Clinical Trial Protocol

	Document Number:	**c14141887-05**
EudraCT No.:	2016-002971-91	
BI Trial No.:	1386.12	
BI Investigational Medicinal Product:	BI 1467335	
Title:	A **R**andomized, double-masked, placebo-controlled exploratory study to evaluate safety, tolerability, pharmacodynamics and pharmacokinetics of **O**rally administered **BI** 1467335 for 12 weeks with a 12 week follow up period in patients with **N**on-proliferative diabetic retinopathy without center-involved diabetic macular edema (ROBIN study)	
Lay Title:	A study that tests BI 1467335 in patients with diabetic eye disease (diabetic retinopathy). It looks at the way BI 1467335 is taken up, the effects it has, and how well it is tolerated.	
Clinical Phase:	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 4)	
Version and Date:	**Version:**	**Date:**
	5.0	11 Apr 2019

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim
Finished product name	Not applicable
Active ingredient name:	BI 1467335
Protocol date	02 Jun 2017
Revision date	11 Apr 2019
Trial number	1386.12
Title of trial:	A **R**andomized, double-masked, placebo-controlled exploratory study to evaluate safety, tolerability, pharmacodynamics and pharmacokinetics of **O**rally administered **BI** 1467335 for 12 weeks with a 12 week follow up period in patients with **N**on-proliferative diabetic retinopathy without center-involved diabetic macular edema (ROBIN study)
Coordinating Investigator:	[redacted] Phone: [redacted] Fax: [redacted]
Trial site(s):	Multi-center trial
Clinical phase:	IIa
Trial rationale:	This study is designed to assess the safety and tolerability of the oral compound BI 1467335 and to investigate the changes in DR lesion morphology. An oral medication capable to treat the moderate/severe stages of NPDR could fill an important gap in which patients with NPDR could receive treatment and thereby their disease progression could be slowed or even reversed.
Trial objective(s):	The primary objective is to evaluate safety and tolerability of 12 weeks treatment of oral BI 1467335 compared to placebo in patients with moderately severe to severe non-proliferative diabetic retinopathy (NPDR) without center-involved diabetic macular edema (CI-DME) and secondary to explore the efficacy of BI 1467335 on improvement of diabetic retinopathy.
Trial design:	Placebo-controlled, double-masked, randomized, parallel design comparison of two groups over 12 weeks of treatment with 12 weeks of follow-up.
Number of patients randomized:	100
Number of patients on each treatment:	50
Diagnosis:	Patients with moderately severe or severe NPDR, i.e. Diabetic Retinopathy Severity Scale (DRSS) level 47 or 53 without CI-DME.

Main in- and exclusion criteria	Male or female patients; of legal age Diagnosis of diabetes mellitus Type 1 or Type 2 Non-proliferative diabetic retinopathy (NPDR) without CI-DME in the study eye at screening with NPDR level 47 or level 53, as determined by the Central reading center (CRC) by using the DRSS Best corrected visual acuity Early Treatment Diabetic Retinopathy Study (ETDRS) letter score ≥ 70 letters in the study eye at screening No evidence of active neovascularization of the iris or angle neovascularization in the study eye No prior pan-retinal photocoagulation in the study eye No history of Diabetic macular edema (DME) or DR treatment with macular laser within 3 months prior to screening, or intraocular injections of medication within 6 months prior to screening, and no more than 4 prior intraocular injections at any time in the past in the study eye
Test product:	BI 1467335 film-coated tablets
dose:	10 mg daily (two 5 mg tablets q.d.)
mode of administration:	p.o.
Comparator products:	Placebo film-coated tablets
dose:	Not applicable
mode of administration:	p.o.
Duration of treatment:	12 weeks of treatment with 12 weeks follow-up
Endpoints:	Primary endpoint is the proportion of patients with ocular adverse events according to Common Terminology Criteria for Adverse Events (CTCAE) over the on-treatment period (over 24 weeks). Secondary endpoints are the proportion of patients with at least 2 steps improvement in the study eye on the DRSS at week 12 compared to baseline, and the proportion of patients with adverse events (according to CTCAE) other than ocular adverse events over the on-treatment period (over 24 weeks)
Safety criteria:	Adverse event reporting, vital signs, 12-lead electrocardiogram (ECG) and standard safety laboratory parameters.
Statistical methods:	The randomization will be stratified by the severity level of the disease under study as assessed by DRSS, i.e. levels 47 or 53. Endpoints related to proportion of patients with improvement in DRSS will be summarized descriptively and will be analyzed using logistic regression adjusting for baseline visual acuity if sufficient numbers of events are observed.. [redacted] All other endpoints will be analyzed using descriptive statistics.

FLOW CHART

Tests and Procedures	**Screening** [23]	**Treatment Period** [1]						**Follow-up period**		
Visit	**1** [21]	**2a Base-line**	**2b** Phone Visit	**3**	**4a**	**4b** Phone Visit	**EOT** [2]	**FU1**	**FU2**	**FU3**
Week			**1**	**4**	**8**		**12**	**16**	**20**	**24**
Day	**-28 to -3** [3]	**1**	**8**	**29**	**57**	**83**	**85**	**EOT**[19] **+28**	**EOT**[19] **+56**	**EOT**[19] **+84**
Time window for visits (days)			±1	±3	±3	±1	+6	±6	±6	±6
Informed consent signed [4]	X [21]									
Informed consent for biobanking [5]	X									
Demographics	X									
Medical history/baseline conditions	X									
Substance use [22]	X	X		X	X		X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X	X	X	X
All AEs/SAEs/ AESIs [20,24]	X	X	X	X	X	X	X	X	X	X
Physical examination	X	X		X	X		X	X	X	X
Vital signs [6]	X	X		X	X		X	X	X	X
Height	X									
Body weight	X	X					X			X
Pregnancy testing [7]	X_S	X_U		X_U	X_U		X_U	X_U	X_U	X_U
Resting ECG [8]	X	X		X	X		X	X	X	X
Ophthalmological exams: [9] Visual acuity (BCVA)	X	X		X	X		X	X	X	X
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Color fundus photography (for DRSS evaluation) [10]	X [21]	X		X	X		X	X	X	X
[redacted]	[redacted]	[redacted]					[redacted]			[redacted]
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
[redacted]	[redacted]	[redacted]		[redacted]	[redacted]		[redacted]	[redacted]	[redacted]	[redacted]
Gonioscopy	X									
In-/Exclusion criteria	X	X								
IRT call [11]	X	X		X	X		X			
Trial medication administration at site		X		X	X		X			
Dispense trial medication		X		X	X					
Collection of trial medication, check of medication compliance				X	X		X			
Dispense trial medication diary [12]		X		X	X					

Tests and Procedures	**Screening** [23]	**Treatment Period** [1]						**Follow-up period**		
Visit	**1** [21]	**2a Base-line**	**2b** Phone Visit	**3**	**4a**	**4b** Phone Visit	**EOT** [2]	**FU1**	**FU2**	**FU3**
Collection / check of trial medication diary				X	X		X			
Reminder to the patient[13]			X			X				
Laboratory tests: Chemistry, hematology, urinalysis	X	X		X	X		X	X	X	X
Infection testing [18]	X									
[redacted]										
Study completion [17]										X

BCVA = Best corrected visual acuity; DRSS = Diabetic Retinopathy Severity Scale; EOT = End of Treatment; ECG = electrocardiography; FU = Follow Up; IRT = Interactive Response Technology; OCT-A = [redacted]; X_S =serum testing; X_U= urine testing; → = preferentially at this particular visit but also possible at later visits.

[1] The medication will be administered once daily, beginning on Day 1 (Visit 2a). Scheduled last day of trial medication intake is Visit EOT where the trial medication will be administered at the site from the kit that the patient returns to the site, unless patient discontinues prematurely for safety reasons or withdraws consent.

[2] This Visit has also to be completed for patients who are withdrawn or who have discontinued the trial early: in case of early discontinuation, visit EOT will be completed as soon as possible after the last trial medication intake instead of the next planned treatment period visit, and the visits FU1, FU2 and FU3 should be performed 4, 8 and 12 weeks after the last trial medication intake, respectively. If patient discontinues prematurely for safety reasons or withdraws consent, trial medication administration and PK collection will not be performed at EOT Visit. Please refer to Section 6.2.3.

[3] The screening period should be kept as short as possible, but the minimum time interval between Screening and Randomization is necessary to allow for receipt of confirmation from the central imaging reading center, laboratory and ECG results.

[4] Prior to any study related procedure; may also be done at an extra visit up to 2 weeks before Visit 1. Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions. Note: Collection of adverse events and other study requirements begin at the time patient signs informed consent.

[5] Serum/plasma and DNA biobanking is optional. To allow the collection of additional blood samples for serum/plasma and DNA biobanking a separate informed consent must be obtained.

[6] Vital signs (to be performed prior to blood collection) include: pulse rate, arterial systolic and diastolic blood pressure and respiratory rate (Section 5.2.2).

[7] Pregnancy testing: at screening serum pregnancy test is done (X_S), and at the other visits as a reflex when urine testing (X_U) is positive.

[8] At screening and follow-up visits 12-lead ECGs should preferentially be performed prior to blood sampling. During the treatment period, ECG should be performed approximately 60 min after trial medication intake. At visits 3 and 4a the ECG may be performed later at that day. ECGs will be recorded after the patients have rested for at least 5 minutes in a supine position. Please refer to Section 5.2.4.

[9] [redacted]

[10] The DRSS evaluation is performed by the independent central imaging reading center.

[11] At visits 2a (randomization call), 3 and 4a, the respective IMP kit number has to be allocated to the patient via IRT. At Visit EOT the IRT call is performed to close out the patient (Termination of medication).

[12] All patients will complete a trial medication diary during the treatment phase to document medication intake and treatment compliance. The diary will be dispensed to the patients and collected and reviewed by site-staff at the following visits. Please refer to Section 6.2.2.

[13] Site staff will call the patient in advance to the Visit 2 and EOT visit to remind of trial medication intake and time recording on the day before the visit. Please also refer to Section 6.2.2.

[redacted]

[17] Study completion of patient participation also needs to be indicated in the eCRF if the patient withdraws prematurely following randomization (see Section 3.3.4).

[18] QuantiFERON® TB test and HBsAg test

[19] If the last day of trial medication intake is different from the EOT visit, the date of the last day of trial medication intake will be used for calculation of the FU visit dates

[20] After the individual patient's end of the trial the investigator should report only any occurrence of cancer, related SAEs and related AESIs of which the investigator may become aware of and only via the SAE form, please see section 5.2.6.2.1.

[21] Screening visit should be performed in two visits. After Informed consent is obtained, fundus photography should be performed and sent to central reading service. If patient is eligible based on the DRSS grading, the patient should return to complete the rest of the screening. In case of scheduling difficulty for certain patients, screening can be performed in one visit. If screening is done as one visit, fundus photography should be performed in line with other ophthalmological examinations.

[22] Alcohol, caffeine and tobacco at screening, Alcohol and caffeine at other visits.

[23] Refer to Section 6.2.1 for re-screening and re-test.

[24] For all ocular AEs (marked as Ocular Event in the CRFs), ocular symptoms present at the time of the event must be reported on the Ocular Symptoms CRF page, including red and/or dry eye, eye pain, flashing lights, floaters, photophobia and watering eyes.

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
ALT	Alanine transaminase, SGPT
AMP	Auxiliary medicinal product
AST	Aspartate transaminase, SGOT
(s)AOC3	(Soluble) Amine oxidase copper-containing 3
AUC	Area under the curve
BCVA	Best Corrected Visual Acuity
BI	Boehringer Ingelheim
BLQ	Below the lower limit of quantification
CA	Competent authority
CI-DME	Center-involved diabetic macular edema
CKD-EPI	Chronic Kidney Disease Epidemiology Collaboration
CML	Clinical Monitor Local
CNV	Choroidal neovascularization
CRA	Clinical Research Associate
CRC	Central reading center
CRO	Clinical Research Organization
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CYP	Cytochrome P450 protein
DILI	Drug-induced liver injury
DM	Diabetes mellitus
DME	Diabetic macular edema
DR	Diabetic retinopathy
DRSS	Diabetic Retinopathy Severity Scale
ECG	Electrocardiography
eCRF	Electronic case report form
EDC	Electronic data capturing
EDTA	Ethylenediaminetetraacetic acid
eGFR	Estimated glomerular filtration rate
EOT	End of treatment
ERG	Electroretinography
ETDRS	Early Treatment Diabetic Retinopathy Study
EudraCT	European clinical trials database
[redacted]	[redacted]
FAS	Full Analysis Set
FU	Follow-up
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
HbA1c	Glycosylated hemoglobin
HIV	Human Immunodeficiency Virus
IB	Investigator's Brochure

ICF	Informed Consent Form
IEC	Independent Ethics Committee
IOP	Intraocular pressure
IRB	Institutional Review Board
IRMA	Intraretinal microvascular abnormalities
IRT	Interactive Response Technology
ISF	Investigator Site File
IVT	Intravitreal treatment
LC-MS/MS	Liquid chromatography tandem mass spectrometry
M	Metabolite(s)
MAO-B	Monoamine oxidase B
MedDRA	Medical Dictionary for Regulatory Activities
MMRM	Mixed-effect Model for Repeated Measures
MRD	Multiple raising dose
NOA	Not analyzed
NOAEL	No Observed Adverse Effect Level
NOR	No valid result
NOS	No sample available
NPDR	Non-proliferative diabetic retinopathy
[redacted]	[redacted]
OIR	Oxygen induced retinopathy
OPU	Operative Unit
PD	Pharmacodynamic
PDR	Proliferative diabetic retinopathy
[redacted]	[redacted]
p.o.	per os (oral)
PRP	Panretinal photocoagulation
q.d.	quaque die (once a day)
QT	Sum of QRS complex, ST segment and T wave on ECG
QTc(V, F)	Heart-rate corrected QT interval (V=using Van de Water's formula, F=using Fridericia's formula)
REP	Residual Effect Period
RIMA	Reversible inhibitor of MAO-A
PTM	Planned time
SAE	Serious Adverse Event
[redacted]	[redacted]
SOP	Standard operating procedure
SRD	Single raising dose
SSAO	Semicarbazide-sensitive amine oxidase
STZ	Streptozotocin
SUSAR	Suspected Unexpected Serious Adverse Reactions
TCM	Trial Clinical Monitor
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper Limit of Normal
VA	Visual acuity

VAP-1	Vascular adhesion protein-1
VEGF	Vascular endothelial growth factor
WOCBP	Woman of childbearing potential

1. INTRODUCTION

Boehringer Ingelheim (BI) is developing BI 1467335, an oral, small-molecule inhibitor of amine oxidase copper-containing 3 (AOC3) also known as vascular adhesion protein-1 (VAP-1) and semicarbazide-sensitive amine oxidase (SSAO) for the indication non-proliferative diabetic retinopathy (NPDR) without center-involved diabetic macular edema (CI-DME).

1.1 MEDICAL BACKGROUND

Diabetes mellitus (DM) denotes a heterogeneous group of disease which share common elements of hyperglycemia due to lack of insulin (Type 1) or glucose intolerance due to insulin deficiency, impaired effectiveness of insulin action, or both (Type 2). The chronic hyperglycaemia of diabetes is associated with long-term damage, dysfunction and failure of various organs, foremost the eyes, kidneys, nerves, heart, and blood vessels.

In 2015, about 415 million people suffered from diabetes worldwide (of which 95% had Type 2 diabetes), and this number is predicted to increase to 642 million patients by the year 2040 with particularly large increases in prevalence observed in the developing world [R16-4703]. Duration of diabetes is a major risk factor associated to the development of diabetic retinopathy (DR). In the USA, the prevalence rate of DR is estimated at 28.5% of the patients with diabetes aged 40 and older [R16-3206, R12-1768]. Worldwide prevalence is estimated at 34.6%. Approximately 10% (range between 5-15%) of the patients with diabetes also suffer from diabetic macular edema (DME). DME is the leading cause of visual loss in the diabetic population. It affects central vision and can lead to decline in vision ranging from slight visual blurring to blindness, substantially affecting independence and quality of life. In about 20-25% of the patients with DME, vision is impaired to a level of 20/40 or worse.

The molecular mechanisms by which diabetes leads to DR and DME includes possible roles for hyperglycemia-induced oxidative stress, polyol pathway activation, and production of advanced glycation end products [R17-0333]. However, the exact mechanism is unclear. At the early phase of the disease the patient might be asymptomatic and the retina appear to be normal on clinical routine examination, however, on more detailed testing, the retinal thickness is reduced due to neuronal loss, and the color vision and contrast sensitivity are all abnormal. In the NPDR stages, the vascular retina begins to become abnormal, the vascular wall becomes weaker, and small microaneurysms are formed (this is mild NPDR). These microaneurysms start to leak fluid into the retina, leading to the formation of exudates and further dysfunction of the retinal neurons. Some of retinal blood vessels start to become occluded and localised hypoxia endure. Vascular sluggish leads to venous changes and haemorrhages, whilst hypoxia induces new vessel formation, initially in form of intraretinal microvascular abnormalities (IRMA) (this is moderate or severe NPDR) and eventually neovascularisation outside the retina (proliferative diabetic retinopathy, PDR).

