Mini Statistical Analysis Plan: CA-005

Study Title:	LIBERATE: A Clinical Evaluation of the Eclipse™ System, a Vaginal Bowel Control (VBC) Therapy for Fecal Incontinence in Women
Study Number:	CA005
Study Phase:	3
Study Design	Multicenter, open-label, prospective trial uses within-subject control
Product Name:	Eclipse™ System
Indication:	Fecal Incontinence
Statistician:	Venita DePuy, PhD Bowden Analytics, Apex NC
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Clinical Events Committee Chair:	Robert Gutman, MD
Final Date:	March 25, 2018

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2 SIGNATURE PAGE

Study Title: LIBERATE: A Clinical Evaluation of the Eclipse™ System, a Vaginal Bowel Control (VBC) Therapy for Fecal Incontinence in Women

Study Number: **CA005**

Statisticians: Venita DePuy

I have read this report and confirm that to the best of my knowledge it accurately describes the conduct and results of the study.

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3 LIST OF ABBREVIATIONS AND DEFINITIONS OF TERMS

BM	bowel movement
BMI	body mass index (kg/m^2)
CEC	Clinical Events Committee
CRF	case report form
FI	fecal incontinence
FIQOL	Fecal Incontinence Quality of Life
IQR	interquartile range
ITT	Intent-to-Treat
PGI-I	Patient Global Impression of Improvement
PP	Per-Protocol Population
TVL	total vaginal length
UADE	unanticipated adverse device effect
UTI	urinary tract infection

4 INTRODUCTION

The Eclipse System is a vaginal bowel control therapy intended to provide bowel control for women with fecal incontinence. Manufactured by Pelvalon, Inc. (Sunnyvale, CA), it is comprised of a non-surgical device placed in the vagina (referred to as the "Eclipse Insert") and a pressure-regulated pump which is used to inflate and deflate the Insert. A Sizing Kit, for use during the fitting process, and an evaluation Insert (referred to as the Trial Insert) are also provided. Please refer to Section 1 of the LIBERATE study protocol for additional background information on the Eclipse System, its mechanism of action, and prior clinical research including the LIFE Study (Protocol CA003), as well as epidemiology, causes, and treatment of FI.

The previous LIFE Study assessed safety and effectiveness of the Eclipse System (including the Eclipse Insert and Pump) after 1 month of use with some subjects opting to extend treatment out to 3 months of use. The rationale for conducting this study is to characterize safety and effectiveness among treatment responders with longer-term follow up than the LIFE Study. Since the previous trial demonstrated a stable treatment effect and an acceptable safety profile between 1 and 3 months it is expected that use of the device between 3 and 12 months will demonstrate a similar safety and effectiveness profile throughout the duration of use.

5 TRIAL OBJECTIVES

5.1 Primary Objective

The primary objective of the study is to evaluate the durability of the safety and effectiveness of the Eclipse™ System after 3 and 12 months of use in a responder population.

6 STUDY DESIGN AND CONDUCT CONSIDERATIONS

6.1 Study Design

This is a multicenter, open-label, prospective trial which uses within-subject control to evaluate the safety and effectiveness of the Eclipse System in women with fecal incontinence.

Subjects may participate in this study if they meet eligibility criteria shown in Table 2 of the protocol. Appropriate subjects are adult females suffering from Fecal Incontinence (FI). Fecal incontinence is defined as the involuntary loss of liquid or solid stool that is a social or hygienic problem. Due to the non-surgical, low risk, reversible nature of this treatment, subjects are not required to have previously attempted/failed other treatment methods. Note that final eligibility for enrollment into the Treatment Period involves several screening assessments, including demonstration that the subject is an initial responder to the therapy.

Subjects who qualify via the Baseline diary will proceed with the first fitting visit. Subjects who are successfully fit with the Eclipse System and qualify via the Test Diary are considered responders and will be eligible for treatment. Each site is expected to contribute approximately 7-25% of the total treatment-eligible subjects unless authorized in writing to over-enroll by the Sponsor. Enrollment is competitive until overall enrollment target is reached or study termination by the Sponsor.

