

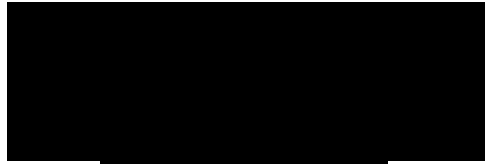






**CLINICAL TRIAL PROTOCOL**

<b>Document Number:</b>	<b>c03441881-03</b>	
<b>EudraCT No.:</b>	2015-003529-33	
<b>BI Trial No.:</b>	1320.22	
<b>BI Investigational Product:</b>	BI 1026706	
<b>Title:</b>	A randomized, double-masked, placebo-controlled exploratory study to evaluate pharmacodynamics, safety and tolerability of orally administered BI 1026706 for 12 weeks in patients with mild visual impairment due to center-involved diabetic macular edema (DME)	
<b>Brief Title:</b>	Safety and effect on central retinal thickness of BI 1026706 in patients with diabetic macular edema	
<b>Clinical Phase:</b>	II a	
<b>Trial Clinical Monitor:</b>	 Phone:  Fax: 	
<b>Coordinating Investigator:</b>	 Phone:  Fax: 	
<b>Status:</b>	Final Protocol	
<b>Version and Date:</b>	Version 2.0	Date: 07 Mar 2016
<b>Page 1 of 65</b>		
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## CLINICAL TRIAL PROTOCOL SYNOPSIS



















<b>Name of company:</b>		Boehringer Ingelheim	
<b>Name of finished product:</b>		-	
<b>Name of active ingredient:</b>		BI 1026706	
<b>Protocol date:</b> 16 Dec 2015	<b>Trial number:</b> 1320.22		<b>Revision date:</b> 07 Mar 2016
<b>Title of trial:</b>	Randomized, double-masked, placebo-controlled exploratory study to evaluate pharmacodynamics, safety and tolerability of orally administered BI 1026706 for 12 weeks in patients with visual impairment due to center-involved diabetic macular edema (DME)		
<b>Coordinating Investigator:</b>	 Phone:  Fax: 		
<b>Trial site(s):</b>	Multi-centre trial		
<b>Clinical phase:</b>	Phase IIa		
<b>Objective(s):</b>	To investigate pharmacodynamics, safety and tolerability of oral BI 1026706 in patients with diabetic macular edema (DME).		
<b>Methodology:</b>	Randomized, double-masked, placebo-controlled, parallel design comparison of BI 1026706 versus placebo group over 12 weeks.		
<b>No. of patients:</b>			
<b>total entered:</b>	100		
<b>each treatment:</b>	50		
<b>Diagnosis:</b>	Patients with vision impairment due to center-involved DME		
<b>Main criteria for inclusion:</b>	<b>Main Inclusion criteria:</b> <ul style="list-style-type: none"> <li>• Age ≥ 18 years</li> <li>• Male or female of non-childbearing potential</li> <li>• Diabetes mellitus type 1 or type 2 with stable antidiabetic medication (stable medication defined as: no change in oral antidiabetic medication and/or no initiation of intensive</li> </ul>		

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<b>Name of active ingredient:</b>		BI 1026706	
<b>Protocol date:</b> 16 Dec 2015	<b>Trial number:</b> 1320.22		<b>Revision date:</b> 07 Mar 2016
		<p>insulin treatment within 3 months prior to randomization or plans to do so in the next 4 months)</p> <ul style="list-style-type: none"> <li>• Center-involved DME with central subfield thickness (CSFT) <math>\geq 300 \mu\text{m}</math> on SD-OCT in the study eye, confirmed by CRC</li> <li>• Best corrected visual acuity ETDRS letter score in the study eye <math>\leq 84</math> and <math>\geq 70</math>.</li> </ul> <p><b>Main Exclusion criteria:</b></p> <ul style="list-style-type: none"> <li>• Macular edema considered to be due to other causes than DME</li> <li>• Additional eye disease in the study eye that, in the opinion of the Investigator, might affect macular edema or could compromise or alter visual acuity during the course of the study</li> <li>• Anterior segment and vitreous abnormalities in the study eye that would compromise the adequate assessment of the visual acuity or an adequate examination of the posterior pole</li> <li>• Intraocular surgery in the study eye within 4 months prior to randomization or planned intraocular surgery, including cataract, during the study period</li> <li>• Proliferative diabetic retinopathy or iris neovascularisation in the study eye</li> <li>• Aphakia in the study eye</li> <li>• Any indication that requires immediate treatment with anti-VEGF or with laser photocoagulation during the study period as per Investigator's judgment</li> <li>• History of prior laser photocoagulation or other surgical, intravitreal or peribulbar treatment in the study eye within 4 months prior to randomization, either for DME or an ocular condition other than DME</li> <li>• History of fluocinolone acetonide intravitreal implant in the study eye</li> </ul>	

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<b>Name of active ingredient:</b>		BI 1026706	
<b>Protocol date:</b> 16 Dec 2015	<b>Trial number:</b> 1320.22		<b>Revision date:</b> 07 Mar 2016
		<ul style="list-style-type: none"> <li>• Application of intraocular corticosteroids in the study eye within 2 years prior to randomization in phakic eyes or 9 months in pseudophakic eyes</li> <li>• Systemic anti-VEGF or pro-VEGF treatment within 4 months prior to randomization</li> <li>• Patients with a clinically relevant abnormal screening haematology, blood chemistry, or urinalysis</li> <li>• Renal impairment with estimated CrCL (as calculated by Cockcroft-Gault equation) &lt; 30 mL/min at screening</li> <li>• Myocardial infarction or unstable angina pectoris within 3 months before randomization.</li> </ul>	
<b>Test product(s):</b>	BI 1026706 film-coated tablet		
<b>dose:</b>	100 mg twice daily (b.i.d.); total daily dose 200 mg		
<b>mode of administration:</b>	p.o.		
<b>Comparator products:</b>	Placebo film-coated tablet		
<b>dose:</b>	Not applicable		
<b>mode of administration:</b>	p.o.		
<b>Duration of treatment:</b>	12 weeks (84 days)		
<b>Endpoint</b>	The primary endpoint is the change from baseline in central subfield thickness (CSFT) in DME patients at week 12 as assessed by Spectral-Domain Optical Coherence Tomography (SD-OCT).		
<b>Safety criteria:</b>	Adverse events, visual acuity, vital signs (blood pressure, pulse rate), physical examination, weight, 12-lead ECG and clinical laboratory parameters.		
<b>Statistical methods:</b>	For the primary endpoint, change from baseline in CSFT at 12 weeks, restricted maximum likelihood estimation based on mixed-		

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<p>effect model for repeated measures (MMRM) analysis will be used to obtain adjusted means for the treatment effects. This model will include treatment and week as discrete fixed effects, baseline CSFT as continuous fixed effects, as well as the interaction between week and treatment and the interaction between week and baseline CSFT.</p> <p>All other endpoints will be analysed via MMRM or descriptive statistics.</p>			

## FLOW CHART

Investigations/Tests and Procedures	Screening Period	Randomized Treatment Period					Follow-up Period
	1	2a	2b Phone Visit	3	4	5/EOT <sup>1</sup>	6/End of Study <sup>2</sup>
<b>Visit</b>	1	2a	2b Phone Visit	3	4	5/EOT <sup>1</sup>	6/End of Study <sup>2</sup>
<b>Study Week</b>			1	4	8	12	16
							
Informed consent	X						
Review of in-/exclusion criteria	X	X					
Demographics	X						
Medical history / baseline conditions	X						
Adverse events	X	X	X	X	X	X	X
Concomitant therapy	X	X	X	X	X	X	X
Physical examination	X	X		X	X	X	X
Body height	X						
Body weight	X	X				X	X
Vital signs (BP, PR)	X	X		X	X	X	X
12 lead-ECG	X	X		X	X	X	X
Safety dipstick urine test	X	X		X	X	X	X
Safety laboratory blood tests <sup>4</sup>	X	X		X	X	X	X
PK blood sampling <sup>5</sup>		X		X	X	X	
Pharmacogenetic (PGx) blood sample for genotyping <sup>6</sup>		X					
Informed consent DNA banking <sup>7</sup>	X	→					
DNA banking blood sample		X <sup>7</sup>	→				
Biomarker blood sampling		X				X	
<b>Ophthalmological exams:<sup>8</sup></b>							
							
Slit lamp	X	X		X	X	X	X
SD-OCT	X	X		X	X	X	X
							
Ocular tonometry	X					X	
Collect/check study drug diary				X	X	X	
Collection of study drug / Drug accountability check				X	X	X	
Compliance check				X	X	X	
IRT Randomization call		X					
Dispense study drug kits		X		X	X		
Dispense study drug diary		X		X	X		
Administration of study drugs at site		X		X	X		
Study completion <sup>9</sup>							X

BP = blood pressure; EOT = End of treatment; IRT = Interactive Response Technology; PR = pulse rate.

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█ [REDACTED]

█ [REDACTED]

█ [REDACTED]

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█ [REDACTED]

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## ABBREVIATIONS

ADME	Absorption, Distribution, Metabolism and Excretion
AE	Adverse Event
AESI	Adverse Event of Special Interest
AUC	Area under the curve
█	█
b.i.d.	bis in die (twice daily dosing)
BCRP	Breast Cancer Resistance Protein
█	█
BP	Blood Pressure
CA	Competent Authority
CI	Confidence Interval
C <sub>max</sub>	Peak plasma concentration
C <sub>min</sub>	Minimum plasma concentration
CML	Local Clinical Monitor
C <sub>pre</sub>	Pre-dose trough concentration
CRA	Clinical Research Associate
CRC	Central Reading Center
CrCL	Creatinine Clearance
CRF	Case Report Form
CRO	Contract Research Organisation
CSFT	Central subfield foveal thickness
CTP	Clinical Trial Protocol
CTR	Clinical Trial Report
CTX	Carboxy-terminal collagen crosslinks
CYP	cytochrome P 450
DDI	Drug-drug interaction
DILI	Drug Induced Liver Injury
DM	Diabetes mellitus
DME	Diabetic Macular Edema
DR	Diabetic retinopathy
eCRF	Electronic Case Report Form
EOT	End of Treatment
ETDRS	Early Treatment Diabetic Retinopathy Study
EudraCT	European Clinical Trials Database
█	█
FAS	Full Analysis Set
FU	Follow Up
5-HT2B	5-Hydroxytryptamine 2B
GCP	Good Clinical Practice
GI	Gastrointestinal
HV	Healthy Volunteer
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IOP	Intraocular Pressure

IRB	Institutional Review Board
IRT	Interactive Response Technology
ISF	Investigator Site File
IVT	intravitreal
MedDRA	Medical Dictionary for Drug Regulatory Activities
MMRM	Mixed-effect model for repeated measures
MRD	Multiple Rising Dose
NOAEL	No Observed Adverse Effect Level
NSAID	Nonsteroidal anti-inflammatory drugs
PD	Pharmacodynamics
P-gp	permeability glycoprotein
PGx	Pharmakogenetics
P1NP	procollagen type I N-terminal propeptide
PK	Pharmacokinetics
p.o.	per os (oral)
PoCM	Proof of clinical mechanism
PR	Pulse Rate
PTM	Planned Time
RDC	Remote Data Capture
REML	Restricted Maximum Likelihood Estimation
REP	Residual effect period, after the last dose of medication with measurable drug levels or pharmacodynamic effects still likely to be present
RPED	Retinal pigment epithelium detachment
SAE	Serious Adverse Event
SD-OCT	Spectral-domain Optical Coherence Tomography
SOP	Standard Operating Procedure
SPC	Summary of Product Characteristics
SRD	Single rising dose
TCM	Trial Clinical Monitor
TS	Treated Set
TSAP	Trial Statistical Analysis Plan
ULN	Upper limit of normal
VEGF	Vascular Endothelial Growth Factor

## 1. INTRODUCTION

BI 1026706 is a [REDACTED] proposed by Boehringer Ingelheim (BI) for the treatment of diabetic macular edema (DME), an ocular complication of diabetes mellitus (DM). DME is the most common cause of moderate to severe vision loss in diabetic patients, substantially affecting independence and quality of life.

### 1.1 MEDICAL BACKGROUND

DME is the leading cause of vision loss in persons aged 20 to 74 years and the leading cause of blindness in diabetic patients. The disease affects central vision and can lead to decline in vision ranging from slight visual blurring to blindness. DME develops in approximately 20% of diabetic patients within 15 years following the diagnosis of diabetes. About 8.7 million patients suffer from DME worldwide, with about 50% of those having early stages of vision impairment in line with the targeted patient population ([R15-1951](#)).

The exact pathogenesis of DME is only incompletely understood. The disease is characterized by intraretinal and subretinal accumulations of fluid due to the leakage of intraretinal fluid from perifoveal abnormal retinal capillaries or microaneurysms. Increased vasopermeability occurs as a result of breakdown of the blood-retinal barrier (BRB) due to many factors. DME is not a condition that develops independently from other diabetic findings. Rather, it is closely associated with the degree of diabetic retinopathy (DR) that is present, and the duration and type of diabetes that the patient has ([R15-5250](#)). Recent evidence indicates that DR is a neurovascular disease of the retina. There is a strong relationship between the development of DR and chronic hyperglycaemia which triggers a sequence of events causing vascular endothelial dysfunction ([R15-5221](#)), but the pathology extends beyond a pure microvasculopathy and includes oxidative stress and inflammatory mechanisms, such as increased nitric oxide (NO) production and release of pro-inflammatory cytokines ([R15-5222](#), [P08-12095](#)). Both oxidative stress and inflammation result in up-regulation of cytokines, chemokines and growth factors like vascular endothelial growth factor (VEGF), which are associated with deleterious effects on vascular and neuronal cells and increase of retinal capillary permeability and subsequent retinal edema ([R15-5246](#)).