Patients with NPDR without center-involved DME (CI-DME) are in general not displaying visual impairment. Visual impairment usually occurs with the development of CI-DME. It is important to distinguish DME and CI-DME in terms of treatment, as the latter is usually treated with anti-vascular endothelial growth factor (anti-VEGF). While DME is known to

occur at any point during the course of DR, it is associated with the degree of diabetic retinopathy that is present: Visual function is usually assessed by testing visual acuity (VA) using specialized reading charts (e.g. the Early Treatment Diabetic Retinopathy Study (ETDRS) chart and Snellen acuity chart). The term best corrected visual acuity (BCVA) means the best possible vision achieved by the patient after corrective prescription glasses are used. Snellen acuity chart is commonly used in optician shop for prescription glasses, however, ETDRS chart is becoming the gold standard for clinical trial (e.g. the ETDRS visual acuity score of 85 or Snellen 20/20 representing normal vision).

As vision is still good in patients with NPDR without CI-DME, the usual standard of care is currently observation until either CI-DME or PDR develops. Upon onset of CI-DME, intravitreal injection with anti-VEGF therapy is indicated, such as aflibercept (Eylea®) or ranibizumab (Lucentis®). Patients who progress to PDR without DME are indicated for panretinal photocoagulation (PRP), which is associated with an initial vision loss but better long-term effects on vision compared to no treatment. Therefore, it is recommended to initiate PRP only in specific cases with severe or very severe NPDR [R17-0368].

Ranibizumab (Lucentis®) was recently approved by the FDA for treatment of DR with and without DME. Aflibercept is indicated for treatment of DR is in patients who have CI-DME.

Few trials are currently investigating treatment options for patients with NPDR who do not have CI-DME. One trial is the EUROCONDOR study, which investigates the effects of somatostatin and brimonidine (neuroprotective agents) on patients with mild NPDR or absence of DR (i.e. less than level 20 on the severity scale) where anti-VEGF and laser therapy are not indicated. The preliminary results showed topical treatment with somatostatin and brimonidine seems not useful for preventing the development of neurodegeneration, at least in a period of 2 years of follow-up. Topical treatment with somatostatin and brimonidine is effective in arresting the progression of neurodegeneration after excluding patients in the low quartile of IT values (best retinal function). That is, in those patients in whom some degree of neurodegeneration is already present. Somatostatin has a positive effect in microvascular disease by arresting or maintaining the number of microaneurysms in comparison with placebo [R17-1803].

Another ongoing study (recruitment started in January 2016) is Protocol W from the Diabetic Retinopathy Clinical Research Network, [ClinicalTrials.gov identifier: NCT02634333] which will investigate the effect of aflibercept vs placebo on the progression of patients with moderate to severe NPDR (no CI-DME) to PDR or onset of CI-DME. Estimated time of completion of the first primary endpoint (i.e. progression of disease) is 2020.

Lastly, the Panorama study in patients with moderate to severe NPDR without CI-DME has also started in 2016 [ClinicalTrials.gov identifier: NCT02718326]. The primary endpoint is 2-step improvement in Diabetic Retinopathy Severity Scale (DRSS) at 6 and 12 months.

As patients with NPDR without CI-DME generally still have good vision, their disease may go unnoticed in regions with limited check up by ophthalmologists. Retinal camera is now commonly used for screening of diabetic patients, and identification of these patients is now common in developed nations. Furthermore, it is expected that smartphones with specialized

lenses can image the retina, which will allow easier detection of DR in the coming years. Normally, NPDR patients will progress to proliferative stages of the disease or onset of CI-DME, triggering treatment with PRP, intravitreal injections with anti-VEGF therapies and/or focal/grid photocoagulation therapy [P12-13318]. Anti-VEGF injections are invasive and expensive, and more importantly patients need frequent monitoring and multiple visit to the retinal specialists. On average, patients with CI-DME need 9 to 10 injections in the first 12 months of treatment [R15-5225]. Laser treatment for PDR, especially PRP, is associated with risks of developing retinal side effects, including peripheral and central visual field loss, and mild visual loss. Furthermore, despite these treatments, many patients would still have bleeding inside the eye leading to visual loss from a few days to a few months, and about 15% of patients required surgical removal of the blood, risking significant visual loss [R17-0293].

Therefore, there is a great need for medications, in particular for patients with NPDR without CI-DME, which are non-invasive such as an oral compound, which will slow progression or even reverse the retinal damage. A 2-step improvement of DRSS was shown to be possible by monthly injection of anti-VEGF agents in patients with moderate or severe NPDR as well as CI-DME [R17-0367]. The study was aimed to treat CI-DME, but the improvement of the retinopathy was a bonus. The FDA approved the anti-VEGF agents as a treatment of diabetic retinopathy in patients with CI-DME.

The moderately severe / severe NPDR without CI-DME group is considered to be the most appropriate target group. Patients with CI-DME and / or PDR, would normally be treated with anti-VEGF agents and / or PRP laser. In patients with milder NPDR, it is more difficult to get improvement due to the ceiling effect.

Treatment with an oral AOC3 inhibitor is anticipated to become first-line therapy for patients with moderate / severe NPDR without CI-DME. There are current studies using anti-VEGF agents to treat these target patients using 2 steps improvement of DRSS as an endpoint.

1.2 DRUG PROFILE

AOC3 is a glycosylated trans-membrane protein with oxidative activity towards primary amines [R15-6139]. It is mainly expressed on endothelial cells, smooth muscle cells and adipocytes [R15-5788]. In the eye, AOC3 immunoreactivity can be found in the arteries of the optic nerve, retina and choroid [R17-1787]. Under inflammatory conditions, the protein is exposed at the extracellular membrane of endothelial cells towards the lumen of the vessels, where immune cells can recognize and bind to the extracellular part of the enzyme, which leads to e.g. reduced rolling velocity of neutrophils on the endothelium [R15-2803]. The enzymatic activity is essential for the support of immune cell transmigration towards the interstitium. Besides the membrane-bound form, a soluble form of AOC3 (sAOC3) can be found in plasma as well as in the vitreous. The sAOC3 consists mainly of the extracellular enzymatic domain of AOC3. Shedding from the membrane is catalyzed by metallo-proteinases, which are increased under endothelial stress and inflammation [R15-5787]. Elevated levels of sAOC3 can be found in patients suffering from diabetes, atherosclerosis, myocardial infarction and nonalcoholic steatohepatitis. Especially in proliferative diabetic

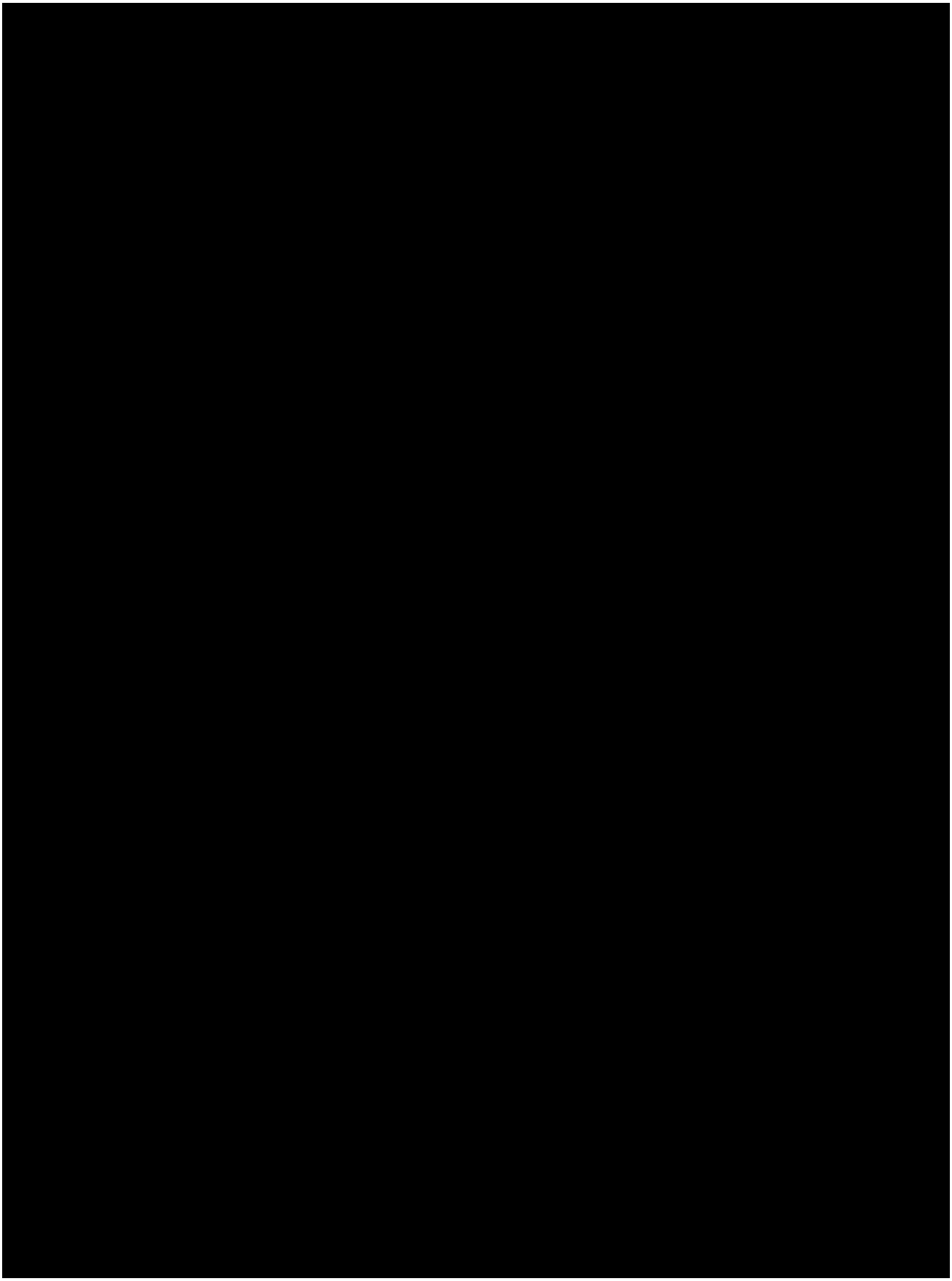
retinopathy, soluble AOC3 is elevated in plasma as well as in the vitreous of patients [R15-5787].

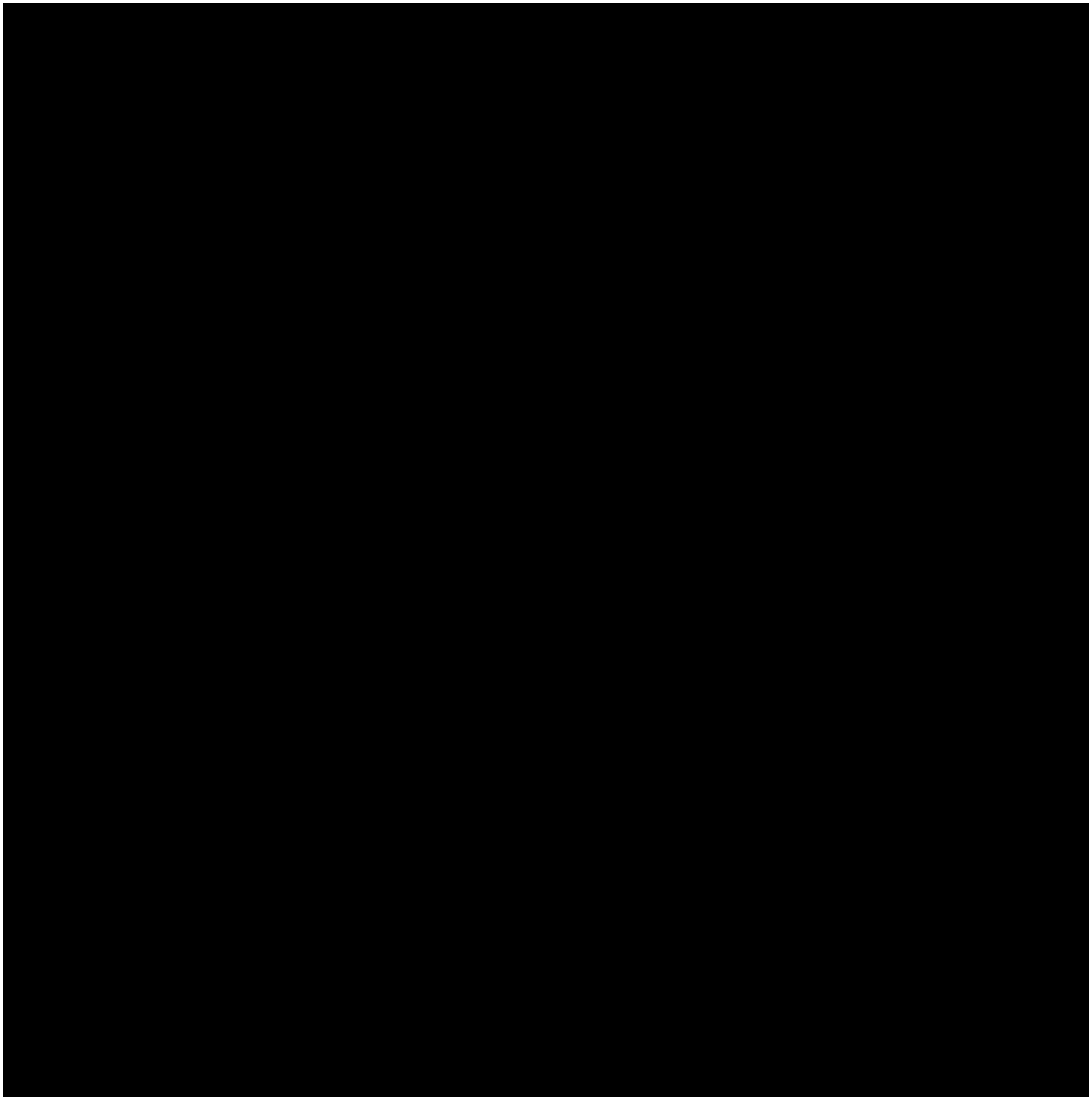
In preclinical studies, it was shown that AOC3 is involved in the migration of lymphocytes, granulocytes, leukocytes and macrophages to the site of inflammation [R15-6045; R15-6047; R15-6048; R15-5654]. Inhibition of AOC3 by an antibody or small molecule reduced inflammation in a variety of disease models [R15-1863; R15-6059; R15-1868; R15-6056; R15-6058]. In support of the role of AOC3 as a mediator of inflammation, AOC3-deficient mice have impaired rolling and transmigration of leukocytes and reduced recruitment of granulocytes to sites of inflammation [R15-6045; R15-2803].

Several literature experiments with AOC3 enzyme inhibitors in pre-clinical models of diabetes induced vascular permeability and diabetic retinopathy have been published. A model of streptozotocin (STZ) induced diabetes exhibited increased plasma sAOC3 levels as well as retinal vascular permeability as measured by fluorescein extravasation [R15-1862]. Treatment of rats with reversible AOC3 inhibitors reduced the vascular permeability in a dose dependent manner. In a model of laser-induced choroidal neovascularization (CNV), treatment with AOC3 inhibitor reduced macrophage infiltration in the lesions as well as the lesion size in a dose dependent manner [R16-5320]. Further, the pathological neoangiogenesis could be reduced in an oxygen induced retinopathy (OIR) mouse model by the treatment with reversible AOC3 inhibitors [R17-1786].

The observed effects of BI 1467335 on models of ocular diseases argue for an improvement of neuronal function and prevention of pathologic neoangiogenesis by AOC3 inhibition.

The data therefore argue for the treatment of patients with NPDR and progression to PDR with BI 1467335 for the prevention of loss of visual acuity due to neuronal dysfunction and neovascularization.





For a more detailed description of the BI 1467335 profile please refer to the current Investigator's Brochure (IB) which is included in the Investigator Site File (ISF).

1.3 RATIONALE FOR PERFORMING THE TRIAL

The current standard of care for patients with NPDR without DME is mostly observation until the disease progresses significantly, while the treatment options in these advanced stages are either aggressive (laser treatment) and can damage the retina, or they are costly and invasive (anti-VEGF injection therapy). Therefore, there is a large unmet medical need for:

- Drugs affecting disease progression and/or addressing the neurodegenerative aspects of NPDR and PDR, thereby delaying the complications associated to progression to/of PDR, or progression to CI-DME and thereby delaying or preventing the need for intravitreal injections/focal photocoagulation or PRP
- Improved/non-invasive route of administration (i.e. orals, topicals)
- Treatment options for patients refractory to anti-VEGF
- Safer treatment options (i.e. no damage to chorioretinal structures)

Thus an oral medication capable to treat the moderate/severe stages of NPDR could fill an important gap in which patients with NPDR could receive treatment and thereby their disease progression could be slowed or even reversed.