The visit schedule is graphically represented in **Error! Reference source not found.**, and the schedule of events shown in Table 1.

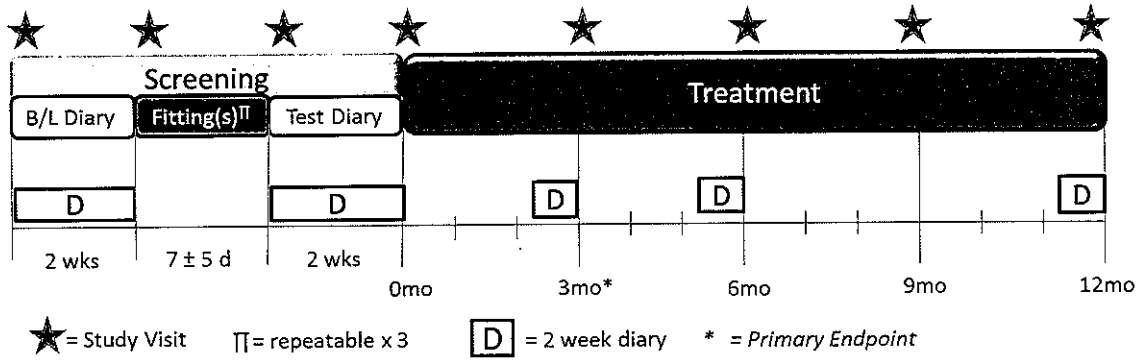

Figure 1. Study Visit Schedule Schematic

Table 1. Schedule of Events

Assessment	Screening Period				Treatment Period (± 2 weeks)T				
	V1	V2	V3	V4	V5	V6	V7	V8	
	Baseline	Fitting Visits*	Fit	Treatment	3 Months	6 Months	9 Months	12 Months /	Unscheduled Visit
Informed Consent	X								
Inclusion/Exclusion Criteria (pregnancy test done at baseline only, if applicable)	X	X	X	X					
Clean catch urine test to r/o UTI+	X	X+							
Demographics & Medical history / FI brochure	X								
FI episode diary dispensed	X		X	X	X		X		
FI episode diary collected & reviewed		X		X	X	X		X	

Assessment	Screening Period				Treatment Period (± 2 weeks)⊤				
	V1	V2	V3	V4	V5	V6	V7	V8	
	Baseline	Fitting Visits*	Fit	Treatment	3 Months	6 Months	9 Months	12 Months / Early Exit	Unscheduled Visit
Device fit check			X		X	X	X	X	X†
Pelvic exam (speculum & digital rectal exam)	X	X	X	X	X	X	X	X††	X†
AE and Con Med review ‡		X	X	X	X	X	X	X	X
St. Mark's (Vaizey) Incontinence Severity Score and FIQOL questionnaire	X				X	X	X	X	
PGI-I questionnaire					X	X	X	X	
Patient Goal questionnaire		X			X	X	X	X	
Device Satisfaction questionnaire					X	X	X	X††	
Cost Utilization survey	X				X			X	

*Fitting visits are repeatable up to 2 more times for a maximum of 3 fitting visits total.

⊤Telephone follow-up calls are required in between each Treatment Visit.

+If clean catch urine test is positive, the test must be repeated until either it, or a urine culture test, is negative before performing a Fitting Visit (Visit 2)

† If clinically indicated.

‡ AEs recorded starting at the first Fitting Visit (Visit 2); Con Meds recorded at baseline and reviewed / updated at every visit.

†† A pelvic exam and Device Satisfaction questionnaire are required at all early study exit visits after the first Fitting Visit (Visit 2).

6.2 Power and Sample Size

As described in Section 3.11 of the study protocol, power calculations were performed based on the primary effectiveness analysis, which tests whether the fraction of treatment responders is significantly greater than 0.40 (H_0: $\pi \leq 0.40$ vs. H_A: $\pi > 0.40$) using a one-sided exact binomial test, based on significance $\alpha = 0.025$ and power $1 - \beta = 0.90$.

