NCT02087085

Study ID: 190342-038

Title: Safety and Efficacy of Brimonidine Posterior Segment Drug Delivery System in Patients with Geographic Atrophy Secondary to Age-related Macular Degeneration

Statistical Analysis Plan Date: 03-Aug-2018

1. Title Page

STATISTICAL ANALYSIS PLAN

Safety and Efficacy of Brimonidine Posterior Segment Drug Delivery System in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration (BEACON Study: 190342-038)

Version 2.0: 2018-08-03

Protocol Number:	190342-038 Amendment 7
Development Phase:	2b
Product Name:	AGN-190342, Brimonidine Drug Delivery System (Brimo DDS®)
Study Statistician:	[redacted]
Sponsor:	Allergan (North America) 2525 Dupont Drive Irvine, California USA 92612 +1-714-246-4500 +1-800-347-4500 Allergan Ltd. 1st Floor, Marlow International, The Parkway, Marlow Buckinghamshire SL7 1YL United Kingdom Tel: +44 (0) 1628 494444 Fax: +44 (0) 1628 494449

2. Table of Contents

2.1 List of Tables

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No table of figures entries found.

3. List of Abbreviations and Definition of Terms

Table 3-1 Abbreviations and Definitions of Terms

Abbreviation/Term	Definition
ACT	anatomical therapeutic chemical
AE	adverse event
AMD	age-related macular degeneration
BCVA	Best-corrected visual acuity
Brimo DDS®	Brimonidine Drug Delivery System
CRC	central reading center
cSLO	confocal scanning laser Ophthalmoscopy
eCRF	electronic case report form
ECG	electrocardiogram
[redacted]	[redacted]
ETDRS	early treatment diabetic retinopathy study
FAF	fundus autofluorescence
GA	geographic atrophy
[redacted]	[redacted]
IOP	intraocular pressure
IR	infrared reflectance
IVRS	interactive voice response system
IWRS	interactive web response system
LLT	lowest level term
LOCF	last observation carried forward
MedDRA	medical dictionary for regulatory activities
mITT	modified intent-to-treat
MMRM	mixed-effects model for repeated measures
NA	non applicable
[redacted]	[redacted]
OC	observed cases
OCT	optical coherence tomography
OD	oculus dexter (the right eye)
OS	oculus sinister (the left eye)
OU	oculus uterque (both eyes)
PCS	potentially clinically significant
PID	patient identification
PP	per-protocol
PRO	patient-reported outcome
PT	preferred term
qFAF	quantitative fundus autofluorescence
SAE	serious adverse event

Abbreviation/Term	Definition
SAP	statistical analysis plan
SD-OCT	spectral-domain optical coherence tomography
[redacted]	[redacted]
SI	*Le Système International d'Unités* (International System of Units)
SOC	system organ class
TEAE	treatment-emergent adverse event
WHO DDE	the World Health Organization drug dictionary enhanced

4. Introduction

This statistical analysis plan (SAP) details comprehensive, technical specifications of the statistical analyses of the efficacy and safety data outlined and/or specified in the final protocol of Study 190342-038 (BEACON) and the most recent amendment (version 7). Specifications of tables, figures, and data listings are contained in a separate document. The SAP for microperimetry [redacted] fundus autofluorescence (FAF) signal intensity, pharmacokinetic/pharmacodynamics (Blood samples for PK), genomic analysis (Blood Samples for Genotypic Analysis and Gene Expression Analysis) and health economics and health outcomes research data [redacted] will be prepared separately.

This document is organized into 3 main sections:

1. Study overview
2. Statistical Methodology and Study Endpoints
3. Data Handling and Analysis Conventions

4.1 Study Design Summary

4.1.1 Overall Design

This is a multicenter, double-masked, randomized, Sham treatment-controlled, 30-month phase 2b study designed to evaluate the safety and efficacy of Brimo DDS in patients with geographic atrophy (GA) secondary to age-related macular degeneration (AMD). Patients will be randomized in a 1:1 ratio to receive 400 µg Brimo DDS, administered by intravitreal injection, or Sham treatment (control). Randomization will be stratified by region (North America, Europe, and Australia) and by atrophic lesion area (≤ 8 mm^2 versus > 8 mm^2) in the study eye as assessed by FAF examination at Screening Visit 1 and quantified by the Central Reading Center (CRC). The study medication will be administered every 3 months from Baseline (Day 1) through Month 21.

The primary efficacy measure, the mean change in atrophic lesion area as assessed with FAF, will be assessed at Month 24. In addition to quantifying structural changes of the retina, functional assessments will be performed using scotopic/mesopic microperimetry, as well as standard and low luminance Best-corrected visual acuity (BCVA) evaluations. Total duration of the study for each patient is 30 months following randomization/treatment. [redacted]

For patients who do not participate in the microperimetry procedure or patients from sites not participating in the microperimetry procedure, there will be only 1 Screening visit, and therefore 13 visits over the study duration.

4.1.2 Number of Participants

According to the study protocol, approximately 300 patients (150 per treatment group) will be enrolled in the study at approximately 40 sites. Two hundred forty patients are expected to reach Month 24 for the primary endpoint assessment. The anticipated dropout rate is 20%.