This study is designed to assess the safety and tolerability of the oral compound BI 1467335 and to investigate the changes in DR lesion morphology as assessed by the DRSS and visual acuity.

[redacted]

1.4 BENEFIT - RISK ASSESSMENT

BI 1467335 has not been previously investigated in patients with NPDR or other ocular diseases, and the sponsor is not aware of any clinical studies on the effects of orally administered AOC3 inhibitors in patients with NPDR. Although NPDR without CI-DME is currently only observed until either CI-DME or PDR develops, a safe and easy to administer compound to slow further disease progression would be beneficial to avoid invasive treatments in advanced stages. Treatments such as intravitreal injections require multiple injections over time and come with procedural risks, such as endophthalmitis, vitreous hemorrhage, retinal detachment, traumatic cataract, and increased intraocular pressure (IOP).

[redacted]

[redacted]

Planned treatment is 12 weeks with 10 mg q.d. The 10 mg dose was selected based on the available data and currently available PK and toxicology data support the administration of BI 1467335 for 12 weeks. The planned 12 week treatment duration is considered sufficient to observe potential impact of BI 1467335 in patients with NPDR without CI-DME.

This study also includes a 12-week follow-up observation period after stopping the trial medication. While, based on its half-life, BI 1467335 is expected to be eliminated from the blood much earlier, the 12-week follow-up was chosen due to irreversible binding of the BI 1467335 to its target. This 12-week follow-up would allow observation of any prolonged effects of BI 1467335.

This is a newly developed drug at an early stage of testing and therefore an individual benefit cannot be guaranteed. As with any new drug, unknown or unexpected adverse events may occur. Patients enrolled in this study will have a 50% chance of receiving placebo or receiving the active drug. It is not known whether there will be any benefit on objective parameters such as the level of severity determined by the DRSS or on clinical symptoms such as visual acuity for those patients following 12 weeks of treatment with BI 1467335. This is a trial of short duration, and the assignment to the placebo arm is not associated with a higher risk to the patient due to slow progression of the NPDR. However, both patients on active drug as well as patients on placebo may receive rescue treatment according to local clinical standard of care if their visual acuity worsens significantly or if a clinically significant progression of NPDR is detected during the trial (please also refer to Section 4.2.1).

While individual patients may benefit through study procedures (monthly assessment of disease severity, safety monitoring), they may also contribute to a better understanding of the underlying disease, disease management, or better drug development in the future.

Ophthalmological exams used in this study are non-invasive and are standard procedures used in ophthalmological practice and will be used in this study according to usual medical practice. Some of the examinations, like BCVA, are used commonly even in healthy people for visual correction, [redacted]

[redacted]

[redacted]
will be excluded from further examinations (see Section 3.3.4).

Some of the examinations require pupil dilatation, which may lead to temporary light sensitivity and impaired vision. This is frequently done with ophthalmological exams and ophthalmological clinics should have sufficient experience for handling this (patient instructions, disposable eye coverings, etc.).

[redacted]

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 5.2.6.1.4, adverse events of special interest.

Continuous safety monitoring will be performed in regular Medical Quality Review Meetings according to the sponsor's Standard operating procedures (SOPs) (please refer to Section 8.7).

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective is to evaluate ocular and systemic safety and tolerability of BI 1467335 as well as whether BI 1467335 monotherapy has a potential to improve retinal lesions in patients with moderately severe NPDR (DRSS level 47) or severe NPDR (DRSS level 53), without CI-DME.

2.1.2 Primary endpoint

- Ocular safety of BI 1467335 as assessed by the proportion of patients with any ocular adverse events (according to Common Terminology Criteria for Adverse Events (CTCAE) as defined in Section 5.2.6.1.5) over the on-treatment period (over 24 weeks) (see Section 7.3.4).
  This is no safety issue.

2.1.3 Secondary endpoints

- Proportion of patients with at least 2 steps improvement in the study eye on the DRSS at week 12 compared to baseline.
- The proportion of patients with adverse events other than ocular adverse events over the on-treatment period (over 24 weeks) (according to CTCAE).
  This is no safety issue.

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL TRIAL DESIGN AND PLAN

The trial is a randomized, double-masked, placebo-controlled, parallel-group, multicenter proof of clinical principle study. Patients will be enrolled into the study once they have signed the informed consent form. Due to high probability of patients screen failing due to DRSS grading on fundus photography, screening should be performed in two parts. Fundus photography should be performed first, and if patients are eligible based on the fundus photography results, patients should return to complete the rest of the screening examinations. In case of scheduling difficulty for certain patients, screening can be performed in one visit. Patients become eligible for randomization if they have met all inclusion and none of the exclusion criteria. Randomized patients will take 10 mg q.d. of BI 1467335 or matching placebo from Day 1 to Day 85 (12 weeks). Following conclusion of a 12-week treatment period, or upon withdrawal from trial medication, all patients will be eligible to receive local standard of care therapy at the discretion of the investigator. Patients will be followed up at three follow-up visits until twelve weeks after the End of treatment visit (EOT).

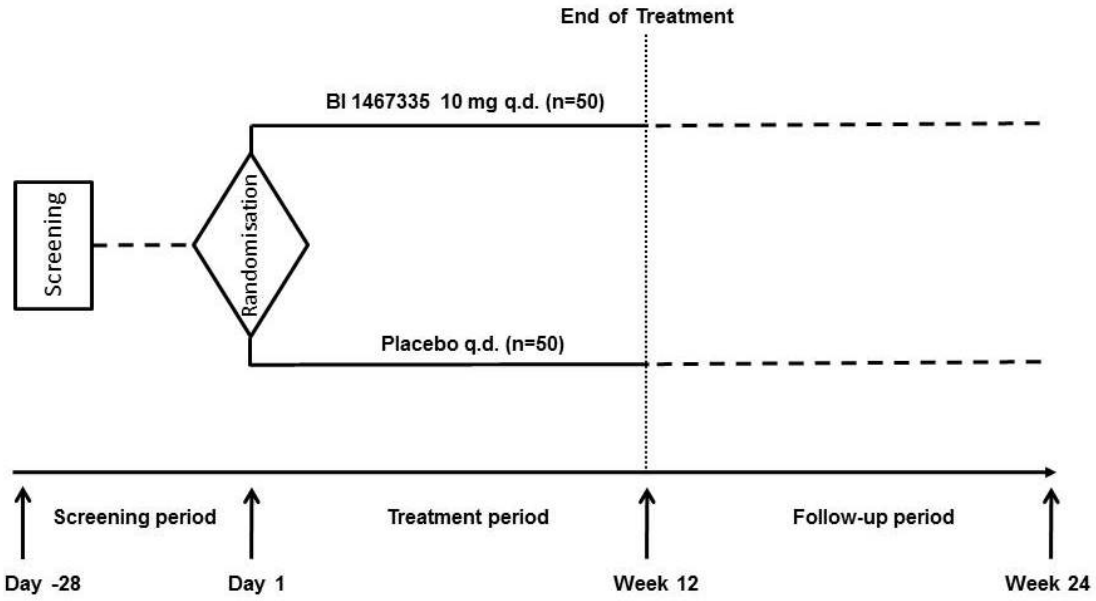


Figure 3.1: 1 Trial design

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

A randomized, double-masked placebo-controlled design is chosen for this trial in order to evaluate safety, tolerability, pharmacokinetics and pharmacodynamics of 10 mg q.d. of BI 1467335 in patients with moderately severe NPDR (DRSS level 47) or severe NPDR (DRSS level 53) without CI-DME. Because currently there is no efficacious therapy available

for this patient group at this stage of the disease, this trial aims to improve the level of disease severity at early time points in the course of the disease.

The treatment period of 12 weeks is deemed adequate to evaluate safety and tolerability, and is covered by currently available toxicology data.
A placebo control arm was chosen for this trial in order to compare BI 1467335 and placebo regarding safety and tolerability in patients with NPDR. Approximately equal numbers of patients will be randomized to both treatment groups. Randomization will be stratified by the level of disease severity (please refer to Section 7) based on DRSS levels 47 or 53 as this may have impact on the expected effects regarding the primary outcome.

3.3 SELECTION OF TRIAL POPULATION

A sufficient number of male and female patients with DM either type 1 or type 2 and NPDR without CI-DME will be screened to ensure the randomization of 100 patients from approx. 20-25 study sites. For consistent evaluation of endpoints only prequalified study sites will participate, and retina images ([redacted] fundus photography, [redacted] will be evaluated by an independent central reading center (CRC).

It is expected that around 4-5 patients will be randomized at each study site. If enrolment is delayed, additional sites may be recruited. Permission to enroll more than 15 patients per site must be obtained from the Trial Clinical Monitor (TCM) at BI. This will only be allowed after a careful review of the enrolment status and of the site.

Screening of patients for this trial is competitive across all countries within the study, 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.

Re-screening and re-testing is described in Section 6.2.

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

If a patient is enrolled in error (does not meet all inclusion criteria or meets one or more exclusion criteria on the day of enrolment), the sponsor should be contacted immediately.

3.3.1 Main diagnosis for trial entry

Patients with NPDR without CI-DME at the Screening visit are eligible for inclusion if they fulfil all of the inclusion criteria (Section 3.3.2) and none of the exclusion criteria (Section 3.3.3). Only one study eye per patient may be enrolled according to Section 3.3.1.1 (Study eye criteria). Ophthalmologic evidence of NPDR without CI-DME with DRSS levels 47 or 53 in the study eye needs to be confirmed by the CRC.

Please refer to Section 8.3.1 (Source Documents) for the documentation requirements pertaining to the inclusion and exclusion criteria.

3.3.1.1 Study eye criteria

The following procedure is to be applied for the selection of the study eye at baseline:

- If only one eye meets all of the inclusion and none of the exclusion criteria, this eye will qualify for the study eye. The fellow eye will be examined for evaluation of safety.
- If both eyes in an individual patient meet all of the inclusion criteria and none of the exclusion criteria, the eye with the higher (=worse) DRSS level at screening will qualify for the study eye.
    - If both eyes show the same DRSS level, the eye with the worse BCVA letter score (as assessed by ETDRS chart at screening) will qualify for the study eye;
    - If both eyes show the same DRSS level and the same BCVA letter score, the eye with the clearer lens will qualify for the study eye;
    - If both eyes show exactly the same conditions mentioned above, the left eye will be selected to be the study eye.

3.3.2 Inclusion criteria

1. Of legal age (according to local legislation, usually ≥ 18 years) at screening
2. Male or female patients. Women of childbearing potential (WOCBP)[1] must be ready and able to use two methods of contraception with at least one of them being a highly effective method of birth control per ICH M3 (R2) that result in a low failure rate of less than 1% per year when used consistently and correctly. A list of contraception methods meeting these criteria is provided in the patient information.
3. Diagnosis of diabetes mellitus (type 1 or type 2):
    - Documented diabetes by American Diabetes Association (ADA) and/or World Health Organization criteria
4. Glycosylated hemoglobin (HbA1c) ≤ 12% at screening
5. Non-proliferative diabetic retinopathy (NPDR) without center-involved diabetic macular edema (CI-DME) in the study eye at screening with NPDR level 47 or level 53, as determined by the CRC by using the DR severity scale (DRSS)
6. Best corrected visual acuity ETDRS letter score ≥ 70 letters in the study eye at screening
7. Media clarity, pupillary dilation and individual cooperation sufficient for adequate retinal examination including fundus photographs [redacted]
8. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the trial

[1] A woman is considered of childbearing potential (WOCBP), i.e. fertile, following menarche and until becoming post-menopausal unless permanently sterile.
Permanent sterilisation methods include hysterectomy, bilateral salpingectomy and bilateral oophorectomy.
Tubal ligation is NOT a method of permanent sterilisation.
A postmenopausal state is defined as no menses for 12 months without an alternative medical cause.

3.3.3 Exclusion criteria

1. Cataract surgery performed within 6 months prior to screening or planned during the trial in the study eye; or any additional eye disease in the study eye that, in the opinion of the investigator, could compromise or alter visual acuity during the course of the study (e.g. vein occlusion, uncontrolled intraocular pressure (IOP) >24 mmHg on optimal medical treatment, glaucoma with visual field loss, uveitis or other ocular inflammatory disease, vitreomacular traction, monocular vision, history of ischemic optic neuropathy, or genetic disorders such as retinitis pigmentosa)
2. Active center-involved DME (CI-DME) on clinical examination and OCT central subfield thickness in the study eye above 300 µm as measured by Optovue OCT or above 320 µm as measured by Heidelberg OCT.
3. Anterior segment and vitreous abnormalities in the study eye that would compromise the adequate assessment of the best corrected visual acuity or an adequate examination of the posterior pole
4. Evidence of neovascularization on clinical examination including active neovascularization of the iris (small iris tufts are not an exclusion) or angle neovascularization in the study eye, ruled out by gonioscopy (documented in the last 4 weeks before screening or performed at screening)
5. Prior pan-retinal photocoagulation (defined as ≥ 100 burns placed previously outside of the posterior pole) in the study eye
6. Treatment of either CI-DME or DR with macular laser within 3 months prior to screening, or intraocular injections of medication within 6 months prior to screening, and no more than 4 prior intraocular injections in the study eye at any time in the past
7. Patients treated with MAO inhibitors or drugs that may have potential side effects due to MAO inhibition, as described in Section 4.2.2.1.
8. Current or planned, during the trial, use of medications known to be toxic to the retina, lens or optic nerve, or cause vision loss (see Section 4.2.2.1)
9. Patients who must or wish to continue the intake of other restricted medications (see Section 4.2.2.1) or any drug considered likely to interfere with the safe conduct of the trial
10. Estimated Glomerular filtration rate (eGFR) < 60 mL/min/1.73m^2 calculated by Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) equation at screening, or where the investigator expects filtration rate is likely to drop below 60 mL/min/1.73m^2 during the trial
11. Alanine transaminase (ALT) or aspartate transaminase (AST) greater than 2.0-fold the upper limit of normal, or total bilirubin > 1.5x upper limit of normal.
12. Uncontrolled arterial hypertension defined as a single measurement of systolic blood pressure >180 mmHg, or two consecutive measurements of systolic blood pressure > 160 mmHg and/or diastolic blood pressure >100 mmHg on optimal medical regimen at screening. If blood pressure is brought to ≤ 160/100 mmHg by antihypertensive treatment until randomization, individual can become eligible.

13. Wolff-Parkinson-White Syndrome, baseline QTcF > 450 ms (Fridericia's formula), family history of long QT, or on medication prolonging QT time at screening or planned initiation during the trial
14. Diagnosis of a serious or unstable systemic or eye disease and other conditions that, in the clinical judgment of the investigator, are likely to interfere with the analyses of safety and efficacy in this study. Patients with an expected life expectancy of less than 2 years are also excluded.
15. Active known or suspected chronic or relevant acute infections, such as HIV (Human Immunodeficiency Virus)\viral hepatitis, or tuberculosis. QuantiFERON® TB test and HBs Ag test will be performed during screening. Patients with a positive test result may participate in the study if further work up (according to local practice/guidelines) establishes conclusively that the patient has no evidence of active infection.
16. Any documented active or suspected malignancy or history of malignancy within 5 years prior to screening, except appropriately treated basal cell carcinoma of the skin or in situ carcinoma of uterine cervix.
17. Chronic alcohol or drug abuse or any condition that, in the investigator's opinion, makes them an unreliable study participant or unlikely to complete the trial
18. Known hypersensitivity to any component of the trial drug and/or allergy to fluorescein dye
19. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomization or planned during the trial, e.g. hip replacement
20. Currently enrolled in another investigational drug trial, or less than 30 days or 5 times half-life of the investigational drug, whichever is longer, since ending another investigational drug trial from the screening visit in this trial or receiving other investigational treatment(s); patients participating in a purely observational trial will not be excluded.
21. Previous randomization in this trial
22. Women who are pregnant, nursing, or who plan to become pregnant while in the trial
23. Any other clinical condition that, in the opinion of the investigator, would jeopardize patient safety while participating in this clinical trial.

3.3.4 Withdrawal of patients from therapy or assessments

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

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

Measures to control the withdrawal rate include careful patient selection, appropriate explanation of the trial requirements and procedures prior to randomization, 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 Electronic Case Report Form (eCRF). If the reason for discontinuation is death, this should be reported on the SAE form as well, regardless of causal relationship.

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 (see Section 4.2.2.1)
- The patient can no longer be treated with trial medication for other medical reasons (such as eye surgery, adverse events, other diseases, or pregnancy)
- Worsening of the disease that requires eye treatment or procedures prohibited in the trial (see Section 4.2.2.1)
- 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.
- Patient develops QTcF > 500 ms or change from Visit 1 > 60 ms.

Given the patient's agreement, the patient will undergo the procedures for early treatment discontinuation and follow up as outlined in the Flow Chart and Sections 6.2.2. and 6.2.3.