Based on the LIFE study, we anticipate an 85.6% success rate among study completers and conservatively estimate 21.3% dropout within 3 months, resulting in an estimated 67% response rate in this study. With as few as 40 subjects in the ITT cohort, the study has ≥90% power to detect a response rate greater than 40%.

Additional subjects, up to the maximum of 150 subjects, will be enrolled through a specified end date in order to provide a more robust analysis.

Withdrawal from the study during the Screening Period is estimated to be substantial due to the baseline diary completion and device fitting requirements. Subjects who are successfully fit with the Eclipse System and successfully complete the Screening Period will be eligible for treatment. Therefore, an estimated 160 to 600 subjects may be recruited into this study in order to achieve 40 to 150 subjects who successfully enter the Treatment Period.

We estimate the subject dropout rate between the start of the Treatment Period and the 12 month visit to be 33%, yielding approximately 25 to 100 subjects completing 12 months of study participation. In a 12-month study of non-surgical management of stress urinary incontinence the dropout rate over this same time period was approximately 36%.[1]

6.3 Randomization Procedure

This is a single-arm, open-label study in which subjects serve as their own controls. No randomization was performed.

6.4 Efficacy Measures

The primary efficacy measure is the number of FI episodes as measured on a 2-week bowel diary.

A subject is classified as a treatment responder if she has a ≥ 50% reduction in the average number of FI episodes per week, as compared to the baseline evaluation period.

Subject-reported outcomes related to symptoms and quality of life, as reported by the St. Mark's (Vaizey) Incontinence Severity Score and FIQOL, and the Patient Global Impression of Improvement (PGI-I) scores are also evaluated.

6.5 Safety Measures

Safety will be assessed using device-related adverse events and device-related serious adverse events. Adverse events will be adjudicated by a Clinical Events Committee (CEC). Please reference the CEC Charter ver. 2.0 for a detailed description of the adverse event adjudication process.

[1] Richter, et al. non-surgical management of stress urinary incontinence: ambulatory treatments for leakage associated with stress (ATLAS) trial. Clinical Trials 2007; 4: 92-101.

6.6 Pharmacokinetic Parameters

No pharmacokinetic parameters will be assessed.

6.7 Completion and Discontinuation

Subjects must complete at least 12 of the 14 consecutive days of the Baseline Diary and have documented at least 4 episodes of major or minor soiling (not staining) on their Baseline Diary. If either of these criteria is not met, or the subject is discontinued for any other reason prior to being fit with the Eclipse System, then the subject is categorized as a pre-fitting discontinuation, and a screen failure.

Eligible subjects then proceed with the Initial Fitting Visit. If a subject cannot obtain a suitable fit during this visit, and/or decides to withdraw, then the subject is categorized as a post-fitting discontinuation, and a screen failure.

Subjects who discontinue the trial after the Initial Fitting Visit, such as those who are deemed to not have a suitable fit during Fit Confirmation Visits or unsuccessful fittings on Repeat Fitting Visits, are also categorized as post-fitting discontinuations, and screen failures.

Subjects who achieve a successful fit but do not meet the Visit 4 Test Diary criteria (as described in protocol section 2.6.8), or who decide withdraw at or before Visit 4, are similarly categorized as post-fitting discontinuations, and screen failures.

Subjects who successfully meet the Visit 4 Test Diary criteria and successfully complete Visit 4 will enter the Treatment Period. These subjects are considered to be enrolled in the study, and any discontinuations after Visit 4 will be considered early terminations. The date of early termination and main reason for discontinuation will be recorded.

7 STUDY POPULATIONS

This study evaluates the durability of the efficacy and safety of the Eclipse System.

7.1 Subject Disposition and Visit Participation

All subjects who sign an informed consent will be classified as either screen failures (those who terminate prior to or at Visit 4, as defined in Section 6.7) or enrolled subjects.

7.2 Analysis Populations

The Safety Population will include all subjects exposed to any part of the Eclipse System during or after Visit 2 (Initial Fitting Visit). This will include all subjects who

were unsuccessfully fitted, and screen failures. This will be the primary analysis population for all safety analyses.

The Test Population will include all subjects who are successfully fit with the Eclipse Insert and successfully completed a Test Diary.

