

Clinical Investigational Plan

LIBERATE:

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

Protocol: CA005
Revision: D
Date: 09 Feb 2017

Study Sponsor:
Pelvalon, Inc.
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Sunnyvale, CA 94085

LIBERATE Protocol Synopsis

Study Objective	To evaluate the durability of the safety and effectiveness of the Eclipse™ System after 3 and 12 months of use.
Study Design	Multi-center, prospective, within-subject control, open label clinical trial
Sites/ Subjects	Up to 150 treatment-eligible subjects may be enrolled into the 12 month Treatment Period at up to 15 clinical sites in the United States
Study Population	Adult females diagnosed with fecal incontinence (FI)
Study Duration	Screening Period: 5 - 7 weeks* Treatment Period: 12 months * Screening may be extended by up to an additional 6 weeks to allow for estrogen pre-treatment, if required
Primary Endpoint	The proportion of treatment responders, defined as a $\geq 50\%$ reduction in the average number of FI episodes per week, as compared to baseline, at the 3 month time point in the ITT population
Secondary Endpoints	<ol style="list-style-type: none"> 1. Proportion of treatment responders at the 3, 6 and 12 month time points in the per protocol (PP) population 2. Change from baseline in mean scores on subject-reported outcomes related to symptoms and quality of life as reported by St. Mark's (Vaizey) Incontinence Severity Score, and FI Quality of Life (FIQOL) 3. Patient Global Impression of Improvement (PGI-I) scores at the 3, 6, 9 and 12 month time points
Safety Endpoint	Safety of the Eclipse System is assessed by the number of device-related (Eclipse System) adverse events, and device-related serious adverse events.
Subgroup Analyses	< 65 years of age versus ≥ 65 years of age
Inclusions: General Eligibility Criteria	<ol style="list-style-type: none"> 1. Female sex 2. Age 19 years or older 3. History of FI for at least 6 months 4. Subject willing and able to give written informed consent to participate in the study 5. Subject can read, write and communicate fluently in English (the study diaries, questionnaires and instructions are only provided in English) 6. Subject willing and able to comply with visit schedule 7. Subject is able to physically manage the insertion and removal of the Insert¹
Exclusions: Pregnancy Exclusion Criteria	<ol style="list-style-type: none"> 8. Vaginal childbirth within the last 18 months 9. Currently pregnant or planning pregnancy during the study period 10. A positive pregnancy test or, if at risk of pregnancy (i.e. of childbearing potential), does not have a documented method of birth control.
Exclusions: Physical / Pelvic Exam Criteria	<ol style="list-style-type: none"> 11. Presence of fecal impaction on pelvic exam ² 12. Presence of an open wound or tear in the vagina or anus on pelvic exam ² 13. Atrophic vaginal tissue that would inhibit the comfortable wearing of a vaginal insert, as determined by symptoms or visualization on pelvic exam ² 14. Current vaginal infection requiring treatment on pelvic exam ² 15. Current urinary tract infection requiring treatment ³

<p>Exclusions: Current / Prior FI Treatments</p>	<ol style="list-style-type: none"> 16. Supervised anal sphincter exercises/pelvic floor muscle training with or without biofeedback within the last 3 months and unwillingness to abstain from such for duration of study participation 17. Use of home e-stim devices to stimulate pelvic floor muscles and unwillingness to abstain from such use for duration of study participation 18. Percutaneous Tibial Nerve Stimulation (PTNS) treatment within the last 3 months and unwillingness to abstain from such for duration of study participation 19. Injectable bulking agents (e.g. Solesta®) for treatment of FI within the last 3 months and unwillingness to abstain from such for duration of study participation 20. Current sacral nerve stimulator (SNS) implant (Interstim®) used within the last 3 months. If SNS unit is implanted, there must be documented evidence that the device has been turned "off" for the past 3 months and the patient must agree to abstain from use for duration of study 21. Presence of an artificial bowel sphincter implant 22. Active participation in another bowel or pelvic floor disorder investigational study, if the treatment could affect use of the Eclipse System, its safety or effectiveness, or otherwise confound the results of this study
<p>Exclusions: Prior Surgeries</p>	<ol style="list-style-type: none"> 23. History of surgical diversion or removal of any portion of the bowel, except appendectomy or cholecystectomy 24. History of bariatric surgery 25. Hysterectomy within the last 6 months 26. Native tissue repair for pelvic organ prolapse within past 6 months 27. Any history of reconstructive mesh surgery for pelvic organ prolapse or FI (mesh mid urethral slings are allowed) 28. Urinary incontinence surgical procedure within past 6 months 29. Colorectal/anal surgery such as rectopexy, sphincteroplasty, graciloplasty within the last 12 months
<p>Exclusions: Concurrent Medical Conditions</p>	<ol style="list-style-type: none"> 30. Chronic (greater than 6 months) abdominal pain in the absence of diarrhea 31. Inflammatory bowel disease (IBD) such as Crohn's Disease or Ulcerative Colitis 32. Grade III or IV hemorrhoids 33. Congenital anorectal malformation 34. Chronic watery diarrhea (3 or more loose stools per day for 4 weeks or more) unmanageable by drugs or diet as primary cause of FI per review of subject history and baseline diary 35. Laxative use as primary cause of FI 36. Chronic (greater than 3 months) fecal impaction requiring ongoing treatment 37. Rectal prolapse (mucosal or full thickness) 38. Chronic (greater than 6 months) rectal, anal or pelvic pain 39. History of chronic or recurrent UTIs (2 or more positive cultures within the last 6 months or 3 or more positive cultures within the last year) 40. History of chronic or recurrent vaginal infections (4 or more per year) within the past year 41. Any pelvic organ prolapse that extends beyond the plane of the hymen 42. Concurrent use of an intra-vaginal pessary or other device that would interfere with the Eclipse™ Insert placement or wearing 43. Presence of any urogenital or colorectal fistula involving the vagina, history of a recurrent fistula, or history of a prior failed or complicated fistula repair. A remote history (≥12 months) of a single, well-healed fistula repair is allowed. 44. Anal or pelvic (colorectal or genitourinary) malignancy within past five years 45. History of pelvic irradiation for cancer 46. Life expectancy of less than three years

Exclusions: Concurrent Medical Conditions (cont.)	47. Uncontrolled and complicated autoimmune or inflammatory disorder such as Systemic Lupus Erythematosus, Sjogren's Syndrome, Rheumatoid Arthritis, or AIDS, that could have a confounding effect on FI severity or frequency during a yearlong study participation 48. Neurological disorders known to affect bowel continence, such as advanced Multiple Sclerosis or Parkinson's disease 49. Subject has an unstable condition (e.g. psychiatric disorder, recent history of substance abuse) or otherwise thought to be unreliable or incapable of complying with the requirements of the study protocol 50. Any other significant medical condition or lifestyle factor or confounder that the investigator believes would interfere with study participation and/or increase subject risk or interpretation of the primary or secondary endpoints
Inclusions: Baseline Diary	51. At least 4 episodes of FI recorded during the 2-week Baseline Diary ¹ 52. At least 12 out of 14 consecutive days of diary data recorded on the Baseline Diary ¹
Inclusions: Device Fitting	53. Successful fitting of the Trial Insert, i.e. device is both stable and comfortable while wearing ¹ 54. Subject is able to physically manage the insertion and removal of the Insert ¹
Inclusions: Test Diary	55. Subject attains a 50% reduction or more in the number of FI episodes while wearing the Trial Insert in the 2-week Fitting Period compared to their 2-week Baseline Period. ¹ 56. At least 12 out of 14 consecutive days of diary data recorded on the Test Diary ¹

¹ These criteria will be assessed at the appropriate follow-up visit.

² Subjects may be treated and re-assessed to qualify for study participation.

³ Subjects should be treated as clinically indicated and may complete their baseline diary, but they must have a documented negative urine dipstick or urine culture test prior to the Initial Fitting at visit 2.

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1 Background

1.1 Epidemiology of FI

Fecal incontinence (FI), also referred to as loss of bowel control or accidental bowel leakage (ABL), is a debilitating condition and a significant unmet need in women's health. Recent studies of community-dwelling women in the U.S. report prevalence rates of 12-25%.^{1,2,3,4,5} The average age of onset is between 47 and 55 years^{2,6}. This condition can be emotionally devastating, resulting in social isolation, and many women are unaware that help is available.

1.2 Causes of FI

The cause of FI is multifactorial, including congenital, neurologic, and traumatic alterations of the continence mechanism. Many women with FI have a history of damage to the pelvic region caused by pregnancy and childbirth. Damage can involve the internal and external anal sphincters, pelvic floor muscles, and associated nerves (e.g., pudendal nerve). Puerperal damage to these structures may not manifest until later in life, possibly due to age-related changes in rectal sensation, compliance, and volume, in addition to further weakening of the sphincters and pelvic floor muscles. Many women with FI have multiple defects in their continence system, making effective treatment particularly difficult.

1.3 Available Treatments

Existing treatments for FI have had limited sustained success. Conservative medical management, such as dietary modification, antimotility agents⁷, and biofeedback⁸, have demonstrated varying degrees of effectiveness, ranging from 50-90% for biofeedback in conjunction with other therapies,^{9,10} Overlapping sphincter repair is one of the most common surgical approaches. However, long-term success rates have been less than 40% and the procedure is usually only applicable for certain, repairable sphincter defects.¹¹ The implantable artificial bowel sphincter is a surgical device that gives the patient dynamic control of the opening and closing of the anorectal canal.¹² This mechanism of dynamic control has shown a 42.6% effectiveness rate, compared to 49.3% for dynamic graciloplasty; however, the high morbidity related to its invasive nature has greatly limited its applicability.¹³ Such surgical interventions also require inpatient hospitalization and prolonged recovery. Recently, sacral nerve stimulation (SNS) has been used to treat FI with up to

¹ Varma MG, Brown JS, Creasman JM, et al. Fecal incontinence in females older than aged 40 years: who is at risk? *Dis Colon Rectum* 2006; 49: 841–851.

² Bharucha AE, Zinsmeister AR, Locke GR, et al. Prevalence and burden of fecal incontinence: a population-based study in women. *Gastroenterology* 2005; 129: 42–49.

³ Boreham MK, Richter HE, Kenton KS, et al. Anal incontinence in women presenting for gynecologic care: prevalence, risk factors, and impact upon quality of life. *Am J Obstet Gynecol* 2005; 192: 1637–1642.

⁴ Brown HW et al. Factors Associated With Care Seeking Among Women With Accidental Bowel Leakage. *Female Pelvic Med Reconstr Surg* 2013;19: 66Y71

⁵ Lawrence JM, Lukacz ES, Nager CW, et al. Prevalence and co-occurrence of pelvic floor disorders in community-dwelling women. *Obstet Gynecol* 2008; 111: 678–685.

⁶ Romano, Carlo Ratto, Giovanni B. Doglietto (ed). *Fecal incontinence: diagnosis and treatment* (1. Ed. ed.). Milan: Springer, 2007.

⁷ Sun W, Donnelly TC. Effects of loperamide oxide on gastrointestinal transit time and anorectal function in patients with chronic diarrhea and faecal incontinence. *Scand J Gastroenterol* 1997;32:34–8.

⁸ Norton C, Chelvanayagam S, Wilson-Barnett J, et al. Randomized controlled trial of biofeedback for fecal incontinence. *Gastroenterology* 2003;125:1320–29.

⁹ Norton C et al. Conservative Management of Fecal Incontinence in Adults. Committee of the International Consultation on Incontinence. Management of fecal incontinence in adults. *Neuro-urolog Urodyn* 2010; 29(1):199-206.

¹⁰ Hayden, D.M. et al. Fecal Incontinence: Etiology, Evaluation, and Treatment. *Clin Colon Rectal Surg* 2011; 24:64-70.

¹¹ Gutierrez et al. Long-term results of anterior sphincteroplasty. *Dis Colon and Rectum* 2004; 47:727-732.

¹² Wong et al. *Dis Colon and Rectum* 2002;45:1139 -1153.

¹³ Belyaev, O, Muller, C. and Uhl, W. Neosphincter Surgery for Fecal Incontinence: A critical and Unbiased Review of the Relevant Literature. *Surg Today* 2006;36:295-303.

83% at 12 months. Its mechanism is not fully understood and is applicable to patients willing to undergo a permanent, surgical implant^{14,15} Injectable bulking agents, such as dextranomer in stabilized hyaluronic acid (Solesta™), have been used to treat FI, with a reported efficacy rate of 52%.¹⁶ Given the risks and limitations associated with current alternatives, most FI patients are resigned to coping with the condition by modifying their lifestyle and using products such as pads and adult diapers.

1.4 Description of the Eclipse System

1.4.1 Overview

The Eclipse System is a vaginal bowel control (VBC) 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.

1.4.2 The Sizing Kit

The Sizing Kit is a set of reusable fitting inserts (Sizers) which consist of the same stainless steel base and medical grade silicone coating as the Eclipse Insert, but without the balloon that is part of the Eclipse system. These reusable Sizers are available in the same base sizes as the Eclipse Insert, and can be reused after reprocessing in accordance with the Instructions for Use (IFU)..

1.4.3 The Trial Insert

Prior to providing the Eclipse Insert to a subject, the clinician will use the Sizers and the Trial Insert to assess appropriate fit of the Eclipse Insert for each subject. The Trial Insert is composed of a base made of medical grade silicone, polycarbonate, and stainless steel, and a balloon made from medical grade silicone and polyurethane.

