part (the SRD part was completed with 15 patients) and up to 27 patients in the MRD part (cohort 1, 2 and 3). Please refer to Section 7.7 for details and justification.

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

3.3.1 Main diagnosis for trial entry

This study enrols patients with subfoveal choroidal neovascularization secondary to wAMD that have insufficiently responded to previous anti-VEGF therapies who meet all inclusion criteria and do not meet any exclusion criterion.

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

SRD part and MRD cohort 1 (treatment-resistant patients with wAMD):

1. Men and women over the age of 55 with active CNV secondary to AMD despite anti-VEGF therapies (at least 3 prior injections with the last injection within 16 to 4 weeks before treatment). Active CNV secondary to AMD is to be defined either by recent fluorescein or OCT angiogram within 4 weeks prior to screening or fluorescein or OCT angiogram obtained prior to first anti VEGF-treatment to confirm the diagnosis and still active according to investigator judgement.
2. Deleted.
3. For MRD part only: Central subfield retinal thickness >300 microns in the study eye on Heidelberg Spectralis Spectral Domain Optical Coherence Tomography (SD-OCT).
4. Presence of sub- and/or intraretinal fluid on SD-OCT in the study eye.
5. Any active CNV with subfoveal leakage in the study eye as determined by OCT
6. No subretinal hemorrhage involving the fovea in the study eye.

7. No significant subfoveal fibrosis or atrophy on SD-OCT in the study eye that, in the opinion of the investigator, is able to prevent improvement in BCVA and/or CSFT.
8. Best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) VA in the study eye between 75 and 24 letters inclusive (approximately 20/32 and 20/320 or 6/9.5 and 6/95) at screening.
9. Best-corrected VA in the non-study eye better than best-corrected VA in the study-eye. If both eyes are eligible and have identical VA the investigator may select the study eye.
10. Male or female patients. 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 and in Section 4.2.1.3.
11. Signed informed consent consistent with ICH GCP guidelines and local legislation prior to participation in the trial, which includes medication washout and restrictions.
12. Not under any administrative or legal supervision or under institutionalization due to regulatory or juridical order.

MRD cohort 2 (treatment-naive patients with wAMD):

1. Not applicable: Adapted to inclusion criterion #13, see below.
2. Not applicable: Deleted.
3. Not applicable: No limitation on central subfield retinal thickness.
4. Not applicable: Adapted to inclusion criterion #14, see below.
5. Not applicable: Adapted to inclusion criterion #14, see below.
6. No subretinal hemorrhage involving the fovea in the study eye.
7. No significant subfoveal fibrosis or atrophy on SD-OCT in the study eye that, in the opinion of the investigator, is able to prevent improvement in BCVA and/or CSFT.
8. Not applicable: Adapted to inclusion criterion #15, see below.
9. Not applicable: Adapted to inclusion criteria #16 and #17, see below.
10. Male or female patients. 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 and in Section 4.2.1.3.
11. Signed informed consent consistent with ICH GCP guidelines and local legislation prior to participation in the trial, which includes medication washout and restrictions.
12. Not under any administrative or legal supervision or under institutionalization due to regulatory or juridical order.
13. Men and women over the age of 55 with treatment-naïve CNV secondary to AMD.
14. Any CNV with subfoveal activity in the study eye defined as evidence of sub- and/or intraretinal fluid, or subretinal hyper-reflective material, or angiographic leakage.
15. Best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) VA in the study eye between 80 and 24 letters inclusive (approximately 20/25 and 20/320 or 6/7.5 and 6/95) at screening.
16. Best-corrected ETDRS VA in the non-study eye 50 letters inclusive (approximately 20/100 or 6/30) or better at screening.
17. If both eyes are eligible at screening, the study eye is the eye with the worse best-corrected VA.

MRD cohort 3 (frequently treated patients):

1-5. Not applicable to cohort 3.
6. No subretinal hemorrhage involving the fovea in the study eye.
7. No significant subfoveal fibrosis or atrophy on SD-OCT in the study eye that, in the opinion of the investigator and with the endorsement of the Sponsor, is able to prevent improvement in BCVA.
8-9. Not applicable to cohort 3.
10. Male or female patients. 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 and in Section 4.2.1.3.
11. Signed informed consent consistent with ICH GCP guidelines and local legislation prior to participation in the trial, which includes medication washout and restrictions.
12. Not under any administrative or legal supervision or under institutionalization due to regulatory or juridical order.
13. Not applicable to cohort 3.
14. Any CNV with subfoveal activity in the study eye defined as evidence of sub- and/or intraretinal fluid, or subretinal hyper-reflective material, or angiographic leakage.
15. Best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) VA in the study eye between 80 and 24 letters inclusive (approximately 20/25 and 20/320 or 6/7.5 and 6/95) at screening.
16. Not applicable to cohort 3.
17. If both eyes are eligible at screening, the study eye is the eye with the worse best-corrected VA.
18. Men and women over the age of 55 with diagnosed wAMD that:
    - require frequent wAMD SoC (28-56 days between the last 3 treatments)
    - have had ≥ 3 previous treatments with IVT SoC (ranibizumab, aflibercept, or bevacizumab) in the study eye
    - had the last SoC injection ≥ 4 weeks, but no more than 8 weeks, before the first administration of the study drug
    - have been on SoC treatment ≥ 6 months and are within 3 years from initial wAMD diagnosis in the study eye

[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. Additional eye disease in the study eye that could compromise best corrected VA (BCVA) with visual field loss, uncontrolled glaucoma (IOP> 24 mmHg on more than 2 consecutive measurements prior to screening), clinically significant diabetic maculopathy, history of ischemic optic neuropathy or retinalvascular occlusion, symptomatic vitreomacular traction, or genetic disorders such as retinitis pigmentosa); history of high myopia > 8 diopters in the study eye. Anterior segment and vitreous abnormalities in the study eye that would preclude adequate observation with SD-OCT.
2. Any prior intraocular surgery in the study eye other then uneventful lens replacement for cataract within 3 months prior to screening.
3. Aphakia or total absence of the posterior capsule. Yttrium aluminum garnet (YAG) laser capsulotomy permitted, more than 1 month prior to enrollment in the study eye.
4. 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).
5. Medical history or condition: Uncontrolled diabetes mellitus, with hemoglobin A1c (HbA1c) > 10%, myocardial infarction or stroke within 12 months of screening, active bleeding disorder, concomitant use of warfarin or anticoagulation therapy (use of anti-platelet therapy such as aspirin is allowed), major surgery within 1 month of screening or when planned within the study period, hepatic impairment, uncontrolled hypertension.
6. Patients with a clinically relevant abnormal screening haematology, blood chemistry, or urinalysis, if the abnormality defines a significant disease as defined in other exclusion criteria. AST or ALT greater than 2.0-fold the upper limit of normal at screening. Patients with total bilirubin 2.5x upper limit of normal at screening.
7. Patient with impaired renal function defined as calculated GFR< 30 mL/min.
8. Significant alcohol or drug abuse within past 2 years per investigator judgement.
9. Participation in trials:
   - Previous participation in this trial.
   - Previous participation in other trials for treatment of wAMD with systemic administration if washout period from last administration is shorter than 3 months.
   - MRD cohorts 1 & 3: Previous participation in other trials for treatment of wAMD with IVT injections in the study eye if washout period from last administration/injection is shorter than 3 months[2].
   - MRD cohort 2: No previous IVT injections for wAMD in the study eye[2].
10. Significant disease or other medical conditions[3] (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.
11. Known hypersensitivity to fluorescein or any of the ingredients used in the Investigational Medicinal Product (IMP) formulation, or any of the medications used.
12. Active intraocular inflammation in the study eye, > 0.5+ anterior chamber cell and/or vitreous haze grading, or history of intraocular inflammation in either eye with previous IVT administration(s) (anterior chamber/haze grading and intraocular imflammation history only applicable to MRD cohort 3).
13. Active infectious conjunctivitis in either eye.

14. Symptoms of active SARS-CoV-2 infection[4].
15. Any history of retinal vein occlusion in the study eye (only applicable to MRD cohort 3).
16. Any previous treatment with brolucizumab or faricimab in either eye (only applicable to MRD cohort 3).
17. Medical history of autoimmune disease that has caused ocular inflammation (only applicable to MRD cohort 3).

[2] Previous participation in other trials with IVT injections allowed if fellow eye was treated.

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

[4] Testing and management of SARS-CoV-2 infection at the discretion of investigators in accordance with local guidelines and policies.

3.3.4 Withdrawal of patients from therapy or assessments

Subjects may potentially be withdrawn from trial treatment or from the trial as a whole ("withdrawal of consent") with very different implications, please see Section 3.3.4.1 and Section 3.3.4.2 below.

Every effort should be made to keep the subjects in the trial: if possible on treatment, or at least to collect important trial data.
Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to first administration of trial medication, as well as the explanation of the consequences of withdrawal.

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

3.3.4.1 Withdrawal from trial treatment

An individual patient is to be withdrawn from trial treatment if:

- The patient wants to withdraw from trial treatment, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product or other trial medication.
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, AEs, other diseases, or pregnancy).
- 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 stick to the trial requirements in the future.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart I, Flow Chart II, Flow Chart III, Flow Chart IV, and Section 6.2.

For all patients the reason for withdrawal from trial treatment (e.g. AEs) must be recorded in the CRF. These data will be included in the trial database and reported.

3.3.4.2 Withdrawal of consent for trial participation

Patients may withdraw their consent for 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 explain the difference between treatment withdrawal and withdrawal of consent for trial participation and explain the options for continued follow up after withdrawal from trial treatment, please see Section 3.3.4.1 above.

3.3.4.3 Discontinuation of the trial by the sponsor

Boehringer Ingelheim (BI) 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. Violation of Good Clinical Practice (GCP), the trial protocol, or the contract impairing the appropriate conduct of the trial.

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 a reason other than a DLE or patients who miss any visit out of Visits 2 to 4 are not evaluable for the occurrence of a DLE within 7 days after drug administration. These patients will be replaced if not decided otherwise by the SMC (in the scenario that there are already 2 DLE evaluable patients in the current dose group; see Section 3.1). Patients who come off study due to a DLE will not be replaced.

MRD part:
In case some subjects do not complete the trial according to the protocol, the trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide if and how many subjects will be replaced.

A replacement subject will be assigned a unique 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

In this trial, the IMP BI 836880 will be switched from an initial trial formulation (CMC1) to an intended final formulation (CMC2). The new formulation will be made available for the treatment of MRD cohort 3.

Table 4.1.1: 1 BI 836880

Substance:	BI 836880
Pharmaceutical formulation:	Solution for IVT injection
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	50 µl BI Solution for injection with a concentration from 5 mg/ml (0.25 mg per dose) to 40 mg/ml (2 mg per dose)
Posology:	SRD part: 1 injection MRD part: 3 injections, each separated by 4 weeks
Route of administration:	IVT injection

Table 4.1.1: 2 Diluent

Substance:	Diluent for BI 836880 concentrate for solution for injection 80 mg/mL, 10 mL/vial
Pharmaceutical formulation:	Diluent
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG
Unit strength:	n/a
Posology:	SRD part: 1 injection MRD part: 3 injections, each separated by 4 weeks
Route of administration:	IVT injection

4.1.2 Selection of doses in the trial

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 subjects 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 Laser CNV model represents a reliable animal surrogate to estimate treatment effects of therapeutics for wAMD [R18-1168]. In an in-house study using such a model (n00256189) 30µg BI 836880 administered IVT into the monkey eye were interpreted to result in clinically meaningful improvement of the respective retinal lesions. The corresponding human dose of 60 µg (0.06 mg) was therefore selected as starting dose as it is likely to already provide a therapeutic benefit over a period of 4 weeks. At the same time this dose is adequately below the observed corresponding NOAEL observed in the cynomolgous monkey of 500 µg (human corresponding dose 1000 µg or 1.0 mg) (n00255516, n00258450, n00254368) leading to a safety margin of more than 15 fold.

For the lower doses a higher relative increase to the next dose (200% and 178%, respectively) was chosen, resulting in dose levels of 0.18 mg and 0.5 mg in order to avoid many small dose steps resulting in an increasing number of trial related IVT injections. For the next dose (1.0 mg) a smaller relative (100%) increase was chosen. If all previous doses are clinically well tolerated one additional dose of 2.0 mg will be tested as one of the development objectives is to find a dose that provides an exposure that has the potential for a decreased injection frequency.

The provisional dose levels to be assigned to separate cohorts of patients are listed in Table 4.1.2: 1.

Table 4.1.2: 1 Provisional dose levels for escalation

Dose level	Proposed dose	Relative increment from previous dose
1	0.06 mg	Starting dose
2	0.18 mg	200%
3	0.5 mg	178%
4	1.0 mg	100%
5	2.0 mg	100%

4.1.3 Method of assigning patients to treatment groups

Recruitment in the trial will be started with the lowest dose group of the SRD part. The MRD part will recruit patients only after the SRD part has been completed and safety of the doses has been established.

In the SRD part, the dose is planned to be escalated in cohorts at the pre-defined provisional dose levels; see Table 4.1.2: 1. Intermediate or lower dose levels, depending on the number of DLEs observed in the study, as long as they fulfil the EWOC criterion, may be investigated if agreed upon between Investigator and Sponsor. At the end of each treatment cohort, BI will convene a meeting with the SMC members. At the dose escalation meeting, the clinical course for each patient in the current dose cohort will be 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 this dose is considered safe based on (the BLRM model and) the clinical course, the recruitment of the next higher dose

group may be started. Therefore, the recruitment of subjects for the dose groups will neither be influenced by the trial personnel nor by any characteristics of the patients, but only by temporal availability.

4.1.4 Drug assignment and administration of doses for each patient

BI 836880 will be administered intravitreously. “BI 836880 concentrate for solution for injection 80 mg/mL” and “Diluent for BI 836880 concentrate for solution for injection 80 mg/mL” and “BI 836880 solution for injection 40 mg/mL” will be provided by BI. The diluent can be used for both drug preparations, “BI 836880 concentrate for solution for injection 80 mg/mL” and for “BI 836880 solution for injection 40 mg/mL”, if required. A site pharmacist or qualified personnel will prepare the ready to use drug product according to the “Instructions to pharmacist/qualified personnel”. The instructions will be provided by BI and will be filed in the ISF.