The Intent-to-Treat (ITT) Population will include all subjects who are successfully fit with the Eclipse Insert, successfully complete Visit 4, and enter the Treatment Period.

The Per-Protocol (PP) Population include all subjects in the ITT population who complete Visit 5, complete at least 10 out of 14 consecutive days of diary data at the 3 month visit, and have no major protocol deviations.

7.3 Protocol Deviations

All protocol deviations will be recorded on the appropriate case report form (CRF). Deviations will be categorized as: consent procedure not followed, eligibility criteria violation, subject diary deviation, study assessment not done, study assessment out of window, visit out of window, visit not done, or other.

All deviations will be reviewed by the sponsor, in conjunction with source documentation as necessary. Prior to database lock, the sponsor will determine which deviations meet the criteria for major protocol deviations.

All major protocol deviations may be summarized by deviation category. All deviations, both major and minor, may be listed by subject.

7.4 Subgroups

No analyses by subgroups will be performed.

8 STATISTICAL ANALYSIS

8.1 General Considerations

Continuous data will be summarized using count (n) the number of non-missing values and mean, median, standard deviation, minimum and maximum as appropriate. The interquartile range (IQR) may also be reported as appropriate. Categorical data will be summarized using counts and frequencies. In general, means and medians will be presented to 1 more decimal place than collected, and standard deviations to 2 more decimal places. Where appropriate, p values will be presented to 4 decimal places.

A one-sided, 2.5% significance level will be used for the primary efficacy endpoint. All p-values, aside from those in the primary efficacy endpoint, are presented for descriptive purposes only. No adjustments will be made for multiple comparisons.

Recorded data may be presented in data listings, aside from cost utilization data which is evaluated under a separate analysis plan. If listed, enrolled subjects will be listed first, followed by screen failures, where appropriate.

8.2 Handling of Missing Data

Subjects are required to complete at least 12 of 14 consecutive days in the Baseline and Test Diaries. If any subject arrives at a 3, 6, or 12 month visit with less than 10 days of completed diary data, they will be given one opportunity to reschedule the follow up visit as soon as possible within the next two weeks while completing a new Treatment Diary for the remainder of the required 14 consecutive day diary period.

Any such partially completed diary information (that does not have additional days completed to total at least 10 of 14 consecutive days) will be listed but summary measures (average FI episodes per week, etc.) will not be calculated. If data is provided for more than 14 days, data from the first 14 consecutive days which has at least 10 days completed will be analyzed.

Missing item results for the FIQOL or St. Mark's (Vaizey) Incontinence Severity score will be handled as described in Sections 11.2.3 and 11.2.4, respectively.

Analyses of treatment response (defined in Section 8.3) utilizing the ITT population, including but not limited to the primary analysis, will classify subjects who do not complete the diary (either partially completed, not completed, or discontinued study prior to that time point) as non-responders for that time point.

No imputation of treatment response will be performed for analyses utilizing the Per-Protocol population (i.e., subjects who do not complete the diary are excluded from analysis).

8.3 Definitions

Baseline measurements are the last recorded values for each parameter prior to the Initial Fitting Visit. Baseline diary measurements, such as average numbers of FI episodes, are based on the entire Baseline Diary. Other assessments are typically recorded at Visit 1.

Change from baseline is calculated as result – (baseline result).

Percent change from baseline is calculated as 100*(change from baseline) / (baseline result). This statistic is represented in tables by **% Δ.**

Study day is calculated as date – Visit 4 date, for visits occurring prior to Visit 4 (the beginning of the Treatment Period), and calculated as date – Visit 4 date + 1, for visits on or after Visit 4. Study day will not be presented for screen failures.

All calculations based on diary data will be calculated based on the entire reported diary period, if the diary was completed for that time period (12+ days for Baseline and Test diary, 10+ days for 3, 6, and 12 month diaries as per Section 8.2). If >14 days were completed for any time period, only the first 14 days will be used for computations. If a diary was repeated as allowed per protocol or Sponsor-approved Protocol Deviation, the calculations will be performed on the repeat diary information only.