The Trial Insert consists of base-balloon configurations sized exactly as the Eclipse Inserts are sized and is intended for short-term use (1-2 weeks). This disposable Trial Insert allows the subject to try one or more Insert sizes (while keeping a fecal incontinence episode diary) during the Fitting Period before qualifying for and committing to the year-long trial of the Eclipse Insert.

A silicone inflation tube connects to the balloon on one end, and to a self-closing luer valve (Valve) and cap on the other end which extends outside of the subject’s vagina. An optional extension tube can be added between the existing tube and the Valve to increase the length. The Valve allows the user to inflate or deflate the balloon with the Pump.

1.4.4 The Eclipse Insert

The Eclipse Insert and the Trial Insert look the same; this Insert is graphically depicted in **Figure 1**.

The Eclipse Insert is provided as a non-sterile unit for use by a single patient and is currently available in a range of base sizes with two (2) different balloon sizes. It is composed of a base made of medical grade silicone and stainless steel, and a balloon made of medical grade silicone and polyurethane.

¹⁴ Leroi et al. Efficacy of sacral nerve stimulation for fecal incontinence: results of a multi-center, double-blind crossover study. *Annals of surgery*, volume 242, number 5, November 2005.

¹⁵ Wexner et al. Sacral nerve stimulation for fecal incontinence: results of a 120-patient, prospective, multi-center study. *Annals of surgery*, volume 251, number 3, March 2010.

¹⁶ Graf et al. Efficacy of dextranomer in stabilised hyaluronic acid for treatment of faecal incontinence: a randomized, sham-controlled trial. *Lancet* 2011; 377: 997-1003.

A silicone inflation tube connects to the balloon on one end, and to a self-closing luer valve (Valve) and cap on the other end which extends outside of the subject's vagina. The Valve allows the user to inflate or deflate the balloon with the Pump. An optional extension tube can be added between the existing tube and the Valve to increase the length.

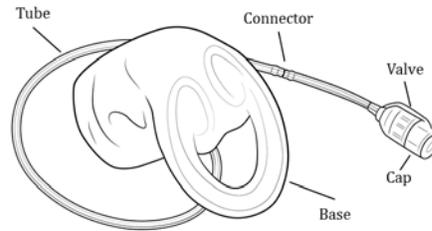


Figure 1. Insert (inflated state)

1.4.5 The Pump

A pressure-regulated Pump (**Figure 2**) is provided to inflate and deflate the Insert. The Pump connects to the Insert via the Valve. The Pump has two ends that connect to the Valve: one end for adding air (labeled with a "+") and the other end for removing air (labeled with a "-"). Air is moved through the Pump by squeezing the pump body. During inflation, the Pump is squeezed seven to ten times. Seven pumping motions are required to adequately fill the balloon. The balloon will not over-inflate because any excess air is vented out by the regulator. When the balloon is fully inflated, the internal pressure is set to the venting pressure of the regulator. Regulators are removable so that different balloon pressures can be achieved. Regulators and pumps are also designed for single-patient use only. Three different Regulators are available that regulate the balloon pressures to within the values listed in **Table 1**. The Pump is packaged without a regulator attached. The "Low", "Medium" and "High" Regulators are shipped separately.

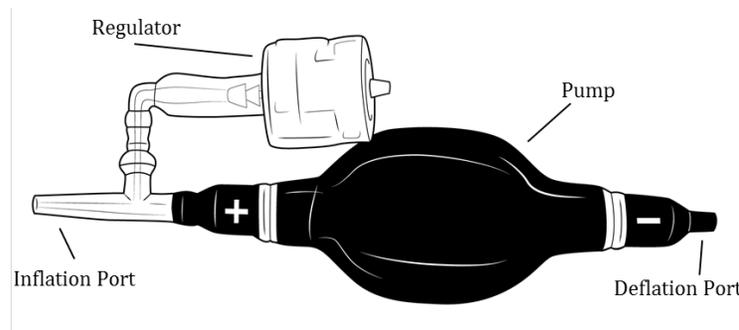


Figure 2. Pump

Table 1. Regulators and Associated Pressures

Regulator	Pressure at Full Inflation (mmHg)
Low	45-57
Medium	70-92
High	114-129

1.5 Mechanism of Action of the Eclipse System

The Insert (refers to both the Eclipse Insert and the Trial Insert) is placed in a position similar to other vaginal devices, such as diaphragms, pessaries, and tampons, whose safety profiles are well-

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established.^{17,18,19} Insertion and removal, and inflation and deflation of the Insert, are under the control of the subject.

The Insert is designed to restore bowel continence in women with FI by replacing the normal continence function provided by the rectum and anal canal, which is complex and multi-factorial. The Insert utilizes the naturally overlapping potential spaces of the vagina and rectum to inhibit (or allow) stool passage in a user-controlled manner. Though separated by the conformable rectovaginal septum, much of the vagina and rectum effectively share the same space. When the rectum fills with stool, it expands, taking up more of this shared space. This is often palpable on a vaginal exam as the vagina conforms to the shape of the expanded rectum. Similarly, when an object is placed in the vagina, it is often palpable in the rectum. The redundant nature of the vaginal tissue makes it naturally conformable without discomfort or strain. The Insert is designed such that when it is placed in the vagina and is in the deflated state, the rectal space is not occupied, allowing stool to pass through normally (see **Figure 3**, left). When the Insert is inflated, the vagina conforms around it, causing a reduction in rectal space, which helps the patient prevent unwanted stool passage (see **Figure 3**, right).

In **Figure 4** the Insert is shown in its deflated state. The base of the Insert is flexible to allow for ease of insertion and removal, as shown in **Figure 5**.

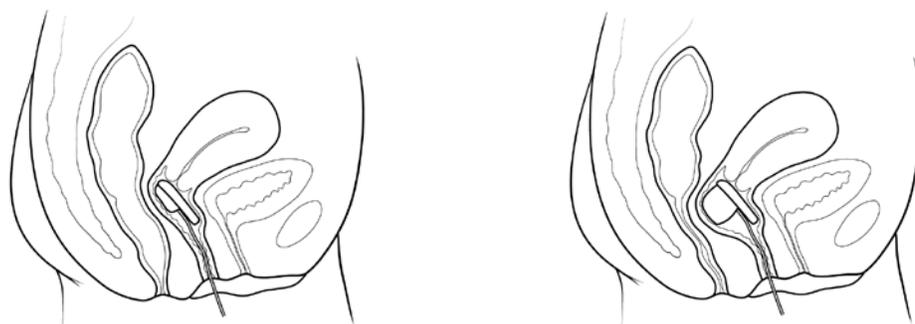


Figure 3. Insert; deflated (left), and inflated (right)

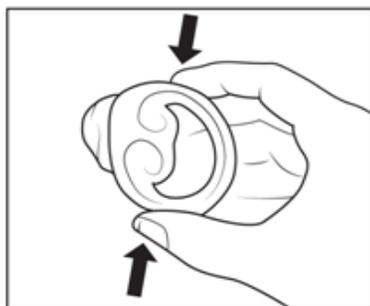


Figure 4. Deflated balloon

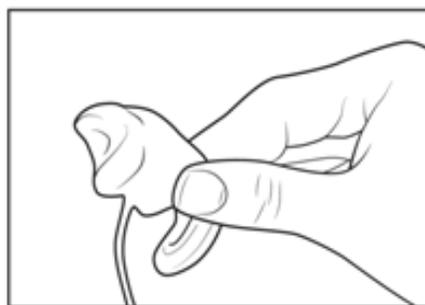


Figure 5. Folded Insert

¹⁷ Lone et al. A 5 year prospective study of vaginal pessary use for pelvic organ prolapse. *Int J Gynecol Obstet.* 114 (2011) 56-59.

¹⁸ Clemons et al. Patient satisfaction and changes in prolapse and urinary symptoms in women who were fitted successfully with a pessary for pelvic organ prolapse. *Am J Obstet Gynecol* (2004) 190, 1025-9.

¹⁹ Bash, et al. Review of vaginal pessaries. *Obstetrical and Gynecological Survey* (2000) 55, 7, p455-460.

1.6 *Prior Investigations*

1.6.1 Feasibility Studies

Two feasibility studies were initially conducted to assess the fit and function of the Eclipse System in female subjects. These studies were approved by each site's Institutional Review Board (IRB) as non-significant risk (NSR) device investigations. In total, 86 subjects were fit with the Insert who wore it for up to 3 months. There were 9 device-related adverse events reported, none of which were classified as serious or unanticipated and all were mild (minor bleeding/lacerations from insertion/removal (3) or minor ecchymosis (6)) and all resolved quickly without medical intervention other than vaginal estrogen cream. Subjects in these studies demonstrated a positive response to the impact of the Eclipse System on their FI symptoms.

1.6.2 LIFE Pivotal Study

The LIFE Study (Protocol CA003) was a multi-center, prospective, open label clinical trial conducted at six (6) centers in the United States. As with the prior studies, all IRBs approved the trial as an NSR investigation. Furthermore, FDA is aware that this and the prior feasibility studies were conducted as NSR investigations and did not object to this categorization. The objective of this pivotal trial was to evaluate the safety and effectiveness of the Eclipse System for the treatment of Fecal Incontinence (FI) in adult women.

A total of 200 female subjects aged 19 to 75 were enrolled in the study between August 2012 and October 2013. Subjects were required to experience ≥ 4 fecal incontinence episodes during a 2 week baseline diary assessment to qualify for participation. Sixty-one (61) subjects met all study eligibility criteria and entered the 1 month Treatment Period to make up the Intent to Treat Cohort. Fifty-six (56) subjects completed the 1 month Treatment Period without major protocol deviations to make up the Per Protocol Cohort.

The primary endpoint was the percent change in the number of episodes of FI experienced while wearing the Insert during the 2-week assessment period (Treatment Period) as compared to the baseline 2-week assessment period. Clinical effectiveness of the Eclipse System (study success) was defined as occurring when at least 40% of the Intent to Treat Cohort demonstrated at least a 50% decrease in the number of FI episodes (recorded in a 2-week patient diary) after 1 month of treatment with the device as compared to the number of FI episodes reported during the Screening Period.

Secondary endpoints were reduction in the number of incontinent days while wearing the device and adverse events. Other endpoints included symptom improvement measured by the Fecal Incontinence Quality of Life (FIQOL), Modified Manchester Health Questionnaire (MMHQ), and Patient Global Impression of Improvement (PGI-I).

At 1 month, 78.7% of the ITT Cohort (95% CI, 66-88%, $p < 0.0001$) met the success criterion; 85.7% (95% CI, 74-94%, $p < 0.0001$) met the success criterion in the Per Protocol analysis and 85.7% of participants considered their bowel symptoms "very much" or "much better". There was significant improvement in all FIQOL (all $p < 0.001$) and MMHQ (all $p \leq 0.007$) subscales.

There were no serious device-related adverse events reported in the trial. Two (2) SAEs were reported, neither of which was related to the study device, a fractured fibula and flu symptoms requiring hospitalization. Among the 117 subjects in the Safety Cohort, 93 AEs in 61 subjects were reported as device-related / possibly device-related, and another 26 AEs were reported in 21 subjects as not / unlikely device-related. All device-related AEs were mild (78%) or moderate (22%) and none required any significant intervention (defined as "intervention to prevent permanent impairment / damage" per the AE CRF). No device-related AEs required surgical treatment to resolve, and only 2

required medical intervention: topical vaginal estrogen for vaginal erythema and a topical antifungal for yeast infection. Modification to pre-existing Estrace usage was also required in some subjects.

1.7 Rationale for this Trial

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.

1.8 Regulatory Status of the Eclipse System

The Eclipse System received marketing clearance from the U.S. Food and Drug Administration (FDA) on November 12, 2015..

1.9 Indications for Use

The Eclipse System is indicated for the treatment of fecal incontinence in adult women.

2 Study Description

2.1 Design

Multi-center, prospective, within-subject control, open label clinical trial.

2.2 Target Population

Subjects may participate in this study if they meet eligibility criteria shown in **Table 2**. Appropriate subjects are adult females suffering from Fecal Incontinence. 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. It is anticipated that up to 625 subjects may need to be screened and consented to yield up to 150 subjects entering the Treatment Period for the effectiveness analysis.

Safety will be evaluated based on all subjects who undergo fitting with the Eclipse System.