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

If a patient becomes pregnant during a trial, study drug must be stopped and patient will follow the same procedure for early treatment discontinuation as outlined above. After the last study follow-up visit, the patient will be followed up until birth or otherwise termination of the pregnancy. Patient's data will be collected and reported in the clinical trial report until last patient last visit and any events thereafter, including outcome of the pregnancy, will be reported in the BI Pharmacovigilance database.

If patient develops clinically significant adverse reaction, judged by the investigator, related to FA procedure, further FA will not be performed for that patient. Patient may continue in the study based on the investigator's assessment.

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 be involved in the discussion with the patient and 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

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 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).

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

4.1.1 Identity of the Investigational Medicinal Products

Table 4.1.1: 1 Test product

Substance:	BI 1467335
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim
Unit strength:	5 mg
Posology	2 tablets once daily
Route of administration:	Oral

Table 4.1.1: 2 Comparator product

Substance:	Placebo to match BI 1467335
Pharmaceutical formulation:	Film-coated tablets
Source:	Boehringer Ingelheim
Unit strength:	Not applicable
Posology	2 tablets once daily
Route of administration:	Oral

4.1.2 Selection of doses in the trial and dose modifications

The pre-clinical data suggests that AOC3 inhibition of 90% or higher is sufficient to translate into a clinical effect on retinal pathology in DR. [redacted]

Thus, 10 mg is a sufficiently high dose to test the potential clinical effect in this exploratory study.

4.1.3 Method of assigning patients to treatment groups

All treatments will be double-masked as to be indistinguishable for the patient as well as for the investigator. After assessment of all inclusion and exclusion criteria, each eligible patient

will be randomized at Visit 2a to receive BI 1467335 or placebo in a 1:1 ratio according to a randomization plan. The assignment will occur in a masked fashion via Interactive Response Technology (IRT). To facilitate the use of the IRT, the investigator will receive all necessary instructions.

Note that the medication number is different from the patient number. Site personnel will enter the medication number in the eCRF.

4.1.4 Drug assignment and administration of doses for each patient

IRT will allocate medication kit numbers at Visit 2a, 3 and 4a. The medication number will be different at each visit. At each visit, the medication box with corresponding medication number must be dispensed to the patient. The amount of trial medication dispensed and returned will be recorded on drug accountability forms.

The first trial medication dose at Visit 2a is given to the patient by the site staff at the investigational site, and trial medication is then dispensed to the patient for home administration (please refer to Section 4.1.4.2).

The medication will be administered once daily, beginning on Day 1 (Visit 2a) until the day of EOT Visit (Day 85 according to the visit schedule), unless patient discontinues prematurely. All treatments will consist of two tablets (BI 1467335 or placebo) to be taken orally approximately at the same time each day. This will not be changed during the entire study treatment period (Visit 2a to EOT).

4.1.4.1 Trial medication administration at the study site

At Visits 2a, 3, 4a and EOT the administration of trial medication is done at the study site under the supervision of the investigator or qualified site staff. Two tablets of the trial drug will be administered with a glass of water after predose blood sampling. The actual visit date and time of trial drug administration at the visit will be recorded in the eCRF at each visit.

At Visits 2a, 3 and 4a, new trial medication boxes will be used for administration of the morning dose at the clinical site and will be dispensed for home administration. At EOT visit trial medication will be taken from the box that the patient returns to the site.

Patients who erroneously take the morning dose of trial medication before coming to the clinic at visits 3 and EOT (with scheduled PK samples) should have the visit rescheduled as soon as possible, ideally on the following day.

The site staff will instruct and remind the patients:

- how to fill in the trial medication diary and to bring the diary to the next visit
- not to take their trial medication at the morning of the next visit as they will be dosed while at the sites after blood samples are taken (as described in Section 6.2.2)
- to bring all trial medication blisters within the box (regardless of whether empty or not) back to the investigational site

4.1.4.2 Trial medication administration at days without site visits

At home, trial medication will be self-administered by the patients. Patients are to be instructed to take the tablets orally with water in the morning at approximately the same time every day. Medication can be taken with or without food. Patients will record the administration dates and times of all doses with the help of a trial drug diary as outlined in the Flow Chart and in Section 6.2.2.

If a dose is missed by more than 8 hours, that dose should be skipped and the next dose should be taken as scheduled. No double doses should be taken and dose reductions are not permitted.

In case medication runs out (or is lost) at home, the patient will go to the site for an additional visit in order to be provided with replacement medication. If a reserve trial medication is needed, the investigator or authorized site staff will assign reserve trial medication via the IRT system.

Patients should be instructed to bring all unused drug and empty study blisters to the study site at every visit during the treatment period.

4.1.5 Masking (blinding) and procedures for unmasking

4.1.5.1 Masking

Patients, investigators and everyone involved in trial conduct or analysis or with any other interest in this double-masked trial will remain masked with regard to the randomized treatment assignments until after database lock with the exceptions noted below. Please refer to Section 4.1.5.2 for rules of breaking the code for patients in emergency situations.

The randomization code will be kept secret by Clinical Trial Support up to database lock. The randomization codes will be provided to bioanalytics prior to last patient out to allow for the exclusion from the analyses of PK samples taken from placebo patients and to a member of the team conducting the interim PK/PD analysis. Bioanalytics will not disclose the randomization code or the results of their measurements until the trial is officially unmasked.

If a planned interim PK/PD analysis is conducted, access to unmasked data required to conduct the planned interim PK/PD analysis will be restricted to members of the trial and project teams who are not directly involved with study conduct. The logistical aspects of conducting the interim PK /PD analysis, and the plan to access interim results will be described in the Interim Analysis Logistics Plan and Results Access Plan.

4.1.5.2 Unmasking and breaking the code

Emergency unmasking will be available to the investigator / pharmacist / investigational drug storage manager via IRT. It must only be used in an emergency situation when the identity of the trial drug must be known to the investigator in order to provide appropriate medical treatment or otherwise assure safety of trial participants. The reason for unmasking must be

documented in the source documents and/or appropriate eCRF page along with the date and the initials of the person who broke the code.

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

4.1.6 Packaging, labelling, and re-supply

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

All trial medication will be contained in medication boxes identified with the trial number and medication number. Each medication box will contain sufficient BI 1467335 tablets or matching placebo for 28 days treatment plus 7 days reserve.

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

4.1.7 Storage conditions

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

If the storage conditions are found to be outside the specified range, the process outlined in the ISF should be followed.

4.1.8 Drug accountability

The investigator, pharmacist 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 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
- Availability of the curriculum vitae of the Principal investigator
- Availability of a signed and dated clinical trial protocol
- Availability of the proof of a medical license for the Principal investigator,
- Availability of Form FDA 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, pharmacist or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the sponsor or warehouse / drug distribution center or alternative disposal of unused products. If applicable, the sponsor or warehouse / drug distribution center 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 / investigational drug storage manager will maintain records that document adequately that the patients were provided the doses specified by the Clinical Trial Protocol (CTP) and reconcile all investigational products received from the sponsor. At the time of return to the sponsor or appointed CRO, the investigator / pharmacist / 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 Other treatments and emergency procedures

As per judgment of the investigator, administration of local standard of care treatment such as Intravitreal Treatment (IVT) or peribulbar injections, or laser or other surgical treatment is allowed in clinically significant worsening of the disease, and should be considered in the event of vision loss of ≥5 letters.

After the end of treatment with trial medication (EOT Visit), standard of care therapy is at the discretion of the investigator. Standard of care therapy is, for the purpose of the present trial, considered a non-investigational medical treatment.

[redacted] Only products that have marketing authorization in the country must be used and administered according to local requirements. Documentation about administration must be available in source documents and will be recorded in ISF. Any side effects of intravenous fluorescein dye will be described in the Patient Information.

4.2.2 Restrictions, warnings and precautions

4.2.2.1 Restrictions regarding concomitant treatment

The following medications are prohibited 5 weeks prior to BI 1467335 dosing and during study participation. In addition BI 1467335 should be discontinued for at least 14 days prior to starting a chronic treatment with these same agents:

- Antidepressants
    - Tricyclic antidepressants such as butriptyline, clomipramine, imipramine, trimipramine, desipramine, dibenzepin, lofepramine, maprotiline, nortriptyline, amitriptyline, amitriptylinoxide, amoxapine,demexiptiline, dimetacrine, dosulepin,

doxepin, fluacizine, imipraminoxide, melitracen, metapramine, nitroxazepine, noxiptiline, pipofezine, propizepine, quinupramine, amineptine, iprindole, opipramol, tianeptine
    - Selective serotonin reuptake inhibitors (SSRIs) such as fluoxetine, fluvoxamine, sertraline, citalopram, escitalopram and paroxetine
    - Serotonin-norepinephrine reuptake inhibitors (SNRIs) such as venlafaxine, duloxetine, atomoxetine, desvenlafaxine, levomilnacipran, milnacipran, sibutramine
- MAO Inhibitors
    - Nonselective MAO-A/MAO-B inhibitors such as isocarboxazid, nialamide, phenelzine, hydracarbazine and tranylcypromine.
    - Selective MAO-A inhibitors such as bifemelane, moclobemide, pirlindole, and toloxatone.
    - Selective MAO-B inhibitors such as rasagiline, selegiline and safinamide.

The following medications are prohibited 2 weeks prior to BI 1467335 dosing and during study participation:
- Meperidine
- Tramadol
- Methadone
- Propoxyphene
- Dextromethorphan
- Cyclobenzaprine
- Sympathomimetic medications including nasal, oral and ophthalmic decongestants and cold remedies
- Bupropion, triptans (almotriptan, rizatriptan, sumatriptan, zolmitriptan, oxitriptan), linezolide, tedizolid, methylene blue, lithium and pethidine

The following drugs are prohibited during the entire duration of the trial:
- Drugs that may affect the retina or the optic nerve, such as quinolones, thioridazine, deferoxamine, ethambutol or vigabatrin: at the time of screening and during the trial.
- Amidarone, methotrexate, systemic glucocorticoids, tetracyclines, tamoxifen, estrogens (excluding oral contraception), anabolic steroids and valproic acid and any medication which prolongs QT time
- Initiation of intensive insulin therapy (switch from regular injections to pump)

Anti-VEGF injection treatment with aflibercept (Eylea®) or ranibizumab (Lucentis®) in the study eye is not allowed to be given in addition to the trial drug. Use of bevacizumab (Avastin®) is not allowed in either the study eye or in the fellow eye, in addition to the trial drug. If the prohibited anti-VEGF intravitreal treatment has to be started during the study prior to the scheduled end of treatment visit, trial medication has to be stopped and the EOT visit has to be performed.

If patients are taking medication that is a Cytochrome P450 protein (CYP) 2D6 substrate, then the patients should be monitored for possible side effects that may result from potential

drug interaction between such medication and trial medication. A list with medication examples will be provided in the ISF.

4.2.2.2 Precautions on diet and life style

Patients should be advised to avoid the consumption of large amounts of tyramine-rich food while taking BI 1467335, such as:

- Aged cheese
- Aged meats
- Soybean products (Soy sauce)
- Red wine
- Beer
- Yeast products
- St John's Wort
- Pickled herring
- Sauerkraut (fermented cabbage)
- Tryptophan supplements

There are no other restrictions on diet, exercise, alcohol consumption or smoking except that the patient's usual habits, including smoking habits and caffeine intake, should be within acceptable daily amounts and not be drastically changed throughout the study conduct. All patients should be on a stable diet and exercise (life style) regimen according to standard of care throughout the study. Assessing the restrictions on diet and life style of study patients is left to the investigator.

4.2.2.3 Contraception requirements

Women of childbearing potential (WOCBP) must use, during the whole trial, two methods of contraception with at least one of them being 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, as described in the patient information.

4.2.2.4 Restrictions regarding gamete donation

Gamete donation must not be performed within 3 months after the end of treatment.

4.3 TREATMENT COMPLIANCE

Patients are requested to bring all remaining trial medication including empty package material with them when attending visits.

Based on tablet counts, treatment compliance will be calculated as shown in the formula below. Compliance will be verified by the Clinical Research Associate (CRA) authorised by the sponsor.

$$\text{Treatment compliance (\%)} = \frac{\text{Number of tablets actually taken} \times 100}{\text{Number of tablets which should have been taken as directed by the investigator}}$$

If the treatment compliance is not between 80-120%, site staff will explain to the patient the importance of treatment compliance.

5. ASSESSMENTS

5.1 ASSESSMENT OF EFFICACY

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

Centrally collected ophthalmological data (color fundus photography, [redacted] will be transferred from the CRC to the sponsor's database. The local measurement data will remain at the study sites as source documents.

If clinically significant worsening is observed in the assessments of efficacy during the study, it will be reported as adverse events in the eCRF and on the SAE form if applicable (please also refer to Section 5.2.6.1.1).

Color Fundus Photography
Seven-field or modified 4-field digital fundus photographs will be obtained from both eyes by a qualified person according to the imaging manual to collect all data for the assessment of the ETDRS Diabetic Retinopathy Severity Scale (DRSS). The images will be sent to the independent CRC who performs the grading on the basis of the DRSS. This scale evaluates retinal hemorrhages, venous beading and IRMA and divides diabetic retinopathy into 13 levels; this scale can be used to describe overall severity of the retinopathy and change in severity over time. In addition, severity of retinopathy in this eye could be assessed as a risk factor by using this grading system [R17-1872].

[redacted]

[redacted]

Visual Acuity measured by ETDRS letter charts
Best corrected visual acuity (BCVA) will be determined by using the ETDRS visual acuity chart starting at a test distance of 4 meters. The BCVA score is the number of letters read correctly by the patient. The assessment will be performed by a trained person under specified conditions regarding examination room and equipment.

[redacted]

5.2 ASSESSMENT OF SAFETY

For the standardized evaluation of ocular safety parameters a complete eye examination will be performed at every visit (please refer to Section 5.2.5.1) next to efficacy parameters (Section 5.1). In addition, the patients will be asked for symptoms that may have occurred since the last study visit, according to Common Terminology Criteria for Adverse Events (CTCAE, see also Section 5.2.6).

5.2.1 Physical examination

A complete physical examination will be performed at the time points specified in the Flow Chart. It includes at a minimum general appearance, neck, lungs, cardiovascular system, abdomen, extremities, and skin. In addition, further physical examination should be performed if clarification of an AE is necessary. The results must be included in the source documents available at the site.

5.2.1.1 Body weight/height

Measurement of height and body weight will be performed at the time points specified in the Flow Chart. The scale used to capture body weight for each patient should remain consistent during the trial. In order to get comparable body weight values, it should be performed in the following way: Shoes and coat/jacket should be taken off and pockets should be emptied of heavy objects (i.e. keys, coins etc.).

5.2.2 Vital signs

Arterial systolic and diastolic blood pressure, respiratory rate (frequency /min) and pulse rate (palpation of the pulse) will be measured after the patient has rested for at least 5 minutes in the sitting position. Measurement of vital signs should precede blood sampling to avoid the impact of blood sampling on the vital measurements. The measured vital signs will be documented in the source documents and recorded in the eCRF.

5.2.3 Safety laboratory parameters

Safety laboratory parameters to be assessed are listed in Table 5.2.3: 1. The following lab parameters will not be determined at each study visit:

- HbA1c: at Visit 1 (screening), Visit 2a (baseline) and EOT only
- Hepatitis B Surface Antigen (qualitative) at Visit 1 (screening) only
- QuantiFERON®-TB at Visit 1 (screening) only

Laboratory samples will be collected by the trial site at the time points indicated in the Flow Chart. All analyses will be performed by a central laboratory.

Reference ranges, instructions regarding sample collection, details about 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 baseline conditions (at screening) or Adverse Events (after start of screening; please also refer to Section 5.2.6.1.1).

In case the criteria for hepatic injury are fulfilled, a number of additional measures will be performed (please see Section 5.2.6.1.4 and the DILI Checklist provided in the ISF). 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.

Urine parameters will be performed by the central laboratory. The urine sediment examination will only be done if the urine dipstick analysis is abnormal.

Urine pregnancy tests will be performed by the site staff.

Table 5.2.3: 1 Safety laboratory parameters

Hematology	Hematocrit (Hct) Hemoglobin (Hb) MCV (mean corpuscular volume) MCH (mean corpuscular hemoglobin) MCHC (Mean Cellular hemoglobin Concentration) Red Blood Cell Distribution Width (RDW) Red Blood Cell Count (RBC) / Erythrocytes	White Blood Cell Count (WBC) / Leukocytes Platelet Count / Thrombocytes Differential Automatic (relative and absolute count): Neutrophils, Eosinophils, Basophils, Monocytes, Lymphocytes
Coagulation	Activated Partial Thromboplastin Time (aPTT) Prothrombin Time (INR) Fibrinogen	

Table 5.2.3: 1 Safety laboratory parameters (cont.)