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

Dose group (mg)	Visit 2 Day 1	Visit 3 Day 8	Visit 4 Day 15	Visit 5 Day 22	Visit 6 Day 29
0.06	X				
0.18	X				
0.5	X				
1.0	X				
2.0	X				

To determine the dose regimen for the next cohort, the available toxicity information (including DLEs and AEs that are not DLEs), PK, PD, as well as the recommendations from the BLRM will be evaluated by the SMC members at the dose decision meeting. The parties must reach a consensus whether further dose escalation is appropriate, or whether to 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 MRD part (the two highest doses established by the SMC as safe and tolerable during the SRD part will be selected)

Dose group (mg)	Visit 2 Day 1	Visit 3 Day 29	Visit 4 Day 57	Visit 5 Day 85	Visit 6 Day 113	Visit 7 Day 141
MRD dose 1	X	X	X			
MRD dose 2	X	X	X			

4.1.5 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.

4.1.6 Masking and procedures for unmasking

4.1.6.1 Masking

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

4.1.6.2 Unmasking and breaking the code

Not applicable.

4.1.7 Packaging, labelling, and re-supply

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

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

4.1.8 Storage conditions

Drug supplies will be kept in their original packaging and in a secure limited access storage area according to the recommended storage conditions on the medication label. A temperature log must be maintained for documentation.
If the storage conditions are found to be outside the specified range, the Clinical Trial Manager (CTM) (as provided in the list of contacts) must be contacted immediately.

4.1.9 Drug accountability

The investigator and/or pharmacist and/or qualified personnel and/or investigational drug storage manager will receive the investigational drugs delivered by the sponsor when the following requirements are fulfilled:

- Approval of the clinical trial protocol (CTP) by the Institutional Review Board (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 (if applicable).

Investigational drugs are not allowed to be used outside the context of this protocol. They must not be forwarded to other investigators or clinics.
The investigator and/or pharmacist and/or qualified personnel and/or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use for each patient, and the return to the sponsor or warehouse /

drug distribution centre or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution centre will maintain records of the disposal.

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

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Restrictions

4.2.1.1 Restrictions regarding concomitant treatment

SRD and MRD cohorts 1 & 2: As per judgement of the investigator, administration of local SoC treatment such as IVT or peribulbar injections, laser, or other surgical treatment is allowed in clinically significant worsening of the disease. After the end of treatment with trial medication (during Follow-up Period, starting at Visit 5), SoC therapy is at the discretion of the investigator. SoC therapy is, for the purpose of the present trial, considered a non-investigational medical treatment.

MRD cohort 3: For the study eye, no other treatment (IVT or otherwise) is allowed during the treatment and follow up periods of the trial unless rescue criteria are met (refer to Section 5.2.2 for rescue treatment criteria), or as deemed medically appropriate during/after Visit 6. Medications listed under the exclusion criteria (Section 3.3.3) are restricted during the trial. SoC therapy is, for the purpose of the present trial, considered a non-investigational medical treatment.

4.2.1.2 Restrictions on diet and life style

None.

4.2.1.3 Contraception requirements

WOCBP are excluded from trial participation.

'WOCBP (partner of a trial participant) must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and correctly if their sexual partner is a man able to father a child:

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

- Bilateral tubal occlusion

Or

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

4.2.2 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

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

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

Centrally collected ophthalmological data (CFP, OCT/OCT-A) will be transferred from the Central Reading Center (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 assessments of efficacy during the study, it will be reported as AE in the eCRF (please also refer to Section 5.2.8).

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

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

Visual Acuity measured by ETDRS letter charts
BCVA will be 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.

5.2 ASSESSMENT OF SAFETY

5.2.1 Dose limiting event

For the SRD part and MRD cohort 1:

A DLE is defined as the occurrence of any of the following events in the study eye:

- Development of sterile endophthalmitis and/or sterile inflammation of the vitreous grade 4+ according to standardization of Uveitis Nomenclature (SUN) working group (WG) grading scheme for anterior chamber cells (see Table 5.2.1: 1) and a duration of 5 or more days between day 1 and day 8
- Visual decrease of more than 15 letters at any given timepoint
- Persistent IOP over 30 mmHg for 3 days
- Signs of vascular occlusion in a 1st (the main branch) or 2nd degree (the vessel after the first bifurcation of the main branch) retinal vessel, including peripheral retinal hemorrhages in the area supplied by the occluded vessel (hemorrhage of the macula would not be included as this is a symptom of the disease).

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

Grade	Cells in Field[1]
0	<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.

DLE criteria are not applicable to MRD cohorts 2 and 3. Should an event involving intraocular inflammation/signs of vascular occlusion, decreases in visual acuity, and/or intraocular pressure occur, the event should only be reported as an AESI as described in Section 5.2.8.1, and not as a DLE.

5.2.2 Time to recurrence

Time to recurrence will be assessed in the MRD part from last trial drug administration to occurrence of any of the following in the study eye, leading to the use of wAMD rescue medication as decided by the investigator:

- Increase in CFST ≥ 75 µm with a decrease in BCVA of ≥ 5 letters compared to Visit 5,
- OR
- Decrease in BCVA of > 5 letters compared to baseline (Visit 2), due to worsening wAMD activity,
- OR
- Decrease in BCVA of ≥ 10 letters compared to the best prior BCVA, due to worsening wAMD activity

The decision to treat with wAMD rescue medication should be documented in the eCRF.

5.2.3 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart I, Flow Chart II, Flow Chart III, and Flow Chart IV. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin. Measurement of height and body weight will be performed at the time points specified in the Flow Charts.

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

Color Fundus Photography
Multi-field digital fundus photographs will be obtained from both eyes by a qualified person according to the imaging manual. For MRD cohort 3, additional color fundus photographs from both eyes will be acquired from the retinal periphery to assess inflammation and from

the central retina to assess vitreous haze. These examinations will be performed at the timepoints defined in the Flow Charts I, II, III, and IV.

5.2.4 Vital signs

Vital signs will be evaluated at the time points specified in the Flow Charts I, II, III, and IV, 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.

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 the Flow Chart I, Flow Chart II, Flow Chart III, and Flow Chart IV. 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 AEs (please refer to Section 5.2.6).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.8.1 and the DILI Checklist provided in the electronic data capture (eDC) system. The amount of blood taken from the patient concerned will be increased due to this additional sampling.

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

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

Hematology • Haematocrit • Haemoglobin • MCV, MCH, RDW, MCHC • Red Blood Cells (RBC) / Erythrocytes • WBC / Leukocytes • Platelet Count / Thrombocytes • Differential Automatic (relative and absolute count): Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes
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) • CK-MB, troponin I (reflex tests if CK is elevated) • Lactate dehydrogenase (LDH) • Lipase • Magnesium • Phosphate • Potassium • Protein total • Sodium • Urea (BUN) • LDL/HDL and total cholesterol • Triglycerides • TSH • Folate

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

Single standard 12 lead ECGs (I, II, III, aVR, aVL, aVF, V1 – V6) will be recorded at the time points described in the Flow Charts. Electrode placement will be performed according to the method of Einthoven/Goldberger (ankles and wrists) and Wilson (chest leads). The recordings will be made using equipment approved or provided by the central ECG vendor. They will be assessed after the subjects have rested for at least 5 minutes in a supine position. ECG recordings at planned time points may be repeated for quality reasons like alternating current artefacts, muscle movements and electrode dislocation. In this case the repeated ECG recordings will be used if quality was better.

All ECGs will be evaluated by the cardiologist of the central ECG vendor, and in addition by a qualified healthcare provider at the site, if available. Clinically relevant abnormal findings will be reported either as baseline condition (if identified at the screening visit) or otherwise as AEs and will be followed up and/or treated as medically appropriate. Additional (unscheduled) ECGs can be recorded for safety reasons at any time based on the judgment of the investigator. For the screening ECG the evaluation needs to be available prior to the final assessment of the in/exclusion criteria.

All ECGs will be transmitted (either electronically (preferred) or via a scanned hard-copy) to the central ECG vendor in order to enable a centralized and independent re-evaluation of all 12-lead ECGs. This re-evaluation will only be done for the screening ECG if needed or if requested by the sponsor. Abnormalities detected during this centralised ECG evaluation will not necessarily qualify as AE.

5.2.7 Other safety parameters

MRD cohort 3 only: Fluorescein angiography (FA) imaging will be obtained from both eyes during Screening by a qualified person according to the imaging manual. Additional FA during Visits 2-8 should be performed at the discretion of the investigator, e.g. if signs of inflammation are observed.

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.

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
- requires prolongation of existing hospitalisation,
- results in persistent or significant disability or incapacity, or
- is a congenital anomaly / birth defect, or
- 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"

Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between 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".**

In accordance with the EMA initiative on Important Medical Events, BI has set up a list of further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.
The latest list of "Always Serious AEs" can be found in the eDC system. These events should always be reported as SAEs as described above.

5.2.8.1.4 Adverse events of special interest (AESIs)

The term 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 above.

The following are considered as AESIs:

Ocular related events (applicable to MRD cohorts 2 & 3)

- Intraocular inflammation events
  - Anterior chamber cells of grade 1+ according to the Standardization of Uveitis Nomenclature (SUN) working group (WG) grading scheme (see Table 5.2.1: 1)
  - Sterile inflammation of the vitreous of 1+ according to the NEI Grading of vitreous haze (see Table 5.2.8.1.4: 1 below)
- Signs of vascular occlusion and inflammation (vasculitis) in the retina, including peripheral retinal hemorrhages in the area supplied by the occluded vessel (hemorrhage of the macula would not be included as this is a sign of wAMD disease)
- Visual acuity decrease of more than 15 letters from the previous visit

- Persistent IOP over 30 mmHg for 3 days after study treatment is administered, despite rescue treatment

Table 5.2.8.1.4: 1 The NEI Grading Scale of Vitreous Haze [R22-2854]

Scale	Description	Clinical findings
0	Nil	None
0.5+	Trace	
1+	Minimal	Posterior pole clearly visible
2+	Mild	Posterior pole details slightly hazy
3+	Moderate	Posterior pole details very hazy
4+	Marked	Posterior pole details barely visible
5+	Severe	Fundal details not visible

Hepatic injury

A hepatic injury is defined by the following alterations of hepatic laboratory parameters:

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

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

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 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 the relationship, 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 diminished).

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 EOT:
  - all AEs (serious and non-serious) and all AESIs.
- After the individual patient's EOT:
  the investigator does not need to actively monitor the patient for AEs but should only report related SAEs and related AESIs of which the investigator may become aware of by any means of communication, e.g. phone call. Those AEs should however, not be reported in the CRF.

5.2.8.2.2 AE reporting to sponsor and timelines

The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form immediately (within 24 hours) to the sponsor's

unique entry point (country specific reporting process will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.

With receipt of any further information to these events, a follow-up SAE form has to be provided. For follow-up information the same rules and timeline apply as for initial information.

5.2.8.2.3 Information required

For each AE, the investigator should provide the information requested on the appropriate eCRF pages and the BI SAE form, if applicable. The investigator should determine the causal relationship to the trial medication.

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

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

If such abnormalities already pre-exist prior to trial inclusion they will be considered as baseline conditions and should be collected in the eCRF only. All (S)AEs, including those persisting after individual patient's EOT must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.

5.2.8.2.4 Pregnancy

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

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

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

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

5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS

5.3.1 Assessment of pharmacokinetics

Date and clock time of drug administration and pharmacokinetic sampling will be recorded in the CRFs. Planned time points for systemic pharmacokinetic samples are listed in Appendix 10.1.

Pharmacokinetic data may additionally be analysed using population pharmacokinetic approach. For this purpose data may also be combined with data from other trials. Modelling activities will be planned and documented separately according to internal and external guidelines and Standard Operating Procedure (SOP).

5.3.2 Methods of sample collection

For the quantification of BI 836880 sample concentrations, at least 3 mL blood will be taken from a forearm vein in a blood drawing tube at time points specified in the Flow Chart I, Flow Chart II, Flow Chart III, Flow Chart IV, and in Appendix 10.1. Samples will be divided into duplicate aliquots and stored frozen at about -70°C at the participating sites or logistics CRO until shipment on dry ice to the bioanalytical laboratory of BI or a BI selected and authorized CRO.

Details about sample collection, preparation, required tubes, labelling of tubes, storage and shipment (frequency and addresses) will be provided in a separate laboratory manual. The 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, and such data will be reported separately. The study samples will be discarded no later than 5 years after the final study report has been generated.

[redacted]

5.3.4 Pharmacokinetic – pharmacodynamic relationship

No formal analysis of a pharmacokinetic/pharmacodynamic relationship is planned. Correlation between drug concentration and response may be made if adequate data are available. In addition, exploratory correlation may also be made between drug concentration and AEs.

Data may also be used to develop pharmacokinetic/pharmacodynamic models using nonlinear mixed effect modelling techniques, if feasible. For this purpose data may also be combined with data from other trials. Modelling activities will be planned and documented separately according to internal and external guidelines and SOP.

5.4 ASSESSMENT OF BIOMARKER(S)

This section refers to exploratory biomarkers. Established biomarkers of efficacy and safety are described and discussed in Sections 5.1 and 5.2.

5.4.1 Plasma derived protein biomarkers

The analysis of the biomarkers free VEGF as well as free/total ANG2 in plasma are exploratory in nature and shall determine the effect of systemic exposure of BI 836880 on the circulating ANG2 and VEGF receptor levels. Participation in the biomarker test is mandatory. Plasma biomarker studies will focus on exploring pharmacodynamic effects.

Methods of sample collection
For quantification of free VEGF and free/total ANG2 5 ml blood will be taken from the forearm vein at those time points specified in the Flow Chart I, Flow Chart II, Flow Chart III, Flow Chart IV, and in Appendix 10.1. Plasma samples for protein biomarkers need to be stored at ≤-70 °C or below. Detailed instructions for sampling, handling, storage, and shipment of the biomarker samples will be provided in the ISF/lab manual. Date and time of sampling will be recorded in the eCRF.

[redacted]

Pharmacodynamic Analysis
The following pharmacodynamic parameters will be determined as further endpoints if feasible:

[redacted]

[redacted]

Biobanking
Participation in biobanking is voluntary and not a prerequisite for participation in the trial. Biobanking will only occur after a separate biobanking informed consent has been given in accordance with local ethical and regulatory requirements (see Section 1.3).

5.4.1.1 Methods and timing of sample collection

For sampling timepoints see Flow Chart II, Flow Chart III, and Flow Chart IV.

DNA banking:
Approx. 8.5 mL blood will be drawn into a PAXgene Blood DNA Tube, preferably at Visit 2.

Plasma banking:
Approx.10 mL blood will be drawn into an Ethylenediaminetetraacetic acid (EDTA blood collection tube.

Serum banking:
Approx. 8.5 mL blood will be drawn into a serum separation tube.
For all biological samples collected, detailed instructions on sampling, preparation, processing, shipment and storage are provided in the laboratory manual. Plasma and serum samples will be stored at an external biobanking facility contracted by the Sponsor; DNA, extracted from the original whole blood sample, will be stored at the Sponsor.