Table 2. List of Inclusion and Exclusion Criteria

Inclusions: General Eligibility Criteria	<ol style="list-style-type: none">1. Female sex2. Age 19 years or older3. History of FI for at least 6 months4. Subject willing and able to give written informed consent to participate in the study5. Subject can read, write and communicate fluently in English (the study diaries, questionnaires and instructions are only provided in English)6. Subject willing and able to comply with visit schedule7. Subject is able to physically manage the insertion and removal of the Insert¹
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<p>Exclusions: Pregnancy Exclusion Criteria</p>	<p>8. Vaginal childbirth within the last 18 months 9. Currently pregnant or planning pregnancy during the study period 10. A positive pregnancy test or, if at risk of pregnancy (i.e. of childbearing potential), does not have a documented method of birth control.</p>
<p>Exclusions: Physical / Pelvic Exam Criteria</p>	<p>11. Presence of fecal impaction on pelvic exam ² 12. Presence of an open wound or tear in the vagina or anus on pelvic exam ² 13. Atrophic vaginal tissue that would inhibit the comfortable wearing of a vaginal insert, as determined by symptoms or visualization on pelvic exam ² 14. Current vaginal infection requiring treatment on pelvic exam ² 15. Current urinary tract infection requiring treatment ³</p>
<p>Exclusions: Current / Prior FI Treatments</p>	<p>16. Supervised anal sphincter exercises/pelvic floor muscle training with or without biofeedback within the last 3 months and unwillingness to abstain from such for duration of study participation 17. Use of home e-stim devices to stimulate pelvic floor muscles and unwillingness to abstain from such use for duration of study participation 18. Percutaneous Tibial Nerve Stimulation (PTNS) treatment within the last 3 months and unwillingness to abstain from such for duration of study participation 19. Injectable bulking agents (e.g. Solesta®) for treatment of FI within the last 3 months and unwillingness to abstain from such for duration of study participation 20. Current sacral nerve stimulator (SNS) implant (Interstim®) used within the last 3 months. If SNS unit is implanted, there must be documented evidence that the device has been turned "off" for the past 3 months and the patient must agree to abstain from use for duration of study. 21. Presence of an artificial bowel sphincter implant 22. Active participation in another bowel or pelvic floor disorder investigational study, if the treatment could affect use of the Eclipse System, its safety or effectiveness, or otherwise confound the results of this study</p>
<p>Exclusions: Prior Surgeries</p>	<p>23. History of surgical diversion or removal of any portion of the bowel, except appendectomy or cholecystectomy 24. History of bariatric surgery 25. Hysterectomy within the last 6 months 26. Native tissue repair for pelvic organ prolapse within past 6 months 27. Any history of reconstructive mesh surgery for pelvic organ prolapse or FI (mesh mid urethral slings are allowed) 28. Urinary incontinence surgical procedure within past 6 months 29. Colorectal/anal surgery such as rectopexy, sphincteroplasty, graciloplasty within the last 12 months</p>

<p>Exclusions: Concurrent Medical Conditions</p>	<p>30. Chronic (greater than 6 months) abdominal pain in the absence of diarrhea 31. Inflammatory bowel disease (IBD) such as Crohn's Disease or Ulcerative Colitis 32. Grade III or IV hemorrhoids 33. Congenital anorectal malformation 34. Chronic watery diarrhea (3 or more loose stools per day for 4 weeks or more) unmanageable by drugs or diet as primary cause of FI per review of subject history and baseline diary 35. Laxative use as primary cause of FI 36. Chronic (greater than 3 months) fecal impaction requiring ongoing treatment 37. Rectal prolapse (mucosal or full thickness) 38. Chronic (greater than 6 months) rectal, anal or pelvic pain 39. History of chronic or recurrent UTIs (2 or more positive cultures within the last 6 months or 3 or more positive cultures within the last year) 40. History of chronic or recurrent vaginal infections (4 or more per year) within the last year 41. Any pelvic organ prolapse that extends beyond the plane of the hymen 42. Concurrent use of an intra-vaginal pessary or other device that would interfere with the Eclipse™ Insert placement or wearing 43. Presence of any urogenital or colorectal fistula involving the vagina, history of a recurrent fistula, or history of a prior failed or complicated fistula repair. A remote history (≥12 months) of a single, well-healed fistula repair is allowed. 44. Anal or pelvic (colorectal or genitourinary) malignancy within past five years 45. History of pelvic irradiation for cancer 46. Life expectancy of less than three years 47. Uncontrolled and complicated autoimmune or inflammatory disorder such as Systemic Lupus Erythematosus, Sjogren's Syndrome, Rheumatoid Arthritis, or AIDS, that could have a confounding effect on FI severity or frequency during a yearlong study participation 48. Neurological disorders known to affect bowel continence, such as advanced Multiple Sclerosis or Parkinson's disease 49. Subject has an unstable condition (e.g. psychiatric disorder, recent history of substance abuse) or otherwise thought to be unreliable or incapable of complying with the requirements of the study protocol 50. Any other significant medical condition or lifestyle factor or confounder that the investigator believes would interfere with study participation and/or increase subject risk or interpretation of the primary or secondary endpoints</p>
<p>Inclusions: Baseline Diary</p>	<p>51. At least 4 episodes of FI recorded during the 2-week Baseline Diary ¹ 52. At least 12 out of 14 consecutive days of diary data recorded on the Baseline Diary¹</p>
<p>Inclusions: Device Fitting</p>	<p>53. Successful fitting of the Trial Insert, i.e. device is both stable and comfortable while wearing ¹ 54. Subject is able to physically manage the insertion and removal of the Insert ¹</p>
<p>Inclusions: Test Diary</p>	<p>55. Subject attains a 50% reduction or more in the number of FI episodes while wearing the Trial Insert in the 2-week Fitting Period compared to their 2-week Baseline Period. ¹ 56. At least 12 out of 14 consecutive days of diary data recorded on the Test Diary ¹</p>

¹ These criteria will be assessed at the appropriate follow-up visit.

² Subjects may be treated and re-assessed to qualify for study participation.

³ Subjects should be treated as clinically indicated and may complete their baseline diary, but they must have a documented negative urine dipstick or urine culture test prior to the Initial Fitting at visit 2.

2.3 Recruitment

Potential study subjects will be recruited primarily from practices of participating investigators. All subject recruitment materials will be reviewed and approved by the Sponsor and the governing IRB prior to use.

An estimated 625 subjects will be recruited into this study across all sites. 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 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.

2.4 Schedule of Events

The scheduled assessments performed at each visit are shown in **Table 3**.

Table 3. Schedule of Events

Assessment	Screening Period				Treatment Period (± 2 weeks) [†]				Unscheduled Visit
	V1	V2	V3	V4	V5	V6	V7	V8	
	Baseline	Fitting Visits*	Fit Confirmation	Treatment Eligibility	3 Months	6 Months	9 Months	12 Months / Study Exit	
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	
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).

2.5 Visit Schedule

The visit schedule is graphically represented in **Figure 6**.

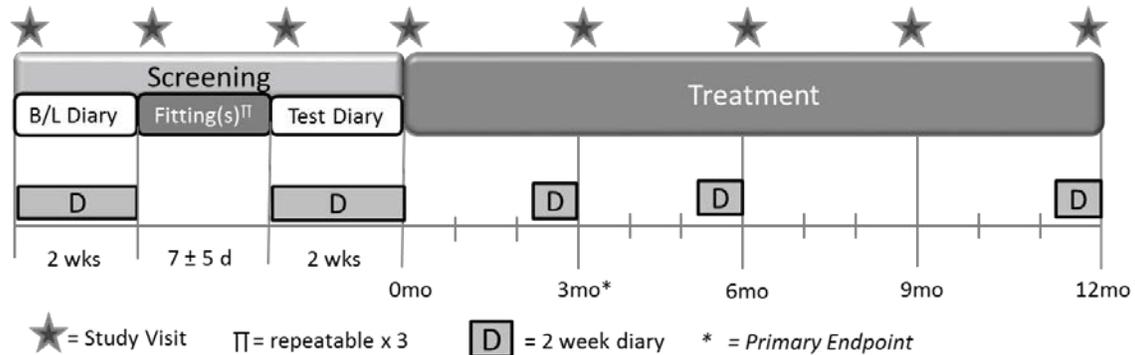


Figure 6. Study Visit Schedule Schematic

2.6 Screening Period

All subjects considered for the trial will be tracked on a screening log. All subjects who are screened and consented will be assigned a unique identification number. Study-specific procedures will be performed only after a subject has signed the informed consent form. It is anticipated that up to 25% of subjects screened will be disqualified due to not meeting the general or pelvic exam inclusion/exclusion criteria, and up to another 25% may fail to meet the baseline FI frequency criteria.

2.6.1 Pre-Screening

Subjects may be recruited and pre-screened by telephone using the appropriate IRB-approved recruitment materials such as a pre-screening telephone script. Once a subject passes the pre-screening criteria they are scheduled for a Baseline Visit.

2.6.2 Visit 1 - Baseline Visit

The trial is fully explained to the subject, and their questions are answered. A copy of the signed informed consent form should be given to the subject and the consent process should be documented within their case history.

After the subject is consented they are evaluated against the study eligibility criteria listed in **Table 2**. If there is any question as to the eligibility of a subject due to unique individual circumstances, the Investigator or research staff should contact the Sponsor's trial management team to discuss the possibility of a waiver. A written confirmation of a waiver must be maintained in the subject record and should be reported to the IRB, if required by the site's IRB reporting requirements. Study waivers are intended to be used judiciously by sites and Sponsor.

The following tasks are completed at this visit:

- Informed Consent obtained
- Inclusion/Exclusion criteria reviewed
- Presentation of FI informational brochure

- Pregnancy test and confirmation of birth control method (if subject is at risk for pregnancy, e.g. of childbearing potential)
- Clean catch urine dipstick for leukocyte esterase or nitrites[†]
- Demographics and Medical History (including baseline concomitant medications)
- Pelvic exam (speculum and digital rectal exam)
- St. Mark's (Vaizey) Incontinence Severity Score
- FIQOL questionnaire
- Cost Utilization survey
- Two week FI Episode Diary (Baseline Diary) dispensed

[†] If subject is positive for leukocyte esterase or nitrites by a clean catch urine dipstick test at baseline, they should be treated as clinically indicated (Note - this is standard of care treatment, not paid for by the study), and continue with screening. However, they must be negative by the same test, or by a urine culture test, at Visit 2 prior to being fit with the device. This test may be repeated at the treating investigator's discretion.

All subjects should be presented with an FI brochure, containing standardized general information about the diagnosis and treatment of Fecal Incontinence during the Baseline Visit²⁰ (**Appendix 7**). Dissemination of this information is meant to standardize the instructions given to each potential subject regarding the maintenance of healthy bowel habits.

In addition, all potential subjects should be counseled to maintain their usual diet and bowel health regimen as much as possible for the duration of their participation in the trial. They should also continue any medications already in use for management of bowel and vaginal health for the duration of their participation. These medications specifically include any intra-vaginal estrogen creams such as Estrace® or Premarin®, and any supplements or medications for fecal incontinence or bowel health, such as fiber, they are using at the time of the Baseline Visit.

Please query subjects regarding any planned dental or medical procedures or travel in the next several months and assess the impact on subject's ability to keep a representative bowel diary and to keep appointments during the screening period (between Visit 1 and Visit 4).

Subjects who are deemed eligible are counseled on proper FI Episode Diary completion, and should demonstrate a satisfactory understanding of how to complete each of the questions in the diary. The subject is instructed to start the Baseline Diary within the next 14 days following the Baseline Visit, and to complete it daily over the next 14 consecutive days. This is to ensure that the training received by the subject on diary completion during the Baseline Visit is fresh in their minds.

If the subject passes the general inclusion/exclusion criteria including the pelvic exam criteria, then they will be scheduled to return for the Initial Fitting Visit as soon as possible within 14 days (-2/+7 days) after their Baseline Visit.

Until a site has been proctored, at the discretion of the Sponsor, there will be an exception made to the 21-day maximum window between Visits 1 and 2 in order to allow for bolus scheduling of two or more subjects at the first fitting visit (Visit 2) without it being considered a protocol deviation.

A subject who presents with vaginal atrophy on initial exam may be prescribed a vaginal estrogen cream such as Estrace® or Premarin® if not contraindicated, and after all risks and benefits have been discussed with the subject (refer to the prescribing information of the relevant vaginal

²⁰ NIH Publication No. 13-4866. Dec. 2012. Available online at http://www.niddk.nih.gov/health-information/health-topics/digestive-diseases/fecal-incontinence/Documents/Fecal_Incontinence_508.pdf

estrogen cream). Subject should return within the next 2 – 6 weeks to be re-assessed by the study clinician at the Initial Fitting Visit.

If the subject fails any other pelvic exam criteria that allow for re-assessment, but they are otherwise eligible, they may be scheduled for the Initial Fitting Visit up to a maximum of 6 weeks from their Baseline Visit, based upon clinician evaluation of the length of time needed for the clinical findings to resolve or stabilize adequately in order for the subject to proceed safely and comfortably with fitting of a vaginal device.

Note: The Baseline Diary should still be started within the next 14 days after the initial Baseline Visit, regardless of the length of time between the Baseline Visit (Visit 1) and the scheduled Initial Fitting Visit (Visit 2). However, subjects will be allowed to repeat (stop and restart) their Baseline diary if during the two weeks recorded there were unusual or exceptional circumstances outside of the subject's control e.g. illness, injury, natural catastrophe, or family emergency. Only the repeat diary data will be used to qualify the subject at Visit 2. Both original and repeat diaries must be retained. Pelvalon should be notified immediately and the rationale for allowing a subject to repeat their diary provided. The case will be evaluated by the Executive Committee, and a documented written approval must be obtained prior to using the repeat diary to calculate the subject's eligibility at Visit 2.

As per the study inclusion criteria, the diary should span 14 consecutive days, with no more than 2 missing days of data between Visit 1 and Visit 2.

2.6.3 Visit 2 - Initial Fitting Visit - 14 days (-2/+7 days) from Baseline Visit

Subjects are first evaluated for the frequency of their FI episodes according to their two-week Baseline Diary. The subject must have completed 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 in order to continue in the trial. If either of these criteria are not met, then the subject is exited from the trial as a screen failure.

Partial days of data entry should be counted as full days for the purposes of calculating eligibility. If the subject continues to qualify for the study based on their FI frequency, they will be asked to undergo a pelvic exam and fitting with the Trial Insert.

For subjects who previously failed any pelvic exam inclusion/exclusion criteria that allow re-evaluation, their Initial Fitting Visit may be extended up to 6 weeks from the Baseline Visit (without being considered a protocol deviation). The previously failed inclusion/exclusion criteria must be re-evaluated during the Initial Fitting Visit pelvic exam, and must be resolved in order for the subject to continue in the trial. Otherwise, they are exited from the study as a screen failure.