Clinical chemistry	Albumin Alkaline phosphatase ALT (alanine transaminase, SGPT) AST (aspartate transaminase, SGOT) γ-GT (gamma-glutamyl transferase) Bicarbonate Bilirubin Total Bilirubin Direct, if total is elevated Bilirubin Indirect, if total is elevated Calcium Chloride Creatinine hsC-reactive protein Creatine kinase (CK) CK-MB, troponin I (reflex tests, only if CK is elevated)	eGFR[1] Glucose Ferritin HbA1c (only at V1, V2a and EOT) Plasma Free fatty acids Lactate dehydrogenase (LDH) Lipase Magnesium Phosphate Potassium Protein total Sodium Urea (BUN) LDL/HDL and total cholesterol Triglycerides
Pregnancy Test	ß-HCG Urine Pregnancy test[2] Serum Pregnancy test[3]	
Infection testing	Hepatitis B Surface Antigen (qualitative) (only at V1) QuantiFERON®-TB (only at V1)	
Urinalysis (dipstick test); albumin content	Urine Nitrite Urine Protein, semiquantitative Albuminuria quantitatively, only if Urine protein is abnormal: Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/ Erythrocytes Urine WBC/ Leukocytes Urine pH Urine creatinine	
Urine Sediment (microscopic examination, only if urine analysis is abnormal)	Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epith Cells Urine Sediment RBC/ Erythrocytes Urine Sediment WBC/ Leucocytes	

1. Estimated Glomerular filtration rate as assessed by the CKD-EPI formula (2009).
2. Urine pregnancy test performed on-site at all dosing visits (predose) as well as EOT and FU (only for female patients of childbearing potential).
3. Serum pregnancy test at screening as well as confirmation of positive urine pregnancy test (only for female patients of childbearing potential).

5.2.4 Electrocardiogram

A centralized ECG assessment will be used for this study. Three ECGs are to be recorded as 12-lead ECGs by a qualified person at the visits outlined in the Flow Chart approximately 60 min after trial drug intake using equipment provided by a central ECG vendor. All ECGs will be printed locally and evaluated by the investigator or a designee; in addition, there is a central cardiologist over-read.

ECGs will be recorded for a10-second duration after the patients have rested for at least 5 minutes in a supine position. Six limb leads, as specified by Einthoven (I, II and III) and Goldberger (aVR, aVL, aVF), and six pre-cordial leads (V1–V6), according to Wilson, will be used. ECGs will be recorded but records may be repeated for quality reasons and the repeated recording will be used for analysis. If necessary, additional ECGs may be recorded for safety reasons. Information about the details of ECG collection will be provided in the ISF.

All three ECGs at screening (used as baseline before the first drug administration), and only the first of the three replicate ECGs at a remaining time points will be evaluated (signed, dated and commented upon) by the treating physician/ investigator. The remaining second and third replicate ECGs will be printed and kept together with other medical records of the patient for additional analyses if required at a later time point.

All ECGs recorded during trial conduct including the baseline ECG will also be transmitted to a vendor for central evaluation and stored at an external central ECG database. Only the first of the three replicate ECGs at a single assessment time will be centrally evaluated and transferred to the sponsor. The results of the centralized evaluation will be sent from the ECG core lab to the sponsor according to a pre-specified data transmission agreement. The remaining second and third replicate ECGs will only be stored at the ECG vendor for additional analyses if required at a later time point

The ECG at the screening visit is regarded as baseline. Clinically significant 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 locally until normal or stable condition. In addition to the AE reports from the investigators, quantitative data (interval lengths) as well as qualitative findings (indicators for arrhythmia, conduction disturbances etc.) will be collected and will be transferred from the ECG reading center to the sponsor.

In the event of any clinical cardiac symptoms (e.g. suspicion of heart rhythm disorders or cardiac ischemia) during the trial, an additional ECG will be recorded at the investigator´s discretion. The ECG recordings will be transmitted to a vendor for central evaluation and stored at an external central ECG database. The electronic versions of the ECGs are regarded as source data.

The results of central reading will be reported to the site. ECGs and the corresponding reports will be evaluated (signed, dated and commented upon) by the treating physician/investigator and stored locally.

The central reader's evaluation of the tracing is considered the official reading for the trial. In case of discrepancies between investigator and central reading, the central evaluation will be valid.

5.2.6 Assessment of adverse events

5.2.6.1 Definitions of AEs

5.2.6.1.1 Adverse event

An adverse event (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 unfavorable and unintended sign (including an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

The following should also be recorded as an AE in the CRF and BI SAE form (if applicable):
- Worsening of the underlying disease or of other pre-existing conditions

- Changes in vital signs, ECG, physical examination, ophthalmological examination and laboratory test results, if they are judged clinically relevant by the investigator.

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

5.2.6.1.2 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 hospitalization, or
- requires prolongation of existing hospitalization,
- 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 judgment which may jeopardize 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 hospitalization or development of dependency or abuse.

5.2.6.1.3 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 5.2.6.2, subsections "**AE Collection**" and "**AE reporting to sponsor and timelines".**

In accordance with the European Medicines Agency 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 Electronic Data Capturing (EDC) system. These events should always be reported as SAEs and as described in 5.2.6.2, subsections "**AE Collection**" and "**AE reporting to sponsor and timelines".**

5.2.6.1.4 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:

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

- an elevation of AST and/or ALT ≥3 fold Upper Limit of Normal (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 RDC. 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 analyzed, if necessary in an unscheduled blood test. Should the results meet the criteria of hepatic injury alert, the procedures described in the DILI checklist should be followed.

5.2.6.1.5 Intensity (severity) of AEs

The intensity (severity) of adverse events should be classified and recorded in the eCRF according to the Common Terminology Criteria for Adverse Events (CTCAE) Version 4.03 dated 14 June 2010 [R10-4848].

5.2.6.1.6 Causal relationship of AEs

Medical judgments 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 etiologies 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.

5.2.6.2 Adverse event collection and reporting

5.2.6.2.1 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 eCRF(s) by the investigator:
- From signing the informed consent onwards through the treatment period and the residual effect period (REP: period after last dose with measurable drug levels and/or pharmacodynamic effects still likely to be present) until the individual patient's end of trial:
    - all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of trial:
    - the investigator does not need to actively monitor the patient for new AEs but should only report any occurrence of cancer and 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 eCRF.

The REP in this study is considered as the entire FU period from last dose administration of trial medication until individual patient's end of trial. All AEs that occurred through the treatment phase until the end of the Follow-up period will be considered as on-treatment (see Section 7.3.4).

5.2.6.2.2 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 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.

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.

5.2.6.2.3 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 and any possible interactions between the trial medication and the AMP (intravenous fluorescein dye).

All (S)AEs, including those persisting after individual patient's end of trial must be followed up until they have resolved, have been assessed as "chronic" or "stable", or no further information can be obtained.
The results must be included in the source documents available at the site.

5.2.6.2.4 Pregnancy

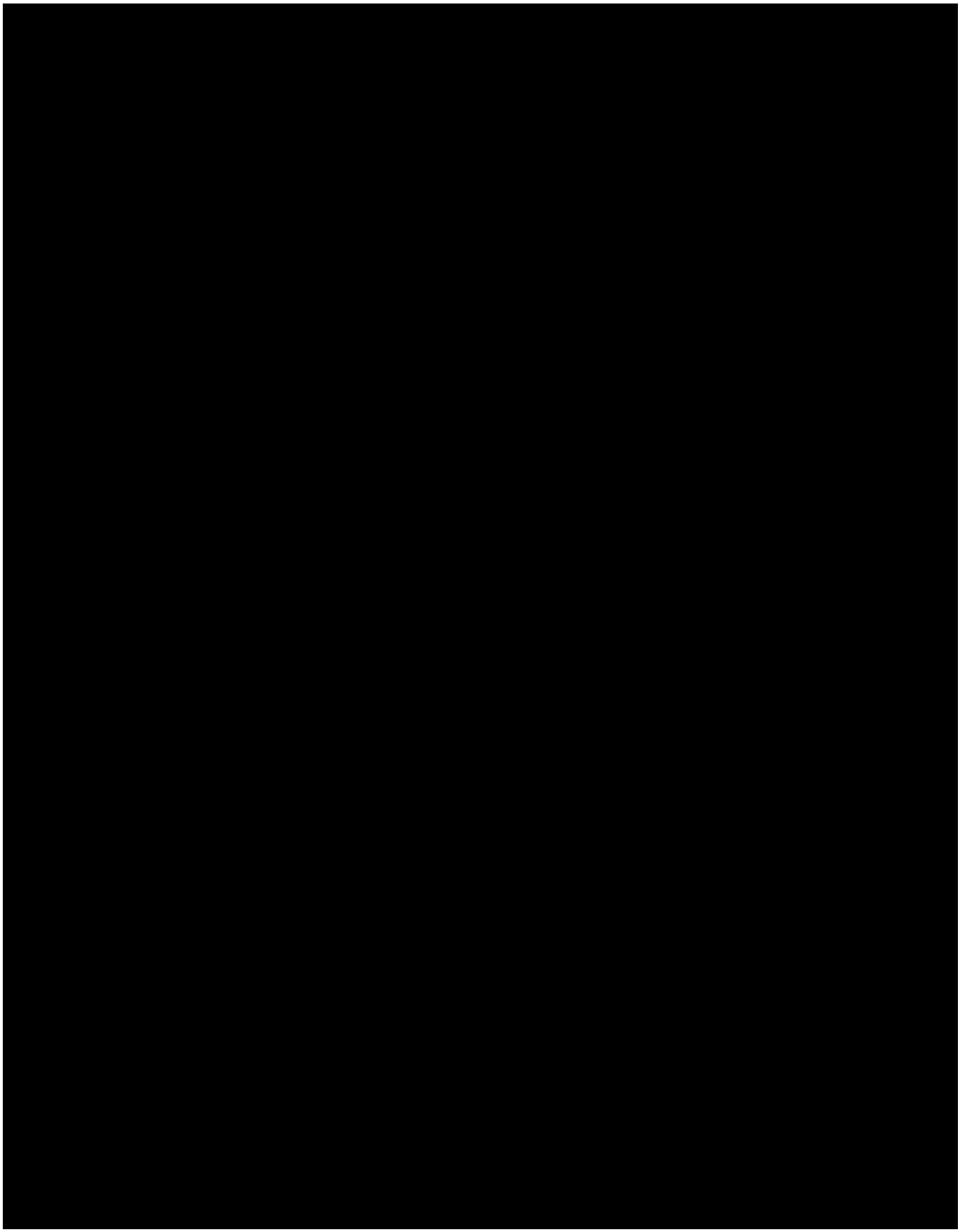
In rare cases, pregnancy might occur in a clinical trial. Once a patient has been enrolled in the clinical trial and has taken trial medication, the investigator must report any drug exposure during pregnancy in a trial participant immediately (within 24 hours) by means of Part A of the Pregnancy Monitoring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

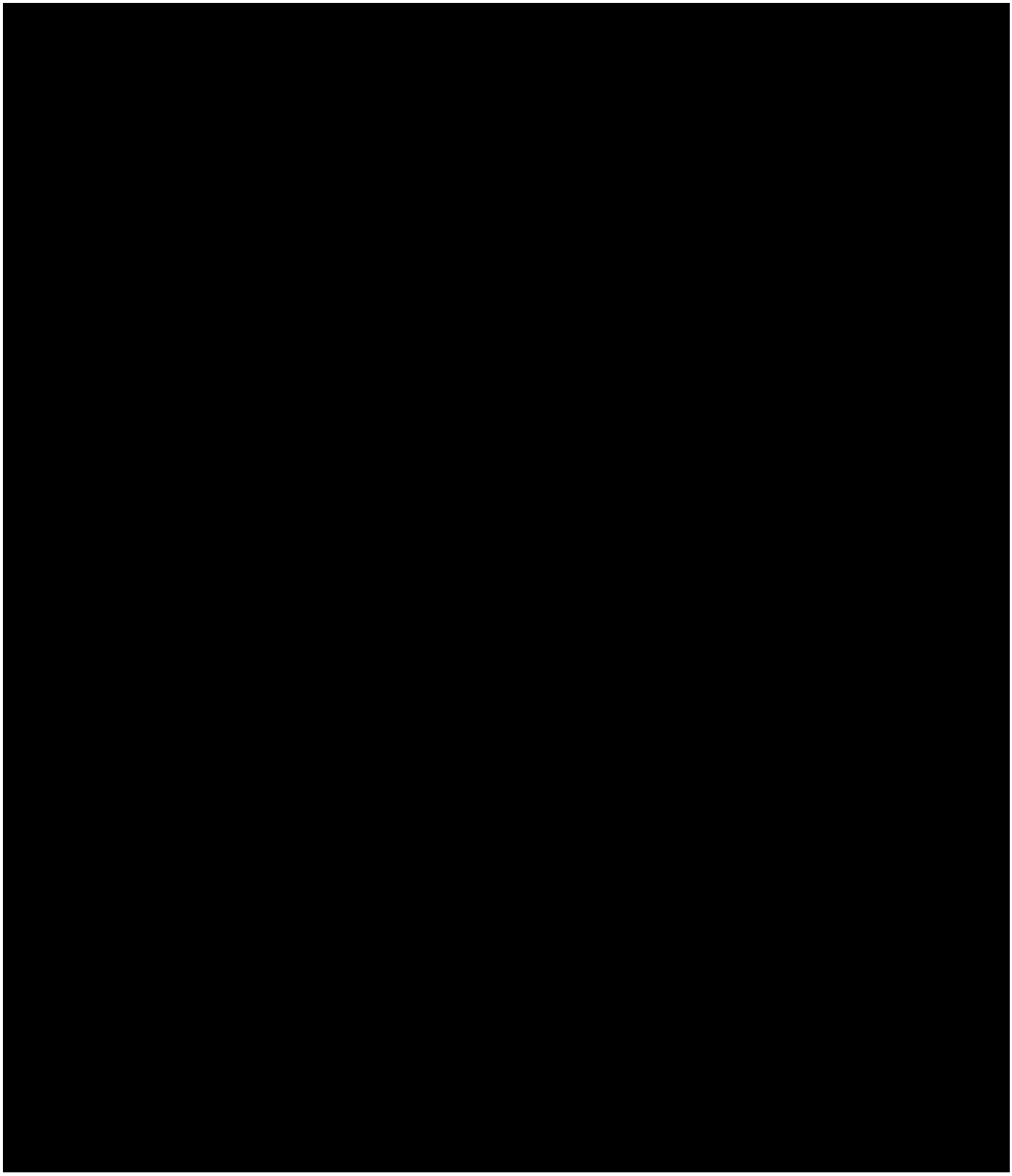
The outcome of the pregnancy associated with the drug exposure during pregnancy must be followed up and reported to the sponsor's unique entry point on the Pregnancy Monitoring Form for Clinical Trials (Part B).

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.

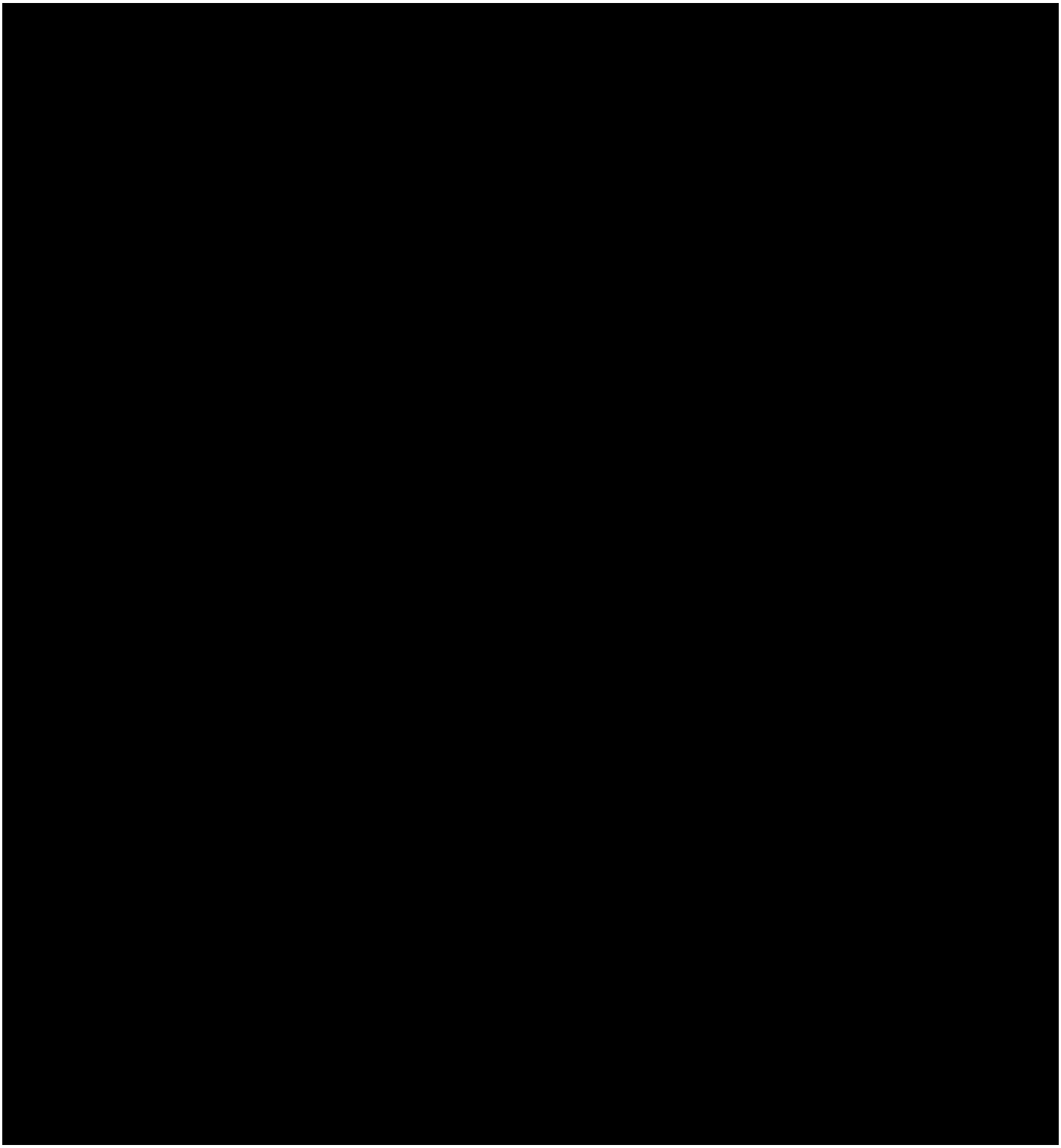
5.3 DRUG CONCENTRATION MEASUREMENTS AND PHARMACOKINETICS





Further details on collection, handling, storage and shipment of biomarker samples will be provided in the laboratory manual in the ISF.