Until 2010, the standard of care for treating clinically significant macular edema was focal/grid laser photocoagulation, reducing the risk of vision loss and increasing the possibility of vision gain compared with no treatment. From 2010, pharmacotherapy in the form of anti-VEGF agents administered by intravitreal injections has proven to be superior to focal/grid laser photocoagulation in decreasing the risk of vision loss and increasing the possibility of vision gain. This led to approval of ranibizumab (Lucentis<sup>®</sup>) in 2010 for the indication DME, and of aflibercept (Eylea<sup>®</sup>) in 2014. In addition, bevacizumab (Avastin<sup>®</sup>), an anti-VEGF agent indicated for the treatment of certain metastatic cancers but not for DME, is frequently used as off-label treatment due to its similar efficacy outcomes and reduced costs ([R15-5248](#)).

Anti-VEGF treatment is characterized by a fast onset of action. After the first injection, about half-maximal efficacy was observed, on average, with a mean improvement in visual acuity

of about 12 letters compared to baseline, as measured by ETDRS letter charts. It was demonstrated that DME patients with a mild vision loss at baseline (i.e., ETDRS best corrected visual acuity (BCVA) of 78 to 69 letters) have shown a mean gain of about 8 letters with an average of 9 intravitreal (IVT) injections after a treatment period of 52 weeks. In patients with more severe vision loss with a baseline vision worse than 69 letters a more prominent mean gain of 14 to 19 letters with a similar number of injections was observed ([R15-5225](#)).

Regarding the safety profile, rare but serious adverse reactions are related to the injection procedure including endophthalmitis, rhegmatogenous retinal detachment and iatrogenic traumatic cataract. Increases in intraocular pressure (IOP) have been noted both pre- and post-IVT treatment, as well as sustained elevations in IOP ([R15-5524](#)). In addition, there is a potential risk of arterial thromboembolic events following intravitreal use of VEGF inhibitors. Based on these safety concerns mostly related to the invasive injection procedure initiation of anti-VEGF treatment would be preferable deferred to more advanced disease stages (i.e., BCVA < 69 letters, approximate Snellen equivalent  $\leq 20/40$ ). So far, there are no other drugs that have been shown to be equally effective ([R15-5223](#)). This leaves treatment opportunities for an easy to administer and safer, such as an oral compound to treat early stages and intervene earlier in the progressive course of DME in order to preserve vision in patients with mild vision impairment due to center-involved DME, characterized by vision loss of up to 15 letters, i.e. ETDRS visual acuity ranging from 84 to 70 letters (approximate Snellen equivalent < 20/20 and  $\geq 20/40$ ).

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### 1.2.1 Toxicology

Repeat-dose toxicity studies in rat and cynomolgus monkeys (maximum feasible dose of 1000 mg/kg) with daily oral administration for up to 13 weeks have revealed no adverse findings or toxicological target organs with clinical relevance. No Observed Adverse Effect Levels (NOAEL) were 1000 mg/kg/day in cynomolgus monkeys, and in the 13-week rat study 400 mg/kg in males and 250 mg/kg in females. However, adverse findings in rats were considered to be not relevant for humans when BI 1026706 is administered as tablets. Based on the revised human therapeutic dose of 25–100 mg b.i.d., corresponding safety margins ( $AUC_{0-24h}$  and  $C_{max}$  based) derived from the 13-week studies are 32× or higher.

### 1.2.2 Clinical Studies

The clinical studies completed so far involve the single rising dose (SRD) study in healthy volunteers (HV) and the MRD study in HVs and patients with osteoarthritis. Overall, these phase I trials evaluating safety, tolerability and PK of BI 1026706 demonstrated that the compound was safe and well tolerated with no unexpected safety signal.

When administered as tablet, BI 1026706 exposure increased dose-proportionally up to 100 mg and less than dose-proportional at higher doses (200 and 400 mg). Food had a minimal impact on  $AUC$  and  $C_{max}$  of BI 1026706 following administration of a 100 mg dose suggesting that tablets could be administered with or without food in upcoming patient trials. For a more detailed description of the drug profile refer to the current Investigator's Brochure (IB) ([c03035551-01](#)) which is included in the Investigator Site File (ISF).

## 2. RATIONALE, OBJECTIVES, AND BENEFIT - RISK ASSESSMENT

### 2.1 RATIONALE FOR PERFORMING THE TRIAL

By inhibiting [REDACTED] a reduction of the edema at the fovea region of patients with DME is expected, resulting in reduction of the abnormal increase of the central retina thickness and, finally, improvement of the central vision. An oral medication capable to treat patients with center-involved DME with mild vision loss could fill the gap in which all patients with DME could be treated properly without the risk of possible complications of current treatment options. Therefore, the target population for BI 1026706 is seen in patients with center-involved DME and as first-line therapy before anti-VEGF treatment initiation.

This phase 2a study is designed to demonstrate a beneficial effect of oral BI 1026706 on retinal lesion morphology for clinical proof of mechanism (PoCM). Therefore, this study will investigate the change in central subfield thickness (CSFT) after 12 weeks of treatment, [REDACTED]. This study is also conducted as a safety and tolerability trial. The duration of treatment in the current trial is longer than that of previous phase I trials and it will therefore serve as a bridging trial between the previous phase I MRD study of 12 days duration performed in healthy volunteers and in patients with osteoarthritis and the planned phase IIb study of 52 week duration in patients with DME.

### 2.2 TRIAL OBJECTIVES

The primary objective of the current PoCM study is to explore the mechanistic of BI 1026706 in the treatment of patients with mild vision impairment due to center-involved DME and to evaluate safety and tolerability of BI 1026706 administered orally twice daily for 12 weeks.

[REDACTED]

Concentrations of BI 1026706 in plasma will be determined to allow for exploratory pharmacokinetics (PK)/pharmacodynamic (PD) correlations to efficacy parameters.

[REDACTED]

Also, safety assessed throughout the study will provide key information regarding the appropriateness of using BI 1026706 as a long-term treatment in DME by extending exposure to 12 weeks in the current study.

[REDACTED]



## 2.3 BENEFIT - RISK ASSESSMENT

BI 1026706 has not been previously investigated in patients with DME or other ocular diseases, and the sponsor is not aware of any clinical studies on the effects of orally administered [REDACTED] in patients with DME. Although DME may be successfully treated in most patients using IVT injections with anti-VEGF biologics, not all patients respond adequately and there is room for additional efficacy. Intravitreal treatment requires multiple injections over time and the procedure carries the risk of endophthalmitis, vitreous hemorrhage, retinal detachment, traumatic cataract, and increased intraocular pressure (IOP). An equally effective oral therapy would be considered an attractive medical advance.

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 CSFT or on clinical symptoms such as vision impairment related to DME for those patients following 12 weeks of treatment with BI 1026706.

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 DME is detected during the trial (please also refer to [Section 4.2.1](#)). Beyond close monitoring of DME symptoms, lesion morphology, clinical laboratory parameters and clinical evaluations there is no specific benefit for these patients. However, the inclusion of a placebo group is essential for the evaluation of the safety and tolerability of BI 1026706 in DME which have not been studied so far.

Given the high unmet need for an effective oral treatment for DME, good clinical tolerability of BI 1026706 coupled with a favorable risk/ benefit ratio supports the conduct of this study. Early pharmacokinetic and safety evaluations of orally administered BI 1026706 demonstrated that treatment was well tolerated at potentially relevant levels and support further clinical development. Safety will be monitored (as described in [Section 5.3](#)) at each clinic visit. This study will therefore provide insight into the safety profile of BI 1026706 in the target population over a longer treatment period of 12 weeks to allow bridging to further studies with longer treatment duration.

The risk of inclusion patients with DME is acceptable based on the data and trial results mentioned in [Section 2.3.2](#) below. The patients participating in this study will be exposed to

- the risks of the study procedures
- the known risks related to exposure to the investigational product
- unknown risks that might be related to exposure to the investigational product.

### 2.3.1 The risks of the study procedures

SD-OCT is an established medical imaging technique that uses eye-safe near-infrared light without damage to the tissue. [REDACTED]

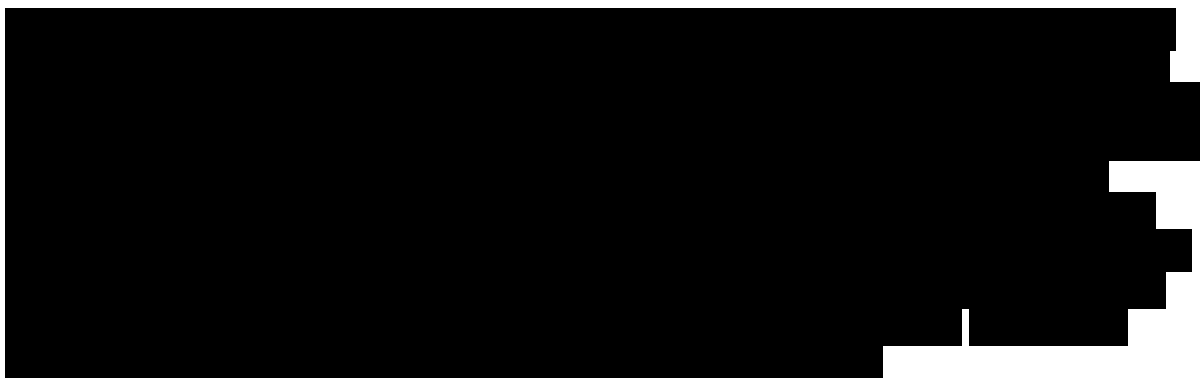
[REDACTED] Other study procedures such as routine ocular examinations, [REDACTED], electrocardiography (ECG) recording, blood pressure measurements or collection of blood are unlikely to cause any adverse events.

### 2.3.2 Drug related risks

BI 1026706 was overall well tolerated at all dose levels (both oral solution and tablet formulation) in the three single dose studies 1320.1, 1320.3, and 1320.13 and in the MRD study 1320.2 in which it was administered for up to 12 days. However, some gastrointestinal effects were observed in subjects treated with high doses (200 or 300 mg q.d.) of oral solution in the MRD study, most likely due to the amount of excipients in the final solution. In this study, a solid tablet formulation will be used.

Based on *in-vitro* data, BI 1026706 exposure may be affected by inhibition or induction of cytochrome P 450 (CYP) 3A4 and permeability glycoprotein 1 (P-gp). The potential of BI 1026706 as a perpetrator of drug-drug interactions (DDI) is expected to be low. A DDI trial (1320.20) to evaluate the impact of CYP 3A4 and P-gp inhibition on the pharmacokinetics of BI 1026706 is ongoing. Specific medication exclusion criteria will ensure that the DDI risk is minimized (see [Section 4.2.2](#)).

Data obtained in the SRD and the MRD trials suggest that renal excretion of unchanged drug is a minor elimination pathway in humans with relative fractions of unchanged drug <4% and <3.5%, respectively (values expressed as GeoMean). Therefore, no accumulation of BI 1026706 is expected in patients with mild to moderate renal insufficiency.



Although rare, a potential for drug-induced liver injury 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 5.3.6.1](#).

Females will only be included in this trial if they are of non-childbearing potential.

Overall BI 1026706 showed an acceptable safety profile supporting a parallel-design in Phase IIa. For further details, please refer to the IB ([c03035551-01](#)).

### 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 mechanism study. Patients will be enrolled into the study once they have signed the informed consent form. Patients become eligible for randomization if they have met all inclusion and none of the exclusion criteria. Entered patients will take 100 mg b.i.d. of BI 1026706 or placebo from Day 1 to Day 84 (12 weeks). Following conclusion of a 12 week treatment period, or upon withdrawal from study medication, all patients will be eligible to receive standard of care therapy at the discretion of the Investigator. Patients will be followed up at the End of Study Visit four weeks after the End of treatment Visit 5/EOT.

The 12 weeks treatment design is described in [Figure 3.1: 1](#).

