Clinical Study Protocol

	Document Number:	**c20065772-02**
EudraCT No.: **EU Trial No:**	NA	
BI Trial No.:	0352-2110	
BI Investigational Product(s):	NA	
Title:	A biomarker evaluation study in patients with geographic atrophy secondary to age-related macular degeneration (AMD) evaluating the use of microperimetry (fundus-controlled perimetry) and Swept Source-OCT in assessing changes in retinal sensitivity and anatomy over time.	
Lay Title:	Geographic Atrophy Biomarker Evaluation Study (GABiE)	
Clinical Phase:	0	
Trial Clinical Monitor:	[redacted] Phone [redacted] Fax [redacted]	
Coordinating Investigator:	[redacted] Tel: [redacted] ; Fax: [redacted] E-mail: [redacted]	
Status:	Final Protocol (Revised Protocol (based on global amendment No. 1))	
Version and Date:	**Version: 2.0**	**Date: 21 Aug 2019**

CLINICAL TRIAL PROTOCOL SYNOPSIS

Company name	Boehringer Ingelheim Pharma GmbH & Co.KG
Finished product name	NA
Active ingredient name:	NA
Protocol date	26 Jul 2018
Revision date	21 Aug 2019
Trial number	0352-2110
Title of trial:	A biomarker evaluation study in patients with geographic atrophy secondary to age-related macular degeneration (AMD) evaluating the use of microperimetry (fundus-controlled perimetry) and Swept Source-OCT in assessing changes in retinal sensitivity and anatomy over time.
Principal Investigator < for single-centre trial or > Coordinating Investigator< for multi-centre trial if applicable >:	[redacted] Tel: [redacted] ; Fax: [redacted] E-mail: [redacted]
Trial site(s):	Multi-center trial
Clinical phase:	0
Objective(s):	To investigate the use of microperimetry and SS-OCT in assessing the natural changes of retinal sensitivity and anatomy in the perilesional zone of geographic atrophy areas in patients with dry age-related macular degeneration.
Methodology:	Biomarker Evaluation Study
Number of patients entered:	50
Number of patients on each treatment:	NA
Diagnosis :	Geographic atrophy in patients with dry age-related macular degeneration.

Main in- and exclusion criteria	Inclusion criteria: • Best Corrected Visual Acuity (BCVA) of 20/63 or better (Snellen equivalent) using ETDRS charts at starting distance of 4 m • Well demarcated area(s) of GA secondary to AMD with no evidence of prior or active choroidal neovascularization (CNV) • At least one patch of GA more than 0.5 disc area (DA) • Sufficiently clear ocular media, adequate pupillary dilation, and fixation to permit quality fundus imaging Exclusion Criteria: • GA in either eye due to causes other than AMD (for example, monogenetic macular dystrophies [e.g., Stargardt disease, cone rod dystrophy] or toxic maculopathies [e.g., chloroquine/hydroxychloroquine maculopathy]) • Receiving active treatment in any studies of investigational drugs for GA/dry AMD
Test product(s):	NA
dose:	NA
mode of administration:	NA
Comparator products:	NA
dose:	NA
mode of administration:	NA
Duration of observation:	12 months
Endpoints	All of the following endpoints will be assessed for the study eye. Primary: • Change from baseline in retinal sensitivity in the junctional zone and in the perilesional zone of the largest atrophic loci as assessed by microperimetry at week 12 • Change from baseline in RPE layers thickness in the junctional zone and in the perilesional zone as measured by SS-OCT at week 12 • Change from baseline in photoreceptor layer thickness in the junctional zone and in the perilesional zone as measured by SS-OCT at week 12 Secondary: • Change from baseline in retinal sensitivity in the junctional zone and in the perilesional zone of the largest atrophic loci as assessed by microperimetry at week 24 and 48 • Change from baseline in RPE layer thickness in the junctional zone and in the perilesional zone as measured by SS-OCT at week 24 and 48

	• Change from baseline in photoreceptor layer thickness in the junctional zone and in the perilesional zone as measured by SS-OCT at week 24 and 48 • Change from baseline in the GA area as measured by FAF at week 12, 24 and 48 • Change in BCVA score as assessed by ETDRS chart at a starting distance of 4 m at week 12, 24 and 48 • Change in LLVA score as assessed by ETDRS chart under low luminance conditions at a starting distance of 4 m at week 12, 24 and 48 • Number of scotomatous points assessed by microperimetry at week 12, 24 and 48 • Change from baseline in the area of choroidal non-perfusion as measured via OCT-A at week 12, 24 and 48
Safety criteria:	Adverse events
Statistical methods:	All endpoints will be evaluated descriptively.

