Boehringer Ingelheim

Non-Interventional Study (NIS) Protocol

Document Number:	N/A
BI Study Number:	**1484.0014**
BI Investigational Product(s):	N/A
Title:	Characterization of patients with Geographic Atrophy (GA) in the US
Brief lay title:	Patients with Geographic Atrophy and their patient journey in the US
Protocol version identifier:	V1.0
Date of last version of protocol:	04-05-2023
PASS:	No
EU PAS register number:	N/A
Active substance:	N/A
Medicinal product:	N/A
Product reference:	N/A
Procedure number:	N/A
Marketing authorisation holder(s):	N/A
Joint PASS:	*NO*
Research question and objectives:	To describe and quantify patients with a GA diagnosis in at least one eye, and the progression to wAMD (including how many receive Anti-Vascular Endothelial Growth Factor (Anti-VEGF) treatment) in both eyes and the progression to GA (in the fellow eye).
Country(-ies) of study:	United States of America

Author/Contact person:	[redacted] [redacted] Phone: [redacted] Email: [redacted]
Marketing authorisation holder(s):	N/A
In case of PASS, add: **MAH contact person:**	N/A
In case of PASS, add: **EU-QPPV:**	N/A
In case of PASS, add: **Signature of EU-QPPV:**	N/A
Date:	

Page 1 of 30

1. TABLE OF CONTENTS

2. LIST OF ABBREVIATIONS

ADR	Adverse Drug Reaction
AE	Adverse Event
AESI	Adverse Event of Special interest
CA	Competent Authority
CCDS	Company Core Data Sheet
CI	Confidence Interval
CML	Local Clinical Monitor
CRA	Clinical Research Associate
CRF	Case Report Form
CTCAE	Common Terminology Criteria for Adverse Events
CTP	Clinical Trial Protocol
eCRF	Electronic Case Report Form
ENCePP	European Network of Centre's for Pharmacoepidemiology and Pharmacovigilance
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GEP	Good Epidemiological Practice
GPP	Good Pharmacoepidemiology Practice
GVP	Good Pharmacovigilance Practices
IB	Investigator's Brochure
IEC	Independent Ethics Committee
IRB	Institutional Review Board
MAH	Marketing Authorization Holder
MedDRA	Medical Dictionary for Regulatory Activities
NIS	Non-Interventional Study
PASS	Post-Authorization Safety Study
SAE	Serious Adverse Event
Anti-VEGF	Anti-Vascular Endothelial Growth Factor
CPT	Current Procedural Terminology
CRT	Central Retinal Thickness
DCC	Distance with correction
DSc	Distance without correction
EHR	Electronic Health Records
EMR	Electronic Medical Records
ETDRS	Early Treatment Diabetic Retinopathy Study
HCPCS	Healthcare Common Procedure Coding System
ICD	International Classification of Diseases
IOI	Intraocular inflammation
I/E	Inclusion/Exclusion
wAMD	Neovascular Age-Related Macular Degeneration
NCC	Near with correction
NSc	Near without correction
OCT	Optical coherence tomography
PH	Pinhole
PHI	Protected Health Information
SD	Standard deviation
SQL	Structured query language
VA	Visual Acuity
GA	Geographic Atrophy
eCNV	Exudative choroidal neovascularization

3. RESPONSIBLE PARTIES

[redacted]

[redacted]

Associate [redacted] of Ophthalmology

[redacted]

4. ABSTRACT

Name of company:	Boehringer Ingelheim
Name of finished medicinal product:	NA
Name of active ingredient:	NA

Protocol date: 05-04-2023	**Study number:** 1484.0014	**Version/Revision:** V1.0	**Version/Revision date:**
Title of study:	Characterization of patients with Geographic Atrophy (GA)		
Rationale and background:	There are many unknowns regarding the natural history of patients with GA, and limited data on the natural history of the disease. Recent results, presented in 2021 [1] [redacted] developed for the treatment of GA found a substantial number of patients with exudative choroidal neovascularization (classified as wAMD throughout the protocol) in the fellow eye or converting to eCNV in the study eye during the studies. These data might have affected the [redacted], and this population of patients may potentially impact the planned activities of BI. In [redacted] clinical trial, a high rate of conversion in the study eye occurred. This high rate of conversion may be influenced by the proportion of patients with wAMD present in the fellow eye. This project aims to provide clarity on the proportion of patients in the real world with GA, eCNV and focuses on both the study eye and fellow eye conversion rates, while also describing functional and imaging results, as well as treatment patterns.		
Research question and objectives:	This study aims to quantify and describe patients with a GA diagnosis in one eye, and progression in the study eye and the fellow eye to wAMD, or to GA (in the fellow eye), and the associated treatment journey.		
Study design:	This is an observational study, using existing data; The [redacted] Database.		
Population:	Patients attending a retina specialist, contributing to the [redacted] Database. Patients will be identified in the database from January 1, 2015, to April 30, 2023. From those, our study population will be patients ≥50 years with a GA diagnosis in at least one eye will be eligible for this study. The study period was selected to be able to identify patients with GA using the ICD-10 codes introduced in that year. The period from January 2015 until October 1st, 2015 will be used to identify patients diagnosed with ICD-9 codes and further classify them as new cases or patients with an previous diagnoses.		
Variables:	A primary outcome variable is visual acuity (VA), reported using converted Early Treatment Diabetic Retinopathy Study (ETDRS) letters. [redacted] Demographic characteristics – including age, gender, patient history, visit history Clinical Characteristics – including ocular comorbidities, lens status, systemic conditions		
Data sources:	The [redacted] database consists of de-identified Electronic Health Records from a geographically diverse panel of 360+ United States based private retinal specialists contributing data from 70+ practices. Over the datasets entire history, there have been about 2 million patients and about 13 million patient visits.		