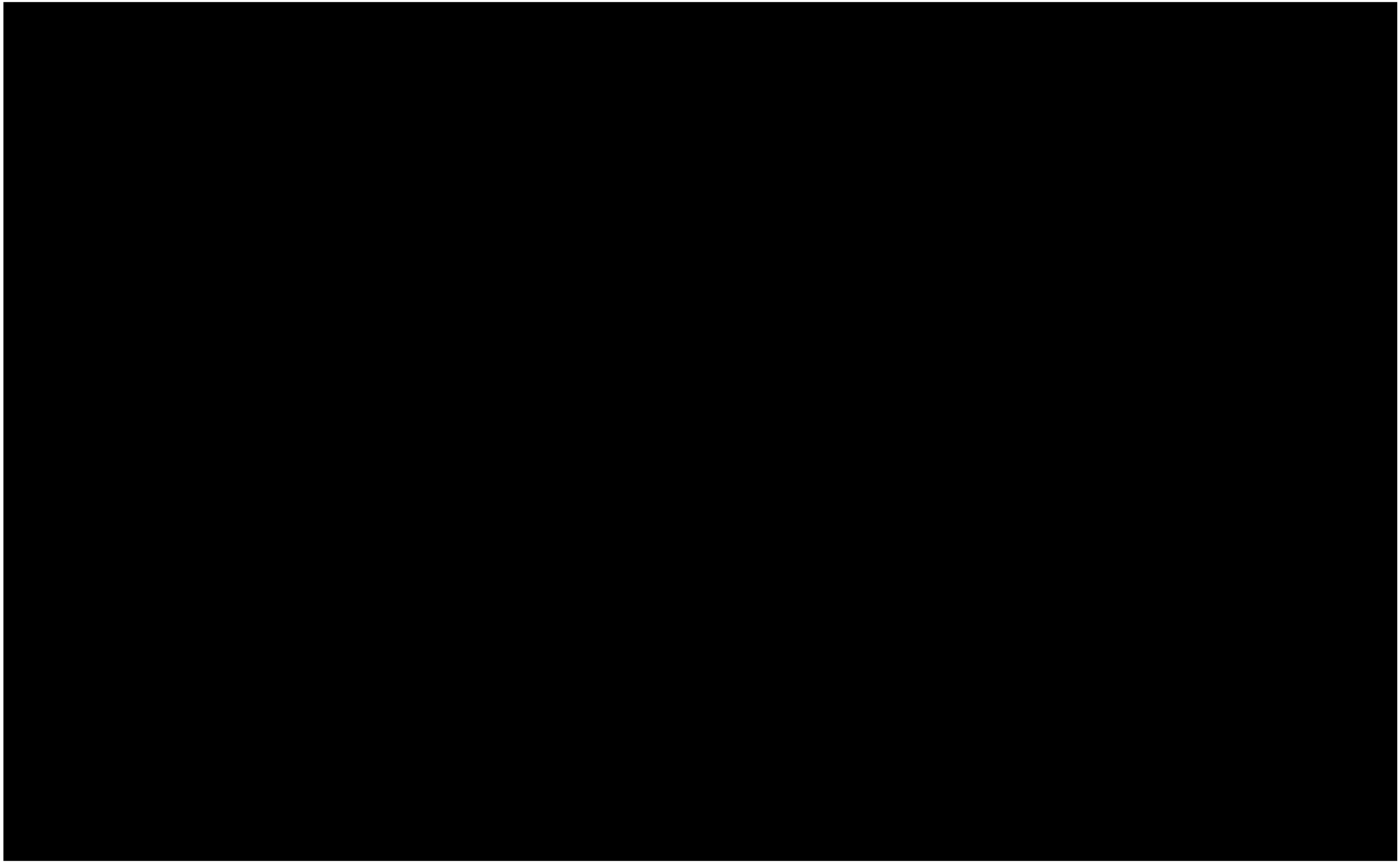
From the patient enrollment monitoring as of September, 2016, total 310 patients were enrolled. Assuming approximately 25% dropout rate based on the survival analysis using Kaplan-Meier estimate, 310 patients will be enough that 240 patients complete the Month 24 visit.

4.2 Study Objectives and Endpoints

Each study objective is presented with corresponding endpoint(s) below:

Objectives	Endpoints
• To compare the efficacy of Brimo DDS with Sham in participants with Geographic Atrophy secondary to AMD.	**Primary Endpoint** • Mean change in atrophic lesion area as assessed with FAF and quantified by the CRC **Secondary Endpoint(s)** • Mean change in low luminance BCVA* as assessed using a 2.0 log unit neutral density filter and the ETDRS visual acuity protocol • Mean change in standard BCVA assessed using the ETDRS visual acuity protocol **Other Endpoint(s)** • Mean change in retinal sensitivity threshold as assessed with scotopic/mesopic microperimetry • [redacted]
• To compare the safety of Brimo DDS with Sham treatment procedure in participants with Geographic Atrophy secondary to AMD.	[redacted]

* Mean change of low luminance deficit will also be calculated.



5. Statistical Methodology and Study Endpoints

5.1 Statistical Methods Planned in the Protocol and Determination of Sample Size

This statistical analysis plan (SAP) will be approved prior to database lock. The SAP expands the statistical section of the protocol and contains a detailed description of methods to analyze data collected in the study. The text portion of the SAP will be included in the CSR report as Appendix 16.1.9.

5.1.1 Statistical and Analytical Plans

Statistical analyses will be conducted using [redacted]

5.1.1.1 Common Conventions

5.1.1.1.1 Analysis Populations

The analysis populations will consist of participants as defined below:

Table 5-1 Analysis Populations

Population	Definition	Study Treatment
Modified Intent-to-Treat (mITT)	All randomized and treated patients with baseline and ≥ 1 postbaseline assessment for geographic atrophy lesion area by FAF, the primary efficacy endpoint.	As randomized
Safety	All patients who received ≥ 1 administration of study treatment	As treated

If a patient is mis-stratified at the randomization, then the patient will be analyzed using the intended stratum in which the patient should belong to.