FLOW CHART

Trial Periods	Screening	Observation Period			
Visit	**1**	**2 (Baseline)**	**3**	**4**	**5**
Weeks	**-4 to -1**		**12**	**24**	**48**
Time window for visits			±2 weeks	±2 weeks	±2 weeks
Informed consent	X				
In/exclusion criteria	X	X			
Demographics	X				
Medical history	X				
[redacted]					
BCVA testing (starting at 4 m)	X	X	X	X	X
Low Luminance Visual Acuity		X	X	X	X
[redacted]					
SD-OCT	X	X	X	X	X
SS-OCT with OCT-A	X	X	X	X	X
[redacted]					
FAF and Near Infrared imaging	X	X	X	X	X
Microperimetry	X[1)]	X	X	X	X
[redacted]					
Concomitant medication	X	X	X	X	X
Concurrent ocular procedures	X	X	X	X	X

1) Microperimetry examination to be executed twice with few minutes of resting
2) Do be performed only after Microperimetry testing has been done in order to avoid that the microperimetry is influenced by the light used for Color Photography.
3) Optional

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ABBREVIATIONS

AE	Adverse Event
AESI	Adverse Event of Special Interest
AMD	Age-related Macular Degeneration
BCVA	Best Corrected Visual Acuity
BI	Boehringer Ingelheim
CI	Confidence Interval
CNV	Choroidal Neovascularization
CRA	Clinical Research Associate
CRC	Central Reading Center
CRF	Case Report Form, paper or electrocic (sometimes referred to as “eCRF”)
CTR	Clinical Trial Report
DA	Disc Area
eDC	Electronic Data Capture
ETDRS	Early Treatment Diabetic Retinopathy Scale
EudraCT	European Clinical Trials Database
FAF	Fundus Autofluorescence
FDA	Food and Drug Administration
GA	Geographic Atrophy
GCP	Good Clinical Practice
IEC	Independent Ethics Committee
IMP	Investigational Medical Product
IRB	Institutional Review Board
IReST	International Reading Speed Test
ISF	Investigator Site File
LLD	Low Luminance Deficit
LLVA	Low Luminance Visual Acuity
MedDRA	Medical Dictionary for Drug Regulatory Activities
NEI VFQ-14	National Eye Institute Visual Function Questionnaire-14
OCT-A	Optical Coherence Tomography Angiography
PGx	Pharmacogenetics
RPE	Retinal Pigment Epithelium
SAE	Serious Adverse Event
SD	Standard Deviation
SD-OCT	Spectral Domain – Optical Coherence Tomography
SS-OCT	Swept Source – Optical Coherence Tomography
TSAP	Trial Statistical Analysis Plan
WHO	World Health Organization
YAG	Yttrium Aluminum Garnet

1. INTRODUCTION

1.1 MEDICAL BACKGROUND

In the developed world, age-related macular degeneration (AMD) is the leading cause of blindness. AMD is a medical condition which may result in blurred or no vision in the center of the visual field. It preferentially affects the central vision, which is needed for reading, driving, recognizing people's faces and color vision. AMD is divided into dry and wet AMD. However, it is better to describe AMD as the early phase which is virtually asymptomatic, intermediate phase with mild visual loss, which can then develop into advanced phase defined as Geographic Atrophy (GA) and / or Neovascular (or wet) AMD leading to significant visual loss. Highlighting the complexity of the disease, in some patients who are first diagnosed to have wet AMD and be treated with anti-VEGF therapy, these patients can then develop GA even after the wet component is under control or stabilized.

The pathogenesis of AMD is not well understood although significant progress has been made in the past few years. Several theories have been put forward, including oxidative stress, mitochondrial dysfunction, choroidal perfusion dysfunction and inflammatory processes. The imbalance between production of damaged cellular components and degradation leads to the accumulation of intracellular lipofuscin and extracellular matrix material, commonly seen clinically as yellow deposit called drusen. Photoreceptor loss occurs overlying the drusen area. Incipient atrophy is demarcated by thinning or pigmentary changes of the Retinal Pigment Epithelium (RPE), the supporting layer of the photoreceptors in the macular area during early disease stages. The interaction between the photoreceptors / RPE and the underlying choroid (the blood supply to the retina) in the disease state is unclear. In the advanced stages of AMD, atrophy of the RPE over a geographic area and/or development of neovascularization result in massive loss of photoreceptors and central vision loss.

1.2 RATIONALE FOR PERFORMING THE STUDY

GA secondary to AMD is an indication with high unmet medical need. Decision making in early clinical trials may be based on quantification of changes in retinal sensitivity or anatomical changes such as thinning of the photoreceptor layer. Retinal sensitivity in a specific area of the retina can be measured by fundus-controlled perimetry (microperimetry). Anatomical changes of retinal or choroidal structures or the RPE can be analysed via OCT imaging, and correlated to changes in light sensitivity.
In order to be able to address future scientific questions, patients will be asked to voluntarily donate biospecimens for banking. If the patient agrees, banked samples may be used for future drug development projects, e.g. to identify patients that are more likely to benefit from a treatment or experience an adverse event (AE), and thereby better match patients with therapies.