5.5 OTHER ASSESSMENTS

5.5.1 Immunogenicity assessment

Methods of ADA sample collection
For the determination of anti-drug antibodies (ADA), approximately 3 mL of blood will be taken from a forearm vein in a blood drawing tube at those time points specified in the Flow Chart I, Flow Chart II, Flow Chart III, Flow Chart IV, and in Appendix 10.1.

Details about sample collection, preparation, storage and shipment are described in the laboratory manual.

[redacted]

[redacted]

5.6 APPROPRIATENESS OF MEASUREMENTS

All other measurements performed during this trial are standard measurements and will be performed in order to monitor patients' safety and to determine pharmacokinetic and pharmacodynamic parameters in an appropriate way. The scheduled measurements will allow monitoring of changes in vital signs, standard laboratory values, and ECG parameters that might occur as a result of administration of trial medication. The safety assessments are standard, are accepted for evaluation of safety and tolerability of an orally administered drug and are widely used in clinical trials. The pharmacokinetic parameters and measurements outlined in Section 5.3 are generally used assessments of drug exposure. The biomarkers and pharmacodynamic parameters and measurements outlined in Section 5.4 and 5.5 are of exploratory nature only.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

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

Before pupil dilation: BCVA assessment and ocular tonometry

After dilation: slit lamp examination, SD-OCT, Fundus photography, OCT- angiography, and FA (FA required at screening or at the discretion of the investigator during subsequent visits, for cohort 3 only).

Additional ocular tonometry may also be performed after treatment at the discretion of the investigator.

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

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

6.2.1 Single Rising Dose Part

6.2.1.1 Screening Visit

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.

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 examination with slit lamp 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.

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

Re-screening:
Patients who do not fulfil all eligibility criteria for a reason that later resolves and allows eligibility criteria to be met within a 12-week period after initial screening visit, can be

rescreened up to one time. For re-screening, patient must be registered in IRT, which will then provide new patient number, and patient must sign new Informed Consent Form (ICF). Imaging of retina (SD-OCT, OCT-A, 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 and end of trial visit 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 other ophthalmologic assessments in the Flow Chart I have been performed (please see Section 4.1.5 for details). An additional tonometry may be performed after IVT injection to monitor intraocular pressure.

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

Visit 8/End of Trial:
The Visit 8/EOT will be performed 14 days after the Visit 7 (see Flow Chart I).
The Visit 8/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 7 should be scheduled as soon as possible, and also Visit 8/EOT should be performed to assess for safety.
If patient refuses to participate at a Visit 7 or Visit 8, the trial completion page of the eCRF has to be filled in.

6.2.2 Multiple Rising Dose Part

6.2.2.1 Screening Visit

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 first treatment visit (Visit 2) may be performed.

If the patient does not meet inclusion/exclusion criteria, the patient must be recorded in eCRF as a screen failure.

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 examination with slit lamp at Visit 1 need to be documented on Baseline Conditions.

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

Re-screening:
Patients who do not fulfil all eligibility criteria for a reason that later resolves and allows eligibility criteria to be met within a 12-week period after initial screening visit, can be rescreened up to one time without new IRT registration. For re-screening beyond this time period (up to one time), patient must be registered in IRT, which will then provide new patient number, and patient must sign new ICF. Imaging of retina (SD-OCT, OCT-A, fundus photography, and/or fluorescein angiography) 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 and end of trial visit MRD 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 other ophthalmologic assessments in the Flow Charts II, III, and IV have been performed (please see Section 4.1.5 for details). An additional tonometry may be performed after IVT injection to monitor intraocular pressure. In the MRD part cohorts 2 and 3, additional safety assessments/visits will be carried out within a week after V2, V3, V4, respectively.

Patients must continue to be followed according to the visit schedule (unless they withdraw consent for further follow-up) in order to collect data at the end of the planned observation period. Unscheduled visits will be possible at the discretion of the investigator at any time for safety reason. The unscheduled visit may include any assessments considered necessary by the investigator. All unscheduled visits should be described and documented in the medical /source record. The investigator may decide to administer standard treatment for wAMD during the follow-up period (for MRD cohort 3 during/after Visit 6) as deemed medically appropriate.

Visit 8/End of Trial:
The Visit 8/EOT will be performed 28 days after the Visit 7 (see Flow Charts II, III, and IV).

The Visit 8/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 want to withdraw consent prior to the end of the trial, Visit 7 should be scheduled as soon as possible, and also Visit 8/EOT should be performed to assess for safety.

If patient refuses to participate at a Visit 7 or Visit 8, the trial completion page of the eCRF has to be filled in.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

This trial will consist of an SRD part followed by an MRD part. Both parts of the trial will be conducted non-randomized, open-label, and uncontrolled. The main objective is to investigate ocular and systemic safety and tolerability as well as disease improvement of BI 836880 after a single IVT injection and after multiple IVT injections of several doses.

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

The model is given as follows:

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

where $\text{logit}(\pi) = \log(\pi/(1-\pi))$, π_d represents the probability of having a DLE in the evaluation period at dose d, $d^* = 2$ 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 200% from the previous dose up to doses of 0.5 mg, and to a maximum of 100% from the previous dose from dose 0.5 mg onwards. Dose escalation will continue up to the 2 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 additional number of patients at this dose level.

Since a Bayesian approach is applied, a prior distribution $f(\theta)$ 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 $f_i(\theta) = \text{MVN}(\mu_i, \Sigma_i)$, 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 0.06 mg would equal 0.01, and the median DLE rate at the maximum feasible dose of 2 mg would equal 0.10. This yields $\mu_1 = (-2.197, -0.380)$. The standard deviations were set such that large uncertainty about the parameter means is reflected, and the correlation was set to 0, thus yielding $\sigma_{1,11} = 2$, $\sigma_{1,22} = 1$ and $\rho_1 = 0$, respectively. The prior weight a_1 for the first component was chosen as 0.9.
2. A high-toxicity weakly informative prior was derived reflecting the case that the compound would be much more toxic than expected. For this prior component, it was assumed that the median DLE rate at the starting dose of 0.06 mg would equal 0.10, and the median DLE rate at 2 mg would equal 0.40. These assumptions yield $\mu_2 = (-0.405, -0.671)$. 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 0.06 mg would equal 0.001, and the median DLE at 2 mg would equal 0.01. These assumptions yield $\mu_3 = (-4.595, -0.417)$. The standard deviations and correlations were set to $\sigma_{3,11} = 5$, $\sigma_{3,22} = 0.01$, therefore almost fixing the slope parameter to its mean. The correlation was set to 0, i.e. $\rho_3 = 0$. The prior weight a_3 for the third component was chosen as 0.05.

A summary of the prior distribution is provided in Table 7.1: 1. Additionally, the prior probabilities of DLEs at different doses, as well as the corresponding probability of targeted and overdosing, are shown in Table 7.1: 2. Graphically, the prior medians with accompanying 95% credible intervals are shown in Figure 7.1: 1. As can be seen from both Table 7.1: 2 and Figure 7.1: 1, the prior medians of the DLE probabilities are in line with the prior medians derived from the weakly informative prior, and the uncertainty around the medians is large, showing the low amount of information this prior provides. This is also supported by the prior sample size, i.e. the information contained in the prior. This is approximately equal to 1.7 patients. A detailed evaluation of the model using hypothetical data scenarios and operating characteristics is provided in Appendix 10.3.

Table 7.1: 1 Summary of prior distribution

Prior Component	Mixture Weight	Mean Vector	SD Vector
1: Weakly inf.	0.900	-2.197 -0.380	2.00 1.00
2: High Tox.	0.050	-0.405 -0.671	2.00 1.00
3: Low Tox.	0.050	-4.595 -0.417	5.00 0.01

Table 7.1: 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%**
0.06	0.917	0.083	0.067	0.151	0.000	0.007	0.599
0.18	0.887	0.113	0.088	0.172	0.000	0.014	0.682
0.5	0.839	0.161	0.119	0.197	0.000	0.030	0.764
1	0.790	0.210	0.154	0.218	0.000	0.053	0.817
2	0.696	0.304	0.212	0.249	0.001	0.101	0.882

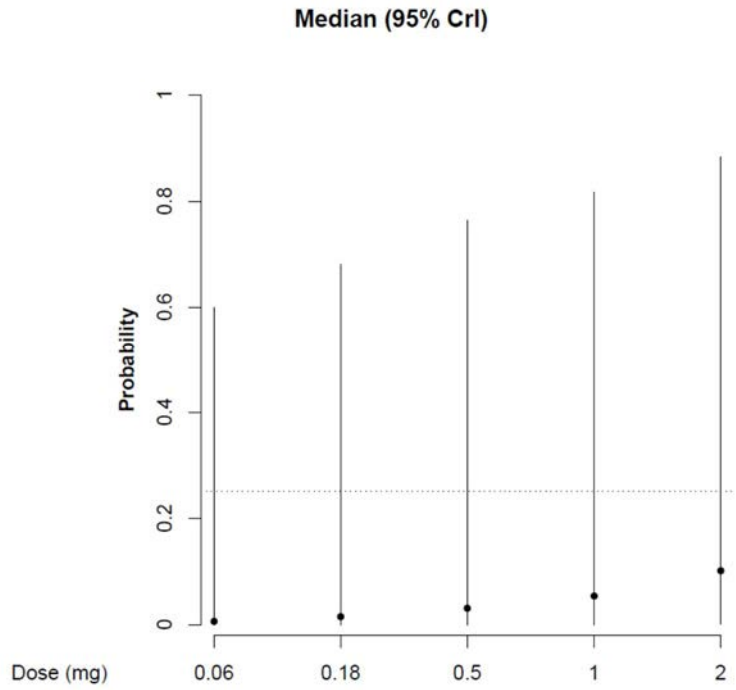

Figure 7.1: 1 Prior medians and 95% credible intervals

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

MRD part
There will be 2 dose groups of the second highest safe (cohort 1) and the highest safe dose level (cohorts 2 and 3) fulfilling the EWOC criterion after completion of the SRD part.

7.2 NULL AND ALTERNATIVE HYPOTHESES

There are no hypotheses tested in this exploratory trial.

7.3 PLANNED ANALYSES

The main analysis populations are defined below. Analyses will be performed by dose/cohort and overall in each trial part. Patients will be analysed according to the assigned treatment, unless otherwise specified. In the SRD part, 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. 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 836880.

Full Analysis Set (FAS; only MRD part)
The FAS will consist of all patients who were treated with at least one dose of BI 836880 and have baseline and on-treatment CSFT measurements for the study eye.

Evaluable Responders' Set (ERS, MRD cohort 3 only)
The ERS will consist of all patients who completed three doses of BI 836880 and have SD-OCT measurements at Week 16 (Visit 6).

In the TSAP, the FAS and ERS definitions may be updated, and further analysis data sets may be defined.

7.3.1 Primary endpoint analyses

No primary efficacy endpoint has been defined for this study.

SRD part:
The primary safety endpoint "Number of patients with ocular DLEs from drug administration until EOT" will be analysed descriptively, based on the TS.

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

MRD 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.

7.3.2 Secondary endpoint analyses

In principle, all secondary endpoints will be analysed descriptively, based on the TS. The analysis of percent change from baseline in CSFT in the study eye at Week 12 (Visit 5) will be done by dose, based on the FAS.

[redacted]

7.3.4 Safety analyses

AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced. For BI 836880, 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 'treatment at onset'.

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

Frequency, severity, and causal relationship of AEs will be tabulated by system organ class and preferred term after coding according to the current version of the MedDRA at the 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.

7.3.5 Pharmacokinetic and pharmacodynamic analyses

The derivation of pharmacokinetic parameters is described in detail in the BI SOP 001-MCS-36-472. The determination of pharmacodynamic parameters AUEC, E_{max}, E_{min} will follow the principles described for the respective PK parameters.

All evaluable patients who received at least one dose of BI 836880 will be included in the pharmacokinetic/ PD analysis. Patients who are considered as not evaluable will be listed with their individual sample concentrations and individual pharmacokinetic/ PD parameters, however, will not be included in descriptive statistics for sample concentrations, pharmacokinetic/ PD parameters or other statistical assessment.

Every effort will be made to include all concentration and response data in an analysis. If not possible, a case by case decision is required whether the value should only be excluded from half-life estimation or the complete analysis.

- If a concentration is only excluded from half-life determination, it will be used for all other calculations (e.g. descriptive statistics) and for graphical presentation.
- If a concentration value is excluded from all calculations, it will not be presented graphically or used for the calculation of descriptive statistics and parameter determination. However, the excluded concentration itself will be listed in the Clinical Trial Report (CTR) associated with an appropriate flag.

Concentrations will be used for graphs and calculations in the format that is reported in the bioanalytical report. Noncompartmental pharmacokinetic analyses of the sample concentration-time data will be performed using a validated software program, e.g. Phoenix WinNonlin. Only concentrations within the validated concentration range will be used for the calculation of pharmacokinetic parameters. For pre-dose samples, the actual sampling time will be set to zero.

Sample concentrations will be plotted graphically versus time for all evaluable subjects as listed in the drug concentration-time tables. For the presentation of the mean profiles, the geometric and arithmetic mean and the planned blood sampling times will be used. If the actual sampling time deviates significantly from the planned time, the corresponding sample concentration will be excluded from the calculation of descriptive statistics.

If the number of patients included allows, the following descriptive statistics will be calculated for analyte concentrations as well as for all pharmacokinetic parameters: N, arithmetic mean, standard deviation, minimum, median, maximum, P10, Q1, Q3, P90, arithmetic coefficient of variation, geometric mean, and geometric coefficient of variation. The data format for descriptive statistics of concentrations will be identical with the data format of the respective concentrations. The descriptive statistics of pharmacokinetic parameters will be calculated using the individual values with the number of decimal places as provided by the evaluation program. Then the individual values as well as the descriptive statistics will be reported with three significant digits in the CTR.

7.4 INTERIM ANALYSES

The sponsor will continuously monitor the safety. In the SRD part, the dose escalation design foresees that the sponsor and the SMC perform regular safety evaluations. Likewise, in the MRD part, the SMC will decide on the dose escalation. These evaluations will be unmasked to dose.

No formal interim analysis of efficacy data is foreseen, although efficacy data when available may be considered as part of the safety evaluations. A preliminary analysis of efficacy data will be performed after the completion of Visit 5 of the first dose group of the MRD part. The preliminary efficacy results will be distributed to the Sponsor’s trial team, but they will not be part of the CTR. A preliminary analysis of PK data will be performed after completion of the SRD part.

7.5 HANDLING OF MISSING DATA

No imputation will be performed on missing efficacy 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.

7.6 RANDOMISATION

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

7.7 DETERMINATION OF SAMPLE SIZE

No formal statistical power calculations to determine sample size were performed for this explorative study.