A **bowel movement (BM)** is defined as any passing of stool reported as a "normal (continent) BM", "minor soil" or "major soil". Staining episodes will be omitted from this definition.

A **fecal incontinence (FI) episode** is defined as any passing of stool reported as a "minor soil" or "major soil". Staining episodes will be omitted from this definition.

Loose stool is defined as a BM with a Bristol stool score of 6 or 7. **Solid stool** will be defined as a BM with a Bristol stool score of 1-5.

The following statistics will be calculated from diary data, for each diary period:

- **Average number of FI episodes per week**: 7 * (# episodes) / (# days of diary entry)
- **Average number of FI episodes while insert in place, per week**: 7 * (# episodes while insert is in place) / (# days of diary entry)
- **Average number of FI days per week**: 7 * (# days with ≥1 FI episode) / (# days of diary entry)
- **Average number of urgent BMs per week**: 7 * (# urgent BMs) / (# days of diary entry)
- **Average number of BMs per week:** 7 * (# BMs) / (# days of diary entry)
- **Average number of loose stool BMs per week:** 7 * (# BMs with Bristol stool scale score of 6 or 7) / (# days of diary entry)
- **Average number of solid stool BMs per week:** 7 * (# BMs with Bristol stool scale score of 1 - 5) / (# days of diary entry)
- **Average number of BM days per week**: 7 * (# days with ≥1 BM) / (# days of diary entry)
- **Average number of episodes per week**: 7 * (# episodes) / (# days of diary entry). Episodes include both BM episodes (normal, minor FI, and major FI) and staining episodes.

- **Average proportion of episode type:** (# episodes of that type) / (# total episodes), where episodes includes both BM episodes and staining episodes

- **Average Bristol score**: (sum of Bristol scores) / (# BMs)

- **Average proportion of loose stools**: (# BMs with Bristol stool scale score of 6 or 7) / (# BMs)

- **Average proportion of solid stools**: (# BMs with Bristol stool scale score of 1 - 5) / (# BMs)

Treatment response is defined as having a ≥50% reduction in the average number of FI episodes per week on the Treatment Diary (3, 6, or 12 months) as compared to the associated Baseline diary.

Subjects are classified into **FI phenotypes** based on the results of the FIQOL at Baseline. Subjects ranking question 2k, "I can't hold my bowel movement long enough to get to the bathroom", as more severe than question 2l, "I leak stool without even knowing it", are classified as *urge-predominant*. Those ranking question 2l as more severe than question 2k are classified as *passive-predominant*. Those ranking both questions the same, when the result is "most of the time" or "some of the time", are classified as *both* predominances. Those ranking both questions as "a little of the time", "none of the time", or "N/A" will not be categorized as having an FI phenotype.

8.4 Interim Analysis

No formal interim analyses are planned.

The sponsor may choose to perform ad hoc analyses during the course of the study. These will not be considered formal interim analyses, and no adjustments to alpha spending will be made.

8.5 Pooling Strategy for Study Sites

Data for all sites will be pooled for all safety and efficacy analyses. Study diary success rates per study period may also be summarized by study site in order to evaluate the consistency of effect of treatment by site.

8.6 Visit Windows/Unscheduled Visits

All data will be listed and summarized by the nominal visit. No visit windowing will be performed.

9 DEMOGRAPHICS AND BASELINE CHARACTERISTICS

All summaries of demographic information will be based on the ITT population.

Demographic information, including age (calculated as the difference between date of informed consent and birthdate, in years), body mass index (BMI), and race/ethnicity, will be summarized. The number and percentage of subjects <65 years of age and ≥ 65 years of age will also be presented.

Medical history such as types of previous urogenital surgeries, current or recent sexual activity, parity, menopause status, Digital Rectal Examination Scoring System (DRESS) resting and squeeze scores, and comorbidities will also be summarized.

Baseline FI characteristics such as FI type, duration of symptoms, previous treatments, self-management, and etiology will also be summarized.

10 CHANGES IN CONDUCT OR PLANNED ANALYSES FROM THE PROTOCOL

This analysis plan was developed in conjunction with CA005 Protocol Revision D, dated 09 Feb 2017. No changes in conduct or planned analysis have occurred.