2. TRIAL OBJECTIVES AND ENDPOINTS

2.1 MAIN OBJECTIVES, PRIMARY AND SECONDARY ENDPOINTS

2.1.1 Main objectives

The main objective of this study is to investigate the use of microperimetry and Swept Source – Optical Coherence Tomography (SS-OCT) in assessing the natural changes of retinal sensitivity and anatomy in the retina of patients with GA.

2.1.2 Primary endpoints

All of the following endpoints will be assessed for the study eye.

- Change from baseline in retinal sensitivity in the junctional zone and in the perilesional zone of the largest atrophic loci as assessed by microperimetry for the evaluation of macular functional response at week 12
- Change from baseline in RPE layer thickness in the junctional zone and in the perilesional zone as measured by SS-OCT at week 12
- Change from baseline in photoreceptor layer thickness in the junctional zone and in the perilesional zone as measured by SS-OCT at week 12

2.1.3 Secondary endpoints

All of the following endpoints will be assessed for the study eye.

- Change from baseline in retinal sensitivity in the junctional zone and in the perilesional zone of the largest atrophic loci as assessed by microperimetry at week 24 and 48
- Change from baseline in RPE layer thickness in the junctional zone and in the perilesional zone as measured by SS-OCT at week 24 and 48
- Change from baseline in photoreceptor layer thickness in the junctional zone and in the perilesional zone as measured by SS-OCT at week 24 and 48
- Change from baseline in the GA area as measured by Fundus Autofluorescence (FAF) at week 12, 24 and 48
- Change in Best Corrected Visual Acuity (BCVA) score as assessed by Early Treatment Diabetic Retinopathy Scale (ETDRS) chart at a starting distance of 4 m at week 12, 24 and 48
- Change in Low Luminance Visual Acuity (LLVA) score as assessed by ETDRS chart under low luminance conditions at a starting distance of 4 m at week 12, 24 and 48
- Number of scotomatous points assessed by microperimetry at week 12, 24 and 48
- Change from baseline in the area of choroidal non-perfusion as measured via Optical Coherence Tomography Angiography (OCT-A) at week 12, 24 and 48

2.2 FURTHER OBJECTIVES AND FURTHER ENDPOINTS

2.2.1 Further objectives

[redacted]

2.2.2 Further endpoints

[redacted]

3. DESCRIPTION OF DESIGN AND TRIAL POPULATION

3.1 OVERALL STUDY DESIGN AND PLAN

This is a US / Europe, multi-center observational study with an enrollment target of 50 patients with GA secondary to AMD who are not receiving treatment for GA.

The observational period is dependent on the potential future availability of approved treatments for GA; in the absence of an approved therapy, this observational study may extend to 12 months. Visual function and anatomic measures will be collected at baseline, 3 months, 6 months, and 12 months. The study will consist of a screening period of up to 28 days (Days –28 to –1) and an observation period of maximally 12 months.

Enrolled patients must satisfy all eligibility criteria at both the screening period and the Day 1 visit. As part of the screening process, the Central Reading Center (CRC) will evaluate color fundus photographs, FAF images, to provide an objective assessment of patient eligibility. Patients must also meet BCVA and other eligibility criteria. Screen-failed patients can rescreen up to two additional times to qualify for study participation. One eye will be chosen as the study eye. If both eyes are eligible, the eye with the better visual function (as determined by the investigator and the patient) will be the study eye; if both eyes have the same visual function, the eye with the larger area of GA will be selected as the study eye (data will be collected on both eyes but analysed for the study eye only).

3.2 SELECTION OF STUDY POPULATION

Screening of patients for this study is competitive, i.e. screening for the study will stop at all sites at the same time once a sufficient number of patients has been screened. Investigators will be notified about screening completion and will then not be allowed to screen additional patients for this study.

3.2.1 Main diagnosis for study entry

Patients with GA secondary to AMD who are not receiving treatment for GA and have not previously receiving active treatment in clinical trials in the indication under invesitigation will be enrolled and followed for up to 12 months. Please refer to section 8.3.1 (Source Documents) for the documentation requirements pertaining to the in- and exclusion criteria.