For subjects who were prescribed an estrogen regimen, if the clinician determines that the vaginal tissue has adequately responded to the vaginal estrogen cream and the subject is willing to continue the use of the estrogen cream throughout the remainder of their study participation, they may continue with the Initial Fitting Visit. Otherwise, they are exited from the study as a screen failure.

The following tasks are completed at this visit:

- Inclusion/exclusion criteria reviewed
- Baseline Diary reviewed
- Patient Goal questionnaire – goal identification
- Pelvic exam (speculum and digital rectal exam)
- Trial Insert fitting
- AEs and Concomitant Medications reviewed

Successful fitting with the Trial Insert is defined as an insert that is stable, in the proper position, provides sufficient rectal occlusion based on a digital rectal exam, and is comfortable for the subject. The clinician may try as many different sizes of the Trial Insert as they and the subject agree are tolerable to the subject at the Initial Fitting Visit. If the subject cannot obtain a suitable fit during this Initial Fitting Visit and/or decides to withdraw, the subject is exited from the trial as a screen failure.

Per the eligibility criteria, during the Fitting Visits the subject must demonstrate the ability to properly insert and remove the Trial Insert and inflate and deflate the Insert as needed using the Pump.

If the subject meets the Baseline Diary and Initial Fitting Visit criteria, they are instructed on proper use and care of the Eclipse System (**Appendix 9**), and are scheduled for a Fit Confirmation Visit within 7 days (-5/+7 days) from the Initial Fitting Visit.

The follow up visit should be scheduled as close to 7 days post-fitting as possible to allow the subject enough time to accommodate to the device. However, the subject should be seen earlier in the window (as soon as possible) if they are experiencing signs of an improper fit (discomfort or lack of effectiveness), a device-related adverse event, or any of the following:

- Foul odor or excessive vaginal discharge
- Any difficulty urinating or defecating
- Significant bleeding not associated with menstruation
- Unusual pelvic pain or discomfort

If the subject is a screen failure based on their Baseline Diary or pelvic exam findings, the subject will be exited from the study without completing the Patient Goal questionnaire or Trial Insert fitting. If the subject is a screen failure based on unsuccessful Trial Insert fitting, any AEs related to the Trial Insert fitting procedure must be reported.

2.6.3.1 Fitting Procedure

The fitting procedure should proceed in accordance with the Eclipse System Instructions for Use (IFU). (**Appendix 8**).

2.6.3.2 Eclipse System Use and Care Instructions

Upon successful fitting with the Trial Insert, a copy of the Eclipse System Use and Care Instructions for LIBERATE Study Subjects (**Appendix 9**) which apply to the Eclipse System (including the Eclipse Insert, Trial Insert, and the Pump) should be reviewed and given to the subject to take home with them.

2.6.4 Telephone Contact (After Initial Fitting Visit)

Within 2-3 days of the Initial Fitting Visit the subject should be contacted by phone to ask about fit and comfort. The next study visit should be confirmed with the subject during this phone call.

2.6.5 Visit 2a / 2b – Repeat Fitting Visits (Optional) – 7 days (-5/+7 days) from the Initial Fitting Visit

Evaluation of fit over multiple visits is standard clinical practice for many vaginal devices as it is often difficult to determine if the device will remain stable and comfortable until the subject wears it during their routine daily activities. A subject may undergo refitting, resulting in being sent home with a different size of the Trial Insert, up to two more times after the Initial Fitting Visit (for a maximum of 3 Fitting Visits in total) before they either exit the trial as a screen failure, or enter the final phase of screening and complete a 2-week Test Diary while wearing the fitted device.

If by the subject's verbal report at the telephone contact following Visit 2 they indicate there may be a problem with the fit of the Trial Insert, the subject can be offered a repeat Fitting Visit. If there are no issues reported or identified during the follow-up pelvic exam, the subject may proceed straight to the Fit Confirmation Visit #3. If a repeat fitting is performed, the following tasks are completed:

- Inclusion/exclusion criteria reviewed
- Pelvic exam (speculum and digital rectal exam)
- Insert fitting as per the Fitting Procedure in **Appendix 8**
- AEs and Concomitant Medications reviewed
- Device satisfaction questionnaire, only if subject is being exited as a screen fail

If a successful fit with the Trial Insert is determined by the clinician to be unattainable, the subject is classified as a screen failure, and the Insert is removed. All remaining scheduled activities for Visit 2a / 2b will still be completed and the subject will be exited from the study.

If a suitable fit is attained with a different sized Trial Insert, then the subject is re-instructed on proper use and care of the Eclipse System (**Appendix 9**), and is scheduled for a Fit Confirmation Visit within 7 days (-5/+7 days) from the Repeat Fitting Visit.

The follow up visit should be scheduled as close to 7 days post-fitting as possible to allow the subject enough time to accommodate to the device. However, the subject should be seen earlier in the window (as soon as possible) if they are experiencing signs of an improper fit (discomfort or lack of effectiveness), a device-related adverse event, or any of the following:

- Foul odor or excessive vaginal discharge
- Any difficulty urinating or defecating
- Significant bleeding not associated with menstruation
- Unusual pelvic pain or discomfort

2.6.6 Telephone Contact (After Repeat Fitting Visits)

Telephone contact should be initiated after any repeat fitting visits following the same guidelines as the Initial Fitting Visit (**Section 2.6.4**).

2.6.7 Visit 3 - Fit Confirmation Visit - 7 days (-5/+7days) from the final Fitting Visit

The subject is evaluated for a continued good fit of the Trial Insert, as described in **Appendix 8** and the following tasks are completed:

- Pelvic exam (speculum and digital rectal exam)
- AEs and Concomitant Medications reviewed
- Device satisfaction questionnaire, only if subject is being exited as a screen fail
- Two week FI Episode Diary (Test Diary) dispensed, only if subject continues to meet all eligibility criteria
- Order the corresponding Eclipse Insert, only if subject continues to meet all eligibility criteria

If per clinician assessment during the pelvic exam a suitable fit with the Trial Insert is deemed to be unattainable, the subject is classified as a screen failure and the Insert is removed. All other scheduled activities for Visit 3 will still be completed (excluding dispensing a Test Diary and ordering the Eclipse Insert) and the subject will be exited from the study.

Based upon the fitting rate observed in the LIFE (CA003) Trial, it is estimated that approximately 24% of subjects who have an Initial Fitting Visit may be disqualified due to not achieving a stable and comfortable fit of the Insert. This fitting rate is comparable to fitting rates observed with other vaginal devices.^{21, 22}

If a successful fit has been confirmed, the subject is re-instructed on proper use and care of the Eclipse System (**Appendix 9**) and on the proper completion of the two week Test Diary, and is scheduled for their final Treatment Eligibility Visit within 14 days (-2/+7days) from the Fit Confirmation Visit.

The subject is instructed to start the Test Diary within the next 7 days following the Fit Confirmation Visit while wearing the Trial Insert. This is to ensure that the training received by the subject on diary completion during the Fit Confirmation Visit is fresh in the subject's mind. If a subject is expecting her menstrual cycle to begin during the next 14 days and she chooses not to wear the Trial Insert during menstruation, she may delay the start of the Test Diary by up to two weeks (without being considered a protocol deviation) since collection of efficacy data would be inappropriate during a period of time when the device is not being worn. The Test Diary should be started the day after menstruation ends.

In addition, subjects will be allowed to repeat (stop and restart) their Test diary if during the two weeks recorded there were unusual or exceptional circumstances outside of the subject's control e.g. illness, injury, natural catastrophe, or family emergency. Only the repeat diary data will be used to qualify the subject at Visit 4. Both original and repeat diaries must be retained. Pelvalon should be notified immediately and the rationale for allowing a subject to repeat their diary provided. The case will be evaluated by the Executive Committee, and a documented written approval must be obtained prior to using the repeat diary to calculate the subject's eligibility at Visit 4.

As per the study inclusion criteria, the diary should span 14 consecutive days, with no more than 2 missing days of data between Visit 3 and Visit 4.

There will be no opportunities to repeat the Test Diary data collection due to missing days of data, but the Treatment Eligibility Visit (Visit 4) may be re-scheduled if interrupted by a menstrual cycle, illness, injury, natural catastrophe, or family emergency to allow for 12-14 days of diary data collection (without it being considered a protocol deviation).

2.6.8 Visit 4 – Treatment Eligibility Visit - 14 days (-2/+7 days) after Visit 3

The following tasks are completed at this visit:

- Two week Test Diary review
- Pelvic exam (speculum and digital rectal exam)
- AEs and Concomitant Medications reviewed
- Device satisfaction questionnaire, only if subject is being exited as a screen fail
- Two week FI Episode Diary (Treatment Diary) dispensed (for use prior to the 3 month visit), only if subject continues to meet all eligibility criteria
- Eclipse Insert dispensed, only if subject continues to meet all eligibility criteria

The Test Diary is assessed for completeness and for the number of fecal incontinence episodes compared to baseline. Subjects who meet the Visit 4 Test Diary inclusion criteria by (a) recording

²¹ Mutone et al. Factors which influence the short-term success of pessary management of pelvic organ prolapse. American Journal of Obstetrics and Gynecology, December, 2005, 193, 89-94.

²² Clemons et al. Risk factors associated with an unsuccessful pessary fitting trial in women with pelvic organ prolapse. American Journal of Obstetrics and Gynecology, 2004. 190, 345-50.

a minimum of 12 out of 14 consecutive days of diary data and (b) achieving a 50% or greater reduction in the average number of FI episodes (major or minor soiling) on their Test Diary compared to their Baseline Diary will be enrolled into the Treatment Period of the study. Partial days of data entry should be counted as full days for the purposes of calculating eligibility.

Subjects who do not meet the Visit 4 Test Diary criteria as described above or who decide to withdraw will be classified as screen failures. If the subject is classified as a screen failure, all other scheduled activities for Visit 4 will still be completed (except for dispensing a Treatment Diary and the Eclipse Insert) and the subject will be exited from the study.

If the subject continues to meet all eligibility criteria, she will be given the same sized Eclipse Insert as the Trial Insert used during the Test Diary, and the used Trial Insert will be disposed of at the site, unless directed otherwise by the Sponsor or unless there is a potential product malfunction associated with the used Trial Insert, in which case it will be returned to the Sponsor for investigation. The subject should continue to use the same Pump. The subject is to be re-counseled on the requirements of the Treatment Period of the protocol, on the proper use and care of the Eclipse System (**Appendix 9**), and on proper completion of the Treatment Diary.

The subject is instructed to complete the Treatment Diary while wearing the Eclipse Insert for a consecutive 14 day (2 week) period just prior to the next scheduled visit at 3 months (\pm 2 weeks) after Visit 4.

2.7 Treatment Period

Subjects who enter the Treatment Period will return for scheduled visits at 3, 6, 9, and 12 months after Visit 4. All eligible subjects will complete a 2-week Treatment Diary during the last 2 weeks prior to the 3, 6 and 12 month visits. There is no Treatment Diary required at the 9 month visit. Subjects will be instructed to complete the diary for 14 consecutive days while wearing the Eclipse Insert. The timing of the start and/or completion of the Treatment Diary may be adjusted by up to 2 weeks (without being considered a protocol deviation) if a subject's menstrual cycle interrupts their wearing of the Eclipse Insert during the two-weeks when the Treatment Diary is scheduled, rendering assessment of effectiveness during this period of time inappropriate.

In addition, subjects will be allowed to repeat (stop and restart) their Treatment Diary if the two weeks recorded were unusual or unrepresentative of their true condition due to circumstances outside of their control e.g. illness, injury, natural catastrophe, or family emergency. Only the repeat diary data will be data entered. Both original and repeat diaries must be retained. Pelvalon should be notified immediately and the rationale for allowing a subject to repeat their diary provided. The case will be evaluated by the Executive Committee, and a documented written approval must be obtained prior to using the repeat diary for data entry.

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. After the second attempt, any non-completed diary will be treated as missing data.

The subject will undergo a pelvic exam at each visit in order to verify proper use of the Eclipse Insert and adequate hygiene, as well as to assess any adverse events.

2.7.1 Telephone Contacts (Between Visit 4 and Visit 5)

The subject should be contacted by phone twice between clinic appointments at one month intervals to ensure she is following the instructions for use, is not experiencing any technical or

medical problems while wearing the Eclipse Insert, and to remind her to complete the Treatment Diary at the required time.

2.7.2 Visit 5 – 3 Months (\pm 2 weeks) after Visit 4

Subjects are evaluated for the frequency of their FI episodes according to their two week Treatment Diary, and are evaluated for continued fit and safety of the Eclipse Insert.

The following tasks are completed at this visit:

- Two week Treatment Diary reviewed
- St. Mark's (Vaizey) Incontinence Severity Score calculated
- FIQOL questionnaire administered
- PGI-I questionnaire administered
- Patient Goal questionnaire administered
- Cost Utilization survey administered
- Device Satisfaction questionnaire administered
- Pelvic exam (speculum and digital rectal exam)
- AEs and Concomitant Medications reviewed
- Two week Treatment Diary dispensed (for use prior to the 6 month visit)

The subject is re-counseled on the requirements of the Treatment Period of the protocol, on the proper use and care of the Eclipse System (**Appendix 9**) and proper completion of the Treatment Diary.

The subject is instructed to complete the Treatment Diary while wearing the Eclipse Insert for a consecutive 14-day (2 week) period just prior to the next scheduled visit.