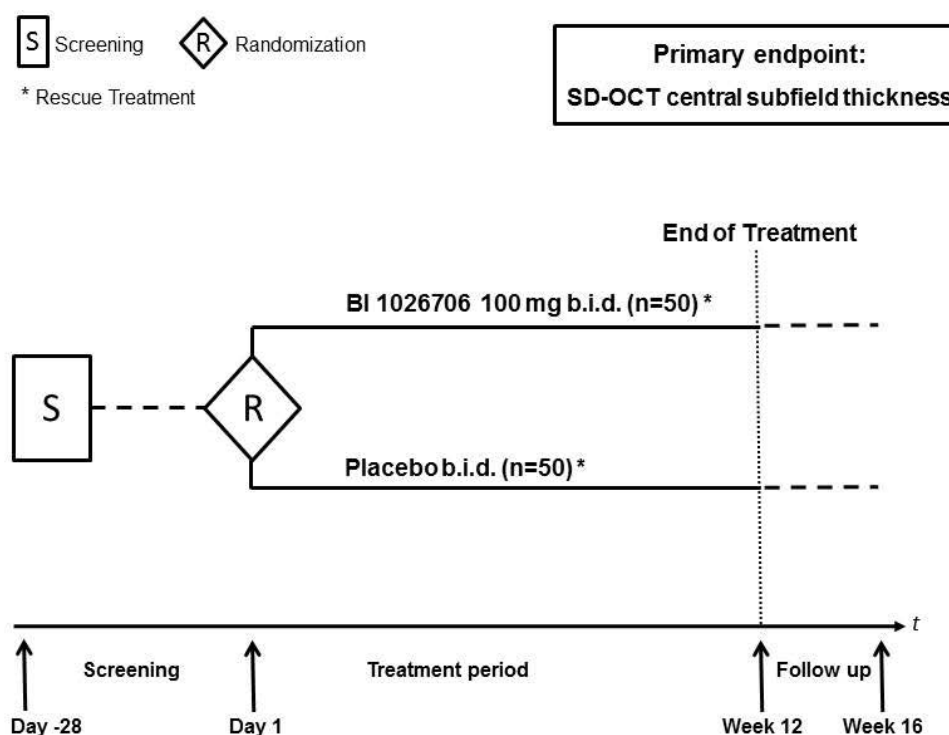


Figure 3.1: 1 Study Design

##### 3.1.1 Administrative structure of the trial

Boehringer Ingelheim 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,
- order the materials as needed for the trial,
- ensure appropriate training and information of local clinical monitors (CML), Clinical Research Associates (CRAs), and Investigators of participating countries.

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

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

A Coordinating Investigator will be nominated and will be responsible to coordinate Investigators at different centres participating in this multicentre trial. Tasks and responsibilities will be defined in a contract. Relevant documentation on the participating (Principal) Investigators and other important participants, including their curricula vitae, will be filed in ISF.

### **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 pharmacodynamics, safety, tolerability and PK of 100 mg b.i.d. of BI 1026706 in patients with mild vision loss due to center-involved DME. Because an efficacious therapy is available for patients with DME who experience at least moderate visual loss (defined as a 15 or more letter score decrease in visual acuity), this trial aims to treat DME patients with only mild vision loss in order to stabilize or even improve central macular edema early in the course of the disorder where it is a reasonable alternative to observe disease progression with the possibility of initiation of rescue treatment at any time during the study.

The study is a short clinical proof of mechanism trial, and given a rather slow progression of DME the duration of the study is considered sufficient to assess the primary outcome of change from baseline in comparison to placebo by SD-OCT in lesion morphology ([R15-5225](#)). The chosen primary outcome is objective with minimal time related effects expected and is therefore appropriate.

A placebo control arm was chosen for this trial in order to compare BI 1026706 and placebo regarding safety and tolerability in patients with DME, which is another important aim of the trial. The treatment period of 12 weeks is deemed adequate to evaluate safety and tolerability, and is covered by currently available 13 weeks toxicology data.

Approximately equal numbers of patients will be randomized to both treatment groups. Randomization will be stratified by previous treatment for DME into treatment naïve versus previously treated patients as this may have impact on the expected effects regarding the primary outcome.

There is the possibility of rescue treatment according to standard of care interventions in the case of significant worsening of clinical and PD parameters at all times during the study for both treatment arms, BI 1026706 and placebo.

### 3.3 SELECTION OF TRIAL POPULATION

A sufficient number of male and female patients with DM either type 1 or type 2 and center-involved DME with mild vision loss will be screened to ensure the randomization of 100 patients from around 44 study sites. The reason for conducting the study with many sites lies with the expected enrolment rate which might be low, as patients are only mildly affected and pure observation is a reasonable option before starting standard intravitreal injection therapy. To take account of the consistent evaluation of endpoints at all sites only prequalified study sites will participate, and SD-OCT images will be evaluated by an independent central reading center (CRC).

It is expected that around 2-3 patients will be randomised at each study site. If enrolment is delayed, additional sites may be recruited. Permission to enrol more than 15 patients per site must be obtained from the 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 study is competitive across all countries within the study, i.e. screening for the study will stop at all sites when it is anticipated that a sufficient number of patients have been screened to yield the desired number of patients randomised to trial treatment. Investigators will be notified when sufficient patients have been screened and when screening is complete, and will not be allowed to recruit additional patients for the study. Patients who have completed Visit 1 procedures prior to notification of the termination of recruitment will be allowed to continue in the study, if they meet all entry criteria and they are able to follow the visit schedule specified in this Clinical Trial Protocol (CTP).

A screening 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.

#### 3.3.1 Main diagnosis for trial entry

Patients with vision loss due to center-involved DME at the Screening visit are eligible for inclusion if they fulfil all of the inclusion criteria and none of the exclusion criteria. Only one study eye per subject may be enrolled. Ophthalmologic evidence of center-involved DME 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 in- 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 exclusion criteria, this eye will qualify for the study eye;

- If both eyes in an individual patient meet all of the inclusion criteria and none of the exclusion criteria, the eye with the larger CSF thickness (CSFT) will qualify for the study

eye; the fellow eye will be examined only for safety reasons and will be not enrolled into the analysis of the primary endpoint;

- If both eligible eyes show the same size of CSFT, the eye with the worse BCVA letter score as assessed by ETDRS chart will qualify for the study eye;
- If both eligible eyes show the same size of CSFT 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 before, the investigator together with the patient may decide which eye will be selected as the study eye.

### 3.3.2 Inclusion criteria

1. Age  $\geq$  18 years
2. Male patients or female patients of non-childbearing potential <sup>1</sup>
3. Diagnosis of DM (type 1 or type 2) as evidenced by one of the following:
  - Current regular use of insulin for the treatment of diabetes
  - Current regular use of oral anti-hyperglycaemia agents for the treatment of diabetes
  - Documented diabetes by American Diabetes Association (ADA) and/or World Health Organization criteria
4. Retinal thickening due to DME involving the center of the macula in the study eye as confirmed by the Investigator on clinical exam
5. DME confirmed on SD-OCT with CSFT  $\geq$  300  $\mu$ m in the study eye at screening, confirmed by CRC
6. Best corrected visual acuity ETDRS letter score in the study eye  $\leq$  84 and  $\geq$  70 at screening
7. Media clarity, pupillary dilation and individual cooperation sufficient for adequate SD-OCT and fundus photographs
8. Signed and dated written informed consent consistent with GCP and local legislation prior to admission to the trial. Medication washout and medication restrictions are allowed only after signed informed consent is obtained.

### 3.3.3 Exclusion criteria

1. Macular edema considered to be due to other causes than DME in the study eye.

An eye should not be considered eligible if:

- The macular edema is considered to be related to ocular surgery, such as cataract extraction, or
  - Clinical examination and/or SD-OCT suggest that vitreoretinal interface abnormalities are contributing to the macular edema, such as a taut posterior hyaloid or epiretinal membrane
2. Additional eye disease in the study eye that, in the opinion of the Investigator, might affect macular edema or could compromise or alter visual acuity during the course of the study (e.g., vein occlusion, uncontrolled intraocular pressure (IOP)  $>$ 24 mmHg on

<sup>1</sup> Women of non-childbearing potential are defined as:

- postmenopausal ( $\geq$  12 months with no menses without an alternative medical cause) or
- permanently sterilized (defined as hysterectomy, bilateral oophorectomy or bilateral salpingectomy).

- 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)
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. An ocular condition is present in the study eye such that, in the opinion of the Investigator, any visual acuity loss would not improve from resolution of macular edema, e.g., foveal atrophy, dense subfoveal hard exudates, pigment abnormalities or fibrosis
  5. Intraocular surgery in the study eye within 4 months prior to randomization or planned intraocular surgery, including cataract, during the study period
  6. History of yttrium aluminium garnet (YAG) laser capsulotomy performed in the study eye within 2 months prior to randomization
  7. Proliferative diabetic retinopathy or iris neovascularisation (including the anterior chamber angle, ruled out by gonioscopy) in the study eye
  8. Aphakia in the study eye
  9. Any indication that requires immediate treatment or for which treatment is expected in the study eye with anti-VEGF or with laser photocoagulation during the course of the study, as per Investigator's judgment
  10. History of prior laser photocoagulation or other surgical, intravitreal or peribulbar treatment in the study eye within 4 months prior to randomization, either for DME or an ocular condition other than DME
  11. History of fluocinolone acetonide intravitreal implant in the study eye
  12. Application of intraocular corticosteroids in the study eye within 2 years prior to randomization in phakic eyes or 9 months in pseudophakic eyes
  13. History of topical steroid or nonsteroidal anti-inflammatory drugs (NSAID) treatment in the study eye within 30 days prior to randomization
  14. Systemic anti-VEGF or pro-VEGF treatment within 4 months prior to randomization
  15. Use of systemic steroids >10 mg prednisone equivalent/day within 4 weeks prior to randomization or known diseases which could require the use of such systemic steroids within the study period
  16. Current or planned, during the study period, use of medications known to be toxic to the retina, lens or optic nerve
  17. Initiation of intensive insulin treatment (multiple daily injections or a pump) within 3 months prior to randomization or plans to do so in the next 4 months
  18. Change in oral antidiabetic medication within 3 months prior to randomization
  19. Patients with a clinically relevant abnormal screening haematology, blood chemistry, or urinalysis, if the abnormality defines a significant disease as defined in other exclusion criteria; AST or ALT greater than 2.0-fold the upper limit of normal; Patients with total bilirubin (TB) or INR > 1.5x upper limit of normal. Laboratory testing may be repeated once during the screening phase
  20. Renal impairment with estimated creatinine clearance (CrCL; as calculated by Cockcroft-Gault equation) < 30 mL/min at screening, or where Investigator expects CrCL is likely to drop below 30 ml/min during the course of the study
  21. Myocardial infarction or unstable angina pectoris within 3 months before randomization



22. Uncontrolled arterial hypertension defined as a single measurement of systolic >180 mmHg, two consecutive measurements of systolic >160 mmHg, or diastolic >100mmHg on optimal medical regimen. If blood pressure is brought ≤160/100 mmHg by antihypertensive treatment, individual can become eligible
23. Significant disease or other medical conditions\* as determined by medical history, examination and clinical investigations at screening that may, in the opinion of the Investigator, result in any of the following:
  - Put the patient at risk because of participation in the study,
  - Influence the results of the study,
  - Cause concern regarding the patient's ability to participate in the study.

\*e.g. cardiac, gastro-intestinal, hepatic, renal, metabolic, dermatologic, neurological, haematological, oncological and psychiatric; history of relevant orthostatic hypotension, fainting spells or blackouts; current chronic or relevant acute infections including external ocular infections in the study eye such as significant blepharitis, chalazion or conjunctivitis; patients with malignancy for which the patient has undergone resection, radiation or chemotherapy within past 5 years. Patients with treated basal cell carcinoma or fully cured squamous cell carcinoma are allowed
24. Patients with a history of and/or active significant alcohol or drug abuse, as assessed by the Investigator
25. Known allergy to any component of the study drug
26. Women of childbearing potential or who are nursing
27. Male patients who do not agree to minimize the risk of female partners becoming pregnant from the first dosing day until 3 months after the trial medication treatment has finished<sup>1</sup>
28. Patients who have participated in another investigational trial within the last 30 days preceding randomization with any drug that has not received regulatory approval or are participating in another trial (patients participating in a purely observational trial will not be excluded)
29. Previous randomization in this trial.

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<sup>1</sup> Male patients who have sexual intercourse with women of childbearing potential will be instructed and must agree to use at least one of the following acceptable forms of effective contraception:

- Established use of oral, injected or implanted hormonal methods of contraception by the female partner of the male patient
- Placement of an intrauterine device (IUD) or intrauterine system (IUS) by the female partner of the male patient
- Use of barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
- Sterilization of the male patient (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).



### **3.3.4 Removal of patients from therapy or assessments**

#### **3.3.4.1 Removal of individual patients**

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

- The patient withdraws consent for study treatment or study participation, without the need to justify the decision.
- The patient needs to take concomitant drugs that interfere with the investigational product in the clinical judgement of the Investigator (please refer to [Section 4.2.2](#)).
- The patient can no longer be treated with trial medication for other medical reasons (such as surgery, adverse events, other diseases, or pregnancy).

Patients who drop out prior to randomization will be considered screening failures. They will be recorded as screening failures in the electronic Case Report Form (eCRF) and no further follow-up is required. The data will be included in the trial database and will be reported.

Patients who discontinue or withdraw from the study after randomization (Visit 2a) will be considered as “early discontinuations” and the reason for premature discontinuation must be recorded in the eCRFs. For patients stopping the treatment prematurely before end of week 12, all investigations according to Visit 5/EOT should be done as soon as possible after stopping the study drug. The End of study Visit (Visit 6) will be performed 28 days after Visit 5/EOT in all patients, as outlined in the [Flow Chart](#) and [Section 6.2.3](#). The data will be included in the trial database and will be reported.

Patients who withdraw or discontinue from the trial after randomization will not be replaced.