3.2.2 Inclusion criteria

1. Signed and dated written informed consent in accordance with ICH-GCP and local legislation prior to admission to the study
2. Age ≥60 years
3. Ability (including a sufficient general health status according to investigators judgement) and willingness to undertake all scheduled visits and assessments including predefined methodology and standards utilizing microperimetry

4. GA secondary to AMD with no evidence of prior or active choroidal neovascularization (CNV) in the study eye
5. GA lesion in the study eye must reside completely within the FAF imaging field (Field 2-30 degree image centered on the fovea)
6. BCVA of 20/63 or better (Snellen equivalent) using ETDRS charts at starting distance of 4 m in the study eye
7. Well demarcated area(s) of GA secondary to AMD with no evidence of prior or active CNV in the study eye
    - The total GA lesion size ≥1.2 mm^2 (approximately ≥0.5 disc area [DA]) and ≤17.78 mm^2 (approximately ≤7 DA) and must reside completely within the FAF imaging field (Field 2−30 degree image centered on the fovea)
    - If GA is multifocal, at least 1 focal lesion must be ≥1.2 mm^2 (approximately ≥0.5 DA)
8. Sufficiently clear ocular media, adequate pupillary dilation, and fixation to permit quality fundus imaging in the study eye

3.2.3 Exclusion criteria

1. GA in either eye due to causes other than AMD (for example, monogenetic macular dystrophies [e.g., Stargardt disease, cone rod dystrophy] or toxic maculopathies [e.g., chloroquine/hydroxychloroquine maculopathy])
2. Receiving active treatment in any studies of investigational drugs for GA/dry AMD in the study eye
3. Mean sensitivity difference > 3 dB between the two microperimetry examinations in the screening visit.
4. History of vitrectomy surgery, submacular surgery, or other surgical intervention for AMD in the study eye
5. Previous laser photocoagulation for CNV, diabetic macular edema, retinal vein occlusion, and proliferative diabetic retinopathy in the study eye
6. Prior treatment with Visudyne®, external-beam radiation therapy, or transpupillary thermotherapy in the study eye
7. History of prophylactic subthreshold laser treatment for AMD in the study eye
8. Previous intravitreal drug delivery in the study eye (e.g., intravitreal corticosteroid injection, anti-angiogenic drugs, anti-complement agents, or device implantation). A single intraoperative administration of a corticosteroid during cataract surgery for cystoid macular edema prophylaxis at least 3 months prior to screening is permitted.
9. RPE tear that involves the macula in either eye
10. Any concurrent ocular or intraocular condition in the study eye (e.g., cataract or diabetic retinopathy) that, in the opinion of the investigator, could do either of the following:
    - Require medical or surgical intervention during the study period to prevent or treat vision loss that might result from that condition
    - If allowed to progress untreated, could likely contribute to loss of at least two Snellen equivalent lines of BCVA during the study period
11. Previous violation of the posterior capsule in the study eye unless it occurred as a result of Yttrium Aluminum Garnet (YAG) laser posterior capsulotomy in association with prior posterior chamber intraocular lens implantation

12. Spherical equivalent of the refractive error in the study eye demonstrating >6 diopters of myopia
13. For patients who have undergone prior refractive or cataract surgery in the study eye, the preoperative refractive error in the study eye should not have exceeded 6 diopters of myopia.
14. Intraocular surgery (including cataract surgery) in the study eye within 3 months preceding Day 1
15. History of glaucoma-filtering surgery in the study eye
16. History of corneal transplant in the study eye
17. Major surgery (major according to the investigator's assessment) performed within 12 weeks prior to randomization or planned within 12 months after screening, e.g. hip replacement
18. Previous enrolment in this study
19. Currently enrolled in another investigational device or drug trial, or less than 30 days since ending another investigational device or drug trial(s), or receiving other investigational treatment(s)

3.2.4 Withdrawal of patients from study participation

3.2.4.1 Withdrawal of consent for study participation

Patients may withdraw their consent for study participation at any time without the need to justify the decision.
This will however mean that no further information may be collected for the purpose of the study and negative implications for the scientific value may be the consequence. Furthermore it may mean that further patient follow up on safety cannot occur.
If a patient wants to withdraw consent, the investigator should explain the difference between treatment withdrawal and withdrawal of consent for study participation and explain the options for continued follow up after withdrawal from study treatment, please see section 3.2.4.1 above.

3.2.4.2 Discontinuation of the study by the sponsor

Boehringer Ingelheim (BI) reserves the right to discontinue the study overall or at a particular study site at any time.

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

4. TREATMENTS

4.1 INVESTIGATIONAL TREATMENTS

No treatments will be administered in this biomarker evaluation study.

4.2 OTHER TREATMENTS, EMERGENCY PROCEDURES, RESTRICTIONS

4.2.1 Other treatments and emergency procedures

There are no special emergency procedures to be followed.