For the SRD part, a maximum of 18 patients will be expected for this trial based on the number of dose levels/cohorts that are tested. Fewer patients might be needed based on the recommendation of the SMC and the criteria specified (see Section 7.1). However, the actual number of patients will depend on the number of dose cohorts tested. Based on the simulation study to evaluate operating characteristics of the BLRM (see Appendix 10.3), about 18 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.

For the MRD part cohort 1 and cohort 2, a size of 10 subjects per dose group is in general considered as sufficient for the exploratory evaluation of multiple dose safety and PK. The drop out rate is expected to be higher for the treatment-naïve patients in cohort 2 as compared to the treatment-resistant patients in cohort 1. To allow for dropouts, 10 to 12 patients will be included in MRD cohort 1 and approximately 16 patients will be included in MRD cohort 2 and 3 combined (in total approximately 42 patients in the trial). In case some subjects do not complete the trial according to the protocol, the trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide if and how many subjects will be replaced.

Further, based on results from [R18-0309] for a comparable patient group and drug product, and based on the inclusion criteria for the current trial, it is assumed that the actual percent decrease in CSFT at Week 12 is above 25%. In Table 7.7: 1, the probability to observe a median percent decrease in CSFT at Week 12 in different pre-defined regions is displayed for a set of scenarios, and for sample sizes 10 and 15, assuming a normal distribution for the percent decrease with standard deviation 16 (also based on the above publication). These results are based on simulations using R Version 3.5.1. Details on the simulation program can be found in the TMF.

Table 7.7: 1 Probability to observe a median percent decrease in CSFT at Week 12 within pre-defined regions based on sample sizes N=10, 15, for different true median percent decreases

N	True Value of Median Percent Decrease [%]	Obs < 18%	Obs in [18,20) %	Obs ≥ 20%
10	13	80.0	8.0	11.9
	19	43.3	13.4	43.3
	25	11.8	8.1	80.1
15	13	83.7	7.8	8.6
	19	42.2	15.6	42.2
	25	8.5	7.9	83.7

Obs: Observed value of median percent decrease in CSFT [%]

For example, if the true median percent decrease in CSFT at Week 12 was 25%, the probability to observe a median percent decrease in CSFT at Week 12 of at least 20% would be around 80%. In contrast, if the true median percent decrease in CSFT at Week 12 was only 13%, then the probability to observe a median percent decrease of at least 20% would be around 12%.

For the MRD cohort 3, no formal sample size calculation has been applied. It is expected that using approximately 12 patients will be sufficient for this cohort.

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 Tripartite Guideline for GCP, relevant BI SOPs, the EU regulation 536/2014 the Japanese GCP regulations (Ministry of Health and Welfare Ordinance No. 28, March 27, 1997) and other relevant regulations.

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 BI 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 will 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 IRB / Independent Ethics Committee (IEC) and 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 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.

The investigator 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 obtains written consent of the patient's own free will with the ICF after confirming that the patient understands the contents. The investigator must sign (or place a seal on) and date the ICF. 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 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. 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 good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the investigator must make three documented attempts 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 the original patient file (please see Section 8.3.2). 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 before sending them to the sponsor.

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
- AEs and outcome events (onset date (mandatory), and end date (if available))
- SAEs (onset date (mandatory), and end date (if available))
- Concomitant therapy (start date, changes)

- 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/or remote monitoring calls 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.

The investigator /institution will allow on-site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access should be granted to all source documents (paper and e-records) including progress notes, copies of laboratory and medical test results. The CRA and auditor 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 ICH GCP.

An adaptive approach to clinical trial monitoring will be utilised. This is initiated by an assessment of the risk associated with the trial combined with identification of critical data and processes. An Integrated Quality and Risk Management Plan documents the strategies involved with the implementation of onsite, offsite and central monitoring activities in order to direct focus to the areas of greatest risk which have the most potential impact to patient safety and data quality. Trial oversight is achieved by regular review of a report of risk which then influences any monitoring adaptations.

The investigator /institution will allow on-site trial-related monitoring, audits, IRB/IEC review and regulatory inspections. Direct access should be granted to all source documents (paper and e-records) including progress notes, copies of laboratory and medical test results

The CRA and auditor 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 ICH GCP.

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

BI is responsible to fulfil their legal and regulatory reporting obligation in accordance with regulatory requirements.
Exemptions from expedited reporting are described in Section 5.2.8.2, if applicable.

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient privacy will be ensured by using patient identification code numbers.
Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the World Health Organization (WHO) GCP handbook.

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 as a result of the trial need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB / IEC and the regulatory authorities.

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

Measures are in place to comply with the applicable rules for the collection, biobanking and future use of biological samples and clinical data, in particular

- Sample and data usage has to be in accordance with the separate biobanking informed consent.
- The BI-internal facilities storing biological samples from clinical trial participants as well as the external banking facility are qualified for the storage of biological samples collected in clinical trials.
- An appropriate sample and data management system, incl. audit trail for clinical data and samples to identify and destroy such samples according to ICF is in place.
- A fit for the purpose documentation (biomarker proposal, analysis plan and report) ensures compliant usage.
- A fit for purpose approach will be used for assay/equipment validation depending on the intended use of the biomarker data.

- Samples and/or data may be transferred to third parties and other countries as specified in the biobanking ICF.

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 Out" (LPO)). The "**Last Patient Drug Discontinuation"** (LPDD) date is defined as the date on which the last patient at an individual trial site ends trial medication (as scheduled per protocol or prematurely). Individual investigators will be notified of Suspected Unexpected Serious Adverse Reactions (SUSARs) occurring with the trial medication until 30 days after LPDD at their site. **Early termination of the trial** is defined as the premature termination of the trial due to any reason before the end of the trial as specified in this protocol.

Temporary halt of the trial is defined as any unplanned interruption of the trial by the sponsor with the intention to resume it.
Suspension of the trial is defined as an interruption of the trial based on a Health Authority request.

The IEC / CA in each participating EU member state will be notified about the trial milestones according to the respective laws.
A final report of the clinical trial data will be written only after all patients have completed the trial in all countries (EU or non-EU) to incorporate and consider all data in the report.
The sponsor will submit to the EU database a summary of the final trial results within one year from the end of a clinical trial as a whole, regardless of the country of the last patient (EU or non-EU).

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by BI.
A CI is responsible to coordinate investigators at the different sites participating in this trial. Tasks and responsibilities are defined in a contract.

A Study Monitoring Committee (SMC) composed of the co-ordinating investigator, participating investigators with treated patients in the cohort that will be evaluated in the meeting and members of the BI trial team and the head of early clinical operations as trial independent member will be established to review individual and aggregated safety data at regular intervals to determine the safety profile and risk/benefit ratio and decide on the next dose level and the next cohort size, or the appropriacy of further enrolment. 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 (CTL), 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 CTM, 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 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 and an IRT vendor will be used in this trial. Details will be provided in the IRT Manual and Central Laboratory Manual, available in the ISF.

9. REFERENCES

9.1 PUBLISHED REFERENCES

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

R13-1509 Eye Diseases Prevalence Research Group. Prevalence of age-related macular degeneration in the United States. Arch Ophthalmol (Chicago) 2004. 122:564-572.

R13-4487 Holz FG, Amoaku W, Donate J, Guymer RH, Kellner U, Schlingemann RO, Weichselberger A, Staurenghi G, SUSTAIN Study Group. Safety and efficacy of a flexible dosing regimen of ranibizumab in neovascular age-related macular degeneration: the SUSTAIN study. Ophthalmology (Rochester) 2011. 118(4):663-671.

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

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

R13-4881 FDA's critical path initiative (page last updated: 12/28/2012). http://www.fda.gov/ScienceResearch/SpecialTopics/CriticalPathInitiative/ucm07668 9.htm (access date: 8 November 2013); Silver Spring: U.S. Food and Drug Administration (2012).

R18-0309 Chakravarthy U, Bailey C, Brown D, Campochiaro P, Chittum M, Csaky K, et al. Phase 1 trial of anti-vascular endothelial growth factor/anti-angiopoietin 2 bispecific antibody RG7716 for neovascular age-related macular degeneration. Ophthalmol Retina 2017. 1(6):474-485.

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

R18-1168 Krzystolik MG, Afshari MA, Adamis AP, Gaudreault J, Gragoudas ES, Michaud NA, et al. Prevention of experimental choroidal neovascularization with intravitreal anti-vascular endothelial growth factor antibody fragment. Arch Ophthalmol (Chicago) 2002. 120(3):338-346.

R21-0692 Khanani AM, Patel SS, Ferrone PJ, Osborne A, Sahni J, Grzeschik S, et al. Efficacy of Every Four Monthly and Quarterly Dosing of Faricimab vs Ranibizumab in Neovascular Age-Related Macular Degeneration - The STAIRWAY Phase 2 Randomized Clinical Trial. JAMA Ophthalmology 2020. 138/9: 964-972.

R22-2854 Nussenblatt RB, Palestine AG, Chan CC, et al. Standardization of vitreal inflammatory activity in intermediate and posterior uveitis. Ophthalmology (Rochester) 1985. 92: 467-471.

9.2 UNPUBLISHED REFERENCES

c21397543 BI 836880 Investigator´s Brochure (wet Age-related Macular Degeneration [wAMD]). Current Version.

n00234399 Pharmacokinetics immunogenicity of BI 836880 in male cynomolgus monkeys after intravenous dosing of BI 836880 (PK-12-1020). 19 May 2014.

n00253677 Efficacy of anti-Ang2/anti-VEGF nanobody BI 836880 in a mouse model of oxygen-induced retinopathy (OIR). MD2016/06/Lab6. 17 Nov 2017.

n00254368 13-Week Toxicity Study of BI 836880 Following Intravitreous Administration in Cynomolgus Monkeys with an 8-Week Recovery, Part: Toxicokinetics. 21 Feb 2018.

n00255516 13-Week Toxicity Study of BI 836880 Following Intravitreous Administration in Cynomolgus Monkeys with an 8-Week Recovery, 16R102. 22 May 2018.

n00256189 Efficacy of BI 836880 in a Monkey Laser-Induced Choroidal Neovascular (CNV) Model Following Intravitreal Injection, 5700737. 17 Nov 2017

n00258450 Pharmacokinetics of BI 836880 after intravitreal administration to Cynomolgus monkeys, A206/16FU(B6007). 29 Sep 2017.

n00259128 Prediction of BI 836880 vitreal pharmacokinetics in Humans. Nov 2017.

001-MCS-36-472 Corporate SOP: Standards and processes for analyses performed within Clinical Pharmacokinetics/Pharmacodynamics. Version 3.0

10. APPENDICES

10.1 TIME SCHEDULE FOR PHARMACOKINETIC (PK) BLOOD SAMPLING

Table 10.1: 1 Time schedule for PK/PD blood sampling during SRD part

Course	Visit	Day	Planned Time [h]	Planned Time [h]	PK BI 836880	ADA	VEGF/ ANG2
1	V2	1	Before IVT administration of BI 836880	-0:05 - -1:00	x	x	x
			Drug administration	0:00			
	V3	4 (+/- 1 day)	3 days after treatment	72:00	x		x
	V4	8 (+/- 2 days)	1 week after treatment	168:00	x		x
	V5	15 (+/- 2 days)	2 weeks after treatment	336:00	x	x	x
	V7	29 (+/- 2 days)	4 weeks after treatment	672:00	x		x
EOT	V8	43 (+/- 2 days)	6 weeks after treatment	1008:00	x	x	x

Table 10.1: 2 Time schedule for PK/PD blood sampling during MRD part

Course	Visit	Day	Planned Time [h]	Planned Time [h]	PK BI 836880	ADA	VEGF/ ANG2
1	V2	1	Before 1st IVT administration of BI 836880	-0:05 (-4 h)	x	x	x
			1st drug administration	0:00			
2	V3	29 (+/- 3 days)	Before 2nd ivt administration of BI 836880	671:55 (-2 h)	x	x	x
			2nd drug adminstration	672:00			
3	V4	57 (+/- 3 days)	Before 3rd ivt administration of BI 836880	1343:55 (-2 h)	x	x	x
			3rd drug administration	1344:00			
FUP	V5	85 (+/- 3 days)	Follow up period	2016:00 (+/- 2 h)	x	x	x
FUP	V6	113 (+/- 3 days)	Follow up period	2688:00 (+/- 2 h)	x		x
FUP	V7	141 (+/- 3 days)	Follow up period	3360:00 (+/- 2 h)	x		x
EOT	V8	169 (+/- 3 days)	End of Trial	4032:00 (+/- 2 h)	x	x	x

10.2 TRIAL BIOMARKER PLAN

Not applicable.

10.3 STATISTICAL APPENDIX INCLUDING MODEL PERFORMANCE AND DATA SCENARIOS

A BLRM with overdose control will be used to guide dose escalation in this study. The BLRM is introduced in Section 7.1, which also specifies the prior for the model. After patients in each cohort have completed the evaluation period of 7 days, the prior distribution will be updated through Gibbs sampling procedures with the accumulated DLE data from the evaluation period. Posterior probabilities for the rate of DLEs will be 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 10.3: 3. In addition, recommendations of the next dose level by the BLRM with overdose control principle are provided under various hypothetical outcome scenarios in early cohorts, to show how it facilitates on-study dose-escalation decisions (see Table 10.3: 1). For simplicity reasons, a cohort size of 3 patients who are all evaluable is assumed.

Hypothetical data scenarios

Hypothetical data scenarios are shown in Table 10.3: 1. These scenarios reflect potential on-study data constellations and related escalation as allowed by the model and the planned dose groups. 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.

For example, scenario 1 represents the case that no DLE is observed in 3 patients at the starting dose of 0.06 mg. In this case, the next planned dose permitted by the model and the 200% escalation rule is 0.18 mg. In contrast, scenario 2 assumes that there is one DLE observed in the first dose group. This would mean overtoxicity from the beginning, and the recommendation would be to stop the trial.

In scenario 3, there is no DLE after the first 2 dose groups, which would allow the trial to continue to the next dose level. In scenario 4, the first DLE occurs in dose group 0.18 mg. Then the recommendation would be to repeat that dose. Scenario 5 shows that the trial would continue to the next dose level 0.5 mg if no additional DLE was observed in the 0.18 mg dose group.

However, if there was another DLE (as in scenario 6), then the recommendation would be to go back to dose 0.06 mg. If there was no further DLE then (scenario 7), one could go up again to dose 0.18 mg. Escalation to the next dose group would only be allowed in case there was no further DLE in this dose group in additional 6 patients (see scenarios 8 and 9). Scenario 10 shows the case where the trial runs through up to the highest possible dose group 2 mg without any DLE and having observed a total of 18 patients (6 were required for the MTD). Scenarios 11 and 12 show that it is even possible to have one DLE in the 2 mg dose group and still to complete the trial with a total of 18 patients. However, if there were 2 DLEs in the highest dose group, then the model would recommend to return to dose 1 mg (scenario 13).