Any leftover samples will be stored and used for not yet specified explorative investigations. These samples will be stored for up to three years after the CTR has been signed and may be used for not yet specified biomarker analyses to enable further characterization of metabolic diseases and their progress, as well as method development and evaluation. Results of these assessments will not be part of the CTR.



[redacted]

5.6 OTHER ASSESSMENTS

Not applicable

5.7 APPROPRIATENESS OF MEASUREMENTS

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

The treatment with BI 1467335 is aiming to improve or stabilize retinal pathology. Therefore, a standard method that captures changes in retinal lesions is used for diagnostic purposes as well as to determine pharmacodynamic effects. The ophthalmological assessments are widely used for the assessment of the retina and other compartments of the eye.

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All trial visits should be initiated preferentially in the morning starting before 9:00 a.m. On scheduled site visits, patients should be instructed to avoid intake of the daily dose of the trial medication at home prior to visiting the site, as they will be dosed at the study site.

All drug administration at the study site will be done under the direct supervision of the study personnel for documentation of precise administration times.

All patient visits should be scheduled according to the Flow Chart. In the event that visits are missed or delayed beyond the time window, the delayed visit should be scheduled as soon as possible and documented with the actual date and the reason for the delayed visit. Subsequent visits should follow the original visit schedule.

If the reason for removal of a patient from the treatment is an adverse event or an abnormal laboratory test result, the patient must be followed until complete resolution or stabilization of the event or until follow-up is agreed adequate by the investigator and BI Clinical Monitor.

Patients should make all efforts to complete the study, which includes the Visit EOT and all follow-up visits FU1, FU2 and FU3. The procedures to be conducted at each visit are provided in the Flow Chart and are further described below.
Regarding removal of patients, please refer to Section 3.3.4.

Order of ophthalmological assessments
For adequate evaluation of the eye fundus it is necessary to dilate the pupil with mydriatic medication according to local standard (please also refer to Section 4.2.1).

- Before pupil dilation, the following assessments have to be performed: BCVA [redacted]
- After pupil dilation, the following assessments will be performed: color fundus photography [redacted]
- [redacted] and slit lamp examination are independent of the dilation.
- Ocular tonometry and gonioscopy (at the screening visit only, if needed per Section 3.3.3 exclusion criterion #4) should be performed after imaging. Goniscopy can also be performed before dilation, if preferred by the investigator.

[redacted]

6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

Study procedures to be performed at each visit are listed in the Flow Chart and in the Appendix 10.2. Additional details regarding visit procedures are provided below.

6.2.1 Screening and run-in period(s)

Informed Consent prior to trial participation
All patients must sign an Informed Consent consistent with ICH-GCP guidelines prior to any study specific procedures. Please refer to Section 8.1 for details.

Screening Period
The Screening period, i.e. the phase before the first administration of the trial drug, starts at Visit 1. The Screening period may be as long as 28 days but should be kept as short as possible. The minimum time interval between Visit 1 and Visit 2a is 3 days to allow receipt of the results of the central imaging reading, safety laboratory and ECG.

Screening visit should be performed in two visits. After Informed consent is obtained, fundus photography should be performed and sent to central reading service. If patient is eligible based on the DRSS grading, the patient should return to complete the rest of the screening. In case of scheduling difficulty for certain patients, screening can be performed in one visit. If screening is done as one visit, fundus photography should be performed in line with other ophthalmological examinations.

[redacted]

Demographics and Baseline Conditions
Information on race will be collected because certain ethnic groups are at higher risk for DR; this demographic information is also required for the calculation of eGFR (CKD-EPI formula).

The following baseline conditions will be specifically asked for: type of DM, arterial hypertension, metabolic syndrome and the level of DR in both eyes (as provided by the CRC). In addition, information will be collected in the eCRF for relevant chronic diseases, current observable conditions and other relevant conditions (as per investigators judgment) which may not be necessarily manifest at the day of examination, e.g., because therapy is given.

Medical History
Information on DR risk factors and factors that may influence AOC3 inhibition will be collected in the eCRF, such as duration of DM, history of arterial hypertension, history of hyperlipidemia, caffeine and alcohol consumption and tobacco use. Furthermore, any previous therapy of DR will be recorded.

In order to collect previous medical reports to keep records of exact dates/diagnoses of relevant medical history or prior medication, up to three documented attempts at different days should be made to get the reports before medical history data will be used.

Level of DR
Images (fundus photographs, angiograms and OCT) have to be sent to the CRC for assessment, see Section 3.3.2.

Re-Screening
Patients who do not fulfil all of the eligibility criteria for a reason that later resolves and all eligibility criteria can be met, can be re-screened up to one time. Patients can also be re-screened if they screen failed due to inclusion/exclusion criteria that has been changed in the current version of the protocol. For rescreening, patient must be registered in IRT, which will then provide new patient number, and patient must sign a new ICF.

Re-testing
Screening evaluations may be repeated once during the screening phase.

IRT
All patients who are screened must be registered with IRT. If the patient results in a screen failure, patient must be recorded as screen failure in IRT as soon as possible and within the 28-day screening period. Details of IRT procedures can be found in the IRT Manual filed in the ISF.

6.2.2 Treatment period(s)

General remarks
As soon as eligibility of enrolled patients is confirmed, patients may enter the study and Visit 2a can be conducted including randomization via IRT.

IRT should not be called in advance of Visit 2a until eligibility is fully confirmed, as randomization of a patient cannot be reserved.

Unscheduled visits will be possible at the discretion of the investigator at any time in order to check the safety of the patient including a potential worsening of ocular function or to perform safety laboratory assessments.

At every site visit during the treatment period (Visits 2a – EOT) patients are asked about their alcohol and caffeine consumption and information is recorded in the eCRF.

Trial drug diary
The patients will be instructed to complete trial drug diaries during the treatment phase to document date and clock time of drug intake at home between the on-site visits. If the trial drug was not administered as planned, the reason should be provided in the diary by the patient.

A new diary will be dispensed to the patients at every visit during the treatment period and will be collected at the following visit by the site (please refer to the Flow Chart). Selected entries, i.e. drug administration dates and times from the 3 days prior to each visit, will be entered in the eCRF by the site.

Visit 2a (Randomization)
At the start of Visit 2a it should be ensured that all Visit 1 procedures have been successfully completed within the past 28 days and eligibility has been confirmed including confirmation of eligibility by the CRC.

Trial medication is administered after predose blood collection. [redacted]

Trial drug kits will be dispensed for home administration, and a trial drug diary will be dispensed to the patients.

Visit 2b (Phone Visit)
This interim phone call will be performed one week after randomization in order to collect AEs, changes in concomitant therapy, and to check handling of the trial drug diary. Patients should be reminded not to take medication in the morning prior to the next visit.

Visits 3 and 4a:
At these visits the trial drug diary will be checked and dates and times of drug administration at the 3 days prior to the visits will be recorded in the eCRF. Unused trial medication, as well as empty blisters and packaging, will be collected.

Visit 4b (Phone Visit)
This interim phone call will be performed in advance to the EOT visit in order to collect AEs, changes in concomitant therapy, and to check handling of the trial drug diary. Patients should be reminded not to take medication in the morning prior to the EOT visit.

End of Treatment (EOT) Visit:
For patients who complete treatment as scheduled, the day of the EOT Visit is the last day of treatment where trial drug will be administered at the site from the kit that the patient returns to the site.

The overall duration of the anticipated treatment period (Randomization to EOT) should not be less than 84 days; therefore the EOT visit is scheduled at Day 85 with a time interval of up to +6 days at maximum.

If the trial drug intake needs to be permanently stopped during the treatment period for any reason prior to the scheduled EOT visit, including that patients are not willing to continue trial drug intake any longer, the EOT visit will be completed instead of the planned treatment period visit as soon as possible after trial drug discontinuation. In this case the patient should be asked to further attend to the follow-up visits and assessments until the end of the trial unless they withdraw consent to participate in the trial. It is important to distinguish between premature trial drug discontinuation, i.e. early discontinuation, and complete withdrawal of consent to participate in further study procedures.

Withdrawal of consent
If a patient is not willing to continue in the trial prior to the end of the trial, Visit EOT should be scheduled and completed instead of the planned treatment period visit as soon as possible. Also one follow-up visit (FU1) should be performed to assess for safety.

If the patient refuses to participate at an EOT Visit and withdraws consent for any reason (without the need to justify the decision), the trial completion page of the eCRF has to be filled in.

All unused trial medication will be collected and trial drug diary will be checked by the site.

If patient discontinues prematurely for safety reasons or withdraws consent, trial medication administration [redacted] will not be performed at EOT Visit.

6.2.3 Follow up period and trial completion

For all patients who had at least one dose of trial medication the follow-up visits FU1, FU2 and FU3 will be performed according to the Flow Chart 4, 8 and 12 weeks after the last intake of trial drug, respectively. If the last day of trial drug intake is different from the EOT visit, the date of the last day of trial drug intake will be used for calculation of the FU visit dates.

Should it be not possible for the patient to attend a follow up visit at the study site, a visit out of time window should be performed as soon as possible; if a visit at the site is not possible at all, at least a phone contact should occur at the scheduled visit time point.
In case that standard of care DR treatment is administered at these visits, this has to be documented in the eCRF.

The FU3 visit is the final visit and the Study completion page in the eCRF has to be entered.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

The trial is a randomized, double-masked, placebo-controlled, parallel-group, multicenter proof of clinical principle study. The primary objective is to evaluate the safety and tolerability of BI 1467335 and to explore the mechanism of BI 1467335 in the treatment of patients with moderately severe NPDR (DRSS level 47) or severe NPDR (DRSS level 53), without CI-DME.

BI 1467335 will be compared to placebo. The primary endpoint is occurrence of ocular adverse events.

The randomization will be stratified by the severity level of the disease under study as assessed by DRSS, i.e. level 47 or 53.

7.2 NULL AND ALTERNATIVE HYPOTHESES

No confirmatory hypothesis testing is planned. This study is considered exploratory.

7.3 PLANNED ANALYSES

The analysis populations are defined below. Patients will be analyzed according to randomized treatment, unless otherwise specified. Important protocol violations and the handling of patients with such violations will be described in the TSAP.

Treated Set (TS)
The Treated Set will consist of all patients who were treated with at least one dose of trial drug (BI 1467335 or placebo).

Full Analysis Set (FAS)
The FAS will consist of all the patients who were randomized, treated with at least one dose of BI 1467335/placebo and have baseline and one on-treatment DRSS assessment.

[redacted]

7.3.1 Primary endpoint analyses

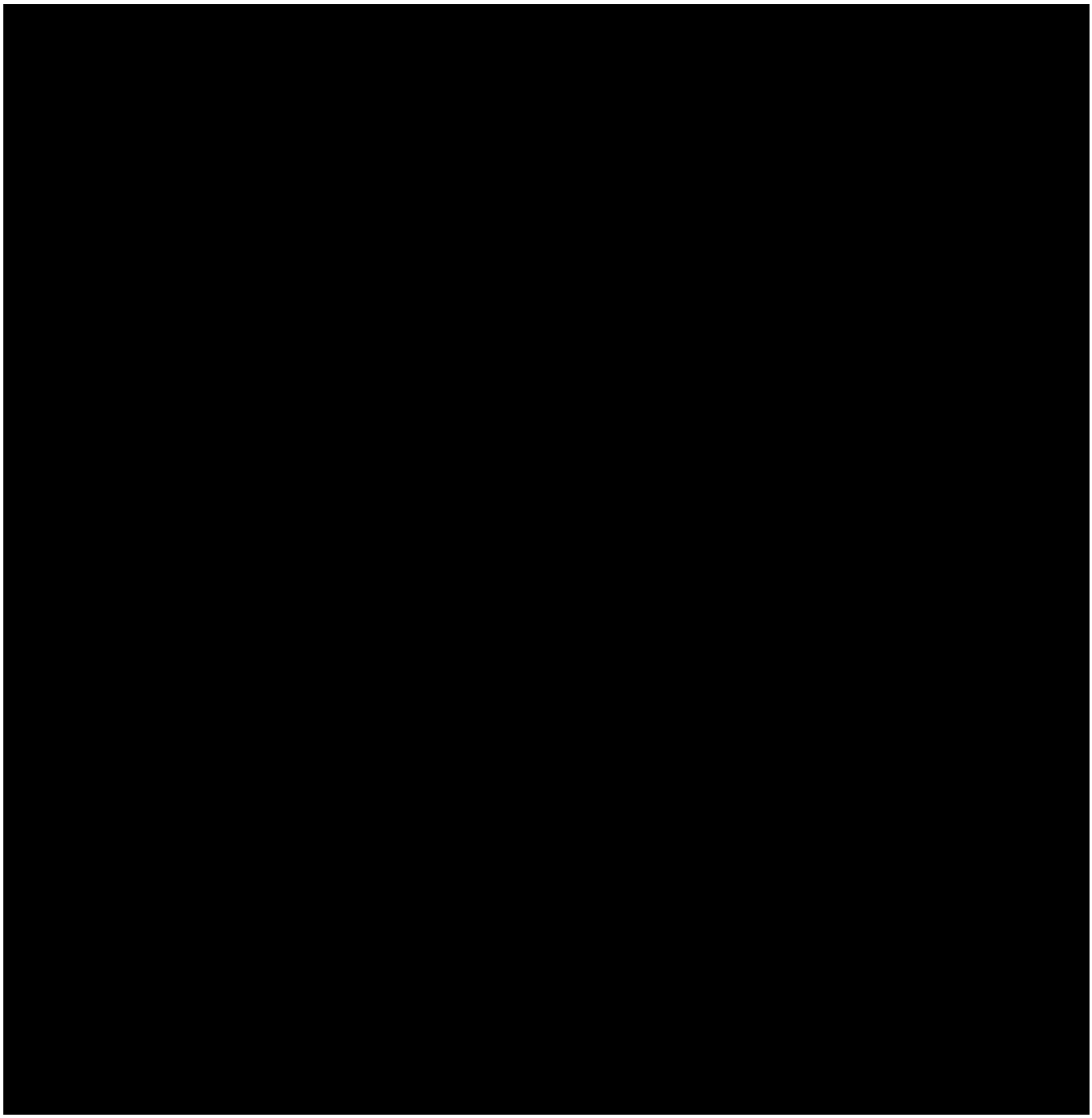
No primary efficacy endpoint has been defined for this study.

For analyses of the primary safety endpoint “proportion of patients with ocular adverse events” over the on-treatment period please refer to Section 7.3.4.

7.3.2 Secondary endpoint analyses

The proportion of patients with at least 2 steps improvement from baseline on the DRSS (Table 10.3: 1) in the study eye at week 12 will be summarized as the frequency and percentage of patients. Logistic regression analyses adjusted for treatment and baseline visual acuity may be performed if a sufficient number of events is observed. Baseline measurements are defined in Section 5.1. The odds ratio and corresponding 95% confidence interval will be presented along with the p-value. The analysis will be performed on the FAS.

For analyses of the secondary safety endpoint “proportion of patients with adverse events other than ocular adverse events” over the on-treatment period, refer to Section 7.3.4.



7.3.4 Safety analyses

All findings noticed at ophthalmological examinations and/or clinically relevant symptoms (according to the judgment of the investigator) which are reported by the patients will be recorded as ocular adverse events according to the CTCAE classification. All adverse events will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA).