Study size:	All patients available in the database and meeting the study criteria will be included. The [redacted] includes approximately 400,000 patient eyes diagnosed with dry AMD, and around 70,000 patients diagnosed with GA during the study period. After the initial feasibility analysis, it is expected, given the study criteria, that there will be around 100,000 eyes included. However, this number might change in the final analysis.
Data analysis:	In this study, both patients and eyes will be considered as the analysis unit. Baseline characteristics will be summarized using descriptive statistics. For continuous variables, the mean, standard deviation, median and range will be presented. For categorical variables frequency and proportion will be used. Variables are identified and calculated at the index diagnosis and throughout the follow-up period for primary outcomes like VA. In the progression analysis, the population will be restricted to patients with a minimum follow–up time (i.e. multiple visits at least one year apart, at least two year), or patients with valid VA reading at the index diagnosis and a second follow-up timepoint. [redacted] The analysis of incident and prevalent calculations will use as the denominator, all patients referred to the retinal specialist. The proportion of patients with a GA diagnosis referred to the retinal specialist will be put into perspective by comparing to other conditions, such as proportion of patients referred to the retinal specialist with a diabetic macular edema (DME) diagnosis, or with a diabetic retinopathy (DR) diagnosis etc. Additionally, extrapolations will be done to approximate to a population-based estimate.
Milestones:	Start of data collection: *05/2023* End of data collection: *06/2023* Final report of study results: *06/2023*

5. AMENDMENTS AND UPDATES

None

6. MILESTONES

Milestone	Planned Date
IRB/IEC approval	*NA*
Start of data collection	*05/2023*
End of data collection	*06/2023*
Registration in the EU PAS register	*NA*
Final report of study results	*06/2023*

7. RATIONALE AND BACKGROUND

GA is the late-stage form of dry age-related macular degeneration (AMD) and responsible for 10-20% of the legally blind cases. Currently, there is only one treatment for GA available for patients, [redacted] is not approved by EMA yet and therefore not available for patients in Europe Patients with wet AMD (wAMD), another advanced form of AMD, can be treated with Anti-VEGF treatment.

Presently, Boehringer Ingelheim (BI) is developing potential treatments for the target population of patients with GA secondary to AMD [redacted]

There are many unknowns regarding the natural history of patients with GA, and limited data on the prevalence, incidence, and progression of the disease. Recent results from clinical trials developing treatments for GA [redacted] found a substantial number of patients with wAMD in the fellow eye or converting to wAMD (20 to 40%) [redacted] the [redacted] a high rate of conversion to wAMD in the study eye occurred. This high rate of conversion may be influenced by the proportion of patients with wAMD present in the fellow eye. This project aims to provide clarity on the proportion of patients in the real world, with GA, wAMD in both study and fellow eyes, and the conversion rates, describing also functional and imaging results and treatment patterns.

8. RESEARCH QUESTION AND OBJECTIVES

Research Question

To quantify and describe patients with a GA diagnosis in at least one eye, [redacted]

Primary objectives
To describe the characteristics* of patients with GA in at least one eye.

To describe characteristics* of the study eye and the fellow eye, at index diagnosis [redacted]

To evaluate and characterize the progression of newly diagnosed patients with GA during each year for 5-year follow-up period. In particular, to describe patients' characteristics, study eye and the fellow eye characteristics over the 5-years follow up. [redacted]

Secondary objectives
To determine the first time occurrence of GA in the study eye, during the study period**.**

To determine the proportion of patients with GA in the study eye, over the study period.

To compare the GA first time occurrence and the proportion of GA, relative to other retinal conditions, and relative to proportion of retinal specialist contributing to [redacted] and the overall US retinal specialist.

To evaluate patients' management (i.e. patients visits and procedures) over the study period.

To describe [redacted] the overall GA population.

9. RESEARCH METHODS

9.1 STUDY DESIGN

This is an observational cohort study based on existing data.

9.1.1 Study population

Study inclusion criteria: All patients ≥50 years, with a GA diagnosis in at least one eye, including in the [redacted] database identified during the study period (January 2015 to April 2023).

Exclusion criteria: Patients without the information of laterality will be excluded.

No other exclusion criteria are applied for the identification of the study population and description of the patients and eye at baseline.

Additional note:

For certain analysis the patient population will be restricted to those with at least 12, 24, 36, 48, or 60 months of history following diagnosis of GA. For the analysis requiring a VA reading, a restriction to those patients with valid VA readings at the index diagnosis and the respective follow-up times will be applied.

For analysis estimating the size of the GA population relative to other retinal diseases, the same timeframe requirements that the study population will be applied. In this population, any patient in the database will be eligible, and the diagnosis of DME, DR or other conditions may be used for subgroup comparisons.

Primary Disease Definitions

In the [redacted] Database, retinal and other diseases are identified using the International Classification of Diseases (ICD), Tenth Revision, Clinical Modification. ICD 10 codes were launched in the USA in October 2015, and are the only version of ICD codes with adequate descriptions of GA and dry AMD severity. As such, only ICD 10 codes will be analyzed in this study and the study period defined above is directly related to the launch of ICD 10 plus a small buffer allowing for physician familiarity.

These codes are entered by the physician at patient visit, with an associated laterality. This, along with the ICD 10 laterality is used in combination to confirm in which eye the disease is occurring. For this study, a patient eye will be considered to have the study disease so long as there is an accompanying ICD code. The primary study diseases to be analyzed are dry AMD, GA and wAMD, and will be identified using the ICD codes in Table 1 below.

Table 1. Study disease definitions-codes.

Study Disease Definitions			
	Dry AMD*	Dry AMD with GA*	wAMD*
ICD 10	H35.311X, H35.312X, H35.313X, H35.319X	H35.3113, H35.3114, H35.3123, H35.3124, H35.3133, H35.3134, H35.3193, H35.3194	H35.321X, H35.322X, H35.323X, H35.329X
ICD 9 (2015 only)	362.51	N/A	362.52

*a comprehensive list of all AMD ICD codes is included in the Appendix

Patients could have simultaneously a diagnosis of wAMD and GA in the same eye. If both conditions are present, wAMD will be described as part of the comorbidities of the study or fellow eye. Patients could also have other ocular comorbidities affecting VA (section 9.3.3), those will be described and for the progression analysis will be analyzed separately.

For the follow-up analysis in the study eye or fellow eye, results will be described for all GA patients, patients with GA and wAMD, and patients with patients with GA only (without wAMD or other ocular comorbidities).

As the progression analysis tracking multiple different metrics across 2 eyes, it will be conducted at the patient level. Bilateral AMD disease is quite common (and will be identified), therefore the following methodology will be used to identify the 'Study' (primary) eye and the 'Fellow' (secondary) eye:

Study Eye – The first study eye in patient history identified with GA in the [redacted] database. GA is the only identifying disease in this case, and wAMD or dry AMD (without GA) in the study eye is not taken into account for study eye definition. If patients are bilaterally diagnosed, the study eye will be selected at random.

Fellow Eye – is defined as the other eye in a patient having their study eye diagnosed with GA. The fellow eye can have dry AMD, wAMD, GA or other retinal conditions. The fellow eye will be followed for progression purposes throughout the study.

Disease Status

Patient eyes will be identified at every visit throughout the study period to estimate the first time occurrence of GA and to estimate the proportion of patient with the disease over the years of the study period. Each visit will be classified as either an incident or a prevalent visit, defined below:

Incident visit – The first visit in patient eye history identified with GA in the [redacted] database. This timepoint also acts as each patients' index diagnosis. The incident visit may only occur once and contribute to one calendar year.