Table 10.3: 1 Hypothetical data scenarios

Scenario	Dose (mg)	# Pat.	# DLE	Current Dose: P(OD)	Next recomm. dose	Next dose:	
						P(TD)	P(OD)
1	0.06	3	0	0.016	0.18	0.968	0.032
2	0.06	3	1	0.308	N/A	N/A	N/A
3	0.06 0.18	3 3	0 0	0.011	0.5	0.964	0.036
4	0.06 0.18	3 3	0 1	0.182	0.18	0.818	0.182
5	0.06 0.18	3 6	0 1	0.074	0.5	0.789	0.211
6	0.06 0.18	3 6	0 2	0.290	0.06	0.874	0.126
7	0.06 0.18	6 6	0 2	0.062	0.18	0.808	0.192
8	0.06 0.18	6 9	0 2	0.105	0.18	0.895	0.105
9	0.06 0.18	6 12	0 2	0.049	0.5	0.773	0.227
10	0.06 0.18 0.5 1 2	3 3 3 3 6	0 0 0 0 0	0.010	2	0.990	0.010
11	0.06 0.18 0.5 1 2	3 3 3 3 3	0 0 0 0 1	0.220	2	0.780	0.220
12	0.06 0.18 0.5 1 2	3 3 3 3 6	0 0 0 0 1	0.098	2	0.902	0.098
13	0.06 0.18 0.5 1 2	3 3 3 3 6	0 0 0 0 2	0.327	1	0.961	0.039

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 10.3: 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 10.3: 2 Assumed true dose-toxicity scenarios

		Dose (mg)				
Scenario		**0.06**	**0.18**	**0.5**	**1**	**2**
1: Prior Med	P(DLE)	0.007	0.014	0.030	0.053	0.101
2: Prior Mean		0.067	0.088	0.119	0.154	0.212
3: High Tox		0.100	0.150	0.200	0.280	0.400
4: Low Tox		0.001	0.005	0.012	0.086	0.127
5: Non-Logistic		0.040	0.010	0.180	0.280	0.360
6: Low-High		0.001	0.011	0.047	0.181	0.500

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 ≤ 200% 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. A minimum number of 15 patients in the trial was required, and the maximum allowed patient number was 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 10.3: 3.

Table 10.3: 3 Simulated operating characteristics

Scenario	% of trials declaring a MTD with true DLE rate in		% of early stopped trials	# Patients	# DLEs
	[0, 0.25) target dosing	[0.25,1] overdosing		Mean (Min-Max)	Mean (Min-Max)
1	94.4	0	5.6	17.97 (3-21)	0.87 (0-4)
2	70.2	0	29.8	15.33 (3-21)	1.80 (0-6)
3	38.8	17.1	44.1	13.55 (3-21)	2.38 (0-6)
4	98.3	0	1.7	17.75 (3-21)	0.99 (0-4)
5	37.8	36.8	16.4	16.42 (3-21)	2.36 (0-6)
6	77.8	7	15.2	18.67 (3-21)	2.41 (0-6)

In scenario 1, which reflects the case that the true dose-toxicity is aligned with prior medians, 94.4% of the simulated trials declared a dose as MTD with true DLT rate in the targeted toxicity range. Note that 5.6% of the simulated trials stopped either because there was no MTD determined after 21 patients had been observed (3.5%) or because of high toxicity (2.1%). This latter is mostly due to the cases that 1 DLT is observed out of 3 patients at the starting dose of 0.06 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 30%). In this case, about 70% of the trials would end with an estimated MTD within the targeted toxicity range, but none in the overdosing range.

In Scenario 3 (high-toxicity scenario), only 38.8 % of the trials trials declared a dose as MTD with true DLT rate in the targeted toxicity range. In 17.1% of the trials, the estimated MTD was in the overdosing range. Scenario 4 (low-toxicity scenario) shows the best results, as would be expected.

Scenarios 5 and 6 showed worse operating characeristics; however, they are reasonable given the quite large deviations from the underlying BLRM.

The mean patient numbers range from 13.6 patients (Scenario 3) to 18.7 patients (Scenario 6), 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.

By reviewing the metrics presented in Table 10.3: 3, it can be seen that the model is generally conservative due to the overdose control criteria. In all scenarios except for the non-logistic case (scenario 5), the probabilities of recommending a dose with true P(DLT) ≥ 25 as MTD

are much smaller than the probabilities of recommending a dose with true P(DLT) < 25% as MTD.

On-study recommendations based on the model are consistent with the clinical decision making process, and should be considered in conjunction with other available clinical information by the BI clinical trial team and study investigators in deciding the dose levels to be tested in order to determine the MTD estimate.
R version 3.3.2 was used for data scenarios and simulations.

10.4 IMPLICATIONS OF CORONAVIRUS DISEASE 2019

At the time of evaluating the fourth dose group of the SRD part in this trial, the COVID-19 pandemic emerged with worldwide impact on daily life. To allow for thorough evaluation of potential additional risks to trial participants in the course of this pandemic, the trial was temporarily put on hold in March 2020. At that timepoint, a total of ten patients had been treated with one single intravitreal injection of BI 836880. Available data did not show dose-limiting events, drug-related adverse events, nor systemic adverse events.

The trial has been re-initiated in July 2020 after potential additional risks for study participants with regard to COVID-19 have been evaluated.

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. No effects related to this MoA on the immune system are currently known. In conclusion, 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. As such, risk mitigation measures, such as measures to reduce patients' exposure will be implemented, if required. Enrolment will only happen when the local situation allows for patients to travel to the trial site, and all precautionary measures (e.g. use of protective personal/patients 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 investigators 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.

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		26 Sep 2019
EudraCT number **EU number**		2017-001221-40
BI Trial number		1336-0007
BI Investigational Product(s)		BI 836880
Title of protocol		Safety, tolerability and pharmacodynamics of single rising intravitreal and multiple rising intravitreal doses of BI 836880 in patients with wAMD (open label, non-randomized, uncontrolled).
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		x
Section to be changed		Flow Chart I
Description of change		ADA sampling at Visit 5 added
Rationale for change		Alignment with Table 10.1: 1
Section to be changed		Flow Chart II
Description of change		ADA sampling added; Footnote (2) corrected
Rationale for change		Alignment with Table 10.1: 2
Section to be changed		2.1.3
Description of change		• Number [N (%)] of patients with any ocular AEs (eye disorders) […] • Percent change from baseline in Central Subfield Thickness (CSFT) at week 12, for each dose • Change from baseline in BCVA at week 12 was changed to • Number [N (%)] of patients with any ocular AEs (eye disorders) in the study eye […] • Percent change from baseline in Central Subfield Thickness (CSFT) in the study eye at week 12, for each dose • Change from baseline in BCVA in the study eye at week 12
Rationale for change		Clarification of the endpoints
Section to be changed		[redacted]

Description of change		[redacted]
Rationale for change		
Section to be changed		3.1, 4.1.2, 7.1, 10.3
Description of change		300% was changed to 200%; 278% was changed to 178%;
Rationale for change		Correction of the calculated relative dose increases
Section to be changed		4.1.6.1 Blinding
Description of change		"Within the central ECG lab, the staff involved with interval measurements will be blinded with respect to the treatment and also with regard to the recording date and time as well as planned time points of the ECGs. The interval measurements for a given patient will be performed in a random and blinded sequence by a single technician. If an interim safety analysis of ECG data is required, a part of the staff of the central ECG lab may be unblinded. This part of the staff will be strictly separated from the blinded staff members who are involved with ECG interval measurements and assessments of ECGs." deleted
Rationale for change		No ECG interval measurements are collected in the data base; open label trial
Section to be changed		5.2.1 Dose Limiting Events
Description of change		Signs of vascular occlusion in the retina, including peripheral retinal hemorrhage (hemorrhage of the macula would not be included

		as this is a symptom of the disease; peripheral retinal hemorrhage may be a sign of vascular occlusion). was changed to Signs of vascular occlusion in a 1st (the main branch) or 2nd degree (the vessel after the first bifurcation of the main branch) retinal vessel, including peripheral retinal hemorrhages in the area supplied by the occluded vessel (hemorrhage of the macula would not be included as this is a symptom of the disease).
Rationale for change		Clarification of the criterion
Section to be changed		5.2.8.1 Definitions of AEs
Description of change		The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form via fax immediately (within 24 hours) to the sponsor's unique entry point (country specific contact details will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and fax the BI SAE form. was changed to The investigator must report SAEs, AESIs, and non-serious AEs which are relevant for the reported SAE or AESI, on the BI SAE form immediately (within 24 hours) to the sponsor's unique entry point (country specific reporting process will be provided in the ISF). The same timeline applies if follow-up information becomes available. In specific occasions the investigator could inform the sponsor upfront via telephone. This does not replace the requirement to complete and send the BI SAE form.
Rationale for change		From 01 Oct 2019 SAEs may be submitted to BI by means other than Fax.
Section to be changed		7.2
Description of change		"There are no hypotheses tested in this exploratory trial." added
Rationale for change		Clarification
Section to be changed		7.3.4
Description of change		"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, QTcB, PR, QRS, RR, and further derived ECG endpoints. The baseline value of an ECG variable is defined

		as the mean of the triplicate ECG measurements prior to drug administration. The derivation of the quantitative and qualitative ECG endpoints and their analyses will be described in the TSAP." deleted
Rationale for change		No ECG interval measurements are collected in the data base; ECGs are only checked for baseline conditions or adverse events.
Section to be changed		10.3
Description of change		The value 0.100 in the specification for the non-logistic scenario in Table 10.3: 2 was changed to 0.010
Rationale for change		Correction

11.2 GLOBAL AMENDMENT 2

Date of amendment		11 Nov 2019
EudraCT number **EU number**		2017-001221-40
BI Trial number		1336-0007
BI Investigational Product(s)		BI 836880
Title of protocol		Safety, tolerability and pharmacodynamics of single rising intravitreal and multiple rising intravitreal doses of BI 836880 in patients with wAMD (open label, non-randomized, uncontrolled).
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		X
Section to be changed		3.3.2 Inclusion criteria
Description of change		Inclusion #1 – State of the art methods for diagnosis of wAMD were included Inclusion #2 – It was clarified that this criterion is only applicable for the MRD part Inclusion #7 – the degree of fibrosis was clarified
Rationale for change		Clarification of Inclusion criteria

11.3 GLOBAL AMENDMENT 3

Date of amendment		06 Oct 2020
EudraCT number **EU number**		2017-001221-40
BI Trial number		1336-0007
BI Investigational Product(s)		BI 836880
Title of protocol		Safety, tolerability and pharmacodynamics of single rising intravitreal and multiple rising intravitreal doses of BI 836880 in patients with wAMD (open label, non-randomized, uncontrolled).
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Clinical Trial Protocol Synopsis: Endpoints, Criteria for PK, Criteria for PD, Safety Criteria
Description of change		'Number [N (%)]' was changed to 'Number' throughout the Clinical Trial Protocol; 'eye disorders' was deleted from 'ocular adverse events' description; 'in the study eye' was added to Endpoints, as applicable; 'Change from baseline in CSFT at week 12' was moved to Criteria for Pharmacodynamics; 'color fundus photography (CFP)' was added as further Criteria for Pharmacodynamics; 'in both eyes' was added to 'Changes from baseline in selected parameters derived from color fundus photography (CFP)/optical coherence tomography (OCT)/OCT-A'; 'in the study eye' was added to Safety Criteria, as applicable.
Rationale for change		Clarification: Adaptations were introduced to more accurately describe respective endpoints and criteria.
Section to be changed		FLOW CHART I (SRD)
Description of change		a) 'Biobanking' and according footnote 3 were deleted. b) New footnote 3 was added: 'Physical examinations will also include measurement of weight and height (height only at Visit 1).'
Rationale for change		a) Clarification: no biobanking will be performed in SRD.

		b) Clarification of physical examinations, according to 5.2.3.
Section to be changed		FLOW CHART II (MRD)
Description of change		a) Additional assessments were added: PK and Biomarker sampling at Visits 6, 7, 8 and additional ADA sampling at Visit 8. b) New footnote 5 was added: 'Physical examinations will also include measurement of weight and height (height only at Visit 1)'.
Rationale for change		a) Extended PK/biomarker sampling to improve characterization of the terminal half-life and target binding duration in plasma of BI°836880 and hence improve modelling of vitreous concentration and target binding. Extended ADA analysis will improve the assessment of the immunogenicity potential of BI°836880 after intral-vitreal administration. b) Footnote 5: Clarification of physical examinations, according to 5.2.3.
Section to be changed		Last Paragraph of 1.2 Drug Profile
Description of change		Addition of: 'Within the trial described here (1336-0007), ten patients had been treated with intravitreal BI 836880 at a time of an initial data cut-off on 24 Mar 2020. Three patients were reported with an AE; all 3 AEs were eye disorders (conjunctival haemorrhage in the study eye, subretinal fluid in the study eye, neovascular AMD in the fellow eye). None of the reported AEs was judged as related to BI°836880 by investigators or fulfilled criteria for dose-limiting events. The AE of neovascular AMD was considered serious.'
Rationale for change		Extract from the current IB to inform that none of the reported AEs was judged as related to IMP in the first 10 patients treated.
Section to be changed		Last Paragraph of 1.4 Benefit-Risk Assessment; Appendix 10.4
Description of change		At the end of 1.4 it was added: 'The implications of the current Coronavirus Disease 2019 (COVID-19) pandemic are summarized in Section 10.4.' To Appendix '10.4 IMPLICATIONS OF CORONAVIRUS DISEASE 2019' was added: 'At the time of evaluating the fourth dose group of the SRD part in this trial, the COVID-19 pandemic emerged with worldwide impact on daily life. To allow for thorough evaluation of potential additional risks to trial participants in

		the course of this pandemic, the trial was temporarily put on hold in March 2020. At that timepoint, a total of ten patients had been treated with one single intravitreal injection of BI 836880. Available data did not show dose-limiting events, drug-related adverse events, nor systemic adverse events. The trial has been re-initiated in July 2020 after potential additional risks for study participants with regard to COVID-19 have been evaluated. 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. No effects related to this MoA on the immune system are currently known. In conclusion, 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. As such, risk mitigation measures, such as measures to reduce patients' exposure will be implemented, if required. Enrolment will only happen when the local situation allows for patients to travel to the trial site, and all precautionary measures (e.g. use of protective personal/patients 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 investigators 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'.
Rationale for change		Clarification that the impact of the current COVID-19 pandemic was carefully evaluated, that the overall benefit – risk assessment is considered to remain positive, and that the trial conduct will follow local instructions and recommendations to mitigate potential risks.