4.2.2 Restrictions

4.2.2.1 Restrictions regarding concomitant treatment

Patients should not be included in an interventional trial for the condition under investigation while being part of this study. There are no other restrictions regarding concomitant treatment to be followed.

4.2.2.2 Restrictions on diet and life style

There are no restrictions regarding diet and lifestyle to be followed.

5. ASSESSMENTS

5.1 ASSESSMENTS OF SAFETY

5.1.1 Physical examination

NA

5.1.2 Safety laboratory parameters

No safety laboratory parameters will be determined.

5.1.3 Assessment of adverse events

5.1.3.1 Definitions of AEs

AE reporting to sponsor and timelines
This study will not use a BI Investigational Medical Product (IMP). All AEs should be collected on the appropriate Case Report Form (CRF) page only.

Adverse event
An AE is defined as any untoward medical occurrence in a patient or clinical study subject and which does not necessarily have to have a causal relationship with this study.

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 study procedures.

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

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

AEs considered "Always Serious"
Cancers of new histology and exacerbations of existing cancer must be classified as a serious event regardless of the duration between discontinuation of the drug and must be reported as described in section 5.1.3.2, subsections "**AE Collection**" and "**AE reporting to sponsor and timelines"**
In accordance with the European Medicines Agency initiative on Important Medical Events, BI has set up a list of further AEs, which by their nature, can always be considered to be "serious" even though they may not have met the criteria of an SAE as defined above.
The latest list of "Always Serious AEs" can be found in the electronic Data Capture (eDC) system. A copy of the latest list of "Always Serious AEs" will be provided upon request.
These events should always be reported as SAEs as described above.

Adverse events of special interest (AESIs)
No AESIs have been defined for this study.

Intensity (severity) of AEs
The intensity (severity) of the AE should be judged based on the following:

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

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

Yes:	There is a reasonable causal relationship between a study procedure and the AE.
No:	There is no reasonable causal relationship between a study procedure and the AE.

5.1.3.2 Adverse event collection and reporting

AE Collection
The investigator shall maintain and keep detailed records of all AEs in the patient files.
The following must be collected and documented on the appropriate CRF(s) by the investigator:

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

Information required
For each AE, the investigator should provide the information requested on the appropriate eCRF pages. The investigator should determine the causal relationship to the study procedures.
If such abnormalities already pre-exist prior to study inclusion they will be considered as baseline conditions and should be collected in the eCRF only.

5.2 ASSESSMENT OF BIOMARKER(S)

This section describes the exploratory biomarkers which will be measured in the study.

For all biomarker endpoint, baseline is defined as the value at Visit 2; if not measured at Visit 2 then baseline is the value at Visit 1. All ophthalmologic examinations will be performed on in the study eye only, as described below.

Centrally collected ophthalmological data (microperiometry, color fundus photography, OCT/OCT-A) will be transferred from the CRC to the sponsor's database. The local measurement data will remain at the study sites as source documents.

Microperimetry
Microperimety is a psychophysical technique allowing for a detailed assessment of function across specific areas of the retina such as the macula. Specific standardized patches of the retina are stimulated with points of light, and the test subject presses a button when he is able to perceive the light spot. In order to assess the light sensitivity at each test location, the stimulus intensity is lowered gradually. The fundus is monitored through an infrared camera and the fixation point is continuously tracked, thereby allowing for mapping the sensitivities of the test spots to the fundus and to images obtained with e.g. FAF imaging.

SS-OCT / SD-OCT-Angiography
The retinal layers and their thickness can be visualized and measured by SS-OCT (for direct comparison SD-OCT imaging will be performed). The assessment will be performed by a qualified person, and only specified OCT equipment will be used. OCT-A is a non-invasive imaging technique that provides high-resolution volumetric blood flow information without the use of dye. The assessment is also performed by a qualified person, and only specified device(s) will be used. OCT images will be sent to an independent CRC for evaluation. A detailed manual for OCT image acquisition and data transmission will be provided.

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

FAF and Near Infrared imaging
FAF is an imaging technology for the morphological assessment of GA. The fluorescence signal predominantly originates from fluorescent material within RPE cells. In eyes with GA, distinctly dark areas are observed where the atrophy of RPE cells leaves an absence of fluorescent signal allowing for a quantification of the size of atrophic regions. Furthermore, FAF may support the prediction of the progression rate of GA via imaging the appearance of the hyperfluorescent junctional zone (i.e., the boundary between dead and surviving RPE regions, which is likely to represent RPE and/or photoreceptor cells which are more likely to become atrophic). Specifically, retinae with junctional zones of the banded or diffuse type are more likely to progress than retinae with focal junctional zones. Therefore, the type of the junctional zone appearance in the FAF can be utilized to define inclusion criteria for this clinical study.