5.1.1.1.2 Study Treatments

The following treatment groups are defined for this study:

- Brimo DDS 400 µg
- Sham

5.1.1.1.3 Statistical Methodology

The methodologies defined below apply as specified to individual endpoints defined in this SAP. When indicated, two-sided 95% confidence intervals and two-sided p-values will be presented. Individual endpoint analyses may specify exceptions (additions or deletions) to these general definitions.

Table 5-2 Statistical Methodology

Methodology	Description
Categorical counts	• Number of participants in individual categories ○ Participants with ≥ 1 qualifying event counted once per individual category

Categorical descriptives	• Number and percentage of participants in individual categories
	  ○ Participants with ≥ 1 qualifying event counted once per individual category
	• Percentage denominator = N1
	  ○ N1 = participants with non-missing value

Methodology	Description
Cumulative descriptives	• Cumulative number and percentage of participants in individual categories by visit o Participants with ≥ 1 qualifying event counted once per individual category • Percentage denominator = number of participants in the population
Continuous descriptives	• N1, mean, standard deviation (SD), median, minimum, maximum • N1 = participants with non-missing value
BCVA CFB categorical change	• BCVA score change from baseline will be classified into the following 5 ordinal categories ranked from the best to the worst changes: 1) ≥ 15 letters improvement; 2) ≥ 5 and < 15 letters improvement; 3) no change (i.e., change between +5 and -5 letters); 4) ≥ 5 and < 15 letters worsening; 5) ≥ 15 letters worsening. • The distribution of the 5 categories at each visit will be summarized by frequency tabulations for each treatment. Treatment comparison will be performed using Mantel-Haenszel statistics for row mean scores differ using the modified ridit scores stratified by GA lesion size at screening visit (<= 8 mm^2, > 8 mm^2).

CFB MMRM	• Continuous descriptives and standard error (SE) for baseline, postbaseline, and values at each analysis visit
	o N1 = participants with non-missing values at both baseline and the specified postbaseline analysis visit
	• CFB will be analyzed with a Mixed Model for Repeated Measures (MMRM). The model includes treatment, study region (North America, Europe, and Australia), analysis visit, and treatment-by-visit interaction as factors as well as the baseline value and baseline value-by-analysis visit interaction as covariates. An unstructured (co)variance structure shared across treatment groups was used to model the within-patient errors (compound symmetry if convergence fails). The Kenward-Roger approximation was used to estimate denominator degrees of freedom and adjust standard errors. Analyses were implemented with SAS PROC MIXED. The following is the sample SAS codes.
	proc mixed;
	class subject treatment time region;
	model Y = baseline treatment time region
	treatment*time baseline*time / ddfm=kr;
	repeated time / sub = subject type = un;
	lsmeans treatment*time / diff slice=time cl ;
	estimate 'treatment difference at tx' treatment -1 1
	treatment * time 0 0 0 0 -1
	0 0 0 0 1/cl;
	run;
	o Least squares (LS) means and standard errors
	o LS mean differences, standard errors, and confidence intervals comparing Brimo DDS vs Sham
	o P-values from contrast t-test comparing Brimo DDS vs Sham
	o N1 = participants with non-missing values at both baseline and the specified postbaseline analysis visit

Nonparametric descriptives	• Number and percentage of patients in individual categories by treatment group • Mantel-Haenszel statistics for row mean scores differ using the modified ridit

Methodology	Description
	scores stratified by GA lesion size at screening visit (<= 8 mm^2, > 8 mm^2).

CFB = change from baseline; AE = Adverse Event

5.1.1.1.4 Missing Data

For efficacy variables, only observed data will be used.

5.1.1.1.5 Site Pooling

Region, defined by geographic proximity, will be summarized as North America, Europe and Australia. Sites will be pooled into these three categories.

5.1.1.2 Demographics

5.1.1.2.1 Analysis Populations

The distribution of participants within the analysis populations will be summarized as follows:

Table 5-3 Analysis Population Summaries

Population	Variable	Timing	Methodology
mITT, and Safety populations	Distribution in total and by treatment group overall and by randomization stratum	—	Categorical counts

5.1.1.2.2 Participant Disposition

Participant disposition encompasses the distribution of participants who enter, complete, and discontinue each specified analysis period, along with eCRF-reported discontinuation reasons from each respective analysis period. Participant disposition will be summarized as follows for the All Randomized Population:

Table 5-4 Participant Disposition Summaries

Parameter	Variable	Timing	Methodology

Dispositions	• Number of participants
	  ○ Screened
	  ○ Randomized
	  ○ Treated
	  ○ Completed
	  ○ Discontinued
	• Reasons for discontinuation
	  ○ Adverse Event
	  ○ Lack of Efficacy
	  ○ Pregnancy
	  ○ Lost to Follow-up
	  ○ Withdrawal by Subject
	  ○ Protocol Violation
	  ○ Other
		Treatment Period[1]	Categorical descriptives

[1] Treatment period will be defined from baseline to Month 30 or early study exit.