#### **3.3.4.2 Discontinuation of the trial by the sponsor**

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

1. Failure to meet expected enrolment goals overall or at a particular trial site
2. Emergence of any efficacy/safety information invalidating the earlier positive benefit-risk-assessment that could significantly affect the continuation of the trial
3. Violation of GCP, the CTP, or the contract disturbing 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 TREATMENTS TO BE ADMINISTERED

#### 4.1.1 Identity of BI investigational product(s) and comparator product(s)

Table 4.1.1: 1 Test product (active drug):

Substance:	BI 1026706
Pharmaceutical formulation:	Film-coated tablets (Formulation B1)
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Str. 65, 88397 Biberach Germany
Unit strength:	100 mg
Posology	Twice daily
Route of administration:	oral

Table 4.1.1: 2 Comparator product (placebo):

Substance:	Placebo to match BI 1026706
Pharmaceutical formulation:	Film-coated tablets (Formulation B1)
Source:	Boehringer Ingelheim Pharma GmbH & Co. KG, Birkendorfer Str. 65, 88397 Biberach Germany
Unit strength:	Placebo to match 100 mg
Posology	Twice daily
Route of administration:	oral

#### 4.1.2 Method of assigning patients to treatment groups

During randomisation visit (Visit 2a) and after the patient's eligibility has been reconfirmed, the treatment will be assigned via Interactive Response Technology (IRT). To facilitate the use of the IRT, the Investigator will receive all necessary instructions.



#### 4.1.4 Drug assignment and administration of doses for each patient

At Visit 2a (Day 1) eligible patients will be randomized to one of 2 double-masked oral treatment groups (BI 1026706 100 mg b.i.d. or placebo matching to the active drug b.i.d., ratio 1:1) using an IRT system. The medication will be administered twice daily, beginning on Day 1 (Visit 2a) until in the evening of the day before Visit 5/EOT (Day 84 according to the visit schedule).

Trial medication is dispensed every month at regularly scheduled study visits (i.e., Visit 2a – 4). The first study medication dose at Visit 2a is given to the patient by the site staff at the investigational site, and trial medication boxes are then dispensed to the patient for home administration (please refer to [Section 4.1.4.2](#)). Study drug kits will contain enough supply to last until the next visit plus some overage. The assigned medication numbers must be entered in the eCRF.

##### 4.1.4.1 Study medication administration at the study site

At Visits 2a, 3 and 4 during the treatment period, the administration of study medication is under the supervision of the Investigator or qualified site staff. One tablet (BI 1026706 or placebo) will be administered with or without a glass of water. At Visit 3 and 4, new study medication boxes will be used for administration of the morning dose at the clinical site after blood sampling (please refer to [Appendix 10.2](#) for details) and will be dispensed for home administration.

##### 4.1.4.2 Study medication administration at home

At home, tablets (BI 1026706 or placebo) will be self-administered by the patients. Patients should be instructed to take their study medication twice daily: one tablet each morning and one tablet each evening, at the same time every day, with or without a glass of water.

To ensure a dose interval of about 12 hours, the medication should be taken every day approximately at the same time between 07:00 and 11:00 a.m. / 07:00 and 11:00 p.m.

If trial medication is not taken at the site, patients will be requested to document the time points of each administration in their study medication diary. If the study drug was not administered as planned, the reason should be provided in the diary by the patient. A new diary will be dispensed at every visit during the treatment phase and will be collected at the following visit by the site (please refer to the [Flow Chart](#)).

No double doses should be taken, and dose reductions are not permitted.

If a scheduled dose is missed by:

- less than 6 hours after the scheduled dose time, the patient must take the missed dose and take all remaining doses at scheduled time. The error must be logged in the Medication diary and reported to the study doctor at the next study visit.
- six (6) hours or more after the scheduled dose time, the patient must skip the missed dose and take the next scheduled dose; subsequent doses must be taken at the scheduled time according to the CTP. The error must be logged in the Medication diary and reported to the study doctor at the next study visit.

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.

The site staff will instruct and remind the patients prior to the next visit

- how to fill in the study medication diary and to bring the diary to the next visit
- not to take their study 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 study medication blisters within the box (regardless of whether empty or not) back to the investigational site.

#### 4.1.4.3 Returning of study medication after home administration

During on-site Visits 3, 4 and 5/EOT, the returned trial medication kits and the patient's diary have to be collected and assessed to determine whether the patient took the medication correctly and the times and dates are filled in. Any discrepancy has to be documented by the Investigator. Regarding calculation of treatment compliance please refer to [Section 4.3](#).

### 4.1.5 Masking and procedures for Unmasking

#### 4.1.5.1 Masking

Masking in this trial is double blind, i.e. 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.

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 pharmacokinetic (PK) samples taken from placebo

patients. Bioanalytics will not disclose the randomization code or the results of their measurements until the trial is officially unblinded.

#### 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 CRF page along with the date and the initials of the person who broke the code.

#### 4.1.6 Packaging, labelling, and re-supply

The trial medication (BI 1026706, placebo) will be provided by the Department of Pharmaceutical Development of Boehringer Ingelheim Pharma GmbH & Co. KG, Biberach, Germany.

The clinical trial supply consists of boxes (treatment kits) labelled with the trial identification and medication kit numbers. Each box will contain 5 blisters, each containing 14 tablets of BI 1026706 or Placebo matching BI 1026706.

The boxes will be labelled according to the country regulatory requirements.

Supply and re-supply will be managed by the IRT system.

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.

#### 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 trial protocol by the IRB / ethics committee,
- Availability of a signed and dated clinical trial contract between the Sponsor and the head of 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.

The Investigator and/or pharmacist and/or investigational drug storage manager must maintain records of the product's delivery to the trial site, the inventory at the site, the use by each patient, and the return to the Sponsor or alternative disposal of unused products.

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 CTP and reconcile all investigational products received from the Sponsor. At the time of return to the Sponsor or appointed contract research organisation (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 CONCOMITANT THERAPY, RESTRICTIONS, AND RESCUE TREATMENT

### 4.2.1 Rescue medication, emergency procedures, and additional treatment(s)

As per judgment of the Investigator, administration of local standard of care treatment such as IVT or peribulbar injections, or laser or other surgical treatment of DME like anti-VEGF, intravitreal or peribulbar corticosteroids or focal/grid macular photocoagulation is allowed in clinically significant worsening of the disease, and may be considered in the event of vision loss of  $\geq 5$  letters or in the event of CSFT increase of  $\geq 10\%$  as compared to the previous visit confirmed by the CRC.

After the end of treatment with study medication (Visit 5/EOT), 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.

### 4.2.2 Restrictions

#### 4.2.2.1 Restrictions regarding concomitant treatment

An overview of restricted medications is provided in [Table 4.2.2.1: 1](#) with examples of individual drugs. However, it remains the Investigators' responsibility to exclude any drugs that are described as potent and moderate CYP/P-gp inhibitors/inducers or sensitive substrates of the given CYP enzymes/P-gp/ Breast Cancer Resistance Protein (BRCP) with a narrow therapeutic window that are not present in the footnotes of [Table 4.2.2.1: 1](#).

Table 4.2.2.1: 1 Restricted medication

Class	Instruction / Explanation
Investigational drugs	<b>Not permitted</b> , see exclusion criterion number 27
Systemic anti-VEGF or pro-VEGF treatment	<b>Not permitted</b> 4 months prior to first trial drug administration (Day 1, Visit 2a) and during the trial
Oral corticosteroids >10 mg prednisone equivalent/day or high potency topical steroids with systemic exposure <sup>1</sup>	<b>Not permitted</b> 4 weeks prior to first trial drug administration (Day 1, Visit 2a) and during the trial (including combinations containing corticosteroids)

Table 4.2.2.1: 1 Restricted medication (continued)

Class	Instruction / Explanation
Drugs that may affect macular edema, such as glitazones, latanoprost, niacin (vitamin B3)	<b>Not permitted</b> 4 weeks prior to first trial drug administration (Day 1, Visit 2a) and during the trial
Drugs that may affect the retina or optic nerve, such as quinolones, thioridazine, deferoxamine, ethambutol, vigabatrin	<b>Not permitted</b> during the trial
Potent and moderate CYP3A4 inhibitors <sup>2</sup>	<b>Not permitted</b> 4 weeks prior to first trial drug administration (Day 1, Visit 2a) and during the trial
Potent and moderate CYP3A4 inducers <sup>2</sup>	
Potent and moderate P-gp inhibitors (drugs causing > 2-fold increase in AUC of sensitive substrate) <sup>2</sup>	
Potent and moderate P-gp inducers (drugs causing > 50% decrease in AUC or 50% increase in clearance of sensitive substrate) <sup>2</sup>	
Sensitive CYP3A4, CYP2B6, CYP2C8, CYP2C9, CYP2C19, P-gp and Breast Cancer Resistance Protein (BCRP) substrates with a narrow therapeutic window <sup>3</sup>	<b>Not permitted</b> 4 weeks prior to first trial drug administration (Day 1, Visit 2a) and during the trial

<sup>1</sup> Use of less than or equal to 10 mg prednisone equivalent per day is allowed if taken as stable medication for at least 4 weeks prior to randomization.

<sup>2</sup> Examples for CYP3A4/P-gp inhibitors/inducers: aprepitant, avasimibe, boceprevir, bosentan, carbamazepine, casopitant, cimetidine, clarithromycin, cobicistat, conivaptan, crizotinib, cyclosporine, ciprofloxacin, diltiazem, dronedarone, efavirenz, enzalutamide, erythromycin, etravirine, fluconazole, genistein, imatinib, indinavir, itraconazole, ketoconazole, lapatinib, ledipasvir, lersivirine, lomitapide, lopinavir, mibefradil, mitotane, nafcillin, nefazodone, netupitant, phenobarbital, phenytoin, posaconazole, quinidine, rifabutin, rifampin, ritonavir, saquinavir, semagacestat, talviraline, telaprevir, telithromycin, thioridazine, tofisopam, troleandomycin, valsopodar, verapamil, voriconazole. Grapefruit juice and Hypericum perforatum (St. John's Wort) are not allowed 5 days prior to randomization and during the trial.

<sup>3</sup> Examples for substrates: CYP3A4: alfentanil, astemizole, cisapride, cyclosporine, diergotamine, ergotamine, fentanyl, pimoziide, quinidine, sirolimus, tacrolimus; CYP2C8: paclitaxel; CYP2C9: warfarin, phenytoin; CYP2C19: S-mephenytoin; P-gp: digoxin; BCRP: methotrexate.

All concomitant medication has to be assessed by the Investigator as to whether it is a moderate or strong inducer or inhibitor of CYP3A4 or P-gp based on the summary of product characteristics (SPC), if applicable. Specific questions of eligibility based on this criterion should be clarified by the clinical monitor prior to inclusion.

Systemic corticosteroids: Use of less than or equal to 10 mg prednisone equivalent per day is allowed if taken as stable medication for at least 4 weeks prior to randomization.

At the day of the visits, patients may take their concomitant medication as usual.

#### 4.2.2.2 Restrictions on diet and life style

Diet and lifestyle restrictions before and after administration of trial medication:

Citrus fruits, in particular grapefruits and Seville oranges (sour or bitter oranges), and their juices as well as products containing St. John's Wort (*Hypericum perforatum*) are not permitted 5 days prior to the first trial drug administration (Day 1, Visit 2a) and until the end of the treatment period (Visit 5/EOT).

Because blood concentrations of lipids will be determined one time during the study at baseline, patients need to have fasted overnight before Visit 2a until blood collection.

Safety blood markers of [REDACTED] on Visits 2a, 5/EOT and 6/End of Study will be taken in the morning together with other blood parameters, prior to administration of trial medication (if applicable). The [REDACTED] samples at subsequent visits should be taken as close as possible to the time of day as the sample taken on Day 1 (Visit 2a). Please refer to [Appendix 10.2](#) for further details.

There are no restrictions concerning food and liquid intake, therefore BI 1026706 may be taken with or without food.

#### 4.2.2.3 Restrictions regarding women of childbearing potential, pregnancy and breastfeeding

Female patients will only be included in this trial if they are of non-childbearing potential and are not pregnant or breastfeeding (see also [Section 3.3](#)).

### 4.3 TREATMENT COMPLIANCE

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

Based on counts, treatment compliance will be calculated as the number of capsules taken, divided by the number of capsules which should have been taken according to the scheduled period, multiplied by 100. Compliance will be verified by the on-site monitor authorised by the Sponsor.

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

The patient will complete a patient diary confirming that trial medication at home has been taken correctly during treatment period. If the number of doses taken is not between 80-120%, site staff will explain the patient the importance of treatment compliance.