Low Luminance Visual Acuity (LLVA)
To determine visual acuity under low luminance condition, the amount of light transmitted is reduced by neutral density filters placed over the eye to be tested, and the subject is asked to read the letters of a ETDRS visual acuity chart which normally illuminated. Because of the filter-reduced luminance, LLVA scores are lower than for BCVA (the magnitude of the difference between BCVA and LLVA is defined as Low Luminance Deficit (LLD). LLVA measurments reveal visual function abnormalities not apparent by measuring standard BCVA alone and might be a more sensitive indicator for the risk of visual decline than assessing only standard BCVA.

[redacted]

5.2.1 Biobanking

[redacted]

6. INVESTIGATIONAL PLAN

6.1 VISIT SCHEDULE

All study visits should take place is pointed out in the Flow Chart and all patients are to adhere to the visit schedule as specified in the Flow Chart.
If any visit has to be rescheduled, subsequent visits should follow the original visit date schedule.

6.2 DETAILS OF STUDY PROCEDURES AT SELECTED VISITS

Patients must sign Informed Consent before any study related procedures are performed. Signing of the Informed Consent is not necessarily the start of the screening visit.
Once Visit 1 procedures are complete inclusion/exclusion criteria must be reviewed. If patient meets inclusion/exclusion criteria, patient should be contacted to schedule next visit. If patient does not meet inclusion/exclusion criteria the patient must be recorded in CRFs as a screen failure.

6.2.1 Observation period

Assessments should be performed as mentioned in Flow Chart, the respective protocol sections and in the imaging manual.

7. STATISTICAL METHODS AND DETERMINATION OF SAMPLE SIZE

7.1 STATISTICAL DESIGN - MODEL

The main objective of this longitudinal observational study is to investigate the use of microperimetry and SS-OCT in assessing the natural changes of retinal sensitivity and anatomy in patients with GA. In addition, changes in several other ophthalmologic measurements over time will be examined.

To this end, point estimates and confidence intervals (CIs) for the primary and secondary endpoints will be determined. Correlations between interesting pairs of outcome measures will be assessed.

7.2 NULL AND ALTERNATIVE HYPOTHESES

It is not planned to test any statistical hypotheses in a confirmatory sense. All statistical analyses are exploratory even if they use confirmatory methods.

7.3 PLANNED ANALYSES

All subjects entering the study will be included in the analyses. Protocol violations will be defined in TSAP. A per-protocol set will be defined accordingly thereafter.

7.3.1 Primary endpoint analyses

For each primary endpoint (see section 2.1.2), baseline is defined as the measurement obtained at Visit 2.

The following descriptive statistics will be calculated for the measurements related to the primary endpoints at each time point, as well as for the changes from baseline: N, arithmetic mean, Standard Deviation (SD), minimum, median, maximum, percentiles, arithmetic coefficient of variation.

Correlations (both Pearson and rank-based) of the changes from baseline of retinal sensitivity in the junctional zone and in the perilesional zone, respectively, of the largest atrophic loci as measured by microperimetry to the following endpoints will be estimated:

- Change from baseline in RPE layer thickness in the junctional zone and in the perilesional zone, respectively, as measured by SS-OCT and by SD-OCT
- Change from baseline in photoreceptor layer thickness in the junctional zone and in the perilesional zone, respectively, as measured by SS-OCT and by SD-OCT
- Changes from baseline in GA area as measured by FAF
- Change from baseline in the area of choroiocapillaris flow deficits as measured via OCT-A at week 12, 24 and 48

Individual data as well as summary statistics will be visualised in respective graphical presentations, e.g. scatter plots or box-plots.

Correlations between the primary endpoints and continuous baseline characteristics will be investigated if necessary.

7.3.2 Secondary endpoint analyses

The secondary endpoints (see Section 2.1.3) will be analysed descriptively.

Correlations between the secondary endpoints and continuous baseline characteristics will be investigated if necessary.

7.3.3 Further endpoint analyses

[redacted]

7.3.4 Safety analyses

AEs will be coded using the Medical Dictionary for Drug Regulatory Activities (MedDRA). Standard BI summary tables and listings will be produced.

AEs recorded prior to Visit 2 will be assigned to the screening period, and AEs occurring after Visit 1 but prior to the study termination date will be assigned to the observation period. Note that AEs occurring after the last per protocol contact but entered before database lock will not be captured in the trial database.

7.3.5 Pharmacokinetic and pharmacodynamic analyses

NA

7.4 INTERIM ANALYSES

No formal interim analysis is planned.
For BI internal decision making, preliminary exploratory analyses will be performed on an ad-hoc basis at selected time points of interest (based on the availability of pre-defined proportions of 12 weeks and 24 weeks data, respectively) before the final database lock. Each of these preliminary analyses will be based on a database snapshot. Details on the analyses will be described in the cumulative statistical analysis plan. Results of these evaluations will be distributed to the project team. No formal preliminary report will be written.