5.1.1.2.3 Protocol Deviations

Protocol deviations will be defined in a separate Protocol Deviation Log, including importance classification. Significant protocol deviations will be summarized as follows:

Table 5-5 Protocol Deviation Summary

Parameter	Variable	Timing	Methodology
Significant protocol deviations	Distribution in all randomized patients in total and by treatment group	—	Categorical descriptives

5.1.1.2.4 Demographics

Demographics will be summarized in total and by treatment group for the mITT population, as follows:

Table 5-6 Demographic Summaries

Parameter	Variable	Timing	Methodology
Age	Age (years) relative to informed consent date	Informed consent	Continuous descriptives
Age group	• < 75 years • ≥ 75 years	Informed consent	Categorical descriptives

Sex, race	• eCRF categories
	• Sex
	• Race
	  ○ White
	  ○ Black
	  ○ Asian
	  ○ Hispanic
	  ○ Other
	• Race group
	  ○ White
	  ○ Non-white
		Screening Visit 1	Categorical descriptives

5.1.1.2.5 Baseline Characteristics

Baseline characteristics will be summarized in total and by treatment group for the mITT population as follows:

Table 5-7 Baseline Characteristic and Stratification Factor Summaries

Parameter	Variable	Timing	Methodology

Baseline characteristics	• Iris Color
	  ○ Blue
	  ○ Green
	  ○ Hazel
	  ○ Brown
	  ○ Other
	• Weight (kg)
	• Height (cm)
	• BMI (kg/m^2)
		Latest assessment in Screening Period or Pretreatment Period	Categorical & Continuous descriptives

Stratification Factors	• Region by Geographic atrophic lesion area in study eye as	Latest assessment in Screening Period or	Categorical descriptives

Parameter	Variable	Timing	Methodology
	assessed by FAF at Screening Visit 1 o North America ▪ ≤ 8 mm^2 ▪ > 8 mm^2 o Europe ▪ ≤ 8 mm^2 ▪ > 8 mm^2 o Australia ▪ ≤ 8 mm^2 ▪ > 8 mm^2	Pretreatment Period	

5.1.1.2.6 Prior and Concomitant Medications

Medications will be coded using the World Health Organization (WHO) Drug Dictionary, March 2016 or newer. Medication will be listed for the Safety Population defined as follows:

Table 5-8 Prior Medication

Parameter	Variable	Timing
Prior medications	Medications taken ≥ 1 time (see below for time definition) before the study treatment start date, regardless of medication end date. A medication will be defined as a prior medication if it satisfies at least one of the following: • The start date is prior to Day 1, regardless of the stop date; • The stop date is prior to or on Day 1, regardless of the start date; or • The start date is marked as "> 1 year ago"	Screening Period

Table 5-9 Concomitent Medication

Parameter	Variable	Timing
Concomitant medications	Medications taken ≥ 1 time (see below for time definition) on or after the study treatment start date, regardless of medication start date. A medication will be defined as concomitant if it satisfies at least one of the following: • The start date is on or after Day 1, regardless of the stop date; • The stop date is after Day 1, regardless of the start date; or • The stop date is marked as ongoing.	Treatment Period

5.1.1.3 Efficacy Analyses

Efficacy analyses will be based on the mITT Population. Baseline for all efficacy endpoints is defined as the last non-missing assessment before the first dose of study treatment.

The following efficacy parameter categorizations are defined:

Table 5-10 Efficacy Assessments

Assessment	Variable

Assessment	Variable
GA lesion area by FAF	GA lesion area (mm^2) as determined by FAF on baseline, Months 6, 12, 18, 24, and 30
Low luminance BCVA	The number of letters read correctly, quantified using a 2.0 log unit neutral density filter
Standard BCVA	The number of letters read correctly, quantified using the EDTRS visual acuity protocol.

5.1.1.3.1 Geographic Atrophy Lesion Area Analyses

Table 5-11 Atrophic Lesion Area Analyses

Endpoint	Variable	Timing[1]	Methodology
Effective Diameter of GA lesion area (mm) of the study eye by FAF[2] (Primary)	• Means, SDs and other descriptives by visit and treatment group • CFB LSMeans, SEs and other descriptives by visit and treatment group • Comparison of CFB LS means by visit	Treatment Period	CFB MMRM
Geographic Atrophy Lesion Area (mm^2) of the study eye by FAF	• Means, SDs and other descriptives by visit and treatment group • CFB LSMeans, SEs and other descriptives by visit and treatment group • Comparison of CFB LS means by visit	Treatment Period	CFB MMRM

[1] Analysis visits defined in Section 6.2.1.

2 Effective diameter (ED) is defined as 2 times square root of GA lesion area divided by π ($ED = 2 * \sqrt{GA\ Area/\pi}$).

5.1.1.3.2 Best Corrected Visual Acuity Analyses

Visual acuity will be recorded on the CRF as the number of letters correctly read. For a given eye, the 4-meter distance (standard) of visual acuity is tested first. If the patient correctly reads at least 20 letters at 4 meters, the visual acuity score will be set as the sum of 30 and the number of letters read correctly. If the patient correctly reads less than 20 letters at 4 meters, the visual acuity is measured again at 1 meter. The visual acuity score will be set to the number of letters read correctly at 1 meter plus the number of letters read correctly at 4 meters.

Table 5-12 Best Corrected Visual Acuity Analyses

Endpoint	Variable	Timing[1]	Methodology
Low luminance BCVA change from baseline in the study eye (Secondary)	• Descriptive summary of baseline & CFB	Treatment Period	CFB MMRM
Low luminance deficit in the study eye (Secondary)	• Descriptive summary of baseline & CFB	Treatment Period	CFB MMRM
Standard BCVA change from baseline in the study eye	• Descriptive summary of baseline & CFB	Treatment Period	CFB MMRM

Endpoint	Variable	Timing[1]	Methodology
(Secondary)			
Standard BCVA change from baseline in the study eye (Secondary)	• Change in postbaseline BCVA scores from the previous visit will be categorized as 1) ≥ 15 letters improvement; 2) ≥ 5 and < 15 letters improvement; 3) no change (i.e., change between +5 and -5 letters); 4) ≥ 5 and < 15 letters worsening; 5) ≥ 15 letters worsening	Treatment Period	BCVA CFB categorical change

[1] Analysis visits defined in Section 6.2.1.