## 5. VARIABLES AND THEIR ASSESSMENT

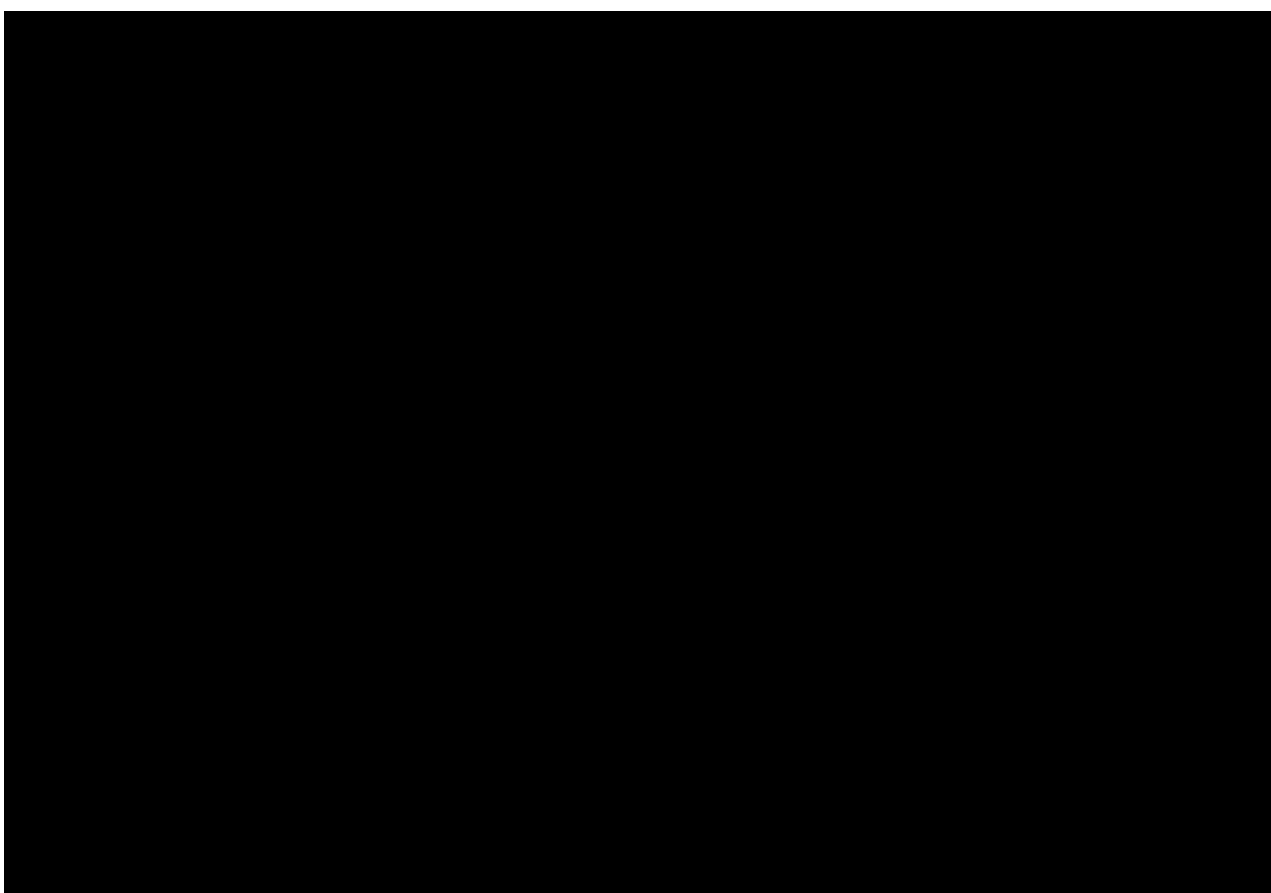
### 5.1 TRIAL ENDPOINTS

#### 5.1.1 Primary Endpoint

The primary endpoint will be the change from baseline in CSFT at week 12, as measured by SD-OCT. Baseline CSFT is determined at Visit 2a.

#### 5.1.2 Secondary Endpoints:

Safety and tolerability of BI 1026706 will be assessed by frequency (in percent) of adverse events over the treatment period.



### 5.2 ASSESSMENT OF EFFICACY

For the endpoints, baseline is defined as the value at Visit 2a, and if not measured at Visit 2a then baseline is the value at Visit 1. Examinations will be performed on both eyes, but efficacy will be assessed only in the study eye. The centrally collected ophthalmological data will be transferred from the CRC to the sponsor's database. The local measurement data will remain at the study sites as source documents.

- Spectral-domain Optical Coherence Tomography (SD-OCT)

The retinal layers and thickness can be visualized and measured by OCT. The assessment will be performed by a qualified person, and only specified OCT equipment will be used. For a given study participant, the same SD-OCT machine type should be used for the duration of the study. OCT images will be sent to an independent CRC for evaluation. A detailed Imaging Manual for image acquisition and data transmission will be provided.

Next to the central foveal subfield also the other subfields of the inner ring (3.0 mm diameter) of the SD-OCT scan will be analyzed in an exploratory manner. The measurements at Visit 2a (Randomization visit) provide baseline values.

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

### 5.3 ASSESSMENT OF SAFETY

Changes in physical examination, vital signs, safety-related findings detected in ophthalmologic examinations, safety laboratory parameters and ECG will be recorded as (S)AEs in the eCRF if they are judged clinically relevant by the Investigator.

#### 5.3.1 Physical examination

A physical examination including height (measured only at Screening), body weight and assessment of the head/neck, skin, upper and lower extremities, thorax, abdomen and nervous system will be carried out by a physician according to the [Flow Chart](#). In addition, further physical examination should be performed if clarification of an AE is necessary. Height/body weight and all clinically significant findings at screening will be documented in the source documents and recorded in the eCRF as baseline conditions.

New findings or worsening of screening conditions at follow-up physical examinations that are, in the opinion of the Investigator, clinically significant or meet other adverse event criteria defined in [Section 5.3.5](#) will be reported as adverse events (AEs).

#### 5.3.2 Vital Signs

Systolic and diastolic blood pressure (BP) and pulse rate (PR) will be measured after the patient has rested for at least 5 min in the sitting position. The measured vital signs will be documented in the source documents and recorded in the eCRF.

### 5.3.3 Ophthalmological examinations

All ophthalmological assessments will be performed for ocular safety in both eyes. Safety-related findings (clinically relevant changes during the study) will be entered in the eCRF as AEs.

The following ophthalmological examinations will be assessed in both eyes in a descriptive way as indicated in the Flow Chart; the results will be entered in the eCRF:


- Slit lamp: The anterior and posterior segment of the eye should be assessed according to local procedure. Evaluation of the posterior pole may be performed by slit lamp evaluation or by indirect ophthalmoscopy, according to local procedures.
- Ocular tonometry: Goldmann applanation tonometry is the preferred method to measure the intraocular pressure (IOP) in both eyes. Tonometry will be performed as the final ophthalmological exam at the visit days in order to avoid influence of the applanation on other ocular assessments.

### 5.3.4 Safety laboratory parameters

Detailed instructions for laboratory safety blood and urine sampling, handling and shipment of samples will be provided in the ISF/laboratory manual.

#### 5.3.4.1 Safety laboratory parameters obtained from blood

The laboratory parameters to be determined in this study are listed in [Table 5.3.4.1: 1](#) and will be performed by a central laboratory. Coagulation parameters will be collected at two visits together with other safety blood parameters. The respective reference ranges will be provided in the ISF. Regarding timing of sampling of safety blood markers please refer to the [Flow Chart](#), [Appendix 10.2](#) and to [Section 6.2](#).



Additional instructions for biomarker sampling, handling and shipment of samples are provided in the ISF.

The central laboratory will send reports to the Investigator. It is the responsibility of the Investigator to evaluate the laboratory reports. Clinically relevant abnormal findings as judged by the Investigator will be reported as adverse events (please refer to [Section 5.3.6](#)). In case the criteria for hepatic injury defined in [Section 5.3.6](#) (protocol-specified adverse events of special interest) are fulfilled, a number of additional measures will be performed (please refer to [Section 5.3.6](#) and 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.

Table 5.3.4.1: 1 Blood samples will be collected for the following tests in accordance with the visit [Flow Chart](#) and [Appendix 10.2](#):

Category	Test name
Chemistry	AST (GOT)
	ALT (GPT)
	Alkaline Phosphatase (AP)
	Creatine Kinase (CK)
	CK-MB, <i>only if CK is elevated</i>
	Gamma-Glutamyl Transferase (GGT/ $\gamma$ -GT)
	Lactic Dehydrogenase (LDH)
	Creatinine
	Creatinine clearance (CrCL) <sup>1</sup>
	Albumin
	Sodium
	Potassium
	Calcium
	Magnesium
	Chloride
	Inorganic phosphate
	Bicarbonate
	Bilirubin Total
	Bilirubin Direct, <i>if total is elevated</i>
	Bilirubin Indirect, <i>if total is elevated</i>
Protein, Total	
Uric Acid	
Glucose, non-fasting (fasting only at Visit 2a)	

<sup>1</sup>Creatinine Clearance according to the Cockcroft-Gault formula

Table 5.3.4.1: 1 Blood samples will be collected for the following tests in accordance with the visit [Flow Chart](#) and [Appendix 10.2](#) (continued):

Category	Test name
<b>Chemistry</b>	HbA1c (only at Visit 2a and Visit 5/EOT) Total cholesterol (only at Visit 2a) LDL cholesterol (only at Visit 2a) HDL cholesterol (only at Visit 2a) Triglycerides (only at Visit 2a)
<b>Coagulation</b>	Activated Partial Thromboplastin Time (=aPTT) (at Visits 2a and 5/EOT) Prothrombin time (Quick and INR) (at Visits 2a and 5/EOT)
<b>Haematology</b>	Haematocrit (Hct) Haemoglobin (Hb) Red Blood Cell Count/ Erythrocytes MCV (mean corpuscular volume) MCH (mean corpuscular haemoglobin) MCHC (Mean Cellular haemoglobin Concentration) Reticulocyte Count White Blood Cells / Leukocytes Platelet Count/ Thrombocytes
	Diff. automatic (manual if diff. automatic is abnormal) <ul style="list-style-type: none"> <li>- Neutrophils</li> <li>- Eosinophils</li> <li>- Basophils</li> <li>- Monocytes</li> <li>- Lymphocytes</li> </ul>
<b>Urinalysis (Stix)</b>	Urine Nitrite Urine Protein, semiquantitative; -> if abnormal, albuminuria will be determined quantitatively Urine Glucose Urine Ketone Urobilinogen Urine Bilirubin Urine RBC/ Erythrocytes Urine WBC/ Leukocytes Urine pH Urine creatinine

Table 5.3.4.1: 1 Blood samples will be collected for the following tests in accordance with the visit [Flow Chart](#) and [Appendix 10.2](#) (continued):

Category	Test name
<b>Albumin content and Urine-Sediment, microscopic examination</b> (both only if urine analysis abnormal)	Urine Albumin content Urine Sediment Bacteria Urine Cast in Sediment Urine Squamous Epith Cells Urine Sediment RBC/ Erythrocytes Urine Sediment WBC/ Leucocytes

#### 5.3.4.2 Safety laboratory parameters obtained from urine

Urine parameters will be performed by the central laboratory. The urine sediment examination will only be done if the urine dipstick analysis is abnormal. Clinically relevant abnormal findings as judged by the Investigator will be reported as adverse events (please refer to [Section 5.3.6](#)).

#### 5.3.5 Electrocardiogram (ECG)

A centralized ECG assessment will be used for this study. All ECGs will be printed locally and evaluated by the Investigator or a designee; in addition, there is a central cardiologist over-read.

Details of the procedure will be included in the ISF. Twelve-lead ECGs (I, II, III, aVR, aVL, aVF, V1-V6) will be recorded using equipment provided by a central ECG vendor. The ECGs will be recorded for a 10-second duration after the patient has rested for at least 5 minutes in a supine position. Electrode placement will be performed according to the method of Einthoven/Goldberger (ankles and wrists). At all time-points indicated in the [Flow Chart](#) single ECG will be recorded, but records may be repeated for quality reasons and the repeat ECG will be used for analysis. Additional ECGs may be collected by the Investigator for safety reasons. Printed ECG-records will be stored at the investigational site.

Clinically relevant abnormal findings as judged by the Investigator will be reported as baseline conditions at screening or as AEs during the trial.

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 transferred from the ECG reading centre to the Sponsor.

#### 5.3.6 Assessment of adverse events

##### 5.3.6.1 Definitions of adverse events

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

### **Adverse reaction**

An adverse reaction is defined as a response to a medicinal product which is noxious and unintended. Response in this context means that a causal relationship between a medicinal product and an adverse event is at least a reasonable possibility. Adverse reactions may arise from use of the product within or outside the terms of the marketing authorization or from occupational exposure. Conditions of use outside the marketing authorization include off-label use, overdose, misuse, abuse and medication errors.

### **Serious adverse event**

A serious adverse event (SAE) is defined as any AE which:

- results in death,
  - is life-threatening (this refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if more severe),
  - requires inpatient hospitalisation or
  - requires prolongation of existing hospitalisation,
  - results in persistent or significant disability or incapacity or
  - is a congenital anomaly/birth defect,
- or
- is to be deemed serious for any other reason if it is an important medical event when based upon 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.

### **AEs considered “Always Serious”**

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

The latest list of “Always Serious AEs” can be found in the RDC system. These events should always be reported as SAEs as described in [Section 5.3.6.2](#).

Cancers of new histology and exacerbations of existing cancer must be reported as a serious event regardless of the duration between discontinuation of the drug and the occurrence of the cancer.

### **Worsening of the underlying disease or of other pre-existing conditions**

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

- Worsening of the underlying disease or of other pre-existing conditions and/or

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

If such abnormalities already pre-exist prior trial inclusion they will be considered as baseline conditions.

#### **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. AESI need to be reported to the Sponsor's Pharmacovigilance Department within the same timeframe that applies to SAE, see [Section 5.3.6.2](#).

The following are considered as AESIs:

- Hepatic injury defined by the following alterations of hepatic laboratory parameters:
  - Elevation of AST and/or ALT  $\geq 3$  fold upper limit of normal (ULN) combined with an elevation of total bilirubin  $\geq 2$  fold ULN measured in the same blood draw sample, and/or
  - Marked peak aminotransferase (ALT, and/or AST) elevations  $\geq 10$  fold ULN.