2.7.3 Telephone Contacts (Between Visit 5 and Visit 6)

The subject should be contacted by phone twice between clinic appointments at one month intervals to ensure she is following the instructions for use, is not experiencing any technical or medical problems while wearing the Eclipse Insert, and to remind her to complete the Treatment Diary at the required time.

2.7.4 Visit 6 – 6 Months (\pm 2 weeks) after Visit 4

Subjects are evaluated for the frequency of their FI episodes according to their two week Treatment Diary, and are evaluated for continued fit and safety of the Eclipse Insert.

The following tasks are completed at this visit:

- Two week Treatment Diary reviewed
- St. Mark's (Vaizey) Incontinence Severity Score calculated
- FIQOL questionnaire administered
- PGI-I questionnaire administered
- Patient Goal questionnaire administered
- Device Satisfaction questionnaire administered
- Pelvic exam (speculum and digital rectal exam)
- AEs and Concomitant Medications reviewed

The subject is re-counseled on the requirements of the Treatment Period of the protocol, and on proper use and care of the Eclipse System (**Appendix 9**). A Treatment Diary is not dispensed at Visit 6 and is not required to be completed by the subject prior to Visit 7.

2.7.5 Telephone Contacts (Between Visit 6 and Visit 7)

The subject should be contacted by phone twice between clinic appointments at one-month intervals to ensure she is following the instructions for use and is not experiencing any technical or medical problems while wearing the Eclipse Insert.

2.7.6 Visit 7 – 9 Months (\pm 2 weeks) after Visit 4

Subjects are evaluated for continued fit and safety of the Eclipse Insert.

The following tasks are completed at this visit:

- St. Mark's (Vaizey) Incontinence Severity Score calculated
 - FIQOL questionnaire administered
 - PGI-I questionnaire administered
 - Patient Goal questionnaire administered
 - Device Satisfaction questionnaire administered
 - Pelvic exam (speculum and digital rectal exam)
 - AEs and Concomitant Medications reviewed
- Two week Treatment Diary dispensed (for use prior to the 12 month visit)

The subject is re-counseled on the requirements of the Treatment Period of the protocol, on proper use and care of the Eclipse System (**Appendix 9**) and proper completion of the Treatment Diary.

The subject is instructed to complete the Treatment Diary while wearing the Eclipse Insert for a consecutive 14-day (2 week) period just prior to the next scheduled visit.

2.7.7 Telephone Contacts (Between Visit 7 and Visit 8)

The subject should be contacted by phone twice between clinic appointments at one month intervals to ensure she is following the instructions for use, is not experiencing any technical or medical problems while wearing the Eclipse Insert, and to remind her to complete the Treatment Diary at the required time.

2.7.8 Visit 8 – 12 Months (\pm 2 weeks) after Visit 4

Subjects are evaluated for the frequency of their FI episodes according to their two week Treatment Diary, and for safety of the Eclipse Insert.

The following tasks are completed at this visit:

- Two week Treatment Diary reviewed
- St. Mark's (Vaizey) Incontinence Severity Score calculated
- FIQOL questionnaire administered
- PGI-I questionnaire administered
- Patient Goal questionnaire administered
- Cost Utilization survey administered
- Device Satisfaction questionnaire administered
- Pelvic exam (speculum and digital rectal exam)
- AEs and Concomitant Medications reviewed

2.7.9 Unscheduled Visits

A subject may return to clinic at any point during the Screening Period or Treatment Period, if needed. During an Unscheduled Visit, the investigator may perform a standard medical interview and physical examination, including a pelvic examination or Insert re-sizing, if appropriate. All assessments, and any abnormal findings, including AEs and/or product malfunctions, will be documented in the appropriate case report forms.

2.8 Re-sizing during Treatment Period

If at any time during or after Visit 5 (the 3-month time point visit), an Insert no longer fits appropriately as assessed by a clinician during a pelvic exam, re-sizing of the Insert may be performed. The Insert may be re-sized at the treatment visit or at an Unscheduled Visit in between Treatment Visits per the following steps:

1. If changing to a different Sized Insert, use one or more of the Sizers to determine the next appropriate sized Trial Insert, and send the subject home with the Trial Insert. Complete a Fitting CRF, and order the corresponding Eclipse Insert from Pelvalon immediately so it arrives in time for the follow-up Fit Confirmation Visit. Complete either the Treatment Pelvic Exam CRF or an Unscheduled Visit CRF, as appropriate.
2. Schedule a follow up visit within 7 days (-5/+7 days) to confirm the Trial Insert fit is comfortable and stable by pelvic exam. The follow up visit should be scheduled as close to 7 days post-fitting as possible to allow the subject enough time to accommodate to the device. However, the subject should be seen earlier in the window (as soon as possible) if they are experiencing signs of an improper fit (discomfort or lack of effectiveness), an adverse event or any of the following:
 - Foul odor or excessive vaginal discharge
 - Any difficulty urinating or defecating
 - Significant bleeding not associated with menstruation
 - Unusual pelvic pain or discomfort
3. If successfully re-sized, dispose of the Trial Insert and dispense the same sized Eclipse Insert and instruct the subject to begin her next Treatment Diary as scheduled. The start of the Treatment Diary should be delayed, if necessary, so that it begins seven days or more after the newly sized Eclipse Insert is dispensed.
4. Steps 1-3 may be repeated as needed.

2.9 Study Exit

A Study Exit CRF will be completed for each subject who is consented in the trial. Participation in the study is considered complete if the subject completes all end-of-study assessments and questionnaires at the final 12 month time point.

A subject's participation may be discontinued early for any of the following reasons:

- Failure to meet screening eligibility criteria at any time after Visit 2
- Withdrawal of consent
- Adverse event preventing further study participation
- Investigator decision / determination that it is in the subject's best interest
- Termination of the study for any reason
- Lost to follow-up: requires documentation of at least 3 attempts to contact the subject by phone and/or email, and a certified letter (with request to return the investigational device)
- Subjects who become pregnant will be discontinued from the trial

For all subjects who were fit with the Eclipse System at Visit 2 and exit the study prior to or at Visit 4 (Treatment Eligibility Visit), AEs and ConMeds will be reviewed and a pelvic exam and the Device Satisfaction questionnaire will be administered, as per **Table 3**.

For subjects who exit the study after Visit 4 (Treatment Eligibility Visit) but before Visit 8 (12 Months) AEs and ConMeds will be reviewed, and a pelvic exam and all required questionnaires per **Table 3** will be administered.

To compensate for time spent during study visits, subjects may receive compensation as detailed in the final IRB-approved consent form and as agreed upon by the Sponsor and the Site per the Clinical Trial Agreement.

2.10 Questionnaires and Surveys

2.10.1 FI Episode Diary

Subjects will be provided a Diary (**Appendix 2**) to record each bowel movement, including the type of episode (normal bowel movement, staining, minor soiling or major soiling), whether the bowel movement was “urgent” (yes or no) and the stool description according to the Bristol Stool Score (ranging from 1 “separate hard lumps” to 7 “liquid consistency with no solid pieces”). The Baseline Diary is dispensed at Visit 1 (Baseline Visit), the Test Diary is dispensed at Visit 3 (Fit Confirmation Visit), and the Treatment Diary is dispensed at Visit 4 (Final Eligibility Visit), and at the 3 month and 9 month scheduled visits during the Treatment Period. The Test Diary and the Treatment Diary also ask if the subject is wearing the Insert at the time of each recorded episode.

Only minor or major soiling are counted towards the number of FI episodes in any two-week diary period, used in the study endpoint analyses (see **Section 3.2**).

2.10.2 St. Mark’s (Vaizey) Incontinence Severity Score

The St. Mark’s (Vaizey) Incontinence Severity Score is a measure of severity of FI symptoms, which has been shown to correlate with improvement in frequency of FI episodes and subjects’ perceptions of relief.^{23,24,25} This score reflects the severity of FI and ranges from 0 (complete continence) to 24 (complete incontinence). The survey will be administered verbally to subjects by site personnel at Visit 1 (Baseline Visit), and at 3, 6, 9 and 12 months during the Treatment Period.

2.10.3 Fecal Incontinence Quality of Life Questionnaire

The Fecal Incontinence Quality of Life (FIQOL) scale (**Appendix 3**) is a 41-item, validated questionnaire completed by the subject.²⁶ FIQOL has 4 subscales: lifestyle, coping/behavior, depression/self-perception and embarrassment. The FIQOL questionnaire will be completed by subjects at Visit 1 (Baseline Visit) and at 3, 6, 9 and 12 months during the Treatment Period.

2.10.4 PGI-I Questionnaire

The Patient Global Impression of Improvement (PGI-I) (**Appendix 4**) is a validated global index that may be used to rate the response of a condition to a therapy on a scale from 1 (Very much better) to 7 (Very much worse). It is a simple, direct, easy to use scale that is intuitively

²³ Vaisey, CJ, et al Gut 1999;44:77-80 doi:10.1136/gut.44.1.77

²⁴ Deutekom M, Terra MP, Dobben AC, Dijkgraaf MG, Felt-Bersma RJ, Stoker J, Bossuyt PM: Selecting an outcome measure for evaluating treatment in fecal incontinence. *Dis Colon Rectum* 2005, 48:2294-2301.

²⁵ Maeda Y. Does the St. Mark's incontinence score reflect patients' perceptions? A review of 390 patients. *Dis Colon Rectum*. 2008 Apr;51(4):436-42

²⁶ Rockwood et al. Fecal Incontinence Quality of Life Scale. *Dis Colon Rectum* 2000;43:9-16.

understandable to subjects and to clinicians. To date it has been most often used to assess the subjects' response to various treatments for urinary incontinence.²⁷ In this study we used the PGI-I questionnaire, replacing urinary incontinence with fecal incontinence, to assess the subject's response to treatment with the Eclipse System for fecal incontinence. The PGI-I questionnaire will be completed by subjects at 3, 6, 9 and 12 months during the Treatment Period.

2.10.5 Patient Goal Questionnaire

At the Visit 2 subjects will be asked to specify a single patient-centered goal describing what a successful improvement in FI symptoms would mean for them. For example, they may identify "confidence in attending social events" or "ability to exercise without incontinence." At the 3, 6, 9 and 12 month visits subjects will rank how well they were able to meet their goal while wearing the Eclipse Insert using a 7-point scale (**Appendix 5**) ranging from "I have met and exceeded my goal" (best case) to "I have moved further away from my goal" (worst case). The patient goal categories are based on results from a survey of women undergoing pelvic floor dysfunction surgery.²⁸

2.10.6 Device Satisfaction Questionnaire

Subjects who are fit at least once with the Trial or Eclipse Insert will be asked to complete a Device Satisfaction Questionnaire (**Appendix 6**). The questionnaire contains questions related to perceptions of device comfort, satisfaction with usage and features, and impact on daily activities.

Subjects who Screen Fail but have been fit at least once with the Insert will be asked to complete this questionnaire just prior to their study exit. Subjects who successfully enter the Treatment Period will be asked to complete this questionnaire at 3, 6, 9 and 12 months during the Treatment Period (or at study exit if they end their participation in the trial early).

2.10.7 Cost Utilization Survey

Subjects will be asked to complete a Cost Utilization survey (**Appendix 10**) in order to capture the direct medical and non-medical (out of pocket) and indirect non-medical costs related to treating FI in the three months prior to Visit 1 (Baseline Visit) and again at the 3 and 12 month time points. The data will be used to perform a cost analysis of the Eclipse System compared to alternative therapies.

3 Statistics

3.1 Study Design

This is a 1-year, multicenter, within-subject control, open-label, single-arm study to evaluate the durability of the safety and effectiveness of the Eclipse™ System after 3 and 12 months of use. All subjects will act as their own control. Subjects will be fitted, and refitted if necessary, with the Trial Insert during the Screening Period. Subjects who successfully complete the Screening Period will be considered as treatment-eligible and will be fitted with the Eclipse Insert and begin the 12 month Treatment Period. Subjects who do not successfully complete the Screening Period will be classified as screen fails and will not continue into the Treatment Period.

²⁷ Yalcin I, Bump R. Validation of two global impression questionnaires for incontinence. *Am J Obstet Gynecol* 2003;189:98-101.

²⁸ Kathie L. Hullfish, Viktor E. Bovbjerg, Jennifer Gibson, William D. Steers Patient-centered goals for pelvic floor dysfunction surgery: What is success, and is it achieved? *American Journal of Obstetrics and Gynecology, Volume 187, Issue 1, July 2002, Pages 88-92*

3.2 Derivations and Definitions

The **baseline period** is the period prior to the Initial Fitting Visit. Results from this period, using either the Baseline Diary or assessments conducted at Visit 1, will be the **baseline results**.

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

Percent change from baseline is calculated as $100 * (\text{change from baseline}) / (\text{baseline result})$.

An **FI episode** is defined as major soiling or minor soiling, but does not include staining alone, as recorded on Baseline Diary, Test Diary or Treatment Diaries, each defined as follows:

- **Staining:** Stain of stool on undergarment, pad, clothing, or skin (does not count as an FI episode).
- **Minor soiling:** Stool leakage that is more than staining, but did not require an immediate change of undergarment, pad, or clothing (e.g. a pebble sized piece of stool or teaspoon of liquid stool).
- **Major soiling:** An accident large enough to require an immediate change of undergarment, pad, or clothing (e.g. most of a bowel movement).

A bowel movement is defined as **urgent** if the subject checks: "I had to rush to the restroom immediately." Note: "Urgent" can be marked regardless of whether you made it to the toilet in time (for a normal bowel movement) or not (resulting in leakage)."