5.1.1.3.3 Exploratory Endpoints and Analyses

[redacted]

- Mean change in retinal sensitivity threshold as assessed with scotopic/mesopic microperimetry

[redacted]

The following exploratory efficacy parameter categorizations are defined:

Table 5-13 Exploratory Efficacy Assessments Variable

Assessment	Variable
Retinal sensitivity threshold by scotopic/mesopic microperimetry	The calculated mean retinal sensitivity (dB) from the BEACON test at baseline, Month 6, 12, 18, 24, and 30.
[redacted]	[redacted]
[redacted]	[redacted]

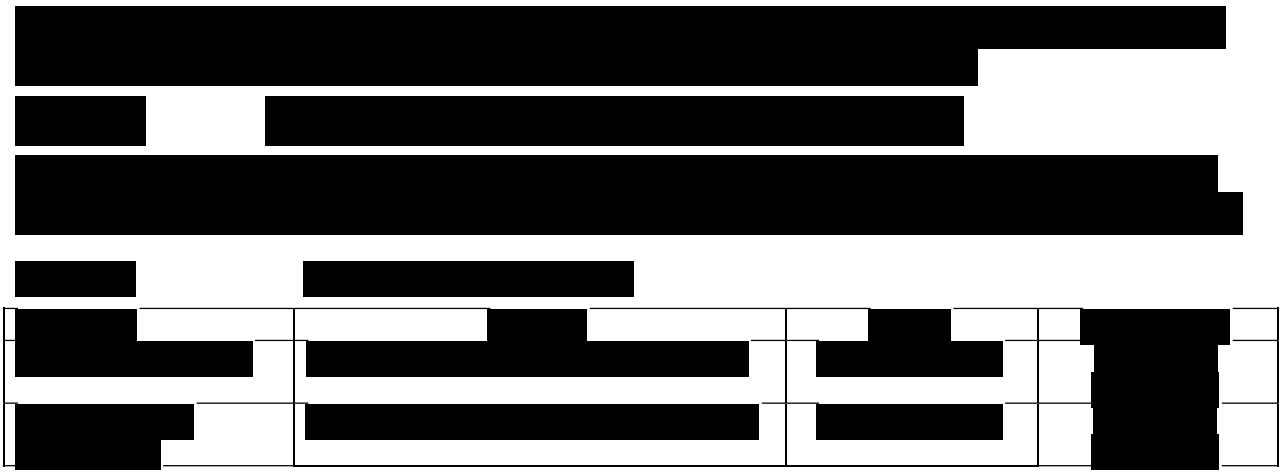
Retinal sensitivity thresholds in the study eye are measured by MP-1S Microperimetry using a grid with 56 stimulus points at baseline, Month 6, 12, 18, 24 and 30. For each subject at each visit, the mean retinal sensitivity by one of the three neutral density filters (0, 1.0, 2.0) is recorded on the CRF. The mean retinal sensitivity data will be analyzed by each of the three neutral density filters and well as the numeric correction. Correction to the retinal sensitivity values will be conducted as follows: if neutral density filter is 0, then keep the recorded value; if the neutral density filter is 1.0, then add 10dB to the non-zero recorded value; if the neutral density filter is 2.0, then add 20dB to the non-zero recorded value.

Table 5-14 Retinal Sensitivity Threshold Analyses

Endpoint	Statistics	Timing	Methodology

The calculated mean retinal sensitivity (dB) by Neutral Density Filter in the study eye from the BEACON test	• Mean, SD and other descriptive statistics by visit and treatment group • Change from baseline Mean, SE and other descriptive statistics by visit and treatment group	Treatment Period	Continuous descriptive

[redacted]



5.1.1.4.2 Adverse Events

The following adverse event (AE) terms are defined:

Table 5-18 AE Terms

Term	Variable
Treatment Emergent (TEAE)	AEs present after the first dose of study treatment or present before the date of the first dose of study treatment and increased in severity or became serious after the first dose of study treatment.
Treatment-Related	Includes TEAEs related to study product or the study procedures as deemed by the study investigator.
Ocular	Ocular AEs will be determined based on the OD and OS checked boxes on the AE module of CRF, and thus are not limited to AEs with SOCs of "Eye."

Unique participants reporting AEs in the following AE categories will be summarized by treatment group for the Safety Population as follows:

Table 5-19 AE Summaries

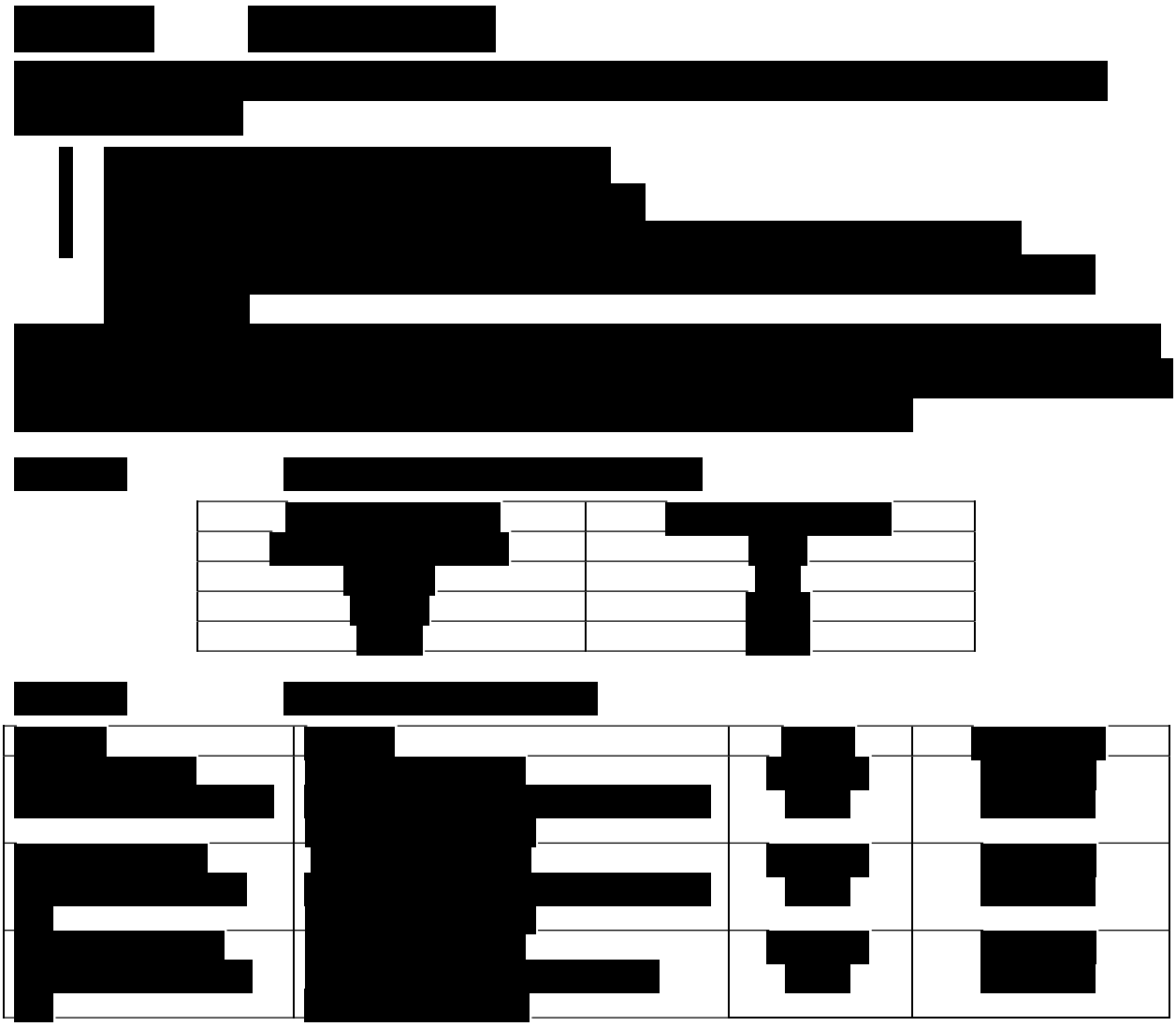
Parameter	Variable	Timing	Methodology
Overall summary	Overall summary only for the following categories: • TEAEs - Ocular - Non-ocular • Treatment-related TEAEs - Ocular - Non-ocular • Serious TEAEs - Ocular - Non-ocular • Deaths • AEs leading to study discontinuation TEAEs by SOC/PT/Severity Treatment Related TEAEs Serious TEAEs AEs leading to study discontinuation	Treatment Period	Categorical descriptives
Ocular	TEAEs by SOC/PT	Treatment Period	Categorical

Parameter	Variable	Timing	Methodology
	Treatment related TEAEs Implant/Study Drug-related TEAEs Injection Procedure-related TEAEs Applicator-related TEAEs		descriptives
Non-ocular	TEAEs by SOC/PT	Treatment Period	Categorical descriptives

If ≥ 1 AE is coded to the same preferred term for the same patient, the patient will be counted only once for that preferred term and strictest causality.
PT and SOC will be ordered by descending frequency by treatment group, ordered from Brimo DDS to Sham, and severity will be ordered by worst severity (maximum severity).

[redacted]

[redacted]



5.1.1.5 Subgroup Analyses

Subgroup analysis will be performed based on baseline GA values for the primary endpoint. The subgroup cutoff value will be chosen based on the the median of baseline GA size to analyze the data properly.

5.1.1.6 Interim Analyses

One interim analysis was conducted when 100% of patients complete the Month-12 visit and 50% of patients complete the Month-18 visit. The study was terminated based on results from the interim analysis.

5.1.2 Determination of Sample Size

Sample size determination was based on previous data or literature (Holz et al, 2010). The following assumptions were made: A GA lesion size of 2.8 mm^2 for the Sham and 2.1 mm^2 for the Brimo DDS groups (a 25% reduction from the Sham treatment) and a common SD of 1.65 mm^2. Under these assumptions, 120 patients will be required in each treatment group to detect the above treatment difference with a power of 90% or greater at the 2-sided t-test with 5%

significance level. With an anticipated dropout rate of 20%, approximately 300 patients will be enrolled such that 240 (120 per group) will complete the Month 24 visit. The sample size calculations are based on the procedure MTTO-1 in nQuery (v6.01).
The sample size assumptions and estimate are summarized as follows:

Table 5-27 Sample Size Assumption

Parameter	Assumption / Estimate
Primary endpoint	Change from baseline in atrophic lesion area in the study eye
Mean difference[1]	0.7 mm^2
SD[1]	1.65 mm^2
α	5%
Sides	2
Power	90%
Dropout rate	20%
N per group	150 (120 completing the Month 24 visit)
N total	300 (240 completing the Month 24 visit)

[1] Based on literature (Holz et al, 2010).