11 EFFICACY

The ITT population will be used as the primary analysis population for efficacy analyses. The PP population is used as a supportive analysis where specified.

11.1 Primary Analysis

The primary analysis will test the following statistical hypotheses for the observed response rate:

$$H_0: \pi = 0.40$$

$$H_A: \pi > 0.40$$

where π is the observed proportion of subjects who are treatment responders at the 3 month time point. An exact binomial test will be used to evaluate whether the response rate is significantly larger than 40%, based on the ITT population. Treatment response is calculated as defined in Section 8.3.

The number and proportion of treatment responders, and its 95% confidence interval, using exact (Clopper-Pearson) confidence limits, will be presented. A p-value for the one-sided upper-tail test of whether the proportion is significantly larger than 0.40, will also be presented. The null hypothesis will be rejected if a sufficient percentage of subjects exhibit treatment response at the 3 month time point. As described in Section 8.2, subjects with missing information will be treated as non-responders for this analysis.

11.2 Secondary Endpoint Analysis

The following analyses will be considered secondary efficacy analyses:

11.2.1 Treatment Response

The primary analysis will be repeated at the 6, and 12 month time points, based on the ITT population. Subjects with missing treatment response information at a time point will be considered non-responders, as described in Section 8.2.

The primary analysis will be repeated at the 3, 6, and 12 month time points, based on the PP population for those time points. Subjects with missing treatment response information at a time point are excluded from the analysis of the PP population at that time point, as described in Section 8.2.

11.2.2 PGI-I

Subjects will rate their control of bowel leakage, as compared to how it was before the Eclipse System, on a 7-point scale (1=Very Much Better, 7=Very Much Worse) at the 3, 6, 9, and 12 month visits.

Scores may be summarized by time point, both continuously and by number and percent of subjects selecting each response, using the PP population.

The average score may be evaluated to see if it is significantly different from a score of 4 (No Change), using the Wilcoxon Signed Rank test.

11.2.3 FIQOL

The FIQOL is administered at Baseline and at 3, 6, 9, and 12 months. The following scoring algorithm is used to create subscale scores for Lifestyle (10 items), Coping/Behavior (9 items), Depression/Self Perception (7 items) and Embarrassment (3 items). Raw item scores are on a 5 point scale for Question 1 (1=Excellent to 5=Poor), 4 point scale for Questions 2a-2m (1=Most of the Time to 4=None of the Time), 4 point scale for Questions 3a-3n (1=Strongly Agree to 4=Strongly Disagree), and 6 point scale for Question 4 (1=Extremely So to 6=Not at All).

- Lifestyle is the average score for questions 2a, 2b, 2c, 2d, 2e, 2g, 2h, 3b, 3l, and 3m, where no more than 4 items are missing

- Coping/Behavior is the average score for questions 2f, 2i, 2j, 2k, 2m, 3c, 3h, 3j, and 3n, where no more than 4 items are missing

- Depression/Self Perception is the average score, where no more than 2 items are missing, of:
  - Question 1 (reverse coded to 5=Excellent to 1=Poor),

- Questions 3d, 3f, 3g, 3i, 3k
- Question 4, multiplied by 0.67 to rescale it to a 4-point range

- Embarrassment is the average score for questions 2l, 3a, and 3e, where no more than 1 item is missing

Subscale scores and their percent changes from baseline will be summarized by visit, based on the PP population.

Changes from baseline in subscale scores will be analyzed separately for each subscale score using a repeated measures model with baseline subscale score as a covariate. Least squares means and associated p-values may be presented for each timepoint during the Treatment Period.

All raw item scores may be listed by subject and visit. Subscale scores and their changes from baseline may be listed separately by subject and visit.

11.2.4 St. Mark's (Vaizey) Incontinence Severity Score

The St. Mark's (Vaizey) Incontinence Severity questionnaire assesses seven aspects of incontinence severity (solid stool incontinence, liquid stool incontinence, gas incontinence, lifestyle alteration, the need to wear a pad or plug, taking constipating medicines, and lack of ability to defer defecation for 15 minutes).