7.5 HANDLING OF MISSING DATA

Missing data will not be imputed.

7.6 RANDOMISATION

NA

7.7 DETERMINATION OF SAMPLE SIZE

The chosen number of 50 patients with GA is assumed to be sufficient for the purpose of investigating the distribution of the microperimetry measurements and their short-term changes in this patient population.

In particular, for this trial a precision (the half-width of the 95% CI) of 0.3 dB for the mean change from baseline in retinal sensitivity has been considered sufficient by the project team. Table 7.5: 1 provides an overview of numbers needed for obtaining a 95% CI for the mean change from baseline in retinal sensitivity with a given half width with at least 90% probability, under various assumptions for the underlying SD. For example, assuming an SD of 0.9, the trial will need 47 patients in order to achieve two-sided 95% CIs for the given precision with a probability of 90%. For an SD of 0.7, the required sample size would be 31. Note that the SD for longitudinal changes from baseline of the retinal sensitivity in 8 patients with GA as seen in Wu et al. [R17-1097] was about 0.62.

Table 7.5: 1 Number of patients needed for obtaining a 95% CI for the mean change from baseline of retinal sensitivity with a given half width with at least 90% probability, for different SD values

	Assumed SD			
Half-width of CI [dB]	0.60	0.7	0.8	0.9
0.20	47	61	77	96
0.25	33	42	53	64
0.30	24	31	39	47

The calculation was performed as described by Julious [R11-5230, Chapter 8] using R Version 3.3.2.

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

The study will be carried out in compliance with the protocol and the ethical principles laid down in the Declaration of Helsinki.

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

The BI transparency and publication policy can be found on the following web page: trials.boehringer-ingelheim.com. The rights of the investigator and of the sponsor with regard to publication of the results of this trial are described in the investigator contract. As a rule, no trial results should be published prior to finalization of the Clinical Trial Report (CTR). The certificate of insurance cover is made available to the investigator and the patients, and is stored in the Investigator Site File (ISF).

8.1 TRIAL APPROVAL, PATIENT INFORMATION, INFORMED CONSENT

This study 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) 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 regulatory and legal requirements of the participating country. Each signature must be personally dated by each signatory and the informed consent and any additional patient-information form retained by the investigator as part of the trial records. A signed copy of the informed consent and any additional patient information must be given to each patient or the patient's legally accepted representative."
The investigator must give a full explanation to study patients based on the patient information form. A language understandable to the patient should be chosen, technical terms and expressions avoided, if possible.
The patient must be given sufficient time to consider participation in the study. The investigator obtains written consent of the patient's own free will with the informed consent form after confirming that the patient understands the contents. The investigator must sign (or place a seal on) and date the informed consent form. If a trial collaborator has given a supplementary explanation, the trial collaborator also signs (or places a seal on) and dates the informed consent.
Re-consenting may become necessary when new relevant information becomes available and should be conducted according to the sponsor's instructions.
The consent and re-consenting process should be properly documented in the source documentation.

8.2 DATA QUALITY ASSURANCE

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

8.3 RECORDS

CRFs for individual patients will be provided by the sponsor.

8.3.1 Source documents

In accordance with regulatory requirements the investigator should prepare and maintain adequate and accurate source documents and trial records that include all observations and other data pertinent to the investigation on each trial patient. Source data as well as reported data should follow good documentation practices and be attributable, legible, contemporaneous, original and accurate. Changes to the data should be traceable (audit trail). Data reported on the CRF must be consistent with the source data or the discrepancies must be explained.
The current medical history of the patient may not be sufficient to confirm eligibility for the trial and the investigator may need to request previous medical histories and evidence of any diagnostic tests. In this case the investigator must make three documented attempts to retrieve previous medical records. If this fails a verbal history from the patient, documented in their medical records, would be acceptable.

8.3.2 Direct access to source data and documents

No regular on-site monitoring visits will be performed. The frequency of site monitoring will be kept to a minimum by assessing all characteristics of the trial, including its nature, objective, methodology and the degree of any deviations of the intervention from normal clinical practice.
The investigator /institution will allow site trial-related monitoring, audits, IRB / IEC review and regulatory inspections. Direct access must be provided to the CRF and all source documents/data, including progress notes, copies of laboratory and medical test results, which must be available at all times for review by the Clinical Research Associate (CRA), auditor and regulatory inspector (e.g. Food and Drug Administration (FDA)). They may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1. The sponsor will also monitor compliance with the protocol and Good Clinical Practice (GCP).
The investigator /institution will allow on-site trial-related monitoring, audits, IRB/IEC review and regulatory inspections. Direct access should be granted to all source documents (paper and e-records) including progress notes, copies of laboratory and medical test results
The CRA and auditor may review all CRFs and informed consents. The accuracy of the data will be verified by direct comparison with the source documents described in section 8.3.1.