Standard BI summary tables and listings will be produced. Consistent with the REP definition in Section 5.2.6.2.1, all adverse events with an onset between start of treatment and last follow up visit will be assigned to the on-treatment period for evaluation. Measurements (such as ECG, vital signs, or laboratory parameters) or AEs will be assigned to treatments (see Section 4.1) based on the actual treatment at the planned time of the measurement or on the recorded time of AE onset (concept of treatment emergent AEs). Therefore, measurements planned or AEs recorded prior to first intake of trial medication will be assigned to 'screening' and those between first trial medication intake until the last follow up visit will be assigned to the treatment period. These assignments including the corresponding time intervals will be defined in detail in the TSAP.

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

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

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

Laboratory data will be analyzed 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 summarized. 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.

Clinically relevant ECG findings will be reported as baseline conditions or AEs. Quantitative and qualitative ECG data from the ECG reading center will be reported descriptively.

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.

[redacted]

7.4 INTERIM ANALYSES

[redacted]

During the conduct of the interim analysis, access to unmasked data will be restricted to members of the trial and project teams not directly involved with study conduct. The results of the interim analysis will not be used to make any adaptions of this trial, like sample size adjustments.

For steps to maintain blinding during the interim analysis see Section 4.1.5.1.

7.5 HANDLING OF MISSING DATA

For the analyses of efficacy endpoints, if a patient misses a visit, the missing data will not be imputed and only on-treatment data will be included.

Additional details on the handling of missing data, including sensitivity analyses of the efficacy endpoints and any imputation rules for further endpoints will be specified in the TSAP prior to unmasking. No imputation is planned for the analysis of AEs, laboratory data or vital signs. Rules for handling missing data are outlined in BI SOPs.

7.6 RANDOMISATION

BI will arrange for the randomization and the packaging and labelling of trial medication. The randomization list will be generated using a validated system, which involves a pseudo-random number generator so that the resulting treatment will be both reproducible and non-predictable. The block size will be documented in the CTR. Access to the codes will be controlled and documented. Procedural aspects of assigning patients to treatment groups and controlling the randomization code are provided in Section 4.1.3 and Section 4.1.5.

7.7 DETERMINATION OF SAMPLE SIZE

The primary endpoint for the trial is occurrence of ocular adverse events.

As this is an exploratory study, no formal sample size calculation has been applied. It is expected that using 50 patients per group will be sufficient to detect clinically relevant signals for ocular events between active treatment and placebo.

Additionally, with DRSS data from 100 patients the probability of seeing at least 2 steps improvement in the study eye on the DRSS at week 12 compared to baseline in 2 patients is approximately 80%, assuming a response rate of 6% on active treatment and 0% response on placebo.

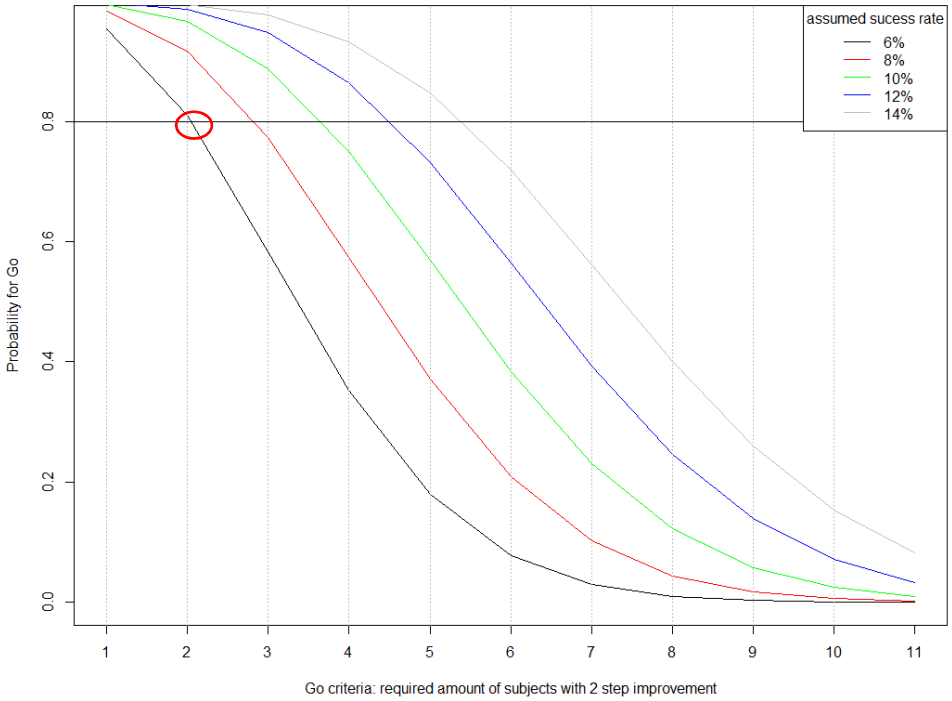


Figure 7.7: 1 Probabilities for seeing different amount of patients with 2 step improvement in DRSS assuming different success rates.

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

The trial will be carried out in compliance with the protocol, the ethical principles laid down in the Declaration of Helsinki, in accordance with the ICH Harmonized Tripartite Guideline for Good Clinical Practice (GCP), relevant BI SOPs, the EU regulation 536/2014 and other relevant regulations. Investigators and site staff must adhere to these principles.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains the responsibility of the 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 a rule, no trial results should be published prior to finalization of the CTR.

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 competent authority (CA) according to national and international regulations. The same applies for the implementation of changes introduced by amendments.

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

The 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 informed consent form after confirming that the patient understands the contents. The investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.

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

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

8.2 DATA QUALITY ASSURANCE

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

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

8.3 RECORDS

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

8.3.1 Source documents

In accordance with regulatory requirements the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). Data reported on the eCRF 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 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 eCRF, data must be derived from source documents, for example:

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

8.3.2 Direct access to source data and documents

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

The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the eCRF 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 eCRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in Section 8.3.1. The sponsor will also monitor compliance with the protocol and GCP.

8.3.3 Storage period of records

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

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

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 and in Section 5.4.1. 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 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.

8.6 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"). 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 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 / competent authority in each participating EU member state will be notified about the trial milestones according to the respective laws.

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

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

8.7 ADMINISTRATIVE STRUCTURE OF THE TRIAL

The trial is sponsored by BI.

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

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 Trial Clinical Monitor, 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 Local Clinical Monitors (CML), CRAs, and investigators of participating countries

The organization of the trial in the participating countries will be performed by the respective local or regional BI-organization (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.

Individual and aggregated safety data will be reviewed in a masked fashion by members of the BI trial team in Medical Quality Review Meetings at regular intervals to determine the safety profile according to the sponsor’s SOPs.

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

Tasks and functions assigned in order to organize, 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, a central imaging reading center, a central ECG service provider and an IRT vendor will be used in this trial. Details will be provided in the respective manuals, available in the ISF.

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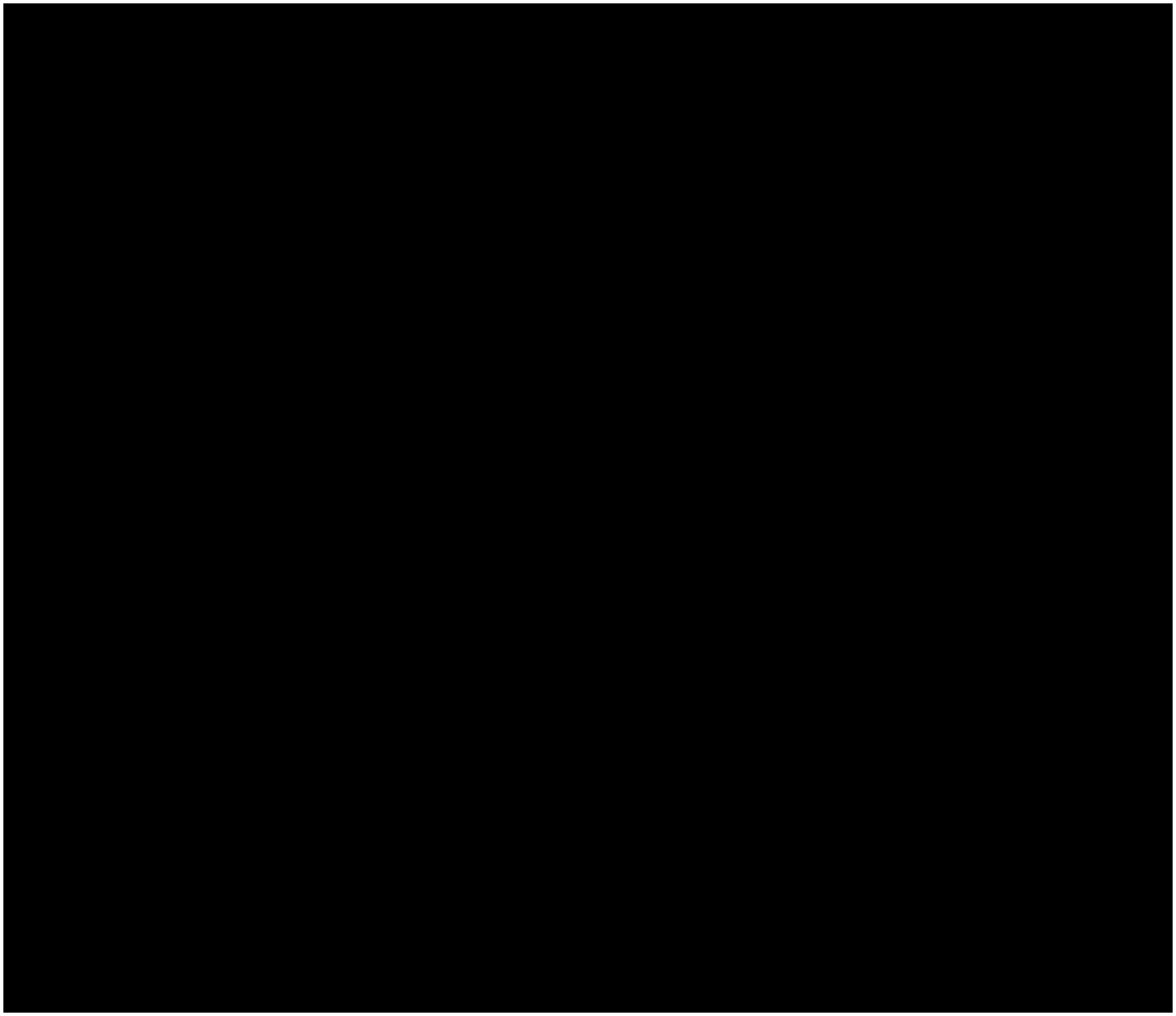

10.3 THE DIABETIC RETINOPATHY SEVERITY SCALE (DRSS)

The DRSS from the Early Treatment Diabetic Retinopathy Study (ETDRS) will be used for the assessment of the level of DR by the Central Reading Center [R17-1872].

Table 10.3: 1 The DRSS for individual eye

Level	Severity	Definition
10	No retinopathy	Diabetic retinopathy absent
20	Very mild NPDR	Microaneurysms only
35	Mild NPDR	Hard exudates, cotton-wool spots, and/or mild retinal hemorrhages
43	Moderate NPDR	43A Retinal hemorrhages moderate (>photograph 1) in four quadrants or severe (≥photograph 2A) in one quadrant
		43B Mild IRMA (<photograph 8A) in one to three quadrants
47	Moderate NPDR	47A Both level 43 characteristics
		47B Mild IRMA in four quadrants
		47C Severe retinal hemorrhages in two to three quadrants
		47D Venous beading in one quadrant
53	Severe NPDR	53A ≥2 level 47 characteristics
		53B Severe retinal hemorrhages in four quadrants
		53C Moderate to severe IRMA (≥photograph 8A) in at least one quadrant
		53D Venous beading in at least two quadrants
		53E ≥2 level 53A-D characteristics
61	Mild PDR	New vessels elsewhere < 0.5 disc area in one or more quadrants
65	Moderate PDR	65A New vessels elsewhere ≥ 0.5 disc area in one or more quadrants
		65B New vessels disc <photograph 10A
71, 75	High-risk PDR	New vessels disc ≥photograph 10A, or New vessels disc <photograph 10A or New vessels elsewhere ≥0.5 disc area plus vitreous hemorrhage or preretinal hemorrhage, or vitreous hemorrhage or preretinal hemorrhage obscuring ≥1 disc area
81, 85	Advanced PDR	Fundus partially obscured by vitreous hemorrhage and either new vessels not gradable or retina detached at the center of the macula

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		18 Jan 2018
EudraCT number **EU number**		2016-002971-91
BI Trial number		1386.12
BI Investigational Product(s)		BI 1467335
Title of protocol		A randomized, double-masked, placebo-controlled exploratory study to evaluate safety, tolerability, pharmacodynamics and pharmacokinetics of orally administered BI 1467335 for 12 weeks with a 12 week follow up period in patients with non-proliferative diabetic retinopathy without center-involved diabetic macular edema
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		☐
Section to be changed		TITLE PAGE CLINICAL TRIAL PROTOCOL SYNOPSIS
Description of change		Study title was updated to add ROBIN study name
Rationale for change		ROBIN was selected as a study name
Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS Statistical methods 7.3.2 Secondary endpoint analyses
Description of change		Added descriptive analysis of secondary efficacy endpoint.
Rationale for change		Add alternate secondary efficacy analysis since too few events may be observed in a study of this size to allow adequate statistical modelling.
[redacted]		[redacted]
Section to be changed		1.4 BENEFIT - RISK ASSESSMENT 3.3.4.1 Withdrawal from trial treatment
Description of change		[redacted]

		[redacted]
Rationale for change		Request from Health authorities
Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS 3.3.2 Inclusion criteria
Description of change		Removal of upper age limit in IN#1
Rationale for change		Request from Health authorities
Section to be changed		3.3.2 Inclusion criteria 4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Removal of diabetic treatment restrictions from IN#3 Removal of restriction of starting new insulin therapy from section 4.2.2.1
Rationale for change		Request from Health authorities
Section to be changed		3.3.2 Inclusion criteria
Description of change		Changing HbA1c inclusion criteria ion IN #4 from 10% to 12%
Rationale for change		To allow inclusion of additional patients since diabetic treatment restriction was removed
Section to be changed		3.3.3 Exclusion criteria
Description of change		Addition of cataract surgery exclusion criteria in EX#1
Rationale for change		Request from Health authorities
Section to be changed		3.3.3 Exclusion criteria
Description of change		Addition ‘suspected’ infections as exclusion criteria in EX#15
Rationale for change		Request from Health authorities
Section to be changed		3.3.4.1 Withdrawal from trial treatment
Description of change		Additional criteria for patient withdrawal based on change in QTc
Rationale for change		Request from Health authorities
Section to be changed		6.2.1 Screening and run-in period(s)
Description of change		The following sentence was added in the Re-Screening paragraph: Patients can also be re-screened if they screen failed due to inclusion/exclusion criteria that has been changed in the current version of the protocol.
Rationale for change		To allow re-screening of patients due to change in inclusion/exclusion criteria.