An overall incontinence severity score, calculated and entered on the CRF, is derived as follows:

- The first 4 questions are scored on a 5-point scale, where 0=Never and 4=Daily

- The next 2 questions (wearing a pad or plug and taking constipating medicines) are scored where 0=No and 2=Yes

- The last question (deferring defecation) is scored where 0=No and 4=Yes

- The item scores are summed to create an overall score on a 24-point scale, where 0 is perfect continence and 24 is total incontinence.

- If any of the items used to create the overall score are missing, the score will be missing. (A missing FI bother item result will not affect the overall score).

An FI bother scale is also administered as part of this assessment. The amount that a subject's bowel control symptoms bothers her on the visit day is ranked on a 4-point scale, where 0=Not at all and 3=Greatly.

The severity score results, changes from baseline and/or percent changes from baseline may be summarized by visit. Changes from baseline in the severity score

will be analyzed using a repeated measures model with baseline severity score as a covariate. Least squares means and associated p-values may be presented for each timepoint during the Treatment Period.

The FI bother scale may be summarized by visit using the PP population. The change from baseline in the FI bother scale, which could take on values of -3 to 3 may also be summarized (continuously) and evaluated using the Wilcoxon Signed Rank test to determine if the average score is significantly different from zero (i.e., no change). The percent change from baseline in FI bother may be summarized as less bothersome (values <0), no change (0), or more bothersome (values >0) by visit.

The individual item scores, overall severity score, and FI bother scale may be listed by subject and visit.

11.3 Additional Analyses of Diary Data

11.3.1 FI Episodes

The average number of FI episodes per week for each subject may be summarized by diary period (Baseline, Test, 3 month, 6 month, 12 month). The change from baseline and percent change from baseline may also be summarized for each Treatment Diary (3 month, 6 month, 12 month).

Percent changes from baseline will be analyzed using a repeated measures model with baseline average number of weekly episodes as a covariate. Least squares means and associated p-values will be presented for each timepoint during the Treatment Period.

The percent change from baseline in FI episodes will be further categorized by degree of improvement (<50% reduction, >= 50% reduction, >75% reduction, and 100% reduction) and the percent of subjects in each category summarized for each Treatment Diary. These analyses will be based on the PP population.

11.4 Exploratory Analyses

No exploratory analyses are planned.

11.5 Subgroup Analyses

Subgroup analyses may be performed by FI phenotype, including but not limited to analyses of FI episodes, FIQOL, St. Mark's (Vaizey), and demgraphic comparisons.

12 SAFETY AND TOLERABILITY

12.1 Adverse Events

All adverse events (AEs) occurring after a subject has been fit with the Eclipse System, at the Initial Fitting Visit, will be recorded. All AEs will be coded into system organ class and preferred term using MedDRA v17.0.

The Clinical Events Committee (CEC) will review all AEs at regular intervals to confirm MedDRA classification and determine the relationship to the study device (not related, unlikely, probable, definite, or unknown). Where appropriate, relationship to the study device will be further classified by component (Eclipse insert, trial insert, sizer, pump, valve, extension tube, regulator). For a more detailed description of the AE review/adjudication and MedDRA coding processes, please refer to the CEC Charter ver. 2.0.

The incidence of adverse events will be summarized by system organ class and preferred term. Subjects will be counted at most one time per system organ class and at most one time per preferred term. For summaries by severity, subjects will be counted at most one time per system organ class and at most one time per preferred term, at the highest recorded severity.

The following summaries will be provided:

- AEs per time period (e.g. fitting vs. treatment)
- AEs related to study device (defined as those categorized by the CEC as being probably or definitely related to study device)
- Serious adverse events (SAEs; if applicable)
- AEs leading to withdrawal from the study
- AEs by severity
- AEs related to study device, by severity

An additional summary of TEAEs, by preferred term, sorted by descending overall frequency, will also be presented.

Data listings, including system organ class and preferred term, will be provided for all AEs, all SAEs, and all AEs related to study device.

Separate listings will be provided for all adjudicated events, and will include all information provided by the CEC.