Section to be changed		Section 2.1.2 Primary endpoint(s), 2.1.3 Secondary endpoint(s), 2.2.2 Further endpoints
Description of change		See also changes introduced to the Clinical Trial Protocol Synopsis. 'Number [N (%)]' was changed to 'Number' throughout the Clinical Trial Protocol; 'eye disorders' was deleted from 'ocular AEs' description. To Further endpoints in SRD part was added: 'color fundus photography (CFP)' and the specification 'for each time point and in both eyes.' Changes in Further endpoints in MRD part: • 'in the study eye' was added to 'Change from baseline in CSFT at week 12' • 'Change from baseline in BCVA in the study eye over time' was added • Further timepoints were added to 'Systemic BI 836880 exposure', i.e., C_{112d} (56 days after last treatment), C_{140d} (84 days after last treatment), and C_{168d} (112 days after last treatment) • Further timepoints were added to 'Systemic free VEGF and ANG2 levels', i.e., E_{112d} (56 days after last treatment), E_{140d} (84 days after last treatment), and E_{168d} (112 days after last treatment) • 'CFP' was added to 'selected parameters', and it was specified 'for each time point and in both eyes'
Rationale for change		Clarification: several adaptations were introduced to more accurately describe respective endpoints.
Section to be changed		Section 3.1 Overall trial design and plan
Description of change		'by the SMC' was added to the sentence 'The two highest doses established as safe and tolerable during the SRD part will be selected to be used in the MRD…'
Rationale for change		Clarification
Section to be changed		Section 3.3.2 Inclusion criteria #1
Description of change		'Screening' was replaced with 'Treatment', as such, respective inclusion criteria #1 reads as follows: '…active CNV secondary to AMD despite anti-VEGF therapies (at least 3 prior injections with the last injection within 12 to 4 weeks before treatment)'
Rationale for change		Clarification; no VEGF therapies at least 4 weeks before treatment (not before screening) is considered adequate
Section to be changed		Section 3.3.2 Inclusion criteria #10

Description of change		'Female subjects must be of non-childbearing potential.' was changed to: 'Male or female patients. 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 and in section 4.2.1.3. [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.'
Rationale for change		Clarification of the definition of childbearing potential and appropriate contraceptive advice for male subjects able to father a child.
Section to be changed		a) Section 4.1.4 and 4.1.9 and b) Table 4.1.4: 2
Description of change		a) 'qualified personnel' was added as an alternative to a site pharmacist to prepare the ready to use drug product and to ensure drug accountability b) 'the two highest doses established by the SMC as safe and tolerable during the SRD part will be selected' was added to the title of the table
Rationale for change		Clarification
Section to be changed		Section 4.2.1.1 Restrictions
Description of change		'EOT' visit was substituted by 'during Follow-up Period, starting at Visit 5'.
Rationale for change		Correction: Standard of care is allowed starting at Visit 5.
Section to be changed		Section 4.2.1.3 Restrictions
Description of change		Header 'Restrictions regarding women of childbearing potential (WOCBP)' was changed to 'Contraception requirements'. Further, it was added: 'WOCBP (partner of a trial participant) must use a highly effective method of birth control per ICH M3 (R2) that results in a low failure rate of less than 1% per year when used consistently and

		correctly if their sexual partner is a man able to father a child. • Combined (estrogen and progestogen containing) hormonal birth control that prevents ovulation (oral, intravaginal, transdermal). • Progestogen-only hormonal birth control that prevents ovulation (oral, injectable, implantable). • Intrauterine device (IUD) or intrauterine hormone-releasing system (IUS). • Bilateral tubal occlusion Or Patients must abstain from male-female sex. This is defined as being in line with the preferred and usual lifestyle of the patient. Periodic abstinence e.g. calendar, ovulation, symptothermal, post-ovulation methods; declaration of abstinence for the duration of exposure to study drug; and withdrawal are not acceptable.'
Rationale for change		Clarification of contraceptive requirements for male subjects with pregnant or non-pregnant WOCBP.
Section to be changed		Section 5.2.1 Dose limiting event
Description of change		Deletion of 'within the evaluation period (7 days after drug administration)', addition of 'in the study eye'
Rationale for change		Correction: timeframe of DLE is not limited to 7 days after drug administration
Section to be changed		Section 5.2.2 Time to recurrence
Description of change		Deletion of 'a) For patients with dry retina after treatment: detection of any new intra- or subretinal fluid. b) For patients with wet retina after treatment: any increase in retinal fluid (excluding Pigment Epithelial Detachments) compared to baseline' and addition of '…in the study eye, leading to the use of wAMD rescue medication as decided by the investigator: - Increase in CFST ≥75 µm with a decrease in BCVA of ≥ 5 letters compared to Visit 5, OR - Decrease in BCVA of > 5 letters compared to baseline (Visit 2), due to worsening wAMD activity, OR

		- Decrease in BCVA of ≥ 10 letters compared to the best prior BCVA, due to worsening wAMD activity'
Rationale for change		Clarification of criteria to accurately determine recurrence leading to the use of rescue medication
Section to be changed		Section 5.3.1 Assessments of pharmacokinetics, MRD part
Rationale for change		Addition of: '• C112d (concentration of the analyte in serum 56 days after the third treatment) • C140d (concentration of the analyte in serum 84 days after the third treatment) • C168d (concentration of the analyte in serum 112 days after the third treatment)'.
Rationale for change		Information about additional PK assessments
Section to be changed		Section 5.4.1 Plasma derived protein biomarkers, MRD part
Rationale for change		Addition of: '• E112d (systemic level of free ANG2 and free VEGF 56 days after the third treatment) • E140d (systemic level of free ANG2 and free VEGF 84 days after the third treatment) • E168d (systemic level of free ANG2 and free VEGF 112 days after the third treatment)'.
Rationale for change		Information about additional biomarker assessments
Section to be changed		Section 6.1 Visit schedule
Description of change		'and ocular tonometry' was added as assessment before pupil dilation. 'Fluorescein angiography' was changed to 'OCT-angiography'. 'Additional ocular tonometry may also happen after treatment on discretion of the investigator' was added.
Rationale for change		Clarification of timepoints for ocular tonometry and correction (fluorescein angiography is not a trial procedure but OCT-A).
Section to be changed		Sections 6.2.1.2 and 6.2.2.2
Description of change		The sentence 'An additional tonometry will be performed after IVT injection to monitor intraocular pressure' was changed to 'An additional tonometry may be performed after IVT injection to monitor intraocular pressure'.
Rationale for change		Correction as tonometry after IVT may happen on discretion of the investigator.
Section to be changed		Section 6.2.2.2 Visit 8/End of Trial
Description of change		'The Visit 8/EOT will be performed 14 days after the Visit 7' was changed to 'The Visit 8/EOT will be performed 28 days after the Visit 7'.

Rationale for change		Correction of the Trial Timelines. A 28 day period is defined as follow-up timeline after Visit 7.
Section to be changed		Section 7.4 Interim analysis
Description of change		Addition of the sentence: 'Likewise, in the MRD part, the SMC will decide on the dose escalation.' Addition of the sentences: 'A preliminary analysis of efficacy data will be performed after the completion of Visit 5 of the first dose group of the MRD part. The preliminary efficacy results will be distributed to the trial team, but they will not be part of the CTR. A preliminary analysis of PK data will be performed after completion of the SRD part.'
Rationale for change		Clarification of preliminary analysis.
Section to be changed		Table 10.1: 2 Time schedule for PK/PD blood sampling
Description of change		Addition of three rows (FUP V6, FUP V7, EOT V8) according to time of sampling.
Rationale for change		To be consistent with the PK, Biomarker, and ADA sampling points introduced in this amendment.

11.4 GLOBAL AMENDMENT 4

Date of amendment		26 Mar 2021
EudraCT number **EU number**		2017-001221-40
BI Trial number		1336-0007
BI Investigational Product(s)		BI 836880
Title of protocol		Safety, tolerability and pharmacodynamics of single rising intravitreal and multiple rising intravitreal doses of BI 836880 in patients with wAMD (open label, non-randomized, uncontrolled).
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Section 3.3.2 Inclusion criteria
Description of change		#1.: Changing '12 weeks' to '16 weeks' #2.: Deleting this criterion #3.: Changing '350 microns' to '330 microns'

Rationale for change		Adaptation of these selected inclusion criteria aims to increase recruitment as initial eligibility criteria were too restrictive. The changes are not considered to have meaningful impact on safety for the patients.
Section to be changed		Section 3.3.3 Exclusion criteria
Description of change		#1.: Specifying 'IOP>24' as 'IOP>24 mmHg on more than 2 consecutive measurements prior to treatment' #3.: Changing '3 months' to '1 month' #9.: Changing to: 'Previous participation in this trial. Previous participation in other trials for treatment of wAMD with systemic administration and/or with IVT injections in the study eye if washout period from last administration/injection is lower than 3 months. Previous participation in other trials with IVT injections allowed if fellow eye was treated.'
Rationale for change		Adaptation of these selected exclusion criteria aims to increase recruitment as initial eligibility criteria were too restrictive. Clarification of the topic 'IOP' and 'previous participation in other trials' in more detail. The changes are not considered to have meaningful impact on safety for the patients.

11.5 GLOBAL AMENDMENT 5

Date of amendment		28 July 2021
EudraCT number **EU number**		2017-001221-40
BI Trial number		1336-0007
BI Investigational Product(s)		BI 836880
Title of protocol		Safety, tolerability and pharmacodynamics of single rising intravitreal and multiple rising intravitreal doses of BI 836880 in patients with wAMD (open label, non-randomized, uncontrolled).
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		

Section to be changed		Cover Page: Clinical phase; Clinical Trial Protocol Synopsis
Description of change		Clinical Phase 'I' was changed to 'I/IIa'.
Rationale for change		MRD cohort 2 will start to evaluate treatment-naïve patients: this population will be the final target population.
Section to be changed		Clinical Trial Protocol Synopsis and section 1.3; section 3.1; section 3.3
Description of change		Number of patients entered/treated: 15 in the SRD part (instead of 18) and 27 in the MRD part (instead of 24; MRD cohort 1 = 12 patients, MRD cohort 2 = 15 patients); total number of patients was not changed. First MRD cohort = 1 mg; second MRD cohort = 2 mg.
Rationale for change		Clarification: The two highest safe and tolerable doses (1 mg and 2 mg) were established with 15 patients in the SRD part; the drop out rate is expected to be higher in the MRD cohort 2 compared to the MRD cohort 1.
Section to be changed		Clinical Trial Protocol Synopsis: Diagnosis
Description of change		Addition of '…treatment-naïve wAMD for MRD cohort 2'.
Rationale for change		Switch to target population in MRD cohort 2.
Section to be changed		Clinical Trial Protocol Synopsis: Main in- and exclusion criteria
Description of change		Addition of: 'For MRD cohort 2: Men and women over the age of 55 with treatment-naïve CNV secondary to AMD.'
Rationale for change		Clarification of main eligibility criteria.
Section to be changed		Clinical Trial Protocol Synopsis: Test product, dose
Description of change		Addition to the MRD part: '1 mg and 2 mg (q4w)'.
Rationale for change		1 mg and 2 mg were selected for the MRD part as the two highest doses established as safe and tolerable during the SRD part.
Section to be changed		Flow Charts
Description of change		Addition of 'Flow Chart III (Multiple Rising Dose Part, Cohort 2'. Examinations/visits as in Flow Chart II with additional safety visits V2a, V3a, and V4a (with slit lamp examination, AE check, and concomitant therapy questionning, respectively) within a week after injection. At these visits, addition of footnote '(6): Additional safety procedures may be performed according to local safety standard practice.'

Rationale for change		As treatment-naïve patients are treated, addition of safety visits/procedures to ensure patient safety.
Section to be changed		1.2 Drug Profile
Description of change		Adaptation of the AE and PK section as follows: 'In the SRD part of the trial described here (1336-0007), 15 patients had been treated with intravitreal BI 836880 and followed up until the end of trial visit. Six patients were reported with an AE after trial drug administration; all of the corresponding 6 AEs were eye disorders (conjunctival haemorrhage in the study eye, subretinal fluid in the study eye, dry eye in the study eye, 2 vitreous floaters in the study eye, neovascular AMD in the fellow eye). None of the reported AEs was judged as related to BI°836880 by investigators or fulfilled criteria for dose-limiting events. The AEs of neovascular AMD and of subretinal fluid were reported as of moderate intensity, the other AEs were rated as mild. The AE of neovascular AMD in the fellow eye was considered serious. All AEs but the neovascular AMD, the subretinal fluid and the dry eye were recovered by the end of follow up. A preliminary pharmacokinetic analysis of the available data from the SRD part of 1336-0007 was conducted. The plasma exposure (C_{max} and AUC) increased in a dose proportional manner and reached gMean C_{max} of 88.0 ng/mL and gMean $AUC_{0-\infty}$ of 20 900 ng· h/mL for the 2 mg dose. Compared with the exposure after intravenous administration of 720 mg BI 836880, the exposure after intravitreal administration was very low (<1/1000). In the MRD part of the trial, two patients of the MRD cohort 1 received three intravitreal doses and one patient of the MRD cohort 1 received two intravitreal doses of BI 836880 at the time of a data cut-off on 28 July 2021. Two patients were reported with an AE after trial drug administration; one of the corresponding 2 AEs was an eye disorder (vitreous floaters in the study eye). None of the reported AEs was judged as related to BI°836880 by investigators or fulfilled criteria for dose-limiting events. Both AEs were reported as of mild intensity.'

Rationale for change		Available data for PK and AEs were incorporated to extend the current information of the drug profile.
Section to be changed		1.3 Rationale for performing the trial
Description of change		Adaption of the paragraph referring to which patients will be included, as follows: 'This trial will consist of a single rising dose (SRD) part and a multiple rising dose (MRD) part including MRD cohorts 1 and 2. Because this is the Fist-in-Human (FiH) application with IVT route of administration, the SRD part and the MRD cohort 1 of this trial will include patients who have not sufficiently responded to anti-VEGF treatment and still have active disease with significant retinal edema after a minimum of three previous injections. After safety has been investigated in SRD and first 3 patients of MRD cohort 1, the MRD cohort 2 will start to evaluate treatment-naïve patients: this population will be the final target population, as it is expected to include the patients that can receive the biggest benefit with IVT administration of BI 836880.'
Rationale for change		Rationale for the inclusion of treatment-naïve patients in the MRD cohort 2.
Section to be changed		1.4 Benefit-Risk Assessment; 9. References
Description of change		Adaptation of the information on RG7716 and addition of reference R21-0692: 'However, IVT administration of an antibody that simultaneously binds to VEGF and ANG2 (faricimab, previously referred to as bispecific antibody RG7716) for treatment of wAMD has previously been tested in humans in a Phase 1 clinical trial [R18-0309], and a Phase 2 clinical trial [R21-0692]. In the Phase 1 trial, the co-adminstration of RG7716 was reported to be well tolerated and to exhibit a favourable safety profile overall [R18-0309]. In addition, there was preliminary evidence of improvements in BCVA and anatomic parameters for this mode of action. In the Phase 2 trial, faricimab maintained vision and anatomic improvements comparable with SoC in wAMD in treatment naïve patients, resulting in the start of Phase 3 trials. These data support that the combination of anti-VEGF and anti-ANG2 can be used safely in patients with wAMD refractory to anti-VEGF monotherapy and in treatment-naïve patients.'