8.3.3 Storage period of records

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

8.4 EXPEDITED REPORTING OF ADVERSE EVENTS

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

8.5 STATEMENT OF CONFIDENTIALITY AND PATIENT PRIVACY

Individual patient data obtained as a result of this trial is considered confidential and disclosure to third parties is prohibited with the exceptions noted below. 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 GCP as outlined in 'Note For Guidance On GCP (CPMP/ICH/13 5/95)
- The BI-internal facilities storing and analysing biological samples and data from clinical trial participants as well as the laboratories' activities for clinical trials sponsored by BI 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 ADMINISTRATIVE STRUCTURE OF THE TRIAL

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

9. REFERENCES

9.1 PUBLISHED REFERENCES

R11-5230 Julious SA. Sample sizes for clinical trials. Boca Raton: Taylor & Francis Group 2010

R17-1097 Wu et al. Longitudinal Changes in Microperimetry and Low Luminance Visual Acuity in Age-Related Macular Degeneration. JAMA Ophthalmol. 2015;133(4):442-448.

10. APPENDICES

Not applicable

11. DESCRIPTION OF GLOBAL AMENDMENT(S)

11.1 GLOBAL AMENDMENT 1

Date of amendment		21 Aug 2019
EudraCT number **EU number**		NA
BI Trial number		0352-2110
BI Investigational Product(s)		NA
Title of protocol		A biomarker evaluation study in patients with geographic atrophy secondary to age-related macular degeneration (AMD) evaluating the use of microperimetry (fundus-controlled perimetry) and Swept Source-OCT in assessing changes in retinal sensitivity and anatomy over time.
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – IRB / IEC / Competent Authority to be notified of change with request for approval		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		X
[redacted]		
Section to be changed		3.3.2. Inclusion criterion #7
Description of change		Well demarcated area(s) of GA secondary to AMD with no evidence of prior or active CNV in the study eye o The total GA lesion size ≥2.54 mm^2 (approximately ≥1 disc area [DA]) and ≤17.78 mm^2 (approximately ≤7 DA) and must reside completely within the FAF imaging field (Field 2–30 degree image centered on the fovea) o If GA is multifocal, at least 1 focal lesion must be ≥0.5 mm^2 (approximately ≥1 DA) was changed to Well demarcated area(s) of GA secondary to AMD with no evidence of prior or active CNV in the study eye o The total GA lesion size ≥1.2 mm^2

		(approximately ≥0.5 disc area [DA]) and ≤17.78 mm^2 (approximately ≤7 DA) and must reside completely within the FAF imaging field (Field 2–30 degree image centered on the fovea) o If GA is multifocal, at least 1 focal lesion must be ≥1.2 mm^2 (approximately ≥0.5 DA)
Rationale for change		A typographical error was erased and GA lesion size for inclusion was changed in order to resemble the later phase study population
Section to be changed		3.3.3. Exclusion criteria #2, 8
Description of change		Criteria were clarified to be applicable to the study eye only
Rationale for change		Clarification
Section to be changed		7.4
Description of change		The process for the use of study data for internal decision making was clarified
Rationale for change		Clarification

11.2 GLOBAL AMENDMENT 2

Date of amendment		
EudraCT number **EU number**		
BI Trial number		
BI Investigational Product(s)		
Title of protocol		
To be implemented only after approval of the IRB / IEC / Competent Authorities		
To be implemented immediately in order to eliminate hazard – **IRB / IEC / Competent Authority to be notified of change with request for approval**		
Can be implemented without IRB / IEC / Competent Authority approval as changes involve logistical or administrative aspects only		
Section to be changed		
Description of change		
Rationale for change		

APPROVAL / SIGNATURE PAGE

Document Number: c20065772 **Technical Version Number:2.0**

Document Name: clinical-trial-protocol-version-02

Title: A biomarker evaluation study in patients with geographic atrophy secondary to age-related macular degeneration (AMD) evaluating the use of microperimetry (fundus-controlled perimetry) and Swept Source-OCT in assessing changes in retinal sensitivity and anatomy over time.

Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed
Author-Clinical Trial Leader	[redacted]	21 Aug 2019 14:06 CEST
Author-Trial Statistician		21 Aug 2019 16:37 CEST
Approval-Team Member Medicine		21 Aug 2019 19:35 CEST
Verification-Paper Signature Completion		22 Aug 2019 14:36 CEST

(Continued) Signatures (obtained electronically)

Meaning of Signature	Signed by	Date Signed