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

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

#### **Intensity of AEs**

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

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

#### **Causal relationship of AEs**

The definition of an adverse reaction implies at least a reasonable possibility of a causal relationship between a suspected medicinal product and an adverse event. An adverse reaction, in contrast to an adverse event, is characterized by the fact that a causal relationship between a medicinal product and an occurrence is suspected.



Medical judgment should be used to determine the relationship, considering all relevant factors, including pattern of reaction, temporal relationship, de-challenge or re-challenge, confounding factors such as concomitant medication, concomitant diseases and relevant history.

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

- The event is consistent with the known pharmacology of the drug
- The event is known to be caused by or attributed to the drug class
- A plausible time to onset of the event relative to the time of drug exposure
- Evidence that the event is reproducible when the drug is re-introduced
- No medically sound alternative aetiologies that could explain the event (e.g. preexisting 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 study drug treatment continues or remains unchanged.

#### 5.3.6.2 Adverse event collection and reporting

##### **AE Collection**

The Investigator shall maintain and keep detailed records of all AEs in their patient files. The following must be collected and documented on the appropriate eCRF by the Investigator:

- From signing the informed consent onwards through the Residual Effect Period (REP) until individual patient's end of study:
  - all AEs (serious and non-serious) and all AESIs.
- After the individual patient's end of study:
  - the Investigator does not need to actively monitor the patient for AEs but should only

report SAEs and AESIs of which the Investigator may become aware of, if considered relevant by the Investigator.

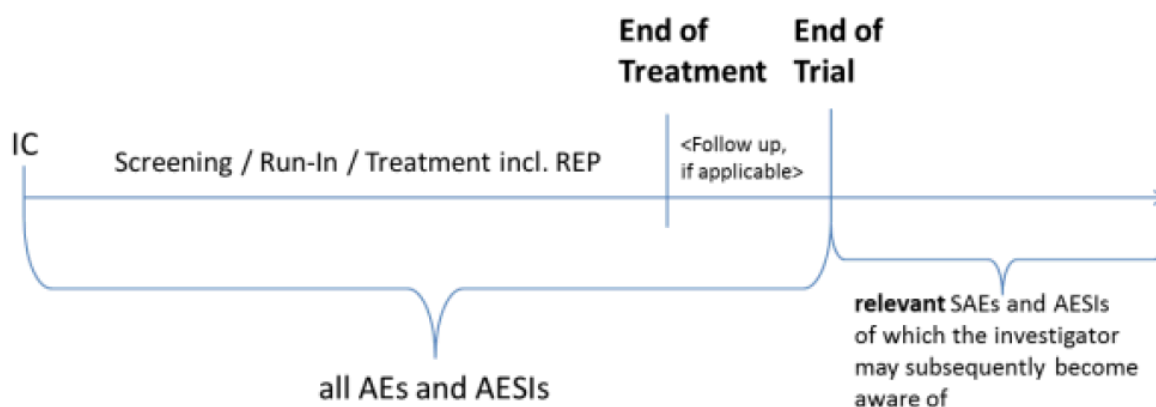


Figure 5.3.6.2: 1 Collection and reporting of AEs/SAEs during the study

The REP is defined as 4 days after the last trial medication application. All AEs which occurred through the treatment phase and throughout the REP will be considered as on treatment; please see [Section 7.3.4](#). Events which occurred after the REP will be considered as post-treatment events.

### 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.

### Information required

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

All (S)AEs, including those persisting after individual patient's end of study must be followed up until they have resolved, have been sufficiently characterized, or no further information can be obtained.

### Pregnancy

Females will only be included in this trial when they are of non-childbearing potential (please see Exclusion criteria). However, measures have to be defined in the event of pregnancy.

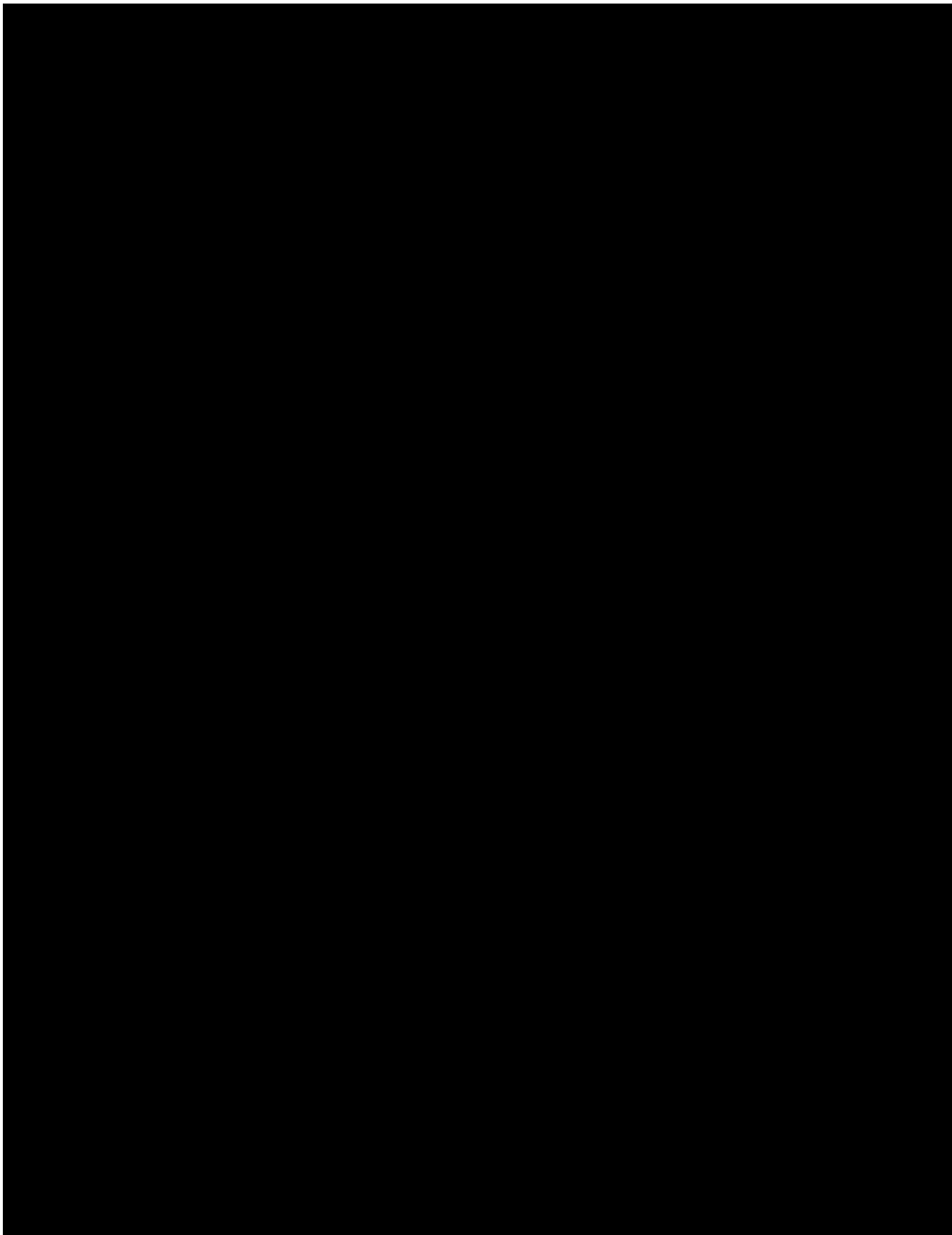
In the unlikely event that a female subject participating in this clinical study becomes pregnant after having taken study medication, the Investigator must report immediately

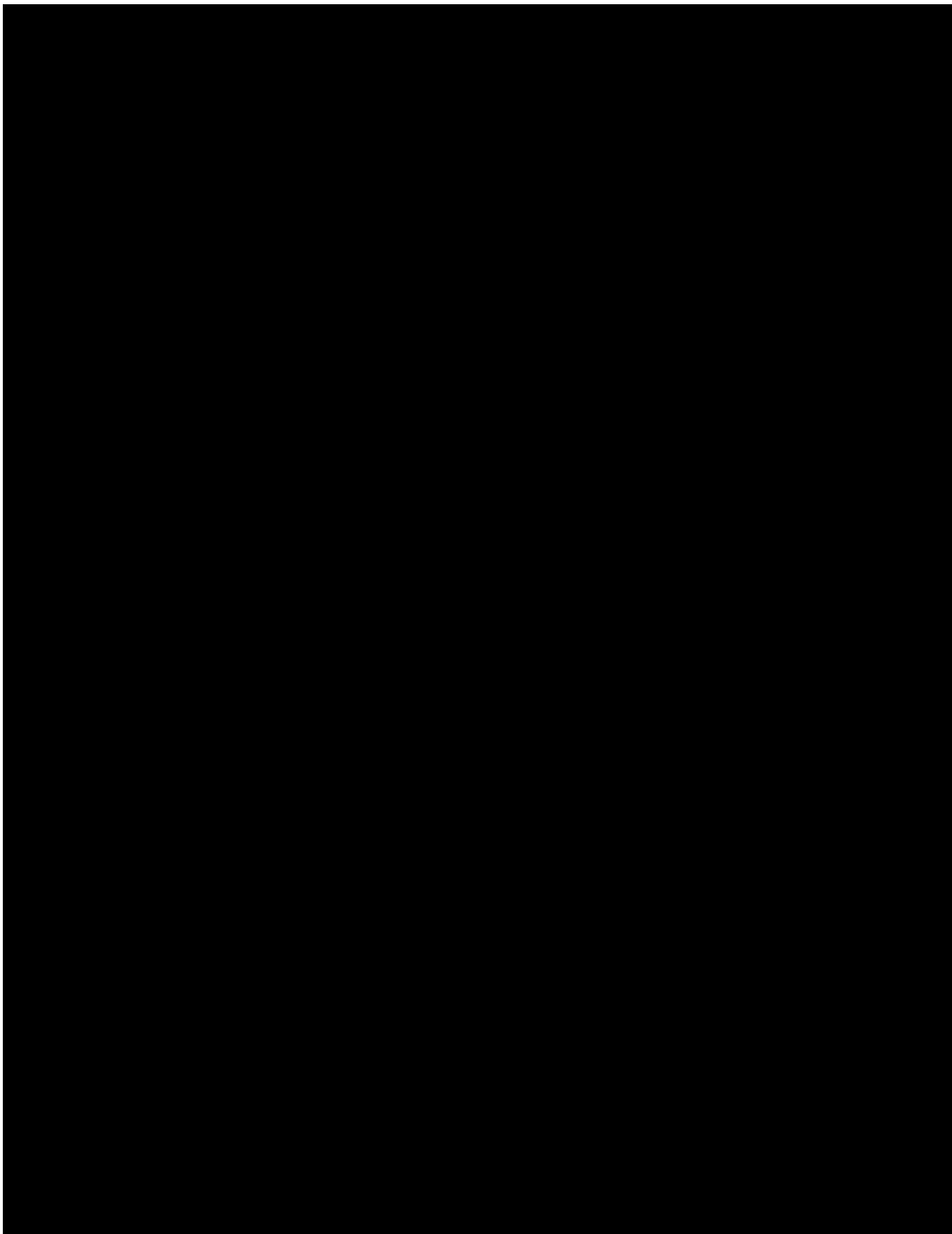
(within 24 hours) a potential drug exposure during pregnancy (DEDP) to the sponsor's unique entry point (country-specific contact details will be provided in the ISF) and study medication must be stopped immediately. The Pregnancy Monitoring Form for Clinical Trials (Part A) should be used.

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).

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.

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





[REDACTED]

[REDACTED]

[REDACTED]

## 5.6 APPROPRIATENESS OF MEASUREMENTS

The measurements performed in this trial are standard measurements and will be performed in order to monitor the pharmacodynamic endpoint as well as ocular and systemic safety aspects and to determine PK parameters in an appropriate way.

The primary outcome of this study is based on SD-OCT measurement which is used as a surrogate for pharmacological activity of BI 1026706. The treatment with BI 1026706 is aiming to reduce formation of edema and vascular leaking and thereby improve or stabilize vision. Therefore, a standard method that captures changes in edema formation is used for diagnostic purposes as well as to determine pharmacodynamic effect. SD-OCT is widely used for the assessment of the layers of the posterior pole of the eye and has proven a valuable measure of the central retinal thickness in DME.

[REDACTED]

Therefore, all measurements applied in this trial are considered by the sponsor to be appropriate.

## 6. INVESTIGATIONAL PLAN

### 6.1 VISIT SCHEDULE

The schedule for trial visits is summarised in the study [Flow Chart](#) including time windows for study visits. All visits are calculated from the date of randomization except for Visit 6/End of Study which is calculated from Visit 5/End of Treatment. 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 will be planned according to the visit schedule.

In the case of medical emergencies, prior approval from the Sponsor for protocol deviations (e.g. visit schedule) will not be required, but the Sponsor should be notified as soon as possible. The relevance of any such protocol deviation will be assessed prior to analysing the data.

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

Patients should make all efforts to complete the study which includes the End of Treatment Visit (Visit 5/EOT) and the follow-up visit 6/End of Study. The procedures to be conducted at each visit are provided in the Flow Chart and further described below.

Regarding removal of patients please refer to [Section 3.3.4](#).

### 6.2 DETAILS OF TRIAL PROCEDURES AT SELECTED VISITS

#### 6.2.1 Screening period

##### 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.

##### Visit 1 (Screening period):

The Screening period, i.e. the phase before the first administration of the trial drug, 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 2 days to allow receipt of the results of the central imaging Reading Center and the central laboratory.

Once DME is confirmed, a patient can be considered for eligibility; gonioscopy may be performed up to 1 month before study entry.

The screening period (see [Flow Chart](#)) includes the following procedures/assessments: check of signed Informed Consent, demographics, review of relevant medical history/baseline conditions at the discretion of the Investigator, current medication and relevant medication history regarding eye specific interventions (e.g., injection therapies, laser) within the last 2 years, inclusion/exclusion criteria, physical exam, body weight and height, vital signs (blood

pressure and pulse rate), ECG, safety laboratory tests collected according to central laboratory instructions, ophthalmological examinations including BCVA, slit lamp, SD-OCT, [REDACTED] and [REDACTED] ocular tonometry (intraocular pressure, IOP) and AE assessment since signed Informed Consent (see [Section 5.3.6](#)). Optional: Informed Consent for DNA banking; this separate consent can be obtained at this visit or at any other visit during the study.

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 anamnestic data will be used.

Images (SD-OCT, [REDACTED]) have to be sent to the CRC for assessment immediately, see [Section 3.3.2](#). The Randomization visit 2a should be performed as soon as possible after the Visit 1, when eligibility of the patient was confirmed.

#### Re-Screening

Patients who do not fulfil all of the eligibility criteria for a reason which later resolves and all eligibility criteria can be met within a 3 month period after initial visit (e.g. time since an exclusionary event), patients can be re-screened up to one time. Imaging of the retina (SD-OCT, [REDACTED]) does not need to be repeated at the re-screening visit if the corresponding criteria for inclusion of the study eye were met at the initial screening visit and the images are not older than 28 days at the re-screening visit; otherwise new images have to be performed.

Patients who cannot be randomized in due time according to the Flow Chart can be re-screened only after approval of the Sponsor.

#### **6.2.2 Treatment period**

The procedures of the visits in the treatment phase will be performed as outlined in the [Flow Chart](#).

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, as randomization of a patient cannot be reserved.

SD-OCT and BCVA as well as blood sampling will always be performed before intake of the trial medication on the respective day.

#### 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.

At Visit 2a (Day 1), patients need to have fasted overnight before this Visit until blood collection.

Visit 2a procedures include review of concomitant therapy, physical exam, body weight, vital signs (blood pressure and pulse rate), randomization, safety laboratory tests, PK, PGx (+



optional DNA banking sample, if Informed Consent is provided) and biomarker blood sampling collected according to central laboratory instructions (please also refer to [Appendix 10.2](#)), AE assessment since last visit (see [Section 5.3.6](#)), ECG and ophthalmological examinations including SD-OCT, visual acuity and slit lamp. Study medication should be taken after blood collection and ocular assessments at the site and study drug kits will be dispensed for home administration.

A trial drug diary will be provided to the patients to record the actual dates and times of drug administration prior to the next scheduled visit to keep records of missed drug intake and to take account of effects on PK trough levels.

#### Visit 2b (Phone Visit)

One week after randomization an interim phone call will be made at Visit 2b to collect AEs, changes in concomitant therapy (if any), and to check handling of the study drug diary.

#### Visit 3 and 4:

At Visits 3 and 4 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 will be collected.

Procedures to be performed at Visits 3 and 4 (see [Flow Chart](#)) include: review of concomitant therapy and AE assessment since last visit (see [Section 5.3.6](#)), physical examination, vital signs (blood pressure and pulse rate), ECG, safety laboratory tests, PK and biomarker blood sampling collected according to central laboratory instructions (please refer to [Appendix 10.2](#)) and ophthalmological assessments.

At Visit 3 (Day 29), in addition, time of breakfast on that day will be captured and also recorded in the eCRF.

Study medication should be taken at the end of the visits at the site from newly assigned kits, and then these kits together with the drug diary will be dispensed for home administration.

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.

When circumstances prevent the proper evaluation of CSFT or visual acuity in the course of the study (e.g., due to recent vitreous haemorrhage), an explanation with a detailed description will be provided in the corresponding eCRF page.

### **6.2.3 End of treatment and Follow-up period**

#### Visit 5/End of Treatment (EOT):

At the time that study drug is permanently stopped for any reason, whether this is done prematurely or because of reaching the end of the treatment period after 12 weeks, the Visit 5/EOT will be completed. The time interval for the regular scheduled Visit 5/EOT is 6 days, i.e. Day 85+5.

When the Investigator decided to permanently discontinue the study medication or became aware that the study medication had been terminated earlier than planned, Visit 5/EOT will be performed as soon as possible. Subsequently, patients should come to the End of Study Visit (Visit 6) four weeks after the premature Visit 5/EOT.

All unused study medication will be collected and study drug diary will be checked. Procedures to be performed include review of concomitant therapy and AE assessment since last visit (see [Section 5.3.6](#)), physical examination, body weight, vital signs (blood pressure and pulse rate), ECG, safety laboratory tests including [REDACTED] and PK blood sampling (please refer to [Appendix 10.2](#)) and ophthalmological examinations according to the [Flow Chart](#).

In case that standard of care DME treatment is administered at this visit, this has to be documented in the eCRF.

#### Visit 6/End of Study:

The Visit 6/End of Study will be performed 28 days after the Visit 5/EOT for all patients who had at least one dose of trial medication (see Flow Chart).

In case that standard of care DME treatment is administered at this visit, this has to be documented in the eCRF.

The Visit 6/End of Study is the final visit and the Trial completion page in the eCRF has to be entered.

#### Withdrawal of consent

If a patient is not willing to continue in the trial and withdraws consent for any reason (without the need to justify the decision) prior to the end of the trial, Visit 5/EOT should be scheduled as soon as possible, and also Visit 6/End of Study should be performed to assess for safety.

If the patient refuses to participate at an EOT Visit, the trial completion page of the eCRF has to be filled in.

## **7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE**

### **7.1 STATISTICAL DESIGN - MODEL**

This is a randomised, double-masked, multi-centre, placebo controlled, parallel group study. The primary objective is to explore the mechanism of BI 1026706 in the treatment of patients with visual impairment due to DME and to evaluate safety and tolerability of BI 1026706.

The superiority of BI 1026706 will be tested against placebo. The primary endpoint of the trial is the change from baseline in CSFT after 12 weeks of treatment.

Restricted Maximum Likelihood Estimation (REML) based Mixed-effects Model for Repeated Measures (MMRM) analysis will be used to obtain adjusted means for the treatment effects. This model will include treatment, previous DME treatment, week and treatment by week interaction as fixed categorical effects. Also, baseline CSFT and baseline CSFT by week interaction as continuous fixed effects. An unstructured covariance matrix will be used to model the within-patient variation.

The randomization will be stratified by the patients' previous DME treatment (naïve versus treated).

### **7.2 NULL AND ALTERNATIVE HYPOTHESES**

The superiority of treatment with BI 1026706 to placebo will be tested for CSFT change from baseline at week 12 by a pairwise comparison against placebo at the  $\alpha=0.05$  level. The population used will be the Full Analysis Set (FAS).

Let  $M_{HA}$  be the mean change from baseline in CSFT ( $\mu\text{m}$ ) after 12 weeks in BI 1026706 group.

Let  $M_{HB}$  be the mean change from baseline in CSFT ( $\mu\text{m}$ ) after 12 weeks in placebo group

The primary objective hypothesis is:

$$H_0: M_{HA} - M_{HB} = 0$$

$$H_1: M_{HA} - M_{HB} \neq 0$$

The test of the null hypothesis will be supported by the 95% confidence interval (CI) for  $M_{HA} - M_{HB}$  and the null hypothesis will be rejected if the CI excludes 0  $\mu\text{m}$ .

### **7.3 PLANNED ANALYSES**

The statistical analysis will be based on the following populations:

Treated Set (TS)

The TS will consist of all patients who were treated with at least one dose of study drug (BI 1026706 or placebo).

#### Full Analysis Set (FAS)

The FAS will consist of all patients who were randomised, treated with at least one dose of BI 1026706/placebo and provided baseline and at least one post-randomization CSFT measurement.

#### Pharmacokinetic analysis Set (PKS)

The PKS will consist of all patients in the TS for whom at least one evaluable BI 1026706 plasma concentration is available.

### 7.3.1 Primary endpoint analyses

The primary analysis of the primary endpoint, change from baseline in CSFT at 12 weeks, will be performed on the FAS. Therefore, all randomised patients who were treated with at least one dose of BI 1026706/placebo, had a baseline and at least one on-treatment CSFT measurement will be included.

Comparisons between treatment groups for the primary endpoint will be based on a mixed effect repeated measures model (MMRM). This model will include treatment, previous DME treatment, week and treatment by week interaction as fixed categorical effects. Also, baseline CSFT and baseline CSFT by week interaction as continuous fixed effects. An unstructured covariance matrix will be used to model the within-patient variation. The SAS procedure MIXED will be used involving the REML and the Kenward-Roger approximation for denominator degrees of freedom. This approach is described in Kenward and Roger ([R10-4391](#)). Adjusted mean values as well as treatment contrasts will be presented together with the 95% CIs and p-values.

The statistical model will be:

CSFT change from baseline = overall mean + continuous baseline CSFT + previous DME treatment + treatment + week + baseline CSFT by week interaction + treatment by week interaction + random error

Baseline CSFT will be defined as the last available CSFT measurement obtained before randomization.

Data obtained after the start of rescue medication will not be used in the primary analysis of the primary endpoint.

### 7.3.2 Secondary endpoint analyses

See [Section 7.3.4](#).



#### 7.3.4 Safety analyses

AEs will be coded using the Medical Dictionary for Regulatory Activities (MedDRA) coding dictionary. Standard BI summary tables and listings will be produced. All AEs with an onset between start of treatment and end of the REP (residual effect period), a period of 4 days after the last dose of trial medication, will be assigned to the treatment period for evaluation. All treated patients will be included in the safety analysis. In general, safety analyses will be descriptive in nature and will be based on BI standards. No hypothesis testing is planned.

Statistical analysis and reporting of AEs will concentrate on treatment-emergent AEs. To this end, all AEs occurring between start of treatment and end of the REP will be considered 'treatment-emergent'. The REP is defined as the time period after the last dose administration of trial medication when measurable drug levels or PD effects are still likely to be present. 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 AEs 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).

Laboratory data will be analysed both quantitatively as well as qualitatively. The latter will be done via comparison of laboratory data to their reference ranges. Values outside the reference range as well as values defined as clinically relevant will be highlighted in the listings.

Clinically relevant ECG findings will be reported as AEs. Quantitative and qualitative ECG data from the ECG reading centre will be reported descriptively.

Treatment groups will be compared descriptively with regard to distribution of parameters as well as with regard to frequency and percentage of patients with abnormal values or clinically relevant abnormal values.

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

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

[REDACTED]

#### 7.4 INTERIM ANALYSES

No interim analysis is planned.

#### 7.5 HANDLING OF MISSING DATA

For the primary analysis of the primary endpoint, if a patient misses a visit, the missing data will not be imputed and only on-treatment data will be included. The mixed effect model will handle missing data based on a likelihood method under the "missing at random assumption". Every randomised patient with at least baseline and one on-treatment measurement will be included in the analysis.

Additional details on the handling of missing data, including sensitivity analyses of the primary endpoint and [REDACTED], will be specified in the TSAP prior to unmasking. No imputation is planned for the analysis of AEs, laboratory data, and vital signs.

#### 7.6 RANDOMIZATION

Patients will be randomised in blocks to double-masked treatment. Approximately equal numbers of patients will be randomised to each treatment group. BI will arrange for the randomization and the packaging and labelling of study 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.

#### 7.7 DETERMINATION OF SAMPLE SIZE

In the Diabetic Retinopathy Clinical Research Network study "Aflibercept, bevacizumab, or ranibizumab for diabetic macular edema" ([R15-5225](#)) the changes from baseline in CSFT at week 12 are estimated to be between 85 and 140  $\mu\text{m}$  for the aflibercept, bevacizumab and ranibizumab treatments. The common standard deviations as week 12 results are not presented. However, standard deviations were estimated from the confidence interval bars presented on the CSFT plots over time.

In order to achieve 80% power and with alpha at the 5% level for a two sided test, the number of patients required to detect a difference in the treatments is given in the table below for a range of mean differences in the treatments and common standard deviations.

Table 7.7: 1                      Sample Size

Mean difference [µm]	Common standard deviation [µm]	Number of patients per arm	Total sample size for the trial
20	20	14	28
30	20	7	14
40	20	5	10
20	30	29	58
30	30	14	28
40	30	8	16
20	40	51	102
30	40	23	46
40	40	14	28

It is assumed that the mean difference is 20 µm and the common standard deviation is 40 µm. Therefore a total sample size of 102 patients is assumed.

Calculations were performed using SAS® 9.3 proc power statistical package.

## **8. INFORMED CONSENT, DATA PROTECTION, TRIAL RECORDS**

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 Standard Operating Procedures (SOPs) and relevant regulations.

Standard medical care (prophylactic, diagnostic and therapeutic procedures) remains in 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 subjects against any immediate hazard, and also of any serious breaches of the protocol or of ICH GCP.

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 Clinical Trial Report.

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, AND INFORMED CONSENT**

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

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

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

### **8.2 DATA QUALITY ASSURANCE**

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



### 8.3 RECORDS

Electronic Case Report Forms (eCRF) 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 subject. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.

The current medical history of the subject may not be sufficient to confirm eligibility for the trial and the Investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the Investigator must make 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.

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

#### 8.3.3 Storage period of records

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

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 regulatory reporting obligation and in accordance to the requirements defined in this CTP.

## 8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. Patient privacy will be ensured by using patient identification code numbers.

Data protection and data security measures are implemented for the collection, storage and processing of patient data in accordance with the principles 6 and 12 of the WHO GCP handbook.

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

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

Measures are in place to comply with the applicable rules for the collection, storage and future use of biological samples from clinical trial participants and the corresponding data, in particular

- A Quality Management System has been implemented to ensure the adherence with the Principles of Good Clinical Practice as outlined in 'Note For Guidance On Good Clinical Practice' (CPMP/ICH/13 5/95)
- The BI-internal facilities storing and analyzing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by Boehringer Ingelheim are regularly audited. The analytical groups and the banking facility are therefore assessed to be qualified for the storage and use of biological samples and data collected in clinical trials.
- Samples and data are used only if an appropriate informed consent is available.

## 8.6 TRIAL MILESTONES

The **start of the trial** is defined as the date of the enrolment of the first patient in the whole trial ("First Patient In").

The **end of the trial** is defined as the date of the last visit (Visit 6/End of study Visit, please refer to [Section 6.2.3](#)) of the last patient in the whole trial ("Last Patient Out").

**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).

## 9. REFERENCES

### 9.1 PUBLISHED REFERENCES

- P08-12095 Adamis AP, Berman AJ. Immunological mechanisms in the pathogenesis of diabetic retinopathy. *Semin Immunopathol.* 2008. 30(2):65-84.
- R10-4391 Kenward MG, Roger JH, The Use of baseline covariates in crossover studies. *Biostatistics* 2010. 11(1):1-17.
- R15-1951 Varma R, Bressler NM, Doan QV, Gleeson M, Danese M, Bower JK, Selvin E, Dolan C, Fine J, Coman S, Turpcu A. Prevalence of and risk factors for diabetic macular edema in the United States. *JAMA Ophthalmol.* 2014. 132(11): 1334-1340.
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- R15-5222 Bhagat N, Grigorian RA, Tulela A, Zarbin M. Diabetic Macular Edema: Pathogenesis and Treatment. *Surv Ophthal.* 2009. 54:1-32.
- R15-5223 Arup D, McGuire PG, Sampathkumar R. Diabetic Macular Edema: Pathophysiology and Novel Therapeutic Targets. *The Eye.* 2015. 122:1375-1394.
- [REDACTED]
- R15-5225 Wells JA, Glassman AR, Ayala AR et al. Aflibercept, Bevacizumab, or Ranibizumab for Diabetic Macular Edema. *N Engl J Med.* 2015. 372:1193-1203.
- [REDACTED]
- R15-5246 Aiello LP, Bursell SE, Clermont A, Duh E. et al. Vascular Endothelial Growth Factor-Induced Retinal Permeability Is Mediated by Protein Kinase C In Vivo and Suppressed by an Orally Effective P-Isoform-Selective Inhibitor. *Diabetes.* 1997. 46:1473-1480.
- [REDACTED]

- R15-5248 Do DV, Nguyen QD, Boyer D, Schmidt-Erfurth U, Brown DM, Vitti R et al. One-year outcomes of the da Vinci Study of VEGF Trap-Eye in eyes with diabetic macular edema. *Opthalmology*. 2012. 119:1658-1665.
- R15-5250 Klein R, Klein BE, Moss SE, Davis MD, DeMets DL. The Wisconsin epidemiologic study of diabetic retinopathy. III. Prevalence and risk of diabetic retinopathy when age at diagnosis is 30 or more years. *Arch Ophtalmol* 1984 April. 102:527-532.
- R15-5524 Bressler SB, Almukhtar T, Borhade A, Bressler NM, Glassman AR, et al. Repeated Intravitreous Ranibizumab Injections for Diabetic Macular Edema and the Risk of Sustained Elevation of Intraocular Pressure or the Need for Ocular Hypotensive Treatment. *JAMA Ophtalmol*. 2015. 133(5):589-597

## **9.2 UNPUBLISHED REFERENCES**

- c03035551-01 [REDACTED] Investigator's Brochure for Chronic Obstructive Pulmonary Disease. BI 1026706. 10 July 2015

## 10. APPENDICES

### 10.1 PHARMACOKINETIC ANALYSES

Pharmacokinetic evaluations will be performed according to the relevant Corporate Procedure of the Sponsor (001-MCS-36-472, current version).

Concentration data identified with NOS (no sample), NOR (no valid result), NOA (not analyzed), and BLQ (below the limit of quantification), will be ignored and not replaced by zero at any time point (applies also to the lag phase including the predose value). Descriptive statistics of concentrations at specific time points will be calculated only when at least 2/3 of the individuals have concentrations within the validated concentration range. The overall sample size to decide whether the “2/3 rule” is fulfilled will be based on the total number of samples intended to be drawn for that time point (i.e. BLQ, NOR, NOS, and NOA are included).

### 10.2 TIME AND VISIT SCHEDULE FOR PK, SAFETY AND BIOMARKER BLOOD SAMPLING

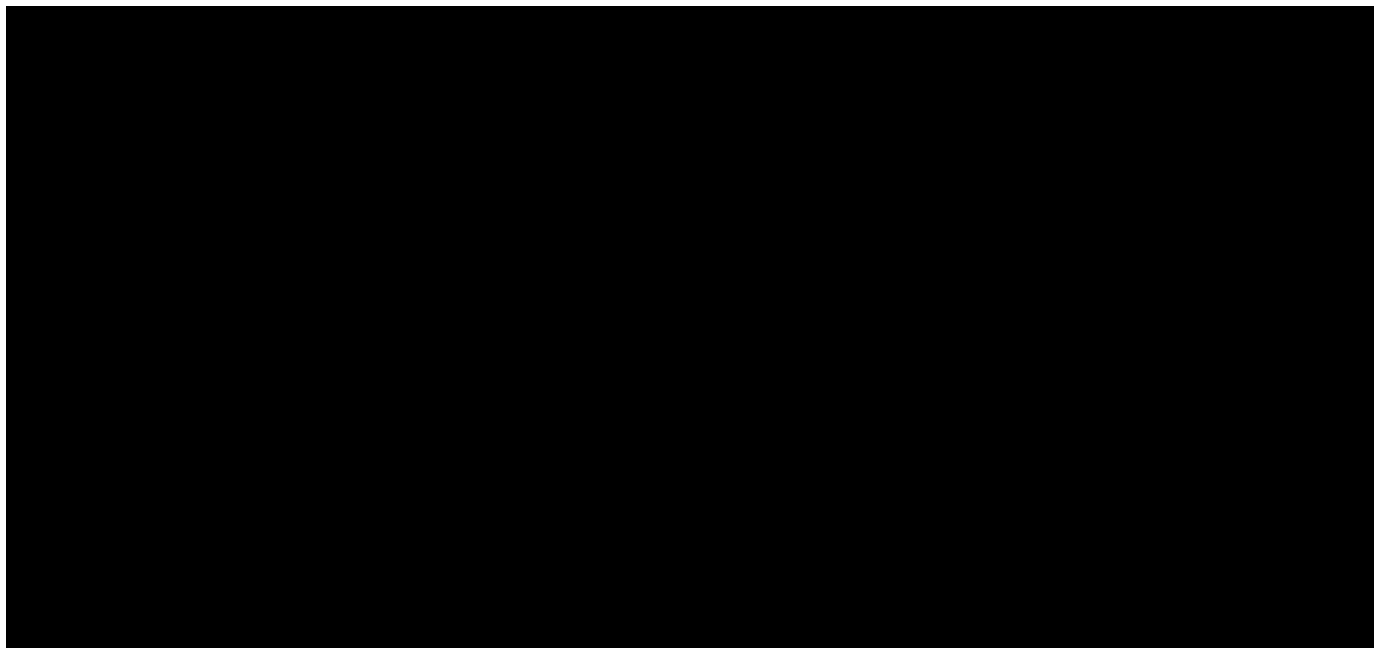
Table 10.2: 1 Time schedule for PK, Safety laboratory including [REDACTED] Biomarker and PGx blood sampling

Visit	Day	Sampling Time Point [hh:min]	CRF Time /PTM	PK	Safety	[REDACTED]	Biomarker sample	PGx
1	-28 to -2				X			
2a	1	Fasting blood collection: <sup>1</sup> Prior to drug administration <sup>2</sup> , between 08:30 a.m. and 10:30 a.m. (±30 min)	- 1:00	X	X	■	X	X
		0:00	0:00	First Drug administration				
3	29 (±3)	Prior to drug administration <sup>2</sup> , between 08:30 a.m. and 10:30 a.m. (±30 min)	- 1:00	X <sup>3</sup>	X			
		0:00	0:00	Drug administration				
		0:45 ± 15 min	0:45	X				
		2:30 ± 30 min	2:30	X				
		3:30 ± 30 min	3:30	X				

<sup>1</sup> Only at Day 1 (Visit 2a) blood collection will be in fasting state.

<sup>2</sup> Drug administration is planned to occur between 07:00 and 11:00 a.m., if possible.

<sup>3</sup> If possible, this sample is to be taken 12 hours ± 60 min after the evening drug intake on the previous day.



## 11. DESCRIPTION OF GLOBAL AMENDMENT(S)

<b>Number of global amendment</b>		1
<b>Date of CTP revision</b>		04 Mar 2016
<b>EudraCT number</b>		2015-003529-33
<b>BI Trial number</b>		1320.22
<b>BI Investigational Product(s)</b>		BI 1026706
<b>Title of protocol</b>		A randomized, double-masked, placebo-controlled exploratory study to evaluate pharmacodynamics, safety and tolerability of orally administered BI 1026706 for 12 weeks in patients with mild visual impairment due to center-involved diabetic macular edema (DME)
<b>To be implemented only after approval of the IRB / IEC / Competent Authorities</b>		<input type="checkbox"/>
<b>To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval</b>		<input type="checkbox"/>
<b>Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only</b>		<input checked="" type="checkbox"/>
<b>Section to be changed</b>		Section 3.3.3
<b>Description of change</b>		<p><b>Change 1: Section 3.3.3, Exclusion criteria</b>  <i>Added:</i>            27. Male patients who do not agree to minimize the risk of female partners becoming pregnant from the first dosing day until 3 months after the trial medication treatment has finished <sup>1</sup></p> <p><i>Numbers of subsequent exclusion criteria changed accordingly.</i></p> <p><b>Change 2: Footnote 1 of Exclusion criteria</b>  <i>Added:</i>  <sup>1</sup> Male patients who have sexual intercourse with women of childbearing potential will be instructed and must agree to use at least one of the following</p>

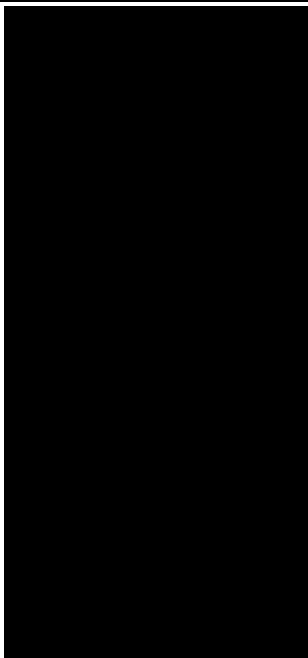



		acceptable forms of effective contraception: - Established use of oral, injected or implanted hormonal methods of contraception by the female partner of the male patient - Placement of an intrauterine device (IUD) or intrauterine system (IUS) by the female partner of the male patient - Use of barrier methods of contraception: Condom or Occlusive cap (diaphragm or cervical/vault caps) with spermicidal foam/gel/film/cream/suppository - Sterilization of the male patient (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate).
<b>Rationale for change</b>		<b>Change 1: Section 3.3.3, Exclusion criterion 27.</b> Specification, to align with Subject Information  <b>Change 2: Footnote 1 of Exclusion criteria</b> Specification, to align with Subject Information

**APPROVAL / SIGNATURE PAGE**
**Document Number: c03441881**
**Technical Version Number:3.0**
**Document Name: clinical-trial-protocol-version-02**

**Title:** A randomized, double-masked, placebo-controlled exploratory study to evaluate pharmacodynamics, safety and tolerability of orally administered BI 1026706 for 12 weeks in patients with mild visual impairment due to center-involved diabetic macular edema (DME)

**Signatures (obtained electronically)**

Meaning of Signature	Signed by	Date Signed
Author-Team Member Medicine		07 Mar 2016 17:12 CET
Author-Trial Clinical Monitor		07 Mar 2016 17:14 CET
Author-Trial Statistician		07 Mar 2016 17:20 CET
Author-Trial Clinical Pharmacokineticist		09 Mar 2016 08:58 CET
Approval-Therapeutic Area 		10 Mar 2016 10:01 CET
Verification-Paper Signature Completion		10 Mar 2016 10:38 CET
Approval-Team Member Medicine		10 Mar 2016 14:01 CET

**(Continued) Signatures (obtained electronically)**

<b>Meaning of Signature</b>	<b>Signed by</b>	<b>Date Signed</b>
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