Rationale for change		Both, Phase I and Phase II data have been published for faricimab that were considered for the benefit-risk evaluation of BI 836880.
Section to be changed		1.4 Benefit-Risk Assessment
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 favorable risk-benefit profile. To the best of the sponsor's knowledge there is currently no product on the market, which is officially approved for intravitreal drug delivery. The needles for preparation of the drug and intravitreal injection are usually silicone oil coated to ease the injection of the needle through the tissue. This carries the potential risk for a silicone oil transfer into the vitreous with the potential risks for occurrence of side effects like vitreous floaters or intraocular inflammation. The overall risk for such events is based on long-term experience with comparable material, and is considered low. However, patients should be made aware of this risk, as reflected in the Informed Consent Form (ICF). To the best of the sponsor's knowledge there is currently no product on the market, which is silicone-free. The recommended syringes are silicone-oil-free and not considered to carry this risk. The IMP handling instructions do not mandate the use of materials from certain manufacturers and 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 836880.'
Rationale for change		Following release of a caution statement by Becton Dickinson (BD), who supply materials for use in this trial, a risk-benefit evaluation and associated mitigation steps was performed and incorporated into the trial protocol.
Section to be changed		1.4 Benefit-Risk Assessment
Description of change		Addition of 'For the MRD cohort 2, treatment-naïve patients will be included based on a positive safety assessment as confirmed by the Safety Monitoring Committee (SMC), after three patients of MRD cohort 1 reaching Visit 5, i.e., one month after the third injection. Treatment-

		naïve patients are the intended final target population for BI 836880, because it is expected that these patients can get the biggest benefit from this treatment.'
Rationale for change		Clarification on MRD cohort 2 as the target population.
Section to be changed		Figure 3.1: 2 Schematic representation of the dose escalation process in the MRD part
Description of change		It was specified: second highest safe dose from SRD = 1 mg (N=12); highest safe dose from the SRD = 2 mg (N=15).
Rationale for change		Two doses have been established, and second MRD cohort changed from N=12 to N=15.
Section to be changed		3.3.2 Inclusion criteria
Description of change		Addition of: 'SRD part and MRD cohort 1:' Addition of: 'MRD cohort 2: 1. Not applicable: Adapted to inclusion criterion #13, see below. 2. Not applicable: Deleted. 3. Not applicable: No limitation on central subfield retinal thickness. 4. Not applicable: Adapted to inclusion criterion #14, see below. 5. Not applicable: Adapted to inclusion criterion #14, see below. 6. No subretinal hemorrhage involving the fovea in the study eye. 7. No significant subfoveal fibrosis or atrophy on SD-OCT in the study eye that, in the opinion of the investigator, is able to prevent improvement in BCVA and/or CSFT. 8. Not applicable: Adapted to inclusion criterion #15, see below. 9. Not applicable: Adapted to inclusion criteria #16 and #17, see below. 10. Male or female patients. 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 and in Section 4.2.1.3 11. Signed informed consent consistent with ICH GCP guidelines and local legislation prior to

		participation in the trial, which includes medication washout and restrictions. 12. Not under any administrative or legal supervision or under institutionalization due to regulatory or juridical order. 13. Men and women over the age of 55 with treatment-naïve CNV secondary to AMD. 14. Any CNV with subfoveal activity in the study eye defined as evidence of sub- and/or intraretinal fluid, or subretinal hyper-reflective material, or angiographic leakage. 15. Best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) VA in the study eye between 80 and 24 letters inclusive (approximately 20/25 and 20/320 or 6/7.5 and 6/95) at screening. 16. Best-corrected ETDRS VA in the non-study eye 50 letters inclusive (approximately 20/100 or 6/30) or better at screening. 17. If both eyes are eligible at screening, the study eye is the eye with the worse best-corrected VA.'
Rationale for change		Adaptation and addition of inclusion criteria specifically for MRD cohort 2.
Section to be changed		3.3.3 Exclusion criteria
Description of change		Adaptation of Exclusion criterion #9 as follows: '9. Participation in trials: • Previous participation in this trial. • Previous participation in other trials for treatment of wAMD with systemic administration if washout period from last administration/injection is shorter than 3 months. • MRD cohort 1: Previous participation in other trials for treatment of wAMD with IVT injections in the study eye if washout period from last administration/injection is shorter than 3 months[2]. • MRD cohort 2: No previous IVT injections for wAMD in the study eye[2]. [2]Previous participation in other trials with IVT injections allowed if fellow eye was treated.'
Rationale for change		Adaptation of this exclusion criterion to clarify differentiate exclusion criteria between MRD cohorts 1 and 2.
Section to be changed		3.3.4.1; 5.; 6.; throughout the protocol

Description of change		Addition of 'and Flow Chart III'.
Rationale for change		Reference to the newly introduced Flow Chart III for MRD cohort 2.
Section to be changed		4.1.4. Drug assignment
Description of change		Addition of 'and "BI 836880 solution for injection 40 mg/mL" '.
Rationale for change		Reference to a new formulation that will become available for use.
Section to be changed		6.2.2.2 Treatment period and end of trial visit MRD part
Description of change		Addition of: 'In the MRD part cohort 2, additional safety assessments/visits will be carried out within a week after V2, V3, V4, respectively.'
Rationale for change		To ensure adequate safety visits/assessments for treatment-naïve patients.
Section to be changed		7.7 Determination of Sample Size
Description of change		Addition of: 'The drop out rate is expected to be higher for the treatment-naïve patients in cohort 2 as compared to the treatment-resistant patients in cohort 1. To allow for dropouts, 12 patients will be included in MRD cohort 1 and 15 patients will be included in MRD cohort 2.'
Rationale for change		Explanation for sample size for cohort 2.
Section to be changed		8.3.2 Direct access to source data and documents
Description of change		Addition of: 'and/or remote monitoring calls'.
Rationale for change		Clarification: Takes into account remote monitoring.
Section to be changed		Table 10.1: 2 Time schedule for PK/PD blood sampling during MRD part; column 'Planned Time [h]'
Description of change		Extension of pre-dose sampling time window to -2 h and of follow-up sampling time window to +/- 2 h.
Rationale for change		To allow higher operational flexibility for PK/PD blood sampling in the MRD part.

11.6 GLOBAL AMENDMENT 6

Date of amendment		25 Oct 2021
EudraCT number **EU number**		2017-001221-40
BI Trial number		1336-0007
BI Investigational Product(s)		BI 836880
Title of protocol		Safety, tolerability and pharmacodynamics of single rising intravitreal and multiple rising intravitreal doses of BI 836880 in patients with

		wAMD (open label, non-randomized, uncontrolled).
To be implemented only after approval of the IRB / IEC / Competent Authorities		X
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		Clinical Trial Protocol Synopsis and throughout the CTP (Sections 1.3; 3.1; 7.7 and Figure 3.1: 2)
Description of change		Specification of cohort sizes in MRD part, i.e., ’10 to 12’ (instead of ‘12’) for MRD cohort 1 and ’10 to 17’ (instead of ‘15’) for MRD cohort 2; illustration that cohort 1 and cohort 2 will run overlapping after the SMC.
Rationale for change		No change of total number of patients, adaptations taking into account a potential higher drop-out rate in treatment-naïve patients where follow-up until EoT is particularly important. Clarification of Figure 3.1: 2.
Section to be changed		Clinical Trial Protocol Synopsis and 3.3.2
Description of change		Incl#3.: Change ‘CSFT > 330 µm’ to ‘CSFT > 300 µm’ for MRD cohort 1.
Rationale for change		Adaptation of this selected inclusion criteria aims to increase recruitment as former eligibility criteria were too restrictive.
Section to be changed		3.1 Overall Trial Design and Plan; MRD part
Description of change		Deletion of ‘Although anti-VEGF gives a fast response in treatment-naïve patients, in this group of patients with wAMD who had not sufficiently responded to anti-VEGF treatment, it is expected that a reduction of fluid in the retina should be observed only after multiple treatments’.
Rationale for change		Misleading sentence as MRD part no longer exlusively consists of patients who had not sufficienly responded to anti-VEGF treatment.
Section to be changed		3.3.2 Inclusion criteria
Description of change		Incl#8: Change ‘ETDRS VA in the study eye between 70 and 24 letters inclusive’ to ‘between 75 and 24 letters inclusive (approximately 20/32 or 6/9.5)’.
Rationale for change		Positive safety data support to broaden this criterion to allow treatment-resistant patients with ETDRS VA up to 75 to be enrolled as well.
Section to be changed		4.1.1. Identity of Investigational Medicinal Product

Description of change		Addition of 'Table 4.1.1: 2' in order to describe the diluent.
Rationale for change		For completeness/clarification: Investigational Medicinal Product includes BI 836880 and diluent.
Section to be changed		4.1.4 Drug assignment and administration of doses for each patient
Description of change		Addition of: 'The diluent can be used for both drug preparations, "BI 836880 concentrate for solution for injection 80 mg/mL" and for "BI 836880 solution for injection 40 mg/mL", if required.'
Rationale for change		Continuation of 1336-0007 1 mg MRD cohort with "BI 836880 solution for injection 40 mg/mL" drug product and diluent if treatment goes beyond February 2022 as the "BI 836880 concentrate for solution for injection 80 mg/mL" drug product expires end of February 2022.
Section to be changed		6.2. Re-Screening
Description of change		Addition of 'without new IRT registration' if re-screen within 12 weeks, 'beyond this time period (up to one time)' with IRT registration.
Rationale for change		Clarification.
Section to be changed		8. Publication Policy
Description of change		Deletion of 'As a rule, no trial results should be published prior to finalization of the CTR.' and addition of 'As per the project publication strategy, interim cohort data will be published as available, while full results will be published after CTR finalization.'
Rationale for change		Clarification.

11.7 GLOBAL AMENDMENT 7

Date of amendment		28 Sep 2022
EudraCT number **EU number**		2017-001221-40
BI Trial number		1336-0007
BI Investigational Product(s)		BI 836880
Title of protocol		Safety, tolerability and pharmacodynamics of single rising intravitreal and multiple rising intravitreal doses of BI 836880 in patients with wAMD (open label, non-randomized, uncontrolled).
To be implemented only after approval of the IRB / IEC / Competent Authorities		X

To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval	
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only	

Section to be changed		Clinical Trial Protocol Synopsis and throughout the CTP (Sections 3.1 Overall trial design and plan; 7.7 Determination of sample size; Figure 3.1: 2)
Description of change		Revision and clarification of patients entered, cohort sizes, and dose groups in MRD part. For number of patients entered (synopsis): '**Approximately** ~~Up to~~ 42; 15 in the SRD part and **approximately** ~~up to~~ 27 in the MRD part' For number of patients on each treatment (synopsis): 'SRD part: 15, in different dose groups MRD part: **11** ~~10 to 12~~ patients in dose group 1 (~~= MRD~~ cohort 1); **approximately 16** ~~10 to 17~~ **patients** in dose group 2**,** (**4 patients from** ~~MRD~~ cohort 2**, 12 patients from cohort 3**).' For Section 3.1: 'The MRD part will consist of a first **part**~~cohort~~ (1 mg) with **11**~~10 to 12~~ treatment-resistant patients ~~and~~**(cohort 1)**, a second **part**~~cohort~~ (2 mg) with **4**~~10 to 17~~ treatment-naïve patients **(cohort 2), and approximately 12 frequently treated patients (cohort 3; inclusion criteria defined in Section 3.3.2).'**, amendment of n numbers and layout of Figure 3.1: 2 For Section 7.7: 'To allow for dropouts, 10 to 12 patients will be included in MRD cohort 1 and **approximately 16**~~10 to 17~~ patients will be included in MRD cohort 2 **and 3 combined** (in total **approximately** ~~not more than~~ 42 patients in the trial). **In case some subjects do not complete the trial according to the protocol, the trial clinical monitor together with the trial pharmacokineticist and the trial statistician are to decide if and how many subjects will be replaced.'** and '**For the MRD cohort 3, no formal sample size calculation has been applied. It is expected that using**

		approximately 12 patients will be sufficient for this cohort.'
Rationale for change		No change of total number of patients. Added the word "approximately" to account for potential variability in number of patients entered and number of patients that are randomized. Reiterated replacement strategy. Patients on each treatment adapted with results from completed SRD and MRD cohorts 1 and 2, 12 patients allocated to cohort 3. Clarification and addition of MRD cohort 3 patients to text in Section 3.1 and Figure 3.1: 2.
Section to be changed		Clinical Trial Protocol Synopsis: Diagnosis
Description of change		Addition of: 'patients within 3 years of initial wAMD diagnosis for MRD cohort 3.'
Rationale for change		Additional requirement of patient population for MRD cohort 3
Section to be changed		Clinical Trial Protocol Synopsis: Main in- and exclusion criteria
Description of change		Addition to main inclusion: 'For MRD cohort 3: Men and women over the age of 55 with active CNV secondary to wAMD that require frequent intravitreal (IVT) treatment (28 to 56 days between treatments) with ranibizumab, aflibercept, or bevacizumab for standard of care for at least 6 months, with the last IVT administration between 4-8 weeks before the first study drug administration.' Addition to main exclusion: 'For MRD cohort 3: Active intraocular inflammation in the study eye, > 0.5+ anterior chamber cell and/or vitreous haze grading, or history of intraocular inflammation in either eye with previous IVT administration(s), history of retinal vein occlusion, previous treatment with brolucizumab or faricimab, and/or medical history of autoimmune disease that has caused ocular inflammation.'
Rationale for change		Update of main eligibility criteria for MRD cohort 3
Section to be changed		Clinical Trial Protocol Synopsis: Test product, dose
Description of change		Addition to the MRD part: '1 mg **(cohort 1)** and 2 mg **(cohort 2 and 3)** (q4w)'
Rationale for change		Clarification of dose groups and cohort allocation
Section to be changed		Clinical Trial Protocol Synopsis: Endpoints & Criteria for Pharmacodynamics; 2.1.3 Secondary