Prevalent visit – all visits following the incident visit in patient eye history while identified with GA in the [redacted] database. Prevalent visits may occur year after year throughout the patients' journey.

Study period
Patients will be identified from January, 2015 to April, 2023.

Selection period: Eligible patients must have at least one GA diagnosis between October 2015 and April 2023. The date of the first GA diagnosis will be considered as index date. For all follow up analysis, eligible patient eyes should be divided in those with at least 12, 24, 36, 48 and 60+ months of follow up. follow up requires multiple visits spanning over the outlined durations and total follow up is defined as the time between incident diagnosis and the final visit in the dataset.

Follow-up period: up to 60-month period following the index diagnosis date of GA (exploratory follow-up of 1, 2, 3, 4, 5 years may be run as cutoff points)

Pre-selection period: January 2015-September 2015. This period will be used to identify patients who have dry AMD using ICD9 coding, and will help to assign patients into the incidence or prevalence status.

9.2 SETTING

9.2.1 Study sites

All data in this study is de-identified, from existing electronical health records from the retinal specialist practices included in the [redacted] Database (US).

The [redacted] database consists of data from a geographically diverse panel of United States based private retina specialists (RS). [redacted] has physician coverage from 2015 onwards, totaling up to 360+ physicians coming from 70+ practices. These practices span across the USA geographically, with the regional distribution as follows: Midwest (20%), Northeast (17%), Southeast (27%), Southwest (11%), West (26%). This collection of practices has contributed 2+ million patients and 13+ million patient visits over the lifetime of [redacted] and is estimated to account for 15-20% of all retina specialists practicing in the USA. This dataset represents a collection of private practicing retina specialists in the USA, no data is collected from hospital or public institutions.

The [redacted] Database therefore includes longitudinal measures of physician findings and patient outcomes. This includes health related outcomes such as deterioration of visual acuity, poor adherence, subretinal fluid, intraocular pressure, and geographic atrophy. Patient phenotypes and individual outcomes can be described by individual comorbidities, demographics, visits, prescriptions, and other relevant clinical characteristics gathered from clinical codes, patient provided information and text mining of patient notes.

Study Subgroups
Following analysis on the overall population, subjects will be placed into subgroups for further analysis. Below are the proposed subgroups which may be subject to modification following data readouts. An initial feasibility will be run to assess each threshold for each subgroup, following which a final subgroup will be chosen. Any analysis (i.e. description of patients characteristics and progression) on subgroups will be defined below.

- Duration of follow up: 1+, 2+ 3+, 4+,5+ years of history
- Newly diagnosed patients with GA vs. patients with an existing GA diagnosis
- Conversion rates over time – Stratify the population into those that either progress/don't progress in the 1+, 2+ 3+, 4+,5+ years of follow up;
- [redacted] in the 1, 2, 3, 4 and 5 years of follow up period.
- Patients [redacted] that do not in the 1, 2, 3, 4 and 5 years of follow up period.

- GA lesion location (sub foveal vs extrafoveal)
- GA lesion size.

9.2.2 Study visits

As this is an observational study based on existing data, no study visit plan is applicable in this study.

9.2.3 Study discontinuation

This is an observational study based on existing data. No enrollment of patients is planned. Boehringer Ingelheim reserves the right to discontinue the study overall at any time for the following reasons:

1. Emergence of any effectiveness/safety information that could significantly affect continuation of the study, or any other administrative reasons
2. Violation of Good Pharmacoepidemiology Practice (GPP), the study protocol, or the contract by a study site, investigator or research collaborator, disturbing the appropriate conduct of the study

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

9.3 VARIABLES

9.3.1 Exposures

Study Treatments

The treatment variables below are identified at the patient eye level and will be used to describe the treatment patterns throughout the analysis. These treatment variables will be analyzed throughout the entire study period. Each treatment type can only occur once per patient eye visit and will be identified at every distinct visit where the following codes are present. Treatment must contain both the Current Procedural Terminology (CPT) codes for intravitreal injection and the J-codes specifying the study treatment (Table 2).

Though not common, it is possible for multiple different treatment types to occur on the same day, in which case both treatments would be captured for analysis i.e., a patient could get a laser and an injection at the same visit.

Table 2. Study Treatment Definitions

Study Treatment Definitions		
Treatment	CPT Code	[redacted]
[redacted]	[redacted]	[redacted], C9214, C9257, Q9977 Eylea- J0178, C9291, Q2046 Lucentis-J2778, C9233 Beovu- J0179

		Susvimo – C9093, J2779 Byooviz- Q5124 Vabysmo- J2777, C9097 Cimerli- C9097, Q5128
Corticosteroids	Intravitreal Injection – 67028	Ozurdex-J7312 Triamcinolone-J3300, J3301 Iluvien-J7313 Yutiq-J7314
Laser	Focal Grid Laser- 67210 Panretinal Photocoagulation-67228	Not Applicable
C3 Inhibitor	[redacted]	J3490, C9399

[redacted] will also accept an incoming procedure medication that is associated to an [redacted]

9.3.2 Outcomes

9.3.2.1 Primary outcomes

- [redacted]

  This study will evaluate the disease progression over time. The main progression endpoints will be for the study eye, [redacted], changes in the GA lesion location, changes in the VA or changes in the size of the GA lesion. For the fellow eye the progression endpoints will also include the developing of GA.
  *Please see Table 1, that includes the disease definitions (dry AMD, GA, and wAMD) based on ICD codes.
- **Position of GA lesion will be assessed over time**. The position of GA lesion will be defined using ICD 10 coding defined below. Any change in location status will be identified as progression of GA

Study Disease Definitions-lesion location		
	GA without Subfoveal Involvement	GA with Subfoveal Involvement
ICD 10	H35.3113, H35.3123, H35.3133, H35.3193,	H35.3114, H35.3124, H35.3134, H35.3194

- **Increase in the size of GA lesion will be assessed over time**. The size of GA lesion will be further defined following feasibility of data availability, with the basis of the lesion size defined using text field extracts. An example of text entries available for classification are defined below. Note that any analysis involving lesion size will need to be run on a subset population where these data are available/documented;
  Small: "Non-Central Geographic Atrophy, Small.";
  Medium: "Moderate Geographic Atrophy (Juxtafoveal)";
  Large: "1.5 DD Central Geographic Atrophy, Large.", "Central Geographic Atrophy, Large.", "4+ Geographic Atrophy."

