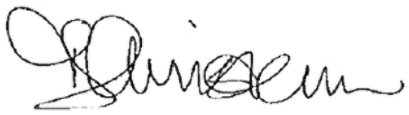
Statistical Analysis Plan
for the
US Early Bird Study (Protocol 6054 – formerly 4039)
NCT03469297

29 Jul 2022

Version 2.0

Approved by: 

Jill Christensen, Clinical Research	29 Jul 2022 Date

1. Introduction

This document outlines intended analyses to characterize the early feasibility of the Beacon Aqueous MicroShunt, Model 2D, in support of a future IDE submission.

In order to provide a comprehensive assessment, data will generally be summarized for all implanted subjects. Due to sample size constraints, no formal statistical hypothesis tests will be specified; however, statistical significance may be assessed in exploratory fashion.

An enrollment flow diagram will summarize the number of subjects who were consented, implanted, screen failed (with reason), withdrawn prematurely (with reason), and study completers.

2. Baseline Demographics and Medical History

Key baseline demographic and medical history variables will be summarized for all consented and implanted subjects. Continuous measures will be summarized using N, mean, standard deviation, median, and range. Categorical measures will be summarized using frequency distributions.

Table X. Summary of Demographic Characteristics

Baseline Characteristic	**N or n/N**	**Mean ± SD (Median) Min, Max or %**
Age (years)	#	##.#
Gender		
Female	#/#	##.#
Male	#/#	##.#
Ethnicity		
Hispanic or Latino		
Not Hispanic or Latino		
Race		
White or Caucasian		
Black or African American		
Asian		
American Indian or Alaska Native		
Hawaiian or Other Pacific Islander		
Other		
Declined to Answer		

Table X. Summary of Demographic Characteristics		
Baseline Characteristic	**N or n/N**	**Mean ± SD (Median) Min, Max or %**
Level of Education		
Did Not Complete High School		
High School		
Attended College		
Undergraduate Degree		
Attended Graduate School		
Graduate Degree		
Other		
Eye Color		
Brown		
Blue		
Green		
Hazel		
Implanted Eye		
OD – Right		
OS – Left		

Table X. Summary of Medical & Ophthalmic History		
Diagnosis/Procedure	**N or n/N**	**Mean ± SD (Median) Min, Max or %**
General Medical History		
Hypertension	#/#	##.#
Diabetes	#/#	##.#
Gout		
Etc		
Ophthalmic History		
Open Angle Glaucoma		
Dry Eye		
Cataract		
Etc		
Ophthalmic Surgical History		
Phacoemulsification		
Selective Laser Trabeculotomy		
Etc		

3. Effectiveness

The primary focus of the analyses is effectiveness. Key effectiveness data will be summarized for completeness and context. The effectiveness assessments will focus on participant experience through 6 months of follow-up following principles of Intent-to-Treat. In these analyses, subjects who have been explanted, with or without re-implant, will be considered treatment failures regardless of status at 6 months. Supportive analyses will include summaries of all protocol visits through 24 months of follow-up that will censor subjects at time of permanent explant or study withdrawal.

Table X. Data of Interest by Subject and Visit					
Subject ID	**Baseline**	**3 Months**	**6 Months**	**12 Months**	**24 Months**

Table X. Endpoint Header: Description of Endpoint				
	Baseline N= X	**6 Months N= X**	**Difference [95% CI]**	**P-value[1]**
Responder Rate	##.#% (#/#)	##.#% (#/#)		
[1] P-value from Chi-square test.				

3.1 Primary Effectiveness

The primary effectiveness parameter includes the following measure in the implanted eye:

- Overall responder rate, with responder defined as achieving at least 20% reduction from baseline in diurnal IOP

3.2 Secondary Effectiveness

Secondary effectiveness parameters of interest in the implanted eye include:

- Mean change from baseline in diurnal IOP
    - Standard deviation, median, range, and sample size at each visit
    - Mean percent reduction, along with median and range, at each visit
- Responder rate, with responder defined as achieving follow-up diurnal IOP less than or equal to 14 mmHg
- Proportion of participants with at least 20% reduction in IOP on the same or fewer IOP-lowering medications
- Change in IOP-lowering medications
    - Mean number of IOP-lowering medications in the implanted eye at each visit and corresponding standard deviation at each visit
    - Overall mean percent reduction at each visit
    - Total number of medications per patient (N/%)
    - Shift table at each visit (decreased, no change, increased)

3.3 Exploratory Effectiveness

Exploratory effectiveness parameters of interest in the implanted and contralateral eye include:

- Changes from baseline in the Schirmer Tear Test
    - Mean and standard deviation in the implanted eye at each visit
    - Shift tables at 6-, 12-, and 24-months according to:
        - 0-5mm: severe
        - >5-10mm: moderate
        - >10-15mm: mild
        - >15: normal

- Treatment satisfaction questionnaire (TSQ)
- Glaucoma progression
    - Summary of changes in visual field in the implanted eye over time
    - Cup/disc ratio in the implanted eye over time

4. Safety Assessment

4.1 All AEs and SAEs

The primary summary of safety will consist of all adverse events (AEs), adverse device effects (ADEs), serious adverse events (SAEs), and unanticipated adverse device effects (UADEs) occurring in the implanted eye through 6 months post-implant, by type, summarized by study and overall. For each reported event, the number of events (# Event), number of participants with an event (n), and the percentage of participants among the total sample size (N) will be summarized. Supportive analyses will include summaries of device-related adverse events and secondary surgical interventions through 24 months of follow-up.

Table X. Summary of Adverse Events		
Event	**# Events**	**% (n/N) Participants**
Adverse Events		
Serious Adverse Events		
Device-Related Adverse Events Possibly Probably Definitely		
Procedure-Related Adverse Events Possibly Probably Definitely		
Study Device and/or Procedure Related Adverse Events		
Serious Study Device and/or Procedure Related Adverse Events		

Table X. Summary of Device-Related Adverse Events			
Participant ID (AE#)	**Description of Event**	**# Events**	**% (n/N) Participants**

Table X. Summary of Secondary Surgical Interventions			
Participant ID (AE#)	**Surgical Intervention**	**# Events**	**% (n/N) Participants**

4.2 Implant Procedure Characteristics

Key implant characteristics will be summarized for each participant. MicroOptx Chief Scientific Officer reviewed all available implant videos to determine if the device implants were corneal or scleral in location.

- Insertion angle (anterior, medial, or posterior)
- Implant position (clock hour)
- Implant location (corneal or scleral)
- Ease of implant (easy, moderate difficulty, difficult)
- Explant (yes, no)
- Re-Implant (yes, no)

Table X. Implant Characteristics by Subject						
Subject ID	**Insertion Angle**	**Implant Position**	**Implant Location**	**Ease of Implant**	**Explant**	**Re-Implant**

4.3 Additional Analyses

Signs of inflammation may indicate insufficient healing of the device within the incisional tract, allowing for micromotion of the implant and increase the risk for adverse events, including endophthalmitis. These signs of inflammation include neovascularization around the implant site, conjunctival hyperplasia (mild, moderate and marked), and partial or complete device extrusion.

Analyses will be conducted to determine whether the implant procedure characteristics described in Section 3.3 contribute to increased inflammation, and whether or not the sign of inflammation was elevated to an adverse event. Further, analyses will be performed to determine the association of inflammation with the outcomes of serious adverse events, device occlusion, and explant.

Analyses will also be conducted to determine whether different anti-inflammatory regimens for inflammation have a differential impact on subsequent adverse events, IOP, diminished flow and device useful life.

5. Subgroup Analyses

Key endpoint data (SAE, SAE or explant, IOP) may be assessed according to pre-defined subgroups. These subgroups include:

- Sex (male, female)
- Race (African American, Caucasian, other)
- Implant location (scleral, corneal)
- Allergies with ocular involvement

Other subgroups may be identified in the course of analysis and will be assessed in a *post hoc* fashion.

6. Other Information

In addition to the described data analysis, the following information will also be presented as part of the safety assessment:

- Updated endothelial cell loss (ECL) analysis
- Individual Participant Summaries for each participant
- Line listing of all adverse events
- Line listing of all protocol deviations

Subject # (Eye)	**BL ECC**	**3 mo ECC**	**6 mo ECC**	**12 mo ECC**	**24 mo ECC**	**3 mo ECC Δ** (%Δ^^)**	**6 moECC Δ (%Δ)**	**12 mo ECC Δ (%Δ)**	**24 mo ECC Δ (%Δ)**
##-## (OD)	####	####	####	####	####	+## (#.#)	+## (#.#)	+## (#.#)	+## (#.#)
##-## (OS)	####	####	####	####	####	+## (#.#)	+## (#.#)	+## (#.#)	+## (#.#)

***** ND = Not Done
^ NA = Not Applicable
****** A positive value indicates higher endothelial cell count relative to baseline reading, while a negative value indicates a loss in endothelial cells (ECL) since baseline
^^ % Δ = (Follow-Up Visit ECC- Baseline ECC)/Baseline ECC * 100