		endpoints; 7.3.2/7.3.3 Secondary/Further endpoint analyses
Description of change		Added week and visit numbers
Rationale for change		Clarification
Section to be changed		Clinical Trial Protocol Synopsis: Statistical Methods; 7.7 Determination of sample size
Description of change		Reworded to make clear that no statistical testing is planned for descriptive statistics Added to 7.7: 'For the MRD cohort 3, no formal sample size calculation has been applied. It is expected that using approximately 12 patients will be sufficient for this cohort.'
Rationale for change		Clarification
Section to be changed		Flow Charts
Description of change		Addition of 'Flow Chart IV (Multiple Rising Dose Part, Cohort 3)'. Examinations/visits as in Flow Chart III with Fundus photos (multi-field and widefield) added to treatment period safety visits. Added fluorescein angiography to Screening with footnote '(7): Fluorescein angiography imaging during Visits 2-8 should be performed at the discretion of the investigator, e.g. if signs of inflammation are observed' Added row to differentiate between multi-field and widefield fundus photos that are required at every visit, rather than at the discretion of the investigator. Changed footnote 4 to 'Vitreous haze assessment to be completed with every examination' Added row with Study Week to all flow charts.
Rationale for change		Adapted to include additional safety measurements required for MRD cohort 3, and for clarity (Study week)
Section to be changed		3.3.4.1; 5.; 6.; throughout protocol
Description of change		Addition of 'and Flow Chart IV' and 'cohort 3'
Rationale for change		Reference to the newly introduced Flow Chart IV and MRD cohort 3
Section to be changed		1.2 Drug profile
Description of change		Updated current summary of clinical safety data including descriptions of 2 SAEs reported in MRD cohort 1. Added references
Rationale for change		Update
Section to be changed		1.3 Rationale for performing the trial
Description of change		Described evidence of efficacy detected during exploratory analysis of interim data in patients

		requiring frequent standard of care which are the target patient population for MRD cohort 3
Rationale for change		Description of exploratory interim data and the unmet medical need for cohort 3 patient population to receive less frequent, higher potency therapy.
Section to be changed		1.4 Benefit-Risk assessment
Description of change		Removed paragraph referring to systemic administration of BI 836880 currently in development for use in oncology Described unmet medical need of frequently treated patient population Described added safety measures: FA imaging during screening, wide angle CFP with vitreous haze assessment at every visit and requirement to report any intraocular inflammation events as AESIs.
Rationale for change		PK data from SRD part showed <1/1000 systemic plasma levels after IVT compared to intraveneous exposure, therefore clinical data is unlikely to be similar/comparable Updates to benefit-risk assessment (favorable)
Section to be changed		[redacted]
Description of change		
Rationale for change		
Section to be changed		3.3.1 Main diagnosis for trial entry; 3.3.2 Inclusion criteria
Description of change		Added to 3.3.1: 'who meet all inclusion criteria and do not meet any exclusion criterion.' Added to 3.3.2: <u>MRD cohort 3 (frequently treated patients):</u> 1-5. Not applicable to cohort 3. 6. No subretinal hemorrhage involving the fovea in the study eye. 7. No significant subfoveal fibrosis or atrophy on SD-OCT in the study eye that, in the opinion of the investigator and with the

		endorsement of the Sponsor, is able to prevent improvement in BCVA. 8-9. Not applicable to cohort 3. 10. Male or female patients. 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 and in Section 4.2.1.3. 11. Signed informed consent consistent with ICH GCP guidelines and local legislation prior to participation in the trial, which includes medication washout and restrictions. 12. Not under any administrative or legal supervision or under institutionalization due to regulatory or juridical order. 13. Not applicable to cohort 3. 14. Any CNV with subfoveal activity in the study eye defined as evidence of sub- and/or intraretinal fluid, or subretinal hyper-reflective material, or angiographic leakage. 15. Best-corrected Early Treatment Diabetic Retinopathy Study (ETDRS) VA in the study eye between 80 and 24 letters inclusive (approximately 20/25 and 20/320 or 6/7.5 and 6/95) at screening. 16. Not applicable to cohort 3. 17. If both eyes are eligible at screening, the study eye is the eye with the worse best-corrected VA. 18. Men and women over the age of 55 with diagnosed wAMD that: • require frequent wAMD SoC (28-56 days between the last 3 treatments) • have had ≥ 3 previous treatments with IVT SoC (ranibizumab, aflibercept, or bevacizumab) in the study eye • had the last SoC injection ≥ 4 weeks, but no more than 8 weeks, before the first administration of the study drug • have been on SoC treatment ≥ 6 months and are within 3 years from initial wAMD diagnosis in the study eye

		Added cohort patient population description to heading for each set of inclusion criteria
Rationale for change		Adaptation and addition of inclusion criteria specifically for MRD cohort 3. Clarification
Section to be changed		3.3.3 Exclusion criteria
Description of change		Added: 9. Participation in trials: • Previous participation in this trial. • Previous participation in other trials for treatment of wAMD with systemic administration if washout period from last administration is shorter than 3 months. • **MRD cohorts 1 & 3**: Previous participation in other trials for treatment of wAMD with IVT injections in the study eye if washout period from last administration/injection is shorter than 3 months[2]. • MRD cohort 2: No previous IVT injections for wAMD in the study eye[2]. **12.** Active intraocular inflammation in the study eye**, > 0.5+ anterior chamber cell and/or vitreous haze grading, or history of intraocular inflammation in either eye with previous IVT administration(s) (anterior chamber/haze grading and intraocular imflammation history only applicable to MRD cohort 3).** 13. Active infectious conjunctivitis in either eye. **14. Symptoms of active SARS-CoV-2 infection[4].** **15. Any history of retinal vein occlusion in the study eye (only applicable to MRD cohort 3).** **16. Any previous treatment with brolucizumab or faricimab in either eye (only applicable to MRD cohort 3).** **17. Medical history of autoimmune disease that has caused ocular inflammation (only applicable to MRD cohort 3).** [2] Previous participation in other trials with IVT injections allowed if fellow eye was treated. [3] e.g. cardiac (including tachycardia), gastro-intestinal, hepatic, renal, metabolic, dermatologic, neurological, haematological, oncological and psychiatric. Patients with malignancy for which the patient has undergone resection, radiation or chemotherapy

		within past 5 years. Patients with treated basal cell carcinoma or fully cured squamous cell carcinoma are allowed. **[4] Testing and management of SARS-CoV-2 infection at the discretion of investigators in accordance with local guidelines and policies.**
Rationale for change		Adaptation of exclusion criterion 9 to clarify differentiate between MRD cohorts 1, 2, and 3. Added/amended exclusion criteria 12, 14-17 to exclude patients with a high potential of developing ocular inflammation from MRD cohort 3.
Section to be changed		3.3.5 Replacement of patients
Description of change		Amended 3.3.5: 'Patients withdrawn before visit 4 for ~~another~~ reason **other** than **a** DLE or patients who miss any visit out of Visits 2 to 4 are not evaluable for the occurrence of a DLE within 7 days after drug administration. These patients will be replaced if not decided otherwise by the SMC (~~because~~**in the scenario that** there are already 2 DLE evaluable patients in the current dose group; see Section 3.1). Patients who come off study due to a DLE will not be replaced.'
Rationale for change		Reworded for clarification, no change to replacement criteria
Section to be changed		4.1.1 Identity of the Investigational Medicinal Products
Description of change		Added: 'In this trial, the IMP BI 836880 will be switched from an initial trial formulation (CMC1) to an intended final formulation (CMC2). The new formulation will be made available for the treatment of MRD cohort 3.'
Rationale for change		Reference to a new formulation that will become available for use.
Section to be changed		4.1.6.1, 4.1.6.2 Blinding and procedures for unblinding; 7.4 Interim Analysis
Description of change		Rephrased all instances of "blinded" to "masked"
Rationale for change		In accordance with current nomenclature for retinopathy studies
Section to be changed		4.2.1.1 Restrictions regarding concomitant treatment; 5.2.2 Time to recurrence; 6.2.2.2 Treatment period and end of trial visit MRD part
Description of change		4.2.1.1 Reworded to: '**SRD and MRD cohorts 1 & 2:** As per judgement of the investigator, administration of local SoC treatment such as IVT or peribulbar injections, laser, or other surgical treatment is allowed in clinically significant worsening of the disease. After the end of treatment with trial medication (during Follow-up Period, starting at

		Visit 5), SoC therapy is at the discretion of the investigator. SoC therapy is, for the purpose of the present trial, considered a non-investigational medical treatment. **<u>MRD cohort 3</u>: For the study eye, no other treatment (IVT or otherwise) is allowed during the treatment and follow up periods of the trial unless rescue criteria are met (refer to Section 5.2.2 for rescue treatment criteria), or as deemed medically appropriate during/after Visit 6. Medications listed under the exclusion criteria (Section 3.3.3) are restricted during the trial. SoC therapy is, for the purpose of the present trial, considered a non-investigational medical treatment.'** Added to 5.2.2: 'The decision to treat with wAMD rescue medication should be documented in the eCRF.' 6.2.2.2 Amended: 'The investigator may decide to administer standard treatment for wAMD during the follow-up period **(for MRD cohort 3 during/after Visit 6)** as deemed medically appropriate.'
Rationale for change		Clarification that SoC therapy should be administered and documented if there is a worsening in disease before Visit 6, and as deemed medically appropriate during/after Visit 6.
Section to be changed		5.2.1 Dose limiting event; 5.2.8.1.4 Adverse events of special interest
Description of change		Added to 5.2.1: Heading to SRD and MRD cohort 1 criteria and 'DLE criteria are not applicable to MRD cohorts 2 and 3. Should an event involving intraocular inflammation/signs of vascular occlusion, decreases in visual acuity, and/or intraocular pressure occur, the event should only be reported as an AESI as described in Section 5.2.8.1, and not as a DLE.' Added to 5.2.8.1.4: detailed AESI criteria for ocular related events (intraocular inflammation, signs of retinal vascular occlusion, decreases in visual acuity, and intraocular pressure). Added NEI grading scale of vitreous haze (Table 5.2.8.1.4: 1)
Rationale for change		Clarification, additional AESI criteria described for cohorts receiving maximum dose (MRD cohorts 2 & 3)

Section to be changed		5.2.3 Physical examination
Description of change		Amended and added to description of color fundus photography: '~~Seven-field or modified 4-~~ **Multi-**field digital fundus photographs will be obtained from both eyes by a qualified person according to the imaging manual. **For MRD cohort 3, additional color fundus photographs from both eyes will be acquired from the retinal periphery to assess inflammation and from the central retina to assess vitreous haze**.'
Rationale for change		Clarification and description of added requirement of multi-field and widefield color fundus photography for cohort 3 (safety requirement)
Section to be changed		5.2.6 Electrocardiogram
Description of change		Amended: 'All ECGs will be evaluated by the cardiologist of the central ECG vendor,~~ or~~ **and in addition** by a qualified~~ cardiologist~~ **healthcare provider** at the site, **if available**.'
Rationale for change		Clarification and to allow operational flexibility. This change is not considered to have an impact to the safety of patients.
Section to be changed		5.2.7 Other safety parameters; 6.1 Visit schedule; 6.2.2.1 Screening Visit
Description of change		Added to other safety parameters: 'MRD cohort 3 only: Fluorescein angiography (FA) imaging will be obtained from both eyes during Screening by a qualified person according to the imaging manual. Additional FA during Visits 2-8 should be performed at the discretion of the investigator, e.g. if signs of inflammation are observed.' Added to visit schedule: 'After dilation: slit lamp examination, SD-OCT, Fundus photography, ~~and~~ OCT- angiography**, and FA (FA required at screening or at the discretion of the investigator during subsequent visits, for cohort 3 only).**' Added to Re-screening: 'Imaging of retina (SD-OCT, OCT-A, fundus photography, **and/or fluorescein angiography**) does not need to be repeated at the re-screening visit'
Rationale for change		Description of added requirement of fluorescein angiography for cohort 3 (safety requirement)
Section to be changed		5.2.8.2.4 Pregnancy
Description of change		Added: 'Similarly, potential drug exposure during pregnancy must be reported if a partner of a male trial participant becomes pregnant. This requires

		written consent of the pregnant partner. Reporting and consenting must be in line with local regulations. The ISF will contain the trial specific information and consent for the pregnant partner.'
Rationale for change		In line with local US amendment 2 requiring written consent of the pregnant partner of a study participant for drug exposure reporting and pregnancy outcome.
Section to be changed		7 Statistical methods and determination of sample size
Description of change		Amended 7.1: 'There will be 2 ~~consecutive cohorts~~ **dose groups** of the ~~highest and the~~ second highest **safe (cohort 1) and the highest safe** dose level **(cohorts 2 and 3)** fulfilling the EWOC criterion after completion of the SRD part.' Amended 7.3: 'Analyses will be performed by **dose/cohort and overall in each** trial part.' Added/amended 7.3: '**Evaluable Responders' Set (ERS, MRD cohort 3 only)** **The ERS will consist of all patients who completed three doses of BI 836880 and have SD-OCT measurements at Week 16 (Visit 6).** In the TSAP, the FAS **and ERS** definitions may be updated, and further analysis data sets may be defined.' Added 7.3.3: 'The analysis of responders in MRD cohort 3 will be based on TS and/or ERS. More details will be described in the TSAP.' Amended 7.7: 'For example, **if the true median percent decrease in CSFT at Week 12 was 25%,** the probability to observe a median percent decrease in CSFT at Week 12 of at least 20% would be around 80%'
Rationale for change		Update/clarification of analytical details regarding newly added MRD cohort 3
Section to be changed		8.1 Trial approval, patient information, informed consent
Description of change		Removed 'or the patient's legally accepted representative'
Rationale for change		In line with local German amendments 1& 2
Section to be changed		Section 1 Introduction; Section 9 References
Description of change		Added: R22-2854, n00253677, n00259128 Updated: draft references with final dates Removed: R07-4722, R09-4830, R16-0366, c02353883, unpublished reference author names

Rationale for change		Update, added references to introduction
Section to be changed		Table 10.1: 2 Time schedule for PK/PD blood sampling during MRD part; column 'Planned Time [h]'
Description of change		Extension of before 1st IVT dose sampling time window to -4 h.
Rationale for change		To allow higher operational flexibility for PK/PD blood sampling

APPROVAL / SIGNATURE PAGE

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Signatures (obtained electronically)

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Approval-Clinical Program [redacted]	[redacted]	29 Sep 2022 09:28 CEST
Approval-[redacted] Medicine		29 Sep 2022 09:49 CEST
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