5.2 Changes in the Conduct of the Study or Planned Analyses

No unplanned analyses were conducted.

5.2.1 Changes in the Conduct of the Study

Prior to database lock, there were no changes in study conduct from what was described in the protocol.

5.2.2 Changes to Analyses Prior to Database Lock

According to the study protocol (section 7.1), mITT and safety populations would be analyzed based on the actual treatment that the patient received (as treated). However, the analysis based on mITT population will be conducted based on the treatment to which the patient was randomized (as randomized), and the analysis based on safety population will be based on the actural treatment received. The deviated patients between randomized and actual treatment received will be listed. In addition, analysis based on per-protocol population (PP) will not be performed.

Presence or absence of reticular drusen measured by near-IR (NiR), instead of area of reticular drusen assessed using NiR images, will be analyzed due to the technical difficulties to measure reticular drusen. GA lesion area by FAF in fellow eye was not obtained and will not be analyzed. Medical and ophthalmic history, the atrophic lesion area assessed with SD-OCT examination, and the location of implants and fragments will be not analyzed due to the changed scope of the analyses.

6. Data Handling and Analysis Conventions

6.1 Study Treatment Conventions

6.1.1 Analysis Days

Treatment days are defined as follows:

Table 6-1 Analysis Day Definitions

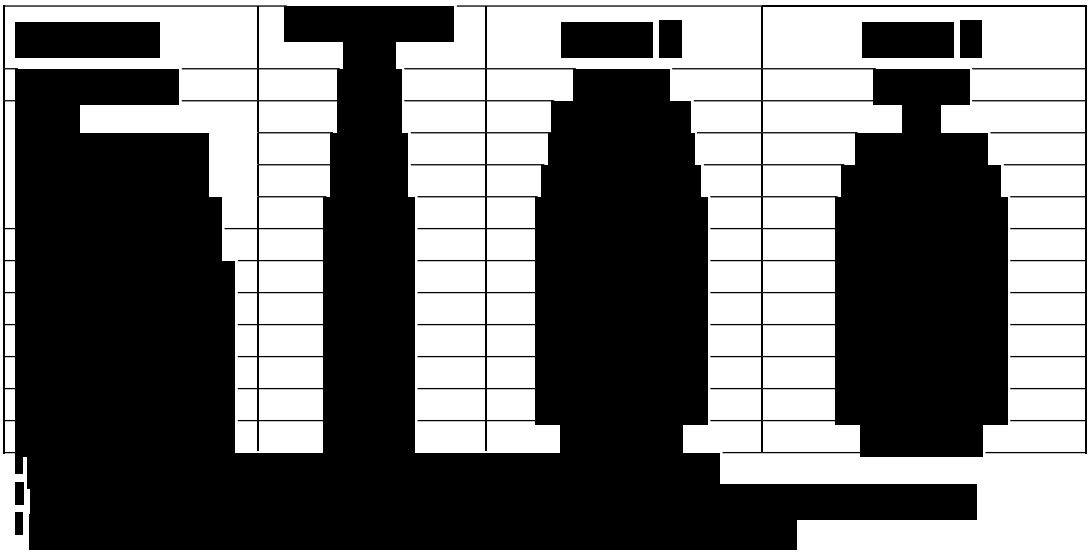
Term	Description
Treatment Day	Relative to treatment start date If analysis date ≥ treatment start date: • Day = analysis date – treatment start date + 1 o Day 1 = treatment start date If analysis date < treatment start date: • Day = analysis date – treatment start date o Day (-1) = day before treatment start date o There is no Day 0

6.1.2 Missing/Incomplete Treatment End Date

Not Applicable.

[redacted]

[redacted]



[redacted]

6.3 Site Pooling

Region, defined by geographic proximity, will be summarized as North America, Europe and Australia. Sites will be pooled into these three categories.

6.4 Missing/Incomplete Date Conventions

Dates may be imputed with year, month, and day values under certain scenarios:

Table 6-4 Imputation Scenarios

Scenario	Complete			Imputable
	Year	Month	Day	
1	Yes	Yes	Yes	Complete
2	Yes	Yes	—	Yes
3	Yes	—	Yes	No[1]
4	Yes	—	—	Yes
5	—	Yes	Yes	No[1]
6	—	Yes	—	No[1]
7	—	—	Yes	No[1]
8	—	—	—	Yes

Scenario	Complete			Imputable
	Year	Month	Day	

[1] Not allowed per database design.

Dates will be imputed initially toward a specified target date for imputable scenarios 2, 4, and 8, and adjusted against the latest reasonable dates. The initial imputed date is determined by the following algorithm:

Table 6-5 Initial Imputed Date Algorithm

Year (YYYY) of Incomplete Date	Month (MM) of Incomplete Date			
	Missing	< Target Month	= Target Month	> Target Month
Missing	Target Date	—	—	—
< Target Year	YYYY-12-31	—	YYYY-MM-LD	—
= Target Year	Target Date	YYYY-MM-LD	Target Date	YYYY-MM-01
> Target Year	YYYY-01-01	—	YYYY-MM-01	—

YYYY = year from incomplete date; MM = month from incomplete date; LD = last day of the month.