The following will be calculated for each diary period using the information entered in the FI Episode Diaries for each subject (Baseline Diary, Test Diary, and Treatment Diaries):

Average number of FI episodes per week: $7 * (\# \text{ episodes}) / (\# \text{ days of diary entry})$

Average number of FI days per week: $7 * (\# \text{ of days with } \geq 1 \text{ FI episode}) / (\# \text{ days of diary entry})$

Screen Failure: A subject who does not successfully complete the Screening Period. This could be due to failing any of the general inclusion/exclusion criteria such as age or FI frequency by baseline diary assessment, unsuccessful fitting (as determined before or at Visit 4), failure to record a minimum of 12 days of diary data after successful fitting (i.e. Test Diary), or failure to demonstrate a 50% or greater reduction in the average number of FI episodes in the Test Diary as compared to the Baseline Diary.

Treatment-eligible Subject (Enrolled): A subject who successfully completes the Screening Period and enters the Treatment period is considered enrolled. This is defined as a subject having a confirmed successful fitting (as determined at Visit 3), having recorded a minimum of 12 out of 14 consecutive days of diary data after a successful fitting (i.e. on their Test Diary), and having demonstrated at least a 50% reduction in the average number of FI episodes in the Test Diary at Visit 4 as compared to the Baseline Diary.

Treatment Responder: An enrolled subject who demonstrates at least a 50% reduction in the average number of FI episodes per week on her Treatment Diary compared to her Baseline Diary is a responder for that time period. An enrolled subject must also have at least 10 out of 14 consecutive days of recorded diary data on her Treatment Diary to be defined as a responder for that time period.

Treatment Non-Responder: An enrolled subject who does not demonstrate at least a 50% reduction in the average number of FI episodes per week on her Treatment Diary compared to her Baseline Diary, is a non-responder for that time period. An enrolled subject with less than 10 out of 14

consecutive days of recorded diary data on her Treatment Diary will also be classified as a non-responder for that time period.

3.3 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 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 will include all subjects in the ITT population who complete Visit 5 (Month 3 Visit), complete at least 10 out of 14 consecutive days of diary data at each time point in the study Treatment Period, and have no major protocol deviations.

3.4 Hypotheses

The null hypothesis is that the proportion of treatment responders at 3 months is no more than 40%, and the alternative hypothesis is that the proportion of treatment responders at 3 months is more than 40%:

$$H_0: \pi \leq 0.40$$

$$H_A: \pi > 0.40$$

3.5 Endpoints

The primary effectiveness endpoint is the proportion of treatment responders at the 3 month time point in the ITT population.

Secondary effectiveness endpoints are:

- The proportion of responders at the 3, 6 and 12 month time points in the PP population.
- The change from baseline in mean scores on subject-reported outcomes related to symptoms and quality of life as reported by St. Mark's (Vaizey) Incontinence Severity Score, and FIQOL at the 3, 6, 9 and 12 month time points
- PGI-I scores at the 3, 6, 9 and 12-month time points

The safety endpoint is the safety of the device, as assessed by the number of device-related (Eclipse System) adverse events and device –related serious adverse events, as adjudicated by the Clinical Events Committee (CEC).

Subjects who are screen failures will not be included in the effectiveness endpoint analysis. However, their data will be reviewed to understand reasons for screen failure. All subjects in whom the device was inserted, even if just for fitting, will be included in the safety analysis. For all screen fail subjects, the Investigator or designee will complete Case Report Forms related to the completed visits and a Study Exit Form.

3.6 Primary Effectiveness Analysis

The primary effectiveness analysis is an exact binomial test to evaluate whether the observed response rate is significantly larger than 40% after the first 3 months of the Treatment Period. The analysis will be performed on the ITT population. Subjects who do not complete at least 10 days of diary data at the 3-month time point and who do not continue in the study will be classified as treatment non-responders.

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.

3.7 Secondary Effectiveness Analyses

The primary effectiveness analysis will be repeated for the 3, 6 month and 12 month time points on the PP population.

Changes from baseline will be evaluated at the 3, 6, 9 and 12 month time points, for the following effectiveness measures, also on the PP population:

- St. Mark's (Vaizey) Incontinence Severity Score
- FIQOL questionnaire subscales

PGI-I scores at 3, 6, 9 and 12 months (assessment not done at Baseline)

3.8 Additional Analyses

The change from baseline in the average (mean) number of FI *episodes per week*, and percent change from baseline, will be evaluated at the 3, 6, and 12 month time points. Negative values represent a decrease in the number of episodes (i.e., improvement), while positive values represent an increase in the number of episodes.

The change from baseline in the average (mean) number of FI *days per week*, and percent change from baseline, will be evaluated at the 3, 6, and 12 month time points. Negative values represent a decrease in the number of days (i.e., improvement), while positive values represent an increase in the number of days.

A cost analysis comparing the Eclipse System to other available therapies will also be performed. This will be described in a separate Statistical Analysis Plan.

3.9 Subgroup Analyses

The primary and secondary analyses will be repeated on the subgroups of < 65 years of age and ≥ 65 years of age.

3.10 Safety Analyses

The number of overall adverse events will be summarized using the Medical Dictionary for Regulatory Activities (MedDRA) system organ class and preferred term and listings will be reviewed at regular intervals by the CEC. Device-related adverse events, and device-related serious adverse events occurring at each time point will be summarized. The CEC adjudicated AEs will be utilized in the safety endpoint analyses

3.11 Power and Sample Size Considerations

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 $\geq 90\%$ 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 quite high 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%.²⁹

4 Adverse Events

Investigators and the Sponsor will carefully track and report adverse events. Any subject who is exposed to the Eclipse System, including the Eclipse Insert, the Trial Insert or Sizers (has any Eclipse System device inserted into their vagina) will be included in the Safety Cohort and Safety Endpoint Analysis.

Adverse event definitions are provided in **Table 4**. Based on clinical experience to date the expectation is a very low risk of serious or unanticipated device-related adverse events.

Table 4. Adverse Event Categories

Term	Definition
Adverse event (AE)	Any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device. This definition includes events related to the study device and events related to any involved procedures.
Serious adverse event (SAE)	<p>Any AE that</p> <ul style="list-style-type: none"> • led to a death, • led to a serious deterioration in the health of the subject that: <ul style="list-style-type: none"> ○ resulted in a life-threatening illness or injury ○ resulted in a permanent impairment of a body structure or a body function ○ required hospitalization or prolongation of existing hospitalization* ○ resulted in medical or surgical intervention to prevent permanent impairment to body structure or function, or to prevent one of the other outcomes (e.g. bronchospasm requiring treatment in an emergency room ○ led to fetal distress, fetal death, a congenital abnormality, or birth defect <p>Note that a planned hospitalization for a pre-existing condition, or a procedure required by the clinical investigational plan, without a serious deterioration in health, is not considered to be an SAE. Note also that continuation of permanent disability (e.g. failure of the Eclipse Insert to improve FI) is not considered an SAE.</p>

²⁹ 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.

Term	Definition
Unanticipated adverse device effect (UADE)	Any serious adverse effect on health or safety or any life-threatening problem or death caused by, or associated with, a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the investigational plan or application (including a supplementary plan or application), or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects. ³⁰

* For purposes of defining a serious adverse event, hospitalization is defined as admission to the hospital for longer than 24 hours or prolongation of a hospital stay due to the adverse event.

4.1 Adverse Event Severity

The investigator will be asked to characterize the severity of each AE as mild, moderate or severe according to definitions provided in **Table 5**.

Table 5. Adverse Event Severities

Term	Definition
Mild	The AE is transient and easily tolerated by the subject.
Moderate	The AE causes the subject discomfort, interrupts the subject's usual activities and requires a visit to a healthcare practitioner.
Severe	The AE causes considerable interference with the subject's usual activities; may be incapacitating and may require hospitalization.

4.2 Adverse Event Association

The relationship of all AEs to the Eclipse System will be reported on the Case Report Forms by the site investigator according to the definitions provided in **Table 6**. Any devices associated with SAEs will be returned in order to facilitate product investigations. Devices associated with non-serious adverse events may also be returned, at the direction of the Sponsor, to assist with product investigations.

Table 6. Adverse Event Relationship to Device

Term	Definition
Definite	Adverse event whose timing is highly plausible for causality and which cannot be explained by other factors
Probable	Adverse event whose timing is reasonable for causality and is unlikely to be explained by other factors
Unlikely	Adverse event whose timing is unlikely for causality and which could be explained by other factors
Not related	Adverse event whose timing makes causality improbable and which could easily be explained by other factors
Unknown	Adverse event whose plausibility of timing cannot be judged or in which information regarding other factors does not exist

4.3 Adverse Event Reporting

Any AEs that occur after a subject has been fit with an Eclipse System device will be recorded on the AE case report form. Pre-existing medical conditions will not be reported as AEs unless there is an increase in severity or frequency of symptoms. All AEs should be followed until they are either resolved or considered by the clinician to be stable or until the subject exits the study and is no longer available for follow up. Relevant source documentation must be available to confirm the occurrence of an AE and must be provided to the Sponsor upon request.

³⁰ 21 CFR 812.3(s)

4.3.1 Adverse Event Coding

All adverse events will be monitored by the Sponsor on an ongoing basis, and checked against the MedDRA coding dictionary for consistency, which will be described in detail in the Data Management Plan.

4.3.2 Clinical Events Committee

A Clinical Events Committee (CEC), comprised of a Medical Monitor and a CEC Chair, will be responsible for the safety oversight of the Trial. The members will be licensed and board certified physicians with experience in female pelvic medicine and reconstructive surgery, including Urogynecology and Obstetrics and Gynecology. They will have experience treating female fecal incontinence and with the functional mechanism of the Eclipse System. Experience as a PI or Sub-Investigator in one or more previous multi-center FI trials is also a pre-requisite. However, they will not be affiliated with an enrolling site in the LIBERATE Trial. Additionally, the CEC members are required to declare any/all conflicts of interest to the Sponsor (as they arise) throughout the duration of the trial.

4.3.3 CEC Adjudication of AEs

The CEC Medical Monitor will review listings of all Sponsor-coded AEs at regular intervals to determine if any clarifications or coding changes are required, or if any additional information is needed in order to make a determination regarding the relationship of an AE to any of the Eclipse System devices. All device-related Serious AEs (SAEs) and Unanticipated Adverse Device Effects (UADEs) will be reviewed by the CEC Chair in a timely manner; all other AEs will be reviewed at monthly and quarterly meetings, as per the CEC Charter.

A summary of all AEs will be provided to the CEC Chair for approval prior to results being utilized in the safety endpoint analyses.

4.3.4 SAE Reporting

All serious adverse events (SAEs) must be reported to the Sponsor within 48 hours of becoming aware of the event, and to the governing IRB per their reporting requirements. The site must maintain detailed information, including copies of de-identified source documents pertaining to the event, on file and provide them to the Sponsor upon request for Medical Monitor review and Clinical Events Committee adjudication.

The Sponsor will review all AEs suspected of being an SAE per Table 4 and will ensure any necessary reporting of the event(s) to investigators and reviewing IRBs as necessary.

4.3.5 UADE Reporting

Unanticipated adverse device effects (UADEs) must be reported to the Sponsor within 48 hours after becoming aware of the event. The site must maintain detailed information, including copies of de-identified source documents pertaining to the event, on file and provide them to the Sponsor upon request for Medical Monitor review and Clinical Events Committee adjudication. In addition, UADEs should be reported to the governing IRB within the timelines required by the IRB.

The study Sponsor will immediately conduct an evaluation of any unanticipated adverse device effect (21 CFR 812.46(b)) and will ensure the necessary reporting of the event(s) to investigators and reviewing IRBs within 10 working days of the Sponsor first becoming aware of the event. If an investigation shows that an unanticipated adverse device effect presents an unreasonable risk to subjects, the Sponsor will terminate the investigation or parts of the investigation presenting that risk as soon as possible. Termination will occur no later than 5 working days after the Sponsor makes this determination and no later than 15 working days after the Sponsor first receives notice

of the effect (21 CFR 812.46(b)(2)). The Sponsor will only resume the investigation after obtaining IRB, and if necessary, FDA approval (21 CFR 812.150(c)).

5 Study Management

Pelvalon, Inc. is the Sponsor of this clinical investigational plan. The LIBERATE study is proposed by the Sponsor as a non-significant risk (NSR) study (see **Section 5.2.1**). Investigational device exemption (IDE) approval from US FDA is not required for an NSR study provided that the reviewing IRBs agree with the NSR designation. NSR studies follow the abbreviated requirements listed in 21 CFR 812.2³¹. These requirements are summarized in **Table 7** and described in more detail below.

Table 7. Abbreviated Requirements for NSR Device Investigations

Labeling per 21 CFR 812.5
IRB approval with NSR determination
Informed consent per 21 CFR 50
Study Monitoring per 21 CFR 812.46
Investigator Recordkeeping per 21 CFR 812.140 (a) (3) (i)
Sponsor Recordkeeping per 21 CFR 812.140(b) (4) and (5)
Investigator Reports required per 21 CFR 812.150 (a) (1), (2), (5), and (7)
Sponsor Reports required per 21 CFR 812.150(b)(1)-(3), (5)-(10)
Prohibition against promotion per 21 CFR 812.7

5.1 Investigational Device Labeling

As per 21 CFR 812.5, the study device packaging includes a label with all required elements, including the statement: “CAUTION – Investigational device. Limited by United States law to investigational use.” In addition, the IFU describes all relevant contraindications, hazards, adverse events, interfering substances, warnings, and/or precautions.

5.2 IRB Approval

Consistent with 21 CFR 56, this clinical protocol and a site-specific informed consent form will be submitted to the local or regional IRB and must be approved by each investigator’s IRB before the investigator may enroll subjects.

This study is proposed as a non-significant risk (NSR) clinical study with regulatory oversight managed by the IRBs of participating centers in the United States. Refer to the Sponsor’s Statement of Non-Significant Risk below in **Section 5.2.1**.

5.2.1 Sponsor Statement of Non-significant Risk

Requirements for NSR studies are described by the FDA in 21 CFR 812 and a corresponding guidance document.³² Devices are categorized as either “significant risk” or “non-significant risk.” A device is classified as non-significant risk if it does not meet the criteria of significant risk as defined below:

According to 21CFR§812.3(m) *Significant risk device* means an investigational device that:

³¹ <http://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/CFRSearch.cfm?CFRPart=812&showFR=1>

(1) Is intended as an implant and presents a potential for serious risk to the health, safety, or welfare of a subject;

(2) Is purported or represented to be for a use in supporting or sustaining human life and presents a potential for serious risk to the health, safety, or welfare of a subject;

(3) Is for a use of substantial importance in diagnosing, curing, mitigating, or treating disease, or otherwise preventing impairment of human health and presents a potential for serious risk to the health, safety, or welfare of a subject; or

(4) Otherwise presents a potential for serious risk to the health, safety, or welfare of a subject.

Pelvalon believes the Eclipse™ System does not meet any of the above criteria, and is therefore a non-significant risk device. Referencing 21CFR§812.3(m) above:

(1) The Eclipse System is not an implant. It can be rapidly removed by the wearer.

(2) The insert does not support or sustain human life.

(3) The insert, in this application, is not of substantial importance in diagnosing, curing, mitigating or treating disease. While it may be of substantial importance in preventing impairment of human health by treatment of fecal incontinence, based on clinical evidence from several prior studies, it does not present a potential for serious risk to the health, safety, or welfare of the subject.

(4) The study design does not introduce any procedures which are experimental. Vaginal inserts such as diaphragms and pessaries are commonly used for a range of gynecologic and female health conditions. Furthermore, the insert may be removed either by the patient or the physician at any time.

As with all prior Pelvalon studies, this study is proposed as a non-significant risk (NSR) clinical study. As detailed in **Section 1.6** “Prior Investigations”, previous studies of the Eclipse System were granted NSR status by all participating site IRBs. Also, FDA is aware of the NSR status of the prior studies and did not disagree with that designation. As a non-significant risk study, this study does not require submission and approval of an investigational device exemption (IDE) from FDA.

5.3 Informed Consent

Investigators will use a study-specific informed consent form which is consistent with regulatory requirements in 21 CFR 50, and will be approved by the governing IRB prior to use. The consent form template, found in **Appendix 1** should be used as a template for each participating site’s consent. The final consent form must be reviewed by the Sponsor prior to submission to the reviewing IRB, and a copy of the IRB approved version must be provided to the Sponsor prior to use in the study.

5.4 Monitoring

The study will be monitored per 21 CFR 812.46 according to the procedures outlined in **Section 5.8.4**.

5.5 Recordkeeping

The Sponsor will ensure that the Investigator maintains the following records including the minimum requirements in **Table 7** for 21 CFR 812.140(a)(3)(i):

- (3) Records of each subject's case history and exposure to the device. Case histories include the case report forms and supporting data including, for example, signed and dated consent forms and medical records including, for example, progress notes of the physician, the individual's hospital chart(s), and the nurses' notes. Such records shall include:
 - i. Documents evidencing informed consent and, for any use of a device by the investigator without informed consent, any written concurrence of a licensed physician and a brief description of the circumstances justifying the failure to obtain informed consent. The case history for each individual shall document that informed consent was obtained prior to participation in the study.

The Sponsor will maintain the following records as required per 812.140(b)(4) and (5):

- (4) The following records, consolidated in one location and available for FDA inspection and copying:
 - The name and intended use of the device and the objectives of the investigation.
 - A brief explanation of why the device is not a significant risk device.
 - The name and address of each investigator.
 - The name and address of each IRB that has reviewed the investigation.
 - A statement of the extent to which the good manufacturing practice regulation in 21 CFR Part 820 will be followed in manufacturing the device.
 - a. Any other information required by FDA.
- (5) Records concerning adverse device effects (whether anticipated or unanticipated) and complaints.

5.5.1 Record Retention

Investigators and Sponsor shall maintain study records for a period of 2 years after the latter of the following two dates: The date on which the investigation is terminated or completed, or the date that records are no longer required for purposes of supporting FDA marketing approval, or such longer period as required by applicable law.

5.6 Reports

The investigator will prepare and submit the following complete, accurate, and timely reports as required per 812.150(a)(1) (2) (5) and (7):

- (1) Unanticipated adverse device effects. An investigator shall submit to the sponsor and to the reviewing IRB a report of any unanticipated adverse device effect occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator first learns of the effect.
- (2) Withdrawal of IRB approval. An investigator shall report to the sponsor, within 5 working days, a withdrawal of approval by the reviewing IRB of the investigator's part of an investigation.
- (5) Informed consent. If an investigator uses a device without obtaining informed consent, the investigator shall report such use to the sponsor and the reviewing IRB within 5 working days after the use occurs.
- (7) Other. An investigator shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

The sponsor shall prepare and submit the following complete, accurate, and timely reports as required per 812.150(b)(1)-(3) and (5)-(10):

- (1) Unanticipated adverse device effects. A sponsor who conducts an evaluation of an unanticipated adverse device effect under 812.46(b) shall report the results of such evaluation to FDA and to all reviewing IRB's and participating investigators within 10 working days after the sponsor first receives notice of the effect. Thereafter the sponsor shall submit such additional reports concerning the effect as FDA requests.
- (2) Withdrawal of IRB approval. A sponsor shall notify FDA and all reviewing IRB's and participating investigators of any withdrawal of approval of an investigation or a part of an investigation by a reviewing IRB within 5 working days after receipt of the withdrawal of approval.
- (3) Withdrawal of FDA approval. A sponsor shall notify all reviewing IRB's and participating investigators of any withdrawal of FDA approval of the investigation, and shall do so within 5 working days after receipt of notice of the withdrawal of approval.
- (5) Progress reports. At regular intervals, and at least yearly, a sponsor shall submit progress reports to all reviewing IRB's.
- (6) Recall and device disposition. A sponsor shall notify FDA and all reviewing IRB's of any request that an investigator return, repair, or otherwise dispose of any units of a device. Such notice shall occur within 30 working days after the request is made and shall state why the request was made.
- (7) Final report. In the case of a device that is not a significant risk device, the sponsor shall submit a final report to all reviewing IRB's within 6 months after termination or completion.
- (8) Informed consent. A sponsor shall submit to FDA a copy of any report by an investigator under paragraph (a)(5) of this section of use of a device without obtaining informed consent, within 5 working days of receipt of notice of such use.
- (9) Significant risk device determinations. If an IRB determines that a device is a significant risk device, and the sponsor had proposed that the IRB consider the device not to be a significant risk device, the sponsor shall submit to FDA a report of the IRB's determination within 5 working days after the sponsor first learns of the IRB's determination.
- (10) Other. A sponsor shall, upon request by a reviewing IRB or FDA, provide accurate, complete, and current information about any aspect of the investigation.

5.7 Additional Investigator Responsibilities

The site Principal Investigator (PI) is responsible for the entire oversight and day-to-day conduct of the investigation and for ensuring that the investigation is conducted according to all signed agreements, the Clinical Investigational Plan, all applicable regulatory requirements and the principles embodied within the Declaration of Helsinki, and any conditions of approval imposed by the IRB. The site PI is also responsible for maintaining control of the investigational devices, and for protecting the rights, safety and welfare of subjects under the investigator's care and for obtaining informed consent in accordance with 21 CFR Part 50.

Additional responsibilities of the Investigator include, but are not limited to:

- Maintaining records of receipt, use or disposition of a device that relate to:
 - The type and quantity of the device, the dates of its receipt, and the lot number.
 - The names of all persons who received, used, or disposed of each device.
 - Why and how many units of the device are returned to the sponsor, or are otherwise disposed of.
- Maintaining subjects records of all relevant observations, including adverse device effects (whether anticipated or unanticipated), information and data on the condition of each subject upon entering, and during the course of, the investigation, including information about relevant previous medical history and the results of all diagnostic tests.
- Maintaining records of dates and reasons for each deviation from the protocol.
- Ensuring that IRB approval is obtained prior the participation of a subject in a clinical trial. Such participation includes obtaining written informed consent.

- Ensuring that the Investigational device is used only under the supervision of an appropriately trained and qualified clinician.
- Returning or disposing of the study supplies at the Sponsor's written request.
- Ensuring that all personnel assisting with the clinical trial are adequately informed and understand their trial-related duties and functions.

Each site should identify a study coordinator for this study. Working with, and under the authority of the site PI, the study coordinator assures that all study requirements are fulfilled, and is the contact person at the site for all aspects of study administration.

Each Investigator must allow direct access to source data/documents for trial related monitoring, audit, IRB review and FDA inspection, if needed. Also, the investigator must allow auditing of their clinical investigational procedure(s).

5.7.1 Device Storage and Accountability

The investigational Eclipse System components will be stored at room temperature at the Investigational Site in a secure location with access limited to study personnel. Any unused devices will be returned to the Sponsor at the completion of the investigational site's participation in the study. Sponsor may request used Trial Inserts (used during the screening period) to be returned to Pelvalon. All used Eclipse Inserts (used during the treatment period) must be returned to the Sponsor at the termination of a subject's participation. All used Inserts must be returned using biohazard packaging materials and labels supplied by the Sponsor, or disposed of at the site at the direction of the Sponsor. The Investigator must maintain records of the receipt and disposition of all devices. A record of the devices used by each subject should be maintained in the subject's record (CRF and source document).

5.7.2 Product Non-conformities and/or User Feedback

The site is responsible for returning used devices (considered bio-hazardous materials) or unused devices that are either non-conforming, related to a potential product malfunction, related to an SAE, or at the direction of the Sponsor, in order to facilitate any necessary product investigations. The Sponsor will provide written instructions for reporting of the non-conformity and/or user feedback, and all necessary materials, including biohazard labels, required for returning these devices to the Sponsor. The site is expected to cooperate with the Sponsor to gather all relevant information in any investigations initiated as a result of a non-conformity or user feedback report.

5.7.3 Investigator Records

Investigator record requirements are described above in **Sections 5.5 and 5.6**. In addition, the investigator will maintain original source documents from which study-related data are derived, which include, but are not limited to:

- Clinic progress notes recording subject's medical history and medications
- Medical records regarding AEs, including treatment and clinical outcome
- Records of non-study related assessments or interventions, such as results of diagnostic tests, and any hospitalizations
- Notes of phone calls and/or correspondence indicating investigational site's attempts to follow study subjects at the required follow-up visits until subject's participation in the study is complete or terminated
- Records relating to subject death (e.g., death certificate, autopsy report/terminal medical records)

5.8 Sponsor Responsibilities

Pelvalon, Inc. is the manufacturer of the Eclipse System and Sponsor of this study. The Sponsor's recordkeeping and reporting responsibilities per 21 CFR 812 are described in **Sections 5.5 and 5.6**. Additional responsibilities include site qualification, site initiation and training, interim monitoring, and close out of the study at participating sites.

5.8.1 Site Qualification

The Sponsor will review investigator qualifications for study participation by site visit or phone call, as needed to determine site suitability for the study. Sites will be evaluated to confirm adequate trained and experienced staff (in general clinical research procedures and the therapeutic area), including a designated study coordinator, and facilities to perform the study according to the requirements of the protocol, as well as an adequate subject population.

5.8.2 Site Initiation and Training

Prior to enrolling any subjects a site initiation visit will be conducted to confirm the site continues to be able to meet the requirements of the trial. All investigators, device fitters and study coordinators will undergo study-specific training prior to or during a Site Initiation Visit, to review the Investigator/site responsibilities and requirements for the study. These include but are not limited to:

- Device use training for clinicians who are fitting the device
- Instructions for Use (IFU)
- Subject Use and Care Instructions
- Clinical Investigational Plan (CIP)
- Regulatory files
- Consenting procedures, including the protection of subject confidentiality
- IRB reporting requirements
- Data entry procedures and guidelines, which may include training in use of an Electronic Data Capture (EDC) system
- Device accountability and storage procedures

Site personnel training will be documented and all study training records will be maintained by the Sponsor.

5.8.3 Site Authorization to Enroll

Sites will be notified in writing by the Sponsor when screening, recruitment and enrollment of subjects may begin. An Authorization to Enroll letter will be sent from the Sponsor to the PI and Study Coordinator once the following minimum requirements have been met:

- CV and medical license is on file for PI
- Clinical Investigational Plan (CIP) Signature Page, signed by the PI, is on file
- Signed Investigator Agreement is on file for PI
- The IRB approval of the investigational plan and informed consent form are on file
- Clinical Trial Agreement between the Site and the Sponsor is fully executed
- Site initiation and training visit is completed and the required training records are on file

Under no circumstances should a site begin recruiting subjects for the study without written authorization to do so from the IRB and the Sponsor.

5.8.4 Interim Monitoring

Periodic site monitoring visits will be performed during the study by a designated study monitor assigned by the sponsor. The purpose of routine monitoring visits is to confirm compliance to the protocol, continued site acceptability in terms personnel staffing and resources, to ensure compliance with the IRB requirements, such as the use of only approved versions of the informed consent form, and to ensure accurate and complete records are being maintained and that CRFs are completed in an accurate and timely manner.