- **Progression of GA by Visual Acuity**

  Change in visual acuity over time will be tracked from the incident date of GA, and assessed on a yearly basis in order to track the progression of GA over time. In this study, visual acuity will be defined as follows:
  [redacted] receives VA data from Snellen charts in over 98% of cases, with some other types (ex. Jaeger, charts) in the remainder. There are no instances of ETDRS being received since all data are coming from private retina clinics. All VA entries are standardized and converted to LogMAR for reporting purposes. [redacted] standard output for VA is in the form of [redacted]
  [redacted] will only compare VA results of a patient if vision is taken by the same measurement method; i.e., if a patient has their vision recorded using a DCC measurement at index diagnosis, for the remainder of the study, only DCC measurements will be accepted for comparison. This is done to ensure that any change in VA is due to actual change in the patients' vision, and not due to them taking a different vision test. Further, where DCC is not available for VA, any other measurements will be used, ensuring the same type of measurement will be used for the same eye to estimate the changes over time. The ranking order for measurement types is DCC ->NCC ->PH ->DSc ->NSc.
  When capturing VA at different time points of interest, a buffer is allowed on either side of the date to increase the chances of each eye coming in for a visit. Should an eye have 2 readings inside the buffer window, the reading closest to the date of interest is taken. The buffers are proposed as follows:
  - Index Diagnosis: +/- 30 days
  - Follow up reading at Month 6, 12, or 18: +/- 30 days
  - Follow up reading at Month 24, 36, 60: +/- 60 days

Incidence (new cases) and prevalence of GA will be captured, based on the ICD 10 diagnosis codes. On a calendar basis, all newly diagnosed patients will be identified and count as incident patients. Patients with a previous diagnosis of GA in the past years (with respect to a given calendar year), will be counted as prevalent cases during that calendar year.

The yearly counts of newly diagnosed or prevalent cases, will help to understand the progression of the overall disease.

9.3.2.2 Secondary outcomes

- **Retinal Disease Related HCRU Outcomes**

Change in physician care over time will be evaluated from the incident date of GA, and assessed on a yearly basis in order to assess if physician habits have changed over time, particularly following September 2021 and additionally following [redacted].

Patient visits: A patient visit (or encounter) is identified in the database any time a patient visits one of the panel physicians. Since the [redacted] database consists only of private practicing retina specialists, these are the only types of visits analyzed in the study.

If a patient visits the physician at a hospital, institution, or has an emergency room admission, the event will not be captured. For all patient visits, it is assumed that both eyes are being seen/assessed even in the primary visit reason is for one particular eye. In this sense, all visits will contribute to both eyes and any outcomes at these visits will be available for assessment.

Treatments: The documentation includes **all treatments** including injections, laser treatments, and other procedures. The type of diagnostic procedure done, and the results of these diagnostics are also recorded for most encounters. For any visit, it is assumed that both eyes are being seen, even if only one eye receives any treatment.

Other medical procedures: for example, cataracts removal, eye lid (ptosis correction), etc.

Checkups: While these eyes may be on a different treatment regimen and are only observed at this visit, the physician will still track **VA, CRT** and perform **other** general check-ups. Common reasons for visits include treatment, check-up, post operative follow up, sudden vision issues, etc. Visit burden to the retina specialist will be analyzed for the duration of the study period and tracked year over year.

Ocular comorbidities (see section 9.3.3.2) will be described over the study period, yearly.

9.3.3 Covariates

9.3.3.1 Demographic Characteristics: The demographic variables below are identified at the patient eye level and will be used to describe the demographic characteristics throughout the analysis. These demographic characteristics will be analyzed at the index diagnosis, unless specified elsewhere.

Age: will be calculated based on DOB from index diagnosis (incident visit).
Sex: identified at index diagnosis, or other visits if not specified.
Diagnosis year: Identified as the calendar year of the index diagnosis.
Months of History: will be defined as the time from index diagnosis to their last record in the database.
Incident Visit: The first visit in the database where one of the study diseases is identified, per eye. This may include Dry AMD, GA and/or wAMD. At incident visits all clinical characteristics, ocular comorbidities, etc. will be also captured.
Prevalent Visit: The first visit during a time period of interest where one of the study diseases is identified, per eye. This may include Dry AMD, GA and/or wAMD. This visit must not be the first diagnosis in the entire patient history. At prevalent visits changes in the clinical

characteristics, ocular comorbidities will be captured and described based on the first prevalent visit per calendar year.

9.3.3.2 Clinical Characteristics

Presence and Type of diabetes (T1DM/T2DM/Unspecified): Any ICD code identifying a specific type of diabetes will be used to identify a patient's diabetes status. The entire patient history prior to or on index diagnosis will be used in the identification process. Diabetes will also be identified based on the systemic drugs a patient is taking. Any type 2 drug will supersede a type 1 drugs. In the event that a patient has conflicting diabetes status using ICD codes and drugs, the ICD code will be used. A list of diabetic drugs can be found in the Appendix.

9.3.3.2.1 Ocular comorbidities defined using ICD codes (where available), listed in Appendix:
Ischemic optic neuropathy
Glaucoma
High myopia-pathologic myopia
Uveitis
Corneal transplant
Incisional glaucoma surgery
Retinal detachment
Vitrectomy
Multifocal choroiditis
Cataracts**: Cataracts presence** are defined using the ICD-9 and -10 codes to be listed in Appendix. Patient eyes will be identified as having cataracts at the index diagnosis.
Phakic Lens is an indication that the subject still has their natural lens intact, in the [redacted] database there will be no way to explicitly identify using "phakic" ICD codes. However, there will be several implicit ways in which phakic will be identified in this study:

-Free-text searches in exam section will be explored, for presence of terms such as 'clear lens', 'cataractous lens' or 'nuclear sclerosis'.

-Any ICD code identifying presence of cataracts or nuclear sclerosis (NS) information not identified on presence of an intra ocular lens will be used a definition for phakic.

Pseudophakic Lens will be defined using a combination of ICD Codes [ICD9] V43.1 or [ICD10] Z96.1[ICD9] 362.83, [ICD10] H35.31, CPT codes and free text searches.

Table 3: Other clinical conditions definitions-codes (ICD 9 and ICD 10)

[redacted]	
[redacted]	[redacted]
[redacted]	[redacted]
[redacted]	[redacted]

9.3.3.3 Other variables

Smoking status will be identified at the patient level (where available). This will be observed at or prior to index diagnosis. Free-text searches will be explored, for presence of terms such as 'Tobacco' or 'Smoker' or 'Smoking'. Smoking status will be identified as one of these categories: Smoker, Ex-Smoker, non-smoker or unknown at index.

Alcohol consumption will be identified at the patient level (where available). This will be observed at or prior to index diagnosis. Free-text searches will be explored, for presence of terms such as 'used to drink daily or '1-2 week' or 'Never. Alcohol consumption status will be identified as one of three categories: Drinker, Ex-Drinker, non-Drinker or unknown at index.

9.4 DATA SOURCES

Founded in 2014, [redacted] is the first-to-market EHR data analytics provider in the retina space. [redacted] was founded by practicing retina specialists and data-analytics experts with the mission to provide real-world insights from analyzing retina practices' electronic health data. [redacted] database consists of de-identified data from EHRs from a geographically diverse panel of United States based private retina specialists. All data comes exclusively from private retina clinics; [redacted] not collect data from hospitals or institutions. [redacted] by an anonymized patient code assigned by the software vendor. Data from multiple sources are organized into the structured database residing in US-based cloud servers. Data is maintained in a secure, password-protected environment using standards associated with personal health information (PHI).

Data Completeness

The Electronic Medical or Health Record represents the entire patient file as maintained by the treating physician and practice with the exception of diagnostic images. Records are continuous regardless of the physician in the practice treating the patient but only to the extent the patient is treated in the same practice. The file is therefore a complete record of the treatments rendered through the practice.
Data completeness within an EHR is entirely dependent on the treating physician recording diagnostic, treatment and other information. Completion rates vary by data element and depend on the treating physician's opinion of the future utility of the information related to that patient's clinical presentation. Crucial visit information such as Procedures, drugs administered, diagnoses, payer, are requires at every visit. Outcomes such as IOP and Visual Acuity are entered at 95+% of visits. Foveal thickness is recorded in approximately 30% of encounters where an OCT scan was taken. [redacted] neither adds nor removes information received. [redacted] receives the key treatment and outcomes information but does not receive every field contained in an EHR. [redacted] does extensive work with physicians analyzing their own data through clinical trials or other projects and have not found inconsistencies between the data and the physician's expectation of the data. This iterative process is an integral step in ensuring data accuracy and completeness of our data.

Capture of Concomitant Medications/Exposure

Medications administered by the treating retina specialist are identified using the structured field containing the relevant J-Code. Each drug is validated during the curation stage. Dates

of administration are the dates of the patient visit describing the treatment delivered. Disease coding is usually restricted to ocular diseases. Items like diabetes, hypertension or statin use must be identified through systemic medications that are received along with the associated procedure record. CPT codes are used in conjunction with J-Codes to enable [redacted] to identify both the procedure performed and all associated medications used. When entering all fields stated above physicians are also required to attach a laterality code. This allows [redacted] to confidently identify diseases, procedures, medications etc. by each specific eye. Anatomical outcomes are captured in our database through data entry fields and through free text fields. Physicians prefer to look at the images rather than a value, and [redacted] does not actively receive the images attached to the charts. [redacted] also receives information on fluid status (subretinal, intraretinal, sub-RPE, edema) which will include primarily present/not present but can also contain the severity level of the fluid. These are obtained and standardized from exam findings in free text fields, where physicians record information found during Optical Coherence Tomography (OCTs), Fluorescein angiographies, etc. Common descriptions of these types of entries are: “Subretinal fluid OD”, “findings consistent with subretinal fluid”.

9.5 STUDY SIZE

During the development of the protocol and while running the projects viability, a feasibility was run on the database identifying both patients and eyes with Dry AMD, and specifically with GA. This analysis was run using only ICD 10 codes and with the use of exam notes. Actual population counts are subject to change based on the dataset available at first data run, but all analysis will be based on the assumption that population sizes are relative to these numbers.

GEOGRAPHIC ATROPHY (PERIOD >=2016) (ICD 10 + Exam Notes)	
# of Patients	72,718
# of Eyes	113,408
Avg months of follow-up	22
# of Patients with visits after 3 years	20,503
# of Eyes with visits after 3 years	31,647

9.6 DATA MANAGEMENT

[redacted] extracts data weekly from various EHR vendors where it is then stored on secure servers accessible only to [redacted] has multiple data warehouses where an iterative standardization is applied to the data to combine different sources and ensure data accuracy.

Once all data cleansing and standardizing has been performed by [redacted], a static dataset is created specifically for the study to ensure there will be no variation in data for its duration. At this point, data accessible for analysis through Microsoft SQL Server Management Studio 18 and the building of the patient population begins. Only after the study population is completed, and all metrics relevant to the analysis have been identified and extracted in aggregated form to excel for further analysis and output generation. The statistical software used for this analysis will be R – version 3.6.3, which will be used for any statistical analysis

performed (t-tests, chi-square test or proportion, Confidence intervals etc.). Graphs and tables will be generated using both R and Excel, where applicable.

No personal data will be provided to Boehringer Ingelheim

9.7 DATA ANALYSIS

9.7.1 Main analysis

All analysis will be performed individually on the study population(s). All study results will be provided in tables, and key findings will be highlighted and summarized. The analyses will be conducted at both the patient and patient eye level, as appropriate.

Analysis for objective:

To describe the characteristics* of patients with GA in at least one eye.

To describe characteristics* of the study eye and the fellow eye, at index diagnosis (i.e., proportion of patients with GA in the fellow eye, [redacted]

All demographics, and clinical characteristics will be summarized at the index diagnosis date (first diagnosis of GA in the study eye).

Characteristics include demographics, comorbidities, comedications (patient level).
And at eye level; AMD, GA, eCNV, other ocular comorbidities, functional parameters i.e. VA. As well as treatments administered prior to or at index.
Summary will include descriptive statistics; continuous variables will consist of mean (SD) and median (IQR) while categorical variables will be described using frequency and proportion. Absolute numbers (n) of the variables (either yes or patients as appropriate) will be always included in the description of the results.

Analysis for objective:

To evaluate and characterize the progression of newly diagnosed patients with GA during a 5-year follow-up period. To describe patients' characteristics, study eye and the fellow eye characteristics, [redacted] or progression of the GA lesion in the study eye. To evaluate changes in VA, to evaluate changes in the lesion location, and lesion size (where available).

Patients with GA will be analyzed as an overall group. Subgroups will be also analyzed separately: only GA, GA and wAMD, GA and other comorbidities, and bilateral GA at baseline.

Ocular comorbidities will also be tracked longitudinally (yearly) from index date (GA diagnosis in the database) to better understand the disease journey.

Disease progression will be analyzed at both patient and each individual eye level. Progression to dry AMD, to GA and to wAMD will be assessed independently using time to event analysis, and also the rate of progression that is seen in the study (2nd, 3rd, 4th, and 5th) years. Bilateral GA eyes at baseline will be evaluated for progression to wAMD

For all time to event metrics, mean (SD), median and range will be summarized, while proportions will be summarized using N (%).

Kaplan Meier or Cox Hazard ratios may be applied when analyzing disease progression.

Additionally, it will be determined how patients progress during the 1,2,3,4,5 years follow up according to the lesion location, and lesion size.

Analysis for objective:

To determine the occurrence of GA in the study eye during the study period (at the 12 (24, 36, 48, 60) month follow up period).

The calculation of the occurrence (new cases) of GA will be tracked against the overall number of patients included in the retinal specialist database ([redacted] database) in a time period (year) as the denominator initially.

The analysis to calculate the prevalent cases will include all patients with a GA diagnosis active in the database in the given time period in the numerator, and all patients included in the retinal specialist database ([redacted] database) will be used as the denominator initially.

Since, this analysis is referring to a population attending a retinal specialist during a given time period and therefore is not a general population-based estimates, in order to give a context to the data, the proportion of other common diagnosis in patients over 50 years or older attending the clinic in the same time period (e.g. diabetic macular edema, diabetic retinopathy, proliferative diabetic retinopathy, and wAMD) will be calculated. The denominator will be all patients attending to the retina specialist in the given time period using the age group category that is applicable in this study (50 years or older).

For the initial calculations, the look back period in 2015 will be used to discard patients with prevalence GA diagnosis in the subsequent years. prior diagnosis will be excluded and only new cases diagnosis in the time period will be considered in the numerator when calculating incidence.

The calculations will be conducted by calendar year, and absolute numbers (n) and correspondent percentage (%) will be provided. As a sub analysis, it will be evaluated if changes occurred after the third quarter of 2021, corresponding with the [redacted]

An additional analysis will be made to extrapolate the prevalent results to a national – US-level. For that analysis, the prevalence of GA will be considering all patients seen by a retina specialist in the given year. With this metric, estimation on a national level will be done using an estimation of all practicing US retina specialists.

When analyzing the rate of progression from dry AMD to GA, a conversion analysis will be done. This will include the overall rate of dry AMD eyes developing GA, along with a Kaplan Meier analysis assessing the rate of conversion over time. This analysis will track progression by month from diagnosis, censor any patient at the final visit in the database, and identify the incident GA diagnosis as an event.

Analysis for objectives:

To evaluate patients' management (i.e. patients visits and procedures) over the study period.

Patients' management
All visits, treatment, checkups, procedures, and other will be summarized across the duration of the study time frame as well as between the index diagnosis and at the 12 (24, 36, 48, 60) month follow up period.
An additional sub analysis will be conducted to evaluate the changes in the frequency of patients visits or procedures, checkups, after the third quarter of 2021 and after [redacted].
Summary will include descriptive statistics; continuous variables will be described by absolute numbers, the mean (SD), median and range, while categorical variables will be described using frequency and proportion. Absolute numbers (n), and correspondent percentage (%) of the variables (either eyes or patients as appropriate) will be always included in the description of the results.

Analysis for objective:
To describe and compare patients' characteristics in different progression subgroups (i.e. those that develop eCNV/those that not), of the overall GA population.

The following groups will be evaluated to better understand progression:
1. Patients that [redacted]
vs. those that do not in the 1, 2, 3, 4 and 5 years of follow up period.
2. Patients that [redacted]
vs. those that do not in the 1, 2, 3, 4 and 5 years of follow up period.
3. Patients with subfoveal lesion location vs. those with extrafoveal lesion location.
For this subgroup of patient's characteristics will be described and compared.

Subgroups will be compared against one another to identify any differences in populations leading to progression. The characteristics will be extracted at the time of assignation to the group i.e. patient do not [redacted] in year one is contributing with his characteristics extracted at year 1 to the group (no progressors), that patient [redacted] at year 5 is contributing with his characteristics extracted at year 5 to the progressor group.

Summary will include descriptive statistics; continuous variables will be described by absolute numbers, the mean (SD), median and range, while categorical variables will be described using frequency and proportion. For discrete demographics or clinical characteristics, chi-squared test of proportion will be done to assess meaningful difference (standardized mean difference SMD may be used as an alternative), while continuous variables will be analyzed using SMD. Following univariate analysis on each metric, a multivariate logistic regression model will be run including relevant metrics identified in the univariate analysis.

Additional information on the analysis is described below:

Patient Demographics (at index and follow up):

N (%); Age, gender, region; Bilateral status, other eye related diagnosis in study and fellow eye; Distribution by months of follow up**;** Concomitant illnesses (diabetes, cataract, etc.)**;** Lesion location and size (along with % capture rate)

Progression : Progression of GA over time; Fellow eye AMD status**;** [redacted] (study and fellow eye) Mean (median/IQR) time to conversion; Conversion to GA (fellow eye) Mean (median/IQR) time to conversion**;** Proportion of patients with wAMD and GA (N, %)

Treatment Characteristics (follow up): Number of visits over time; Number of treatments over time**,** Mean (median) time to study treatment; Type of treatment – Anti-VEGF, Laser, Combination, Mean (median) time on therapy

New cases occurrence and prevalent cases of GA (stratified by index year): N (%)

- Age, gender
- Distribution by months of follow up
- Calculation to the % of patients attending the retinal specialist over the same time period for other retinal conditions i.e. wAMD, DR, dry AMD or DME.

Visual Acuity Outcomes

N (% capture rate); Mean (median) VA at index; Mean (median) VA at month 12; Change in VA from index to the different follow up times, VA distribution by buckets, Change in VA based on progression dates

[redacted]

9.7.3 Safety Analysis

There will be no safety analysis performed in this study

9.8 QUALITY CONTROL

The EMR information [redacted] receives is loaded into the input database unchanged. The incoming data are subject to quality control steps to ensure all the expected data are received and files are complete and readable. Changes in historic data are labeled as such and both original and modified values retained.

Input data are transformed into the operational database through a quality assurance process to ensure the validity of each data point. Metrics are tracked longitudinally to ensure logical consistency visits over visit, and are required to fall within specified limits (thresholds have been set using clinical insight from active retina specialists). Incidental Personal Health Information (PHI) contained in text fields are removed, information in text strings that contain multiple data elements are broken down into separate analyzable and standardized cells. [redacted]

All data shared with BI will be at an aggregated stage, and will be fully de-identified and HIPAA compliant

9.9 LIMITATIONS OF THE RESEARCH METHODS

As with real world data entered during patient encounters, there are limitations due to the entry process and general operations of both physicians and clinics. The [redacted] database includes only data from visits that occurred at the practices contributing to the database. Anything occurring during visits to a retina specialist/ophthalmologist in a different practice, state, country etc. is not captured.
[redacted] does receive information on previous history, referrals, etc. from overall patient history fields in attempt to gain insights on potential previous physicians, however [redacted] completely relies upon the physician to enter these data. This is a limitation of the study regarding the incidence and prevalence of the study diseases.

Retinal specialists are the primary specialty that will observe and treat all forms of AMD. However, there is a portion of mild dry AMD patients who are being observed by their general ophthalmologist. As this study will focus on GA specifically, there should not be a concern with underrepresentation in the database, as it is the most severe form of dry AMD. Out of the 1.6 million eyes with 1+ visit to in the [redacted] in 2022, dry AMD was the most prominent disease with ~180,000 eyes, twice as large as those with wAMD.
While this study will identify newly diagnosed cases of GA and wAMD, there is a possibility that a patient was diagnosed prior by an ophthalmologist or other retina specialist. As these are severe versions of AMD that are handled only by retina specialists in the USA, it is a limitation that must be addressed.
Prevalent cases are less affected as per the study definitions they are being seen over a multiple year span in the same dataset. While it is possible, they are seeing other healthcare

professionals during this time frame, they are continuing to visit their retina specialist for follow up. Patients who leave the panel for any number of reasons (death, moving, poor experience) are only able to be identified as lost to follow up. No other claim can be made on these cases, and for the study purposes they would no longer be included in any analysis from that point onwards.
For portions of the analysis where visual acuity (or other key clinical outcomes) is the primary outcome, patients are only included in the analysis when a visual acuity reading was available. In this way, it is possible that a bias is occurring in patients who are willing to have their vision recorded at every visit, or who are visiting their doctor on a more regular basis. [redacted] can only analyze visits where VA is taken, any visual acuity gains or losses that occur between visits cannot be captured. The last VA taken, or other clinical measures, is not automatically carried forward between visits, or in other words, last observation carried forward or other automatically carried forward outcomes are not utilized as [redacted] standards. These methods are available for exploration, but also carry their own limitations.

Regarding the progression analysis over a 5-year period, one limitation using this database is the length of patient follow-up time. While running feasibility, the [redacted] database showed a mean of 1.9 years of follow up. This however also includes patient who were diagnosed in 2022 for example and do not have the opportunity for 3 years of follow up. One way to address this limitation is to restrict those analysis to those patients with at least two entries with available data on progression during the follow up, however this may have the caveat to reduce the cohort of patients available for analysis. This will be explored during data readouts. Alternative methods of analysis such as Kaplan Meier may be a useful alternative to mitigate bias when analyzing rates over time.

As an overall limitation of the dataset, Data in the EHR is recorded by the physician or scribe under the direction of the physician. Physicians do not tend to enter data that is not directly relevant to the patient's current condition and tend not to enter null information. There is no real time validation of the information entered during the encounter either in terms of completeness or accuracy. However, [redacted] works extensively with the physicians providing analysis of their own data. As such, this is a crucial step in the data validation process, as physicians analyzing their own data over the years has provided insights on better coding, data entry and completeness. This limitation will affect the covariates related to comorbidities outside of retina. The current workaround is to use the systemic medications list provided to identify the treatment of these comorbidities (diabetes, hypertension etc.). However, this field also comes with its own limitation of relying on the physician/patient to provide an accurate summary of each patient's medication list.

9.10 OTHER ASPECTS

9.10.1 Data quality assurance

As this data is retrospective and de-identified in nature, there is no opportunity for patient influence and is therefore exempt from IRB review.
A quality assurance audit/inspection of this study may be conducted by the sponsor. The quality assurance auditor will have access to the database.

9.10.2 Study records

This is a study based on existing data, [redacted] is an existing database that contained the electronical medical records of patients as described in the data source section.

The investigator/institution will permit study-related monitoring, audits, IRB/IEC review and regulatory inspection, providing direct access to all related source data/documents. CRFs/eCRFs and all source documents, including progress notes and copies of laboratory and medical test results must be available at all times for review by the sponsor's clinical study monitor, auditor and inspection by health authorities (e.g. US Food and Drug Administration (FDA)).

9.10.3 Completion of study

This is a study based on existing data, and there is no EC competent for the use of the [redacted] database.

10. PROTECTION OF HUMAN SUBJECTS

This is a study based on existing data and the data analysis will be conducted using anonymized patient level information. The use of the [redacted] database do not require any submission or approval from an Institutional Review Board (IRB).

10.1 STUDY APPROVAL, PATIENT INFORMATION, AND INFORMED CONSENT

The conduct of the study using the [redacted] database does not required of any Institutional Review Board/Independent Ethics Committee approval. No additional Competent Authority should be consulted to the initiation of this NIS. As this study is based on existing data, patients consent is not necessary to be obtained.

10.2 STATEMENT OF CONFIDENTIALITY

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

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 study need to be available for inspection on request by the participating physicians, the sponsor's representatives, by the IRB/IEC and the regulatory authorities (when applicable).

11. ADVERSE EVENT AND SERIOUS ADVERSE EVENT COLLECTION AND REPORTING

Not applicable based on secondary use of data without any potential that any employee of BI or agent working on behalf of BI will access individually identifiable patient data.

12. REPORTING TO HEALTH AUTHORITIES

Adverse event reporting to regulatory agencies are done by the Marketing Authorization Holder (MAH) according to local and international regulatory requirements.

13. PLANS FOR DISSEMINATING AND COMMUNICATING STUDY RESULTS

The rights of the investigators, and of the sponsor with regard to publication of the results of this study are described in the "terms of collaboration" document. As a general rule, no study results should be published prior to finalization of the Study Report.

14. REFERENCES

14.1 PUBLISHED REFERENCES

[2] Wykoff CC, Rosenfeld PJ, Waheed NK, Singh RP, Ronca N, Slakter JS, Staurenghi G, Monés J, Baumal CR, Saroj N, Metlapally R, Ribeiro R. Characterizing New-Onset Exudation in the Randomized Phase 2 FILLY Trial of Complement Inhibitor Pegcetacoplan for Geographic Atrophy. Ophthalmology. 2021 Sep;128(9):1325-1336. doi: 10.1016/j.ophtha.2021.02.025. Epub 2021 Mar 10.PMID: 33711380

[redacted]

15. ANNEX 1. ADDITIONAL INFORMATION

All definitions of variables outlined during the protocol are summarized in an excel file to keep this document concise and for ease of reference. The file has been sent along with the protocol and a link can be found here:

CODES APPENDIX.XLSX

ANNEX 2. REVIEWERS AND APPROVAL SIGNATURES

The NIS Protocol must be sent for review to the following individuals **prior to approval**.

Study Title: Characterization of patients with Geographic Atrophy (GA) in the US

Study Number: 1484.0014

Protocol Version:1.0

I herewith certify that I agree to the content of the study protocol and to all documents referenced in the study protocol.

Position	Name/Date	Signature:
NIS [redacted]	[redacted] 05-May-2023	DocuSigned by: [redacted]
TMM	[redacted] 05-Mai-2023	DocuSigned by: [redacted]
GEpi Group [redacted]		DocuSigned by: [redacted]

DocuSign

Certificate Of Completion

Envelope Id: AEA7567F21644FDD87EB978ADEEAF25F
Status: Completed
Subject: Complete with DocuSign: BI-nis-protocol-[redacted]Geographic Atrophy Final V1.0.docx
Source Envelope:
Document Pages: 30
Signatures: 3
Envelope Originator:
Certificate Pages: 4
Initials: 0
AutoNav: Enabled
EnvelopeId Stamping: Enabled
Time Zone: (UTC+01:00) Amsterdam, Berlin, Bern, Rome, Stockholm, Vienna
[redacted]

Record Tracking

Status: Original
5/5/2023 8:32:01 AM
Holder: [redacted]
[redacted]
Location: DocuSign

Signer Events	Signature	Timestamp
[redacted] Security Level: Email, Account Authentication (None)	DocuSigned by: [redacted] Signature Adoption: Pre-selected Style Using IP Address: [redacted]	Sent: 5/5/2023 8:34:12 AM Viewed: 5/5/2023 8:34:29 AM Signed: 5/5/2023 8:34:56 AM Freeform Signing
Electronic Record and Signature Disclosure: Accepted: 1/3/2023 4:07:01 PM ID: 8d2c88f8-6560-4b16-888c-63d6398c3bf6		
[redacted] Security Level: Email, Account Authentication (None), Login with SSO	DocuSigned by: [redacted] Signature Adoption: Pre-selected Style Using IP Address: 147.161.131.117	Sent: 5/5/2023 8:35:00 AM Viewed: 5/5/2023 9:29:41 AM Signed: 5/5/2023 9:43:18 AM Freeform Signing
Electronic Record and Signature Disclosure: Accepted: 1/6/2023 8:11:50 AM ID: 153a122d-a222-45b2-bfb3-871fca5ee953		
[redacted] Global Epidemiology [redacted] Boehringer Ingelheim Validated Production Security Level: Email, Account Authentication (None)	DocuSigned by: [redacted] Signature Adoption: Pre-selected Style Using IP Address: [redacted]	Sent: 5/5/2023 9:43:23 AM Viewed: 5/5/2023 11:59:11 AM Signed: 5/5/2023 12:00:27 PM Freeform Signing
Electronic Record and Signature Disclosure: Accepted: 8/19/2022 3:23:37 PM ID: e8e4e87e-5a6a-4488-8086-6345ae09ad9e		

In Person Signer Events	Signature	Timestamp

Editor Delivery Events	Status	Timestamp

Agent Delivery Events	Status	Timestamp

Intermediary Delivery Events	Status	Timestamp

Certified Delivery Events	Status	Timestamp

Carbon Copy Events	Status	Timestamp

Witness Events	Signature	Timestamp

Notary Events	Signature	Timestamp

Envelope Summary Events	Status	Timestamps
Envelope Sent	Hashed/Encrypted	5/5/2023 8:34:12 AM
Certified Delivered	Security Checked	5/5/2023 11:59:11 AM
Signing Complete	Security Checked	5/5/2023 12:00:27 PM
Completed	Security Checked	5/5/2023 12:00:27 PM

Payment Events	Status	Timestamps

Electronic Record and Signature Disclosure

Boehringer Ingelheim
Consent to Proceed with Electronic Signatures

This document describes the frame conditions with regard to the use of the DocuSign® system by the authorized user ('you') for electronic signing and/or processing of documents concerning the business with Boehringer Ingelheim International GmbH, Binger Strasse 173, 55216 Ingelheim am Rhein, Germany or any of its affiliated companies ('we, us or Company').
Via the DocuSign® system, you will be able to complete, review, and even print documents you will electronically sign using only your web browser via the link sent to you by e-mail. Before using the DocuSign® system, please make sure that you are able to meet the technical system requirements, which can be accessed via the DocuSign® website. Please read the information below carefully and thoroughly.

Contractual documents and notices may be sent to you electronically

If not otherwise agreed in a given contract between you and us, we will provide electronically to you through your DocuSign® user account all contractual documents, notices and other documents that are required to be provided or made available to you during the course of our business relationship with you. To reduce the chance of you inadvertently not receiving any notice or document, we will provide all of the required notices and documents to you by the contractually agreed method(s) and to the address(es) provided therein. Subject to the provisions of the given contract you may receive documents and notices electronically or in paper format.

Getting paper copies

As long as you are an authorized user of the DocuSign® system, you will have the ability to download and print any documents we send to you through your DocuSign® user account for a limited period of time (usually 30 calendar days) after such documents are first sent to you. In case a mandatory local legal requirements exists, we will provide paper copies of the contractual documents upon your request which has to be sent to the respective Company contact nominated in the contract.

Consequences of changing your mind

In exceptional cases (f.e. contractually agreed option, mandatory local legal requirement) you may be entitled to elect to receive required notices and disclosures only or additionally in paper format. If you decide to exercise a given option you have to liaise with your respective Company contact nominated in the contract by using the address(es) in accordance with the process contractually foreseen.

Changing your e-mail address

If your e-mail address changes please arrange for your new e-mail address to be reflected in your DocuSign® account by following the process for changing e-mail in the DocuSign® system.

Acknowledging your access and consent to receive materials electronically

To confirm to us that you can access this information electronically, please verify that you were able to read this electronic consent and that you (i) also were able to print on paper or electronically save this disclosure for your future reference and access or that you (ii) were able to e-mail this disclosure and consent to an address where you will be able to print on paper or save it for your future reference and access.
By checking the 'I Agree' box, I confirm that:

- I can access and read this CONSENT TO PROCEED WITH ELECTRONIC SIGNATURES document; and

- I can print on paper the disclosure or save or send the disclosure to a place where I can print it, for future reference and access; and
- Until or unless I have notified my respective Company contact as described above, I consent to receive through electronic means all contractual documents, notices and other documents that are required to be provided or made available to me by the Company during the course of the business relationship with you.