6.4.1 Missing/Incomplete Adverse Event (AE), Start Date

AE start dates will be imputed as the minimum of the following:

- Initial imputed date, where target date = Treatment start date
- Complete end date

6.4.2 Missing/Incomplete Medication Start Date

Medication start dates will be imputed as the minimum of the following:

- Initial imputed date, where target date = Treatment start date – 1
- Complete end date

6.4.3 Missing/Incomplete AE/Medication End Date

AE and medication end dates will be imputed as the minimum of the following:

- Initial imputed date, where target date = Treatment end date + 30
- Death date

6.5 Efficacy Endpoint Conventions

Treatment group will be labeled as follows:

Table 6-6 Treatment Group Label in TFL

Treatment Group	Presentation
Brimo DDS® contains 400 µg brimonidine free base ([redacted]	Brimo DDS
Sham	Sham

The following conventions will be applied to the TFLs.

Table 6-7 Programming Conventions

Parameter	Presentation
Decimal places	• Summary statistics: For a measure with x decimal places, min and max have x, mean and median have x+1, STD and CI have x+2 decimal places with proper rounding. For ratios such as compliance rate, and daily average scores with • x decimal places, min, max, mean and median have x, std and CI have x+1 decimal places with proper rounding. • Frequency distribution/incidence rates: % and CI should be rounded to 1 decimal place. • P-value: An un-rounded p-value greater than 0.999 should be reported as >0.999. Similarly, an un-rounded p-value less than 0.001 should be reported as <0.001. An un-rounded p-value can be reported as 1.000 only if it is exactly 1.000. Similarly, an un-rounded p-value can be reported as 0.000 only if it is exactly 0.000. In presentation, p-values should be rounded to the 3rd decimal place unless it is already determined as >0.999, or <0.001, as discussed earlier. All p-values should be reported with 3 decimal places. Missing p-value will be reported as 'N/A'.
P-value approximation	Specify the algorithm of approximation to compute P-values, especially for non-parametric tests (e.g., Wilcoxon rank sum test, Kruskal-Wallis test).

6.6 Safety Endpoint Conventions

6.6.1 Adverse Events

6.6.1.1 Missing Intensity or Relationship

If the investigator is unable to provide the actual values, the following imputations will be applied:

Table 6-8 Missing AE Intensity and Relationship Imputation Algorithms

Missing Value	Imputation	Timing
Intensity	Mild	Screening Period, Pretreatment Period
	Severe	Treatment Period
Relationship	—	Screening Period, Pretreatment Period
	Related	Treatment Period

6.6.2 Repeated or Unscheduled Assessments of Safety Parameters

If end-of-study assessments are repeated or if unscheduled visits occur, the last non-missing post-baseline assessment will be used as the end-of-study assessment for generating summary statistics.

6.7 Imputed Value Listing Conventions

In general, listings will present the actual partial or missing values rather than the imputed values that may be used in endpoint derivation. In instances where imputed values will be presented,

imputed values will be flagged. Actual rules will be fully defined in the table, figure, and data listing specification document.

6.8 Handling Mis-randomization and Mis-stratification

Patients will be randomized by two stratification factors, region (North America, Europe and Australia) and atrophic lesion area (≤ 8 mm2 versus > 8 mm2). If a patient is mis-stratified at the randomization, then the patient will be analyzed using the intended stratum in which the patient should have been randomized.

7. References

Holz, FG, Schmidt-Valckenberg S, Fleckenstein M, Jaffe GJ, Hohman T. Lesion characteristics and progression in the natural history of Geographic Atrophy (GAP) Study. Invest Ophthalmol Vis Sci. 2010; 94:a141.

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Analysis Plan 190342-038 Final Amend 1

Date (DD/MMM/YYYY)/Time (PT)	Signed by:	Justification
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1. Title Page

Safety and Efficacy of Brimonidine Posterior Segment Drug Delivery System in Patients with Geographic Atrophy Secondary to Age-Related Macular Degeneration

(BEACON Study: 190342-038)

STATISTICAL ANALYSIS PLAN ADDENDUM

SAP version history*:*

SAP Version 1.0: February 20, 2017
SAP Version 2.0 Final Amendment: August 3, 2018
SAP Addendum Version 1.0: September 6, 2018
SAP Addendum Version 2.0: March 2019

SUMMARY OF CHANGES

The following planned lesion area by SD-OCT analyses will be conducted post-hoc after the DBL:

1. Table 14.2-1.7 “Geographic Atrophy Lesion Area (mm2) by SD-OCT: Raw and Change from Baseline”

2. Table 14.2-1.8 “Geographic Atrophy Lesion Area (mm2) by SD-OCT: Raw and Change from Baseline; Lesion Area < 4.5 mm2”

3. Table 14.2-1.9 “Geographic Atrophy Lesion Area (mm2) by SD-OCT: Raw and Change from Baseline; Lesion Area >= 4.5 mm2”

Continuous descriptives	• N1, mean, standard deviation (SD), median, minimum, maximum • N1 = number of participants with non-missing value
CFB MMRM	• Continuous descriptives for baseline, postbaseline, and CFB values • Estimates derived from mixed model for CFB value controlling for factors (treatment group, study region, analysis visit), covariate (baseline GA lesion size as measured by SD-OCT) and interaction (treatment group by analysis visit, treatment group by baseline value). o Least squares (LS) means, standard errors, and 95% confidence intervals for within group change from baseline o LS mean differences, standard errors, and confidence intervals vs Placebo o P-values from contrast t-test comparing treatment group vs. Placebo o N1 = participants with non-missing values at both baseline and the specified postbaseline analysis visit