The initial monitoring visit to a site will be scheduled soon after the first 2 to 5 subjects are enrolled in the study. The frequency of subsequent visits will be dependent upon the rate of enrollment and site performance on previous monitoring visits.

Monitoring of the study will be a continuous process conducted in accordance with 21 CFR 812.46 and applicable Sponsor procedures. Monitoring will be performed by qualified Sponsor clinical research personnel, or designees (contract CRAs). The monitors will follow the procedures described within the Monitoring Plan, briefly summarized below:

- Monitors will be qualified by training and experience and may be Sponsor representatives or contractors.
- Remote monitoring of electronic Case Report Forms will occur on an ongoing basis as part of the routine data review and data management activities. Queries will be issued, reviewed and resolved within the electronic data capture (EDC) system on an ongoing basis. Remote monitoring may also be done via review of faxed/scanned diaries, questionnaires, CRFs, and de-identified source documents.
- Onsite monitoring of source documentation, the regulatory binder and device accountability records will occur at regular intervals as subject enrollment and data volume dictates, according to the Monitoring Plan, but no less than once during the trial and again at the end of the trial.
- Monitors will ensure the appropriate reporting of protocol deviations, AEs, SAEs, and UADEs within the case report forms, to the Sponsor and to the governing IRB.
- Monitors will facilitate the requests for, and transmission of, de-identified source documents from the site to the Sponsor, as requested for Medical Monitor review and adjudication of Adverse Events or to support investigations of product non-conformance or complaints.
- If there are significant non-compliance issues at a site, including lack of adherence to the protocol or applicable regulatory requirements, the issues will be discussed with the Investigator and study coordinator and the site will be instructed on how to regain compliance.
- Noncompliance with the signed agreement, the investigational plan, or other applicable regulatory requirements, will be communicated by the monitor to the Sponsor's study management team, and will be documented in the monitoring report and the follow up letter. The monitor and the Sponsor's study management team will work with the site to secure compliance through corrective and preventive action (CAPA) planning and documentation, as necessary.
- In cases of serious or repeated nonconformance the Sponsor may either temporarily or permanently discontinue shipments of the investigational devices to the site, or temporarily or permanently put the site "on hold" for screening and enrolling new subjects. All subjects currently enrolled will continue to be followed as per the protocol until they can be appropriately exited from the study.
- The Sponsor will also ensure that investigators return any unused devices, unless this action would jeopardize the rights, safety, or welfare of a subject.

5.8.5 Site Close-out

At the completion of the last follow-up visit at each site a close-out visit will be performed. At the discretion of the Sponsor, the close out visit may be conducted remotely. The reasons for deciding to conduct a remote close out visit will be transmitted in writing to the applicable site(s) and may

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include low subject enrollment, or cases where all CRFs have been previously monitored. The purpose of the Close-out Visit is to:

- Reconcile all outstanding data queries
- Review the records retention requirements for the study as per **Section 5.5.1**
- Arrange for the return of all study materials to the Sponsor
- Review the final IRB requirements for the study

5.9 Protection of Confidentiality

At all times throughout the clinical investigation, confidentiality will be observed by all parties involved. All data will be secured against unauthorized access. Privacy and confidentiality of information about each subject will be preserved in study reports and in any publication. Each subject participating in this study will be assigned a unique identifier. All CRFs will be tracked, evaluated, and stored using only this unique identifier.

Each site Principal Investigator will maintain a confidential study subject list identifying all enrolled subjects. This list will contain the assigned study subject's unique identifier and name. The investigator bears responsibility for keeping this list confidential. This list will not be provided to the study Sponsor and is only to be used at the study center.

Monitors and auditors will have access to the study subject list and other personally identifying information of study subjects to ensure that data reported in the CRF corresponds to the person who signed the ICF and the information contained in the original source documents. Such personal identifying information may include, but is not limited to the subject's name, address, date of birth, gender, race and medical record number.

NOTE: The subject's name, medical record number or address will NOT be recorded in the monitor's visit report or the database; demographic data that may be recorded include date of birth, race, and gender.

Source documents copied for monitoring purposes by the Sponsor will be identified by using the assigned subject's unique identifier in order to protect subject confidentiality.

The data collected about each subject, and the results of this study, belong to the Sponsor and may be used for business purposes such as in publications, marketing materials, or regulatory submissions. An IRB-approved HIPAA authorization is required to be signed by each subject before their data can be used in the study and their medical records monitored.

5.10 Trial Registration

This trial will be registered on clinicaltrials.gov website. As this device is not yet cleared for commercialization, the publication of study results on the clinicaltrials.gov website will be delayed under the terms of US Public Law 110-85, Title VIII, Section 801.

5.11 Data Collection and Data Management

Study data will be collected using standardized case report forms that may be either paper-based or electronic. If electronic, the electronic data capture (EDC) system will be validated and verified as 21 CFR Part 11 compliant. Sites will be trained in completion of CRFs and the use of the EDC system prior to being issued access to the system.

The Sponsor is responsible for the design and user acceptance testing of the database, and for routine data review, monitoring (remotely and onsite), and query resolution.

5.12 Protocol Deviations

A protocol deviation is defined as any study action taken by study-associated personnel or subjects that is in conflict with the study protocol. All protocol deviations will be documented in the site files, and on the appropriate case report form(s).

The investigator should notify the Sponsor and the IRB immediately if any protocol deviation was necessary in order to protect the life or physical well-being of a subject in an emergency. All protocol deviations should be reported to the governing IRB according to the IRB's requirements.

5.13 Study Suspension or Early Termination

The study may be discontinued at the discretion of the Sponsor either at an individual site or at all sites for reasons including, but not limited to, the following:

- Occurrence of unexpected adverse events or unanticipated adverse device effects
- New scientific information that shows that the study is no longer valid or necessary
- Insufficient recruitment of subjects
- Persistent non-compliance with the protocol
- Persistent non-compliance with IRB or regulatory requirements
- **Business reasons**

If the study is discontinued or suspended prematurely, the Sponsor will promptly notify the following in writing of the termination or suspension and the reason(s) for it:

- All clinical investigator(s)/investigational center(s)
- All governing central IRBs

If the study is discontinued or suspended prematurely, the Investigator(s) will promptly notify the following in writing of the termination or suspension and the reason(s) for it:

- Their governing local IRBs
- The subjects and/or their primary care physicians if deemed necessary by the governing IRB or the Sponsor

5.14 Final Report

A final report will be completed, even if the study is prematurely terminated. At the conclusion of the trial, a multi-center abstract reporting study results may be prepared. The publication of results from any single center experience within the trial is not allowed until the aggregate study results have been published, unless there is written consent from the Sponsor.

6 Risk Analysis

It is anticipated that the risks and benefits of the Eclipse System are comparable to vaginal devices, such as pessaries, currently marketed for gynecologic care. Risks to the subject are minimized by use under the care and instruction of the investigator, regular study visits and because subjects may remove the device at any time as needed. Subjects may experience a change in bowel or urinary habits while using the device. Common side effects related to poor hygiene with the use of vaginal devices are malodorous odor, vaginal discharge and itching. Subjects will be advised to maintain proper hygiene, and on the use and care of the Eclipse System (**Appendix 9**).

Anticipated risks associated with the use of the Eclipse System, as seen in the previous clinical evaluations, include:

- Pelvic Cramping or Discomfort

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- Pelvic Pain
- Vaginal Erythema / Petechiae
- Vaginal Discharge
- Vaginal Abrasion
- Vaginal Bleeding
- Vaginal Spotting
- Vaginal Ecchymosis or Bruising
- Vaginal Irritation
- Yeast Infection (Candidiasis)
- Lower Urinary Tract Infection
- Urinary Incontinence
- Urinary Urgency / Frequency
- Difficulty with Urinary Voiding
- Difficulty with Stool Evacuation

Refer to the IFU (**Appendix 8**) for a list of warnings and precautions.

It is possible that any of these risks or discomforts may occur with greater frequency or severity than previously reported. It is also possible that there are risks that are unknown at this time. As detailed in the background section, previous clinical evaluations of the Eclipse System in over 200 subjects support the low-risk nature of the device and that the risk profile is similar to the risks anticipated with other vaginal devices.

7 Abbreviations

Abbreviation	Meaning
ABL	Accidental Bowel Leakage
AE	Adverse Event
CAPA	corrective and preventive action plan
CEC	Clinical Events Committee
CFR	Code of Federal Regulations
CIP	Clinical Investigational Plan
CRA	Clinical Research Associate
CRF	Case Report Form
EDC	Electronic Data Capture
e-stim	electric stimulation
FDA	Food and Drug Administration
FI	Fecal Incontinence
FIQOL	Fecal Incontinence Quality of Life
H ₀	null hypothesis
H _A	alternate hypothesis
IBD	Irritable Bowel Disease
IDE	Investigational Device Exemption
IFU	Instructions for Use
IRB	Institutional Review Board
ITT	Intent to Treat
MedDRA	Medical Dictionary for Regulatory Activities
mmHG	millimeters of Mercury
MMHQ	Modified Manchester Health Questionnaire
NSR	Non-significant Risk
PGI-I	Patient Global Impression of Improvement
PP	Per Protocol
PTNS	Percutaneous Tibial Nerve Stimulation
SAE	Serious Adverse Event
SNS	Sacral Nerve Stimulation
UADE	Unanticipated Adverse Device Effect
US	United States
UTI	Urinary Tract Infection
VBC	Vaginal Bowel Control

8 Revision Record

Section	Description of Change	Rev C – 10 Dec 2015	Rev D – 09 Feb 2017
Protocol Synopsis	Clarified that enrollment may be <i>up to</i> 150 subjects.	150 treatment-eligible subjects will be enrolled into the 12 month Treatment Period at up to 15 clinical sites in the United States	Up to 150 treatment-eligible subjects may be enrolled into the 12 month Treatment Period at up to 15 clinical sites in the United States
Table of Contents	Updated page numbers.	NA	NA
2.2 Target Population	Clarified that enrollment may be <i>up to</i> 150 subjects. Removed statement that half of subjects enrolled will be 65 or older.	It is anticipated that up to 625 subjects may need to be screened and consented to yield 150 subjects entering the Treatment Period for the effectiveness analysis. Safety will be evaluated based on all subjects who undergo fitting with the Eclipse System. Recruitment will be managed to ensure approximately one half of the subjects who enter the Treatment Period are age 65 and older.	It is anticipated that up to 625 subjects may need to be screened and consented to yield up to 150 subjects entering the Treatment Period for the effectiveness analysis. Safety will be evaluated based on all subjects who undergo fitting with the Eclipse System.
2.3 Recruitment	Clarified that enrollment may be stopped or paused at any time by the Sponsor. Revised individual site enrollment contribution levels from a number cap to a percent of total launched. Removed statement that enrollment may be restricted by sub-group.	Each site is expected to enroll a minimum of 10 and a maximum of 30 treatment-eligible subjects...Enrollment is competitive until overall enrollment target is reached, and recruitment may be restricted by sub- groups to ensure approximately one half of the subjects entering the Treatment Period are <65 years of age and one half are >65 years of age.	Each site is expected to contribute approximately 7-25% of the total treatment-eligible subjects...Enrollment is competitive until overall enrollment target is reached or study termination by the Sponsor.

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Section	Description of Change	Rev C – 10 Dec 2015	Rev D – 09 Feb 2017
3.6 Primary Effectiveness Analysis	Removed references to absolute enrollment numbers to reflect potential interim analyses.	The null hypothesis will be rejected if 72/150 of subjects exhibit treatment response at the 3 month time point.	The null hypothesis will be rejected if a sufficient percentage of subjects exhibit treatment response at the 3 month time point.
3.11 Power and Sample Size Considerations	Added in ranges based on revised enrollment and power estimates. Removed power estimates for non-primary endpoints.	<p>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 150 subjects in the ITT cohort, the study has >90% power to detect a response rate greater than 40%.</p> <p>Withdrawal from the study during the Screening Period is estimated to be quite high 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 625 subjects may be recruited into this study in order to achieve 150 subjects who successfully enter the Treatment Period.</p> <p>We estimate the subject dropout rate between the start of the Treatment Period and the 12 month visit to be 33%, yielding 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</p>	<p>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.</p> <p>Withdrawal from the study during the Screening Period is estimated to be quite high 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.</p> <p>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</p>

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Section	Description of Change	Rev C – 10 Dec 2015	Rev D – 09 Feb 2017
		36%. ³³ The study has a 90% power to detect a response rate greater than 40% at 12 months.	management of stress urinary incontinence the dropout rate over this same time period was approximately 36%.
NA	Minor clarifications and edits to spelling throughout Protocol.	NA	NA

9 Appendices

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Appendix 1 – Informed Consent Form Template
[Incorporated by reference behind this cover sheet]

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Appendix 2 – FI Episode Sample Diaries
[Incorporated by reference behind this cover sheet]

Appendix 3 – FIQOL Questionnaire
[Incorporated by reference behind this cover sheet]

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Appendix 4 – PGI-I Questionnaire
[Incorporated by reference behind this cover sheet]

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Appendix 5 – Patient Goal Questionnaire
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Appendix 6 - Device Satisfaction Questionnaire
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Appendix 7 – FI Information Brochure
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Appendix 8 – Eclipse System Instructions for Use
[Incorporated by reference behind this cover sheet]

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Appendix 9 – Eclipse System Use and Care Instructions for LIBERATE Study Subjects
[Incorporated by reference behind this cover sheet]

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Appendix 10 – Cost Utilization Survey
[Incorporated by reference behind this cover sheet]

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