Section to be changed		FLOW CHART, footnote #14 1.2 DRUG PROFILE 4.1.4.2 Trial medication administration at days without site visits 6.1 VISIT SCHEDULE 6.2.2 Treatment period(s)
[redacted]		[redacted]
[redacted]		[redacted]
Section to be changed		4.1.5.1 Masking 7.4 INTERIM ANALYSES
Description of change		Allow trial and project team members not involved with study conduct to be unmasked for the interim analysis.
Rationale for change		Allow specific trial and project team members to assist with interim PK/PD analysis.
Section to be changed		5.3.2 Methods of sample collection
Description of change		[redacted]
Rationale for change		Error in the protocol.
Section to be changed		Title page
Description of change		'BI Investigational Product' changed to 'BI Investigational Medicinal Product'
Rationale for change		New sponsor protocol template
Section to be changed		CLINICAL TRIAL PROTOCOL SYNOPSIS
Description of change		New Trial rationale section added 'Objective(s)' changed to 'Trial objective(s)' 'Methodology' changed to 'Trial design' 'Number of patients entered' changed to 'Number of patients randomized'
Rationale for change		New sponsor protocol template
Section to be changed		FLOW CHART
Description of change		'Adverse events' changed to 'All AEs/SAEs/AESIs [21]' and corresponding footnote added
Rationale for change		New sponsor protocol template
Section to be changed		1.3 RATIONALE FOR PERFORMING THE TRIAL
Description of change		Some text modifications in the last paragraph

Rationale for change		New sponsor protocol template
Section to be changed		3.3 SELECTION OF TRIAL POPULATION
Description of change		Last sentence was added
Rationale for change		New sponsor protocol template
Section to be changed		3.3.2 Inclusion criteria
Description of change		'Full' age changed to 'legal' age in IN#1
Rationale for change		New sponsor protocol template
Section to be changed		3.3.4 Withdrawal of patients from therapy or assessments
Description of change		Last sentence added
Rationale for change		New sponsor protocol template
Section to be changed		3.3.4.2 Withdrawal of consent for trial participation
Description of change		Last sentence modified to say: If a patient wants to withdraw consent, the investigator should **be involved in the discussion with the patient and** explain the difference …
Rationale for change		New sponsor protocol template
Section to be changed		4.1.2 Selection of doses in the trial and dose modifications
Description of change		Section title changed
Rationale for change		New sponsor protocol template
Section to be changed		4.2.2.3 Contraception requirements
Description of change		Section tile changed from 'Restrictions regarding women of childbearing potential' to 'Contraception requirements'
Rationale for change		New sponsor protocol template
Section to be changed		4.3 TREATMENT COMPLIANCE
Description of change		'as directed by the investigator' was added to the formula for treatment compliance
Rationale for change		New sponsor protocol template
Section to be changed		5.2.4 Electrocardiogram
Description of change		Text that ECGs shoud be performed by a qualified technologist'' was added in the first paragraph.
Rationale for change		New sponsor protocol template
Section to be changed		5.2.6.1 Definitions of AEs
Description of change		Numbering of subsections was added
Rationale for change		New sponsor protocol template

Section to be changed		5.2.6.1.1 Adverse event
Description of change		Last two paragraphs were added
Rationale for change		New sponsor protocol template
Section to be changed		5.2.6.2 Adverse event collection and reporting
Description of change		Numbering of subsections was added
Rationale for change		New sponsor protocol template
Section to be changed		5.2.6.2.1 AE Collection
Description of change		Figure 5.2.6.2:1 was deleted
Rationale for change		New sponsor protocol template
Section to be changed		5.4 ASSESSMENT OF BIOMARKER(S) 5.5 BIOBANKING 5.6 OTHER ASSESSMENTS 5.7 APPROPRIATENESS OF MEASUREMENTS
Description of change		Sections are renumbered without change in the text
Rationale for change		New sponsor protocol template
Section to be changed		8. INFORMED CONSENT, TRIAL RECORDS, DATA PROTECTION, PUBLICATION POLICY, AND ADMINISTRATIVE STRUCTURE
Description of change		Last sentence in the first paragraph was added.
Rationale for change		New sponsor protocol template
Section to be changed		8.2 DATA QUALITY ASSURANCE
Description of change		First paragraph was added
Rationale for change		New sponsor protocol template

11.2 GLOBAL AMENDMENT 2

Date of amendment		20 Mar 2018
EudraCT number **EU number**		2016-002971-91
BI Trial number		1386.12
BI Investigational Product(s)		BI 1467335
Title of protocol		A **R**andomized, double-masked, placebo-controlled exploratory study to evaluate safety, tolerability, pharmacodynamics and pharmacokinetics of **O**rally administered **BI** 1467335 for 12 weeks with a 12 week follow up period in patients with **N**on-proliferative diabetic retinopathy without center-involved diabetic macular edema (ROBIN study)
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 The immediate actions were implemented in the context of a Dear Investigator Letter dated 6 Mar 2018. IRB / IEC / Competent Authorities have been informed. The changes due to this measure are contained in protocol sections 1.2, 2.3, 3.3.3 and 4.2.2.		☑
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		☐
Section to be changed		1.2 DRUG PROFILE
Description of change		Non-clinical safety [redacted]
[redacted]		[redacted]
Section to be changed		1.4 BENEFIT - RISK ASSESSMENT
Description of change		*The following text was added:*

[redacted]		[redacted]
Section to be changed		3.3.3 Exclusion criteria
Description of change		EX#7 was modified
Rationale for change		More detailed list of drugs excluded due to potential MAO-B inhibition was added to Section 4.2.2.1.
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		First two paragraphs were added with additional restricted medications, both as exclusion criteria during screening and as prohibited medication during the trial
Rationale for change		BI 1467335 demonstrated in vitro to be an irreversible inhibitor of MAO-B.
Section to be changed		4.2.2.2 Restrictions on diet and life style
Description of change		*The following text was added:* Patients should avoid consuming food that contains very large amounts of tyramine, such as: • Aged cheese • Aged meats • Soybean products (Soy sauce) • Red wine • Tap (draft) beer • St John's Wort • Pickled herring • Sauerkraut (fermented cabbage) • Tryptophan supplements
Rationale for change		BI 1467335 demonstrated in vitro to be an irreversible inhibitor of MAO-B.
Section to be changed		9.2 UNPUBLISHED REFERENCES
Description of change		References n00257993 and n00259383 were added.
Rationale for change		References for the new text that was added in the

		Section 1.2
Section to be changed		3.3.3 Exclusion criteria
Description of change		IN #2 was modified to add "or Heidelberg OCT"
Rationale for change		To allow the use of Heidelberg OCT device.
Section to be changed		5.1 ASSESSMENT OF EFFICACY
Description of change		[redacted]
[redacted]		
[redacted]		[redacted]
[redacted]		
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Anti-VEGF injection treatment either in the study eye or in the fellow eye is not allowed to be given in addition to the trial drug during the trial. If anti-VEGF intravitreal treatment … *was changed to* Anti-VEGF injection treatment with aflibercept (Eylea®) or ranibizumab (Lucentis®) in the study eye is not allowed to be given in addition to the trial drug during the trial. Use of bevacizumab (Avastin®) is not allowed in either the study eye or in the fellow eye. If the prohibited anti-VEGF intravitreal treatment …
Rationale for change		To allow treatment with aflibercept (Eylea®) or ranibizumab (Lucentis®) in the fellow eye during the trial.
Section to be changed		3.3.4.1 Withdrawal from trial treatment
Description of change		… change from baseline (Visit 2) > 60 ms.

		was changed to: … change from Visit 1 > 60 ms.
Rationale for change		Correction in the protocol. For ECG, the baseline is Visit 1.
Section to be changed		4.1.5.1 Masking
Description of change		… member of the independent team in preparation for interim PK/PD analysis. *was changed to:* … member of the team conducting the interim PK/PD analysis.
Rationale for change		Correction in the protocol.
Section to be changed		4.3 TREATMENT COMPLIANCE
Description of change		If the number of doses taken is not between 80-120%, … *was changed to:* If the treatment compliance is not between 80-120%, …
Rationale for change		Correction in the protocol.

11.3 GLOBAL AMENDMENT 3

Date of amendment		01 Aug 2018
EudraCT number **EU number**		2016-002971-91
BI Trial number		1386.12
BI Investigational Product(s)		BI 1467335
Title of protocol		A **R**andomized, double-masked, placebo-controlled exploratory study to evaluate safety, tolerability, pharmacodynamics and pharmacokinetics of **O**rally administered **BI** 1467335 for 12 weeks with a 12 week follow up period in patients with **N**on-proliferative diabetic retinopathy without center-involved diabetic macular edema (ROBIN study)
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		☐
Section to be changed		FLOW CHART
Description of change		Footnote 21 was added
Rationale for change		Based on the screen failures observed so far, majority of patients screen failed due to DRSS grading. Screening visit should be performed in two visits. Fundus photography would be performed first. If patient is eligible based on the DRSS grading, the rest of the screening will be performed. Splitting the screening would reduce burden of performing the remaining screening procedures for patients who fail DRSS grading.
Section to be changed		3.1 OVERALL TRIAL DESIGN AND PLAN
Description of change		*The following text was added:* Due to high probability of patients screen failing due to DRSS grading on fundus photography, screening should be performed in two parts. Fundus photography should be performed first, and if patients are eligible based on the fundus photography results, patients should return to complete the rest of the screening examinations. In case of scheduling difficulty for certain patients, screening can be performed in one visit.
Rationale for change		See above for splitting screening visit

Section to be changed		6.2.1 Screening and run-in period(s)
Description of change		Screening Period *The following text was added:* Screening visit should be performed in two visits. After Informed consent is obtained, fundus photography should be performed and sent to central reading service. If patient is eligible based on the DRSS grading, the patient should return to complete the rest of the screening. In case of scheduling difficulty for certain patients, screening can be performed in one visit. If screening is done as one visit, fundus photography should be performed in line with other ophthalmological examinations.
Rationale for change		See above for splitting screening visit
Section to be changed		1.4 BENEFIT - RISK ASSESSMENT
Description of change		
Rationale for change		Clarification regarding food and diet precaution

Section to be changed		4.2.2 Restrictions
Description of change		*Section title was changed to:* 4.2.2 Restrictions, warnings and precautions
Rationale for change		Clarification regarding food and diet precaution
Section to be changed		4.2.2.2 Restrictions on diet and life style
Description of change		*Section title was changed to:* 4.2.2.2 Precautions on diet and life style Patients should avoid consuming food that contains very large amounts of tyramine, such as … *was changed to:* Patients should be advised to avoid the consumption of large amounts of tyramine-rich food while taking BI 1467335, such as … • Tap (draft) beer *was changed to:* • Beer • Yeast products
Rationale for change		Clarification regarding food and diet precaution
Section to be changed		ABBREVIATIONS
Description of change		*Following abbreviation was added:* RIMA Reversible inhibitor of MAO-A
Rationale for change		New abbreviation in the protocol
Section to be changed		FLOW CHART footnote 8
Description of change		At visits without medication administration 12-lead ECG … *was changed to:* At screening and follow-up visits 12-lead ECG …
Rationale for change		Clarification
Section to be changed		FLOW CHART
Description of change		"Substance use" line and the corresponding footnote were added
Rationale for change		Substance use was described in the protocol and included in the CRFs. It was added in the FLOW CHART for clarity.
Section to be changed		3.3.3 Exclusion criteria
Description of change		2. Active center-involved DME (CI-DME) on clinical examination and OCT central subfield thickness above 300 µm in the study eye, as measured by Optovue OCT or Heidelberg OCT.

		was changed to: 2. Active center-involved DME (CI-DME) on clinical examination and OCT central subfield thickness in the study eye above 300 µm as measured by Optovue OCT or above 320 µm as measured by Heidelberg OCT.
Rationale for change		Update for Heidelberg OCT cut-off.
Section to be changed		6.2.1 Screening and run-in period(s)
Description of change		… caffeine consumption and tobacco use. *was changed to:* … caffeine and alcohol consumption and tobacco use.
Rationale for change		Clarification
Section to be changed		6.2.2 Treatment period(s)
Description of change		... patients are asked about their caffeine consumption … *was changed to:* … patients are asked about their alcohol and caffeine consumption …
Rationale for change		Clarification
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		Several drug names were corrected
Rationale for change		Errors in the previous protocol version
Section to be changed		4.2.2.1 Restrictions regarding concomitant treatment
Description of change		[redacted]
Rationale for change		
Section to be changed		4.2.2.4 Restrictions regarding gamete donation
Description of change		Section 4.2.2.4 was added
Rationale for change		[redacted]
Section to be changed		3.3.1.1 Study eye criteria
Description of change		… the eye with the higher (=worse) DRSS level at screening will qualify for the study eye; the fellow eye will not be enrolled into the analysis of the key

		secondary endpoint. *was changed to:* … the eye with the higher (=worse) DRSS level at screening will qualify for the study eye;
Rationale for change		Clarification
Section to be changed		4.1.5.1 Masking
Description of change		Access to unmasked data … *was changed to:* If a planned interim PK/PD analysis is conducted, access to unmasked data …
Rationale for change		Clarification regarding interim analysis
Section to be changed		7.4 INTERIM ANALYSES
Description of change		An interim PK/PD analysis will be performed … *was changed to:* An interim PK/PD analysis may be performed …
Rationale for change		Clarification regarding interim analysis
Section to be changed		5.3.4 Pharmacokinetic – pharmacodynamic relationship
Description of change		The pharmacokinetics of BI 1467335 will be investigated … *was changed to:* The pharmacokinetics of BI 1467335 may be investigated … … a pharmacometric PK/PD analysis will be performed … *was changed to:* … a pharmacometric PK/PD analysis may be performed …
Rationale for change		[redacted]
[redacted]		[redacted]
[redacted]		[redacted]
Rationale for change		Clarification
Section to be changed		6.2.1 Screening and run-in period(s)

Description of change		Re-Screening Patients who do not fulfil all of the eligibility criteria for a reason that later resolves and all eligibility criteria can be met within a 12-week period after initial screening visit, can be re-screened up to one time. *was changed to:* Patients who do not fulfil all of the eligibility criteria for a reason that later resolves and all eligibility criteria can be met, can be re-screened up to one time.
Rationale for change		To allow more flexibility in re-screening
Section to be changed		7.3.5 Pharmacokinetic and pharmacodynamic analyses
Description of change		[redacted]
Rationale for change		Clarification
Section to be changed		7.5 HANDLING OF MISSING DATA
Description of change		Rules for handling missing data are outlined in the BI SOP mention in section 10.1. *was changed to:* Rules for handling missing data are outlined in BI SOP.
Rationale for change		Clarification
Section to be changed		10.1 PHARMACOKINETIC ANALYSES
Description of change		[redacted]
Rationale for change		Clarification

11.4 GLOBAL AMENDMENT 4

Date of amendment		11 Apr 2019
EudraCT number **EU number**		2016-002971-91
BI Trial number		1386.12
BI Investigational Product(s)		BI 1467335
Title of protocol		A **R**andomized, double-masked, placebo-controlled exploratory study to evaluate safety, tolerability, pharmacodynamics and pharmacokinetics of **O**rally administered **BI** 1467335 for 12 weeks with a 12 week follow up period in patients with **N**on-proliferative diabetic retinopathy without center-involved diabetic macular edema (ROBIN study)
Global Amendment due to urgent safety reasons		☐
Global Amendment		☑
Section to be changed		FLOW CHART 4.1.4.1 Trial medication administration at the study site 5.3.1 Assessment of pharmacokinetics 5.3.2 Methods of sample collection 6.2.2 Treatment period(s) 10.2 TIME SCHEDULE FOR BI 1467335 PHARMACOKINETIC (PK), PK METABOLITE (M) AND PHARMACODYNAMIC (PD) BLOOD SAMPLING
Description of change		[redacted]
[redacted]		
Section to be changed		FLOW CHART
Description of change		Footnote 23 added
Rationale for change		To clarify rescreening and retesting procedures at screening

Section to be changed		FLOW CHART
Description of change		[redacted]
Rationale for change		[redacted]
Section to be changed		FLOW CHART 5.2.5.1 Ocular safety parameters 6.1 VISIT SCHEDULE
Description of change		Reference to Section 3.3.3 exclusion criterion #4 added to the description of gonioscopy procedure. The flowing sentence was added to Flow chart footnote 9 and Section 6.1: "Goniscopy can also be performed before dilation, if preferred by the investigator."
Rationale for change		Clarification when gonioscopy should be performed.
Section to be changed		ABBREVIATIONS 3.3.3 Exclusion criteria 3.3.4.1 Withdrawal from trial treatment
Description of change		Specification of QTcF formula
Rationale for change		Clarification that QTcF formula is being used for QTc assessments
Section to be changed		3.3.3 Exclusion criteria
Description of change		EX#1 – 'in the study eye' added to cataract surgery language
Rationale for change		Clarification that exclusion related to cataract surgery applies to the study eye.
Section to be changed		3.3.3 Exclusion criteria
Description of change		*EX#6 was changed to:* "Treatment of either CI-DME or DR, with …"
Rationale for change		Clarification
Section to be changed		FLOW CHART
[redacted]		[redacted]

Rationale for change		To emphasize additional information collected for ocular events. This is not a new requirement in the protocol or CRFs.
Section to be changed		6.2.1 Screening and run-in period(s)
Description of change		Laboratory testing may be repeated … *was changed to* Screening evaluations may be repeated …
Rationale for change		Clarification that all screening evaluations can be repeated not just laboratory testing
Section to be changed		7.3.2 Secondary endpoint analyses
Description of change		*The following sentence was deleted:* A sensitivity analysis may be performed excluding observations obtained after the start of rescue medication.
Rationale for change		Such sensitivity analysis cannot be performed since there is no defined rescue medication.
Section to be changed		FLOW CHART 6.2.2 Treatment period(s)
Description of change		[redacted]
[redacted]		[redacted]

APPROVAL / SIGNATURE PAGE

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Document Name: clinical-trial-protocol-version-5

Title: A Randomized, double-masked, placebo-controlled exploratory study to evaluate safety, tolerability, pharmacodynamics and pharmacokinetics of Orally administered BI 1467335 for 12 weeks with a 12 week follow up period in patients with Non-proliferative diabetic retinopathy without center-involved diabetic macular edema (ROBIN study)

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	12 Apr 2019 18:12 CEST
Approval-Team Member Medicine		12 Apr 2019 20:58 CEST
Approval-Clinical Pharmacokinetics		15 Apr 2019 09:45 CEST
Author-Trial Statistician		15 Apr 2019 19:25 CEST
Approval-Therapeutic Area [redacted]		16 Apr 2019 08:27 CEST
Verification-Paper Signature Completion		18 Apr 2019 19:18 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed