# SUMMARY OF SAFETY AND EFFECTIVENESS DATA

## I. GENERAL INFORMATION

**Device Generic Name**: Dextranomer in stabilized sodium hyaluronate

**Device Trade Name:** Solesta®

**Applicant's Name and Address**: Oceana Therapeutics, Inc.
2035 Lincoln Highway, Suite 2150
Edison, NJ 08817

**Date of Panel Recommendation:** December 2, 2010

**Premarket Approval Application (PMA) Number:** P100014

**Date of FDA Notice of Approval:** May 27, 2011

**Expedited:** Not Applicable

The Solesta material was originally approved as Deflux under PMA (P000029) on September 24, 2001, and is indicated for the treatment of children with vesicoureteral reflux (VUR) grades II-IV. The SSED to support that indication is available on the CDRH website and is incorporated by reference here. The biocompatibility testing for the material was originally conducted for the Deflux PMA and was leveraged for Solesta. However, FDA had unique concerns about the use and durability of the product in a different patient population and area of the body, so additional animal studies were conducted as described in Section IX. In addition, manufacturing changes occurred following the Solesta study, and additional pre-clinical testing was conducted to address these changes.

## II. INDICATIONS FOR USE

Solesta is indicated for the treatment of fecal incontinence in patients 18 years and older who have failed conservative therapy (e.g., diet, fiber therapy, anti-motility medications).

## III. CONTRAINDICATIONS

Solesta is contraindicated in patients with any of the following conditions:

- Active inflammatory bowel disease
- Immunodeficiency disorders or ongoing immunosuppressive therapy
- Previous radiation treatment to the pelvic area.
- Significant mucosal or full thickness rectal prolapse
- Active anorectal conditions including: abscess, fissures, sepsis, bleeding, proctitis, or other infections

- Anorectal atresia, tumors, or malformation
- Rectocele
- Allergy to hyaluronic acid based products
- Rectal varices
- Presence of existing implant (other than Solesta) in anorectal region

## IV. WARNINGS AND PRECAUTIONS

The warnings and Precautions can be found in the Solesta® labeling.

## V. DEVICE DESCRIPTION

Solesta consists of dextranomer microspheres, 50 mg/mL, and stabilized sodium hyaluronate, 15 mg/mL, in phosphate buffered 0.9% sodium chloride solution.

Solesta is a sterile, viscous gel contained in a disposable 1 mL assembled glass syringe with a standard luer-lock fitting as shown in Figure 1. The syringe is equipped with a plunger stopper, a plunger rod and a finger grip. A transparent label with indicative volume markings, batch number and expiry date is fitted onto the syringe. The labeled syringe is packed in a pouch and terminally sterilized by moist heat. The final product consists of a carton containing four pouches with syringes, five sterile needles (Sterican®, 21G x 4 ¾ inches, 0.80 x 120 mm), patient record labels and a package insert. The product is for single use.

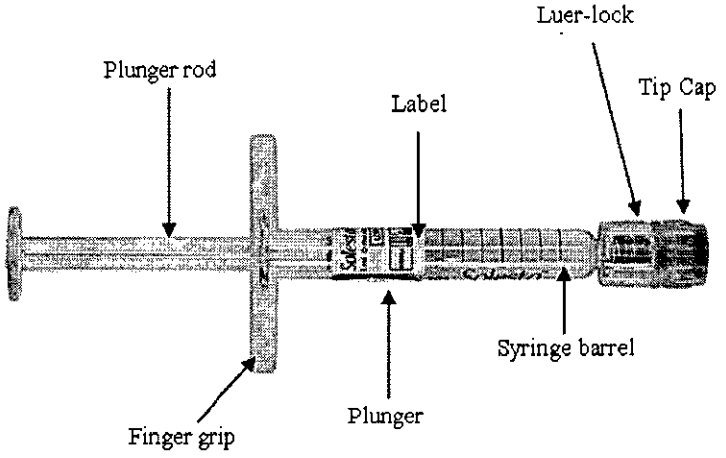


**Figure 1: Annotated photograph of Solesta® device**

Solesta has exactly the same composition as Deflux, which is indicated for treatment of children with vesicoureteral reflux (VUR) grades II-IV and was originally approved in September 2001 under PMA P000029.

### Shelf life and storage

The proposed shelf life of Solesta is 24 months when the device is stored up to 25°C (77°F), protected from sunlight and freezing. Stability data are available to support the shelf life.

**Needle used for injection of Solesta**

The needle used for injection of Solesta is Sterican 21G x 4 ¾ inches, 0.80 x 120 mm, a sterile needle for single use manufactured and CE marked by B. Braun, Germany. The same needle is cleared for marketing in the U.S. under 510(k) Number K072247.

**Complete Composition of Solesta**

The complete composition of Solesta is provided, see Table 1.

**Table 1: Composition of Solesta**

| Ingredients | Each mL contains |
|---|---|
| **Main Ingredients:** | |
| Dextranomer (DX) | 50 mg |
| Sodium hyaluronate, stabilized [a] | 15 mg |
| **Other Ingredients** [b] | |
| Sodium Chloride | 9 mg |
| $KH_2PO_4$ | 0.03 mg |
| $Na_2HPO_4 \times 2H_2O$ | 0.14 mg |
| Water for Injection (WFI) | Add up to 1 mL |

[a] Produced from Sodium Hyaluronate Pharma Grade and BDDE. The sodium hyaluronate is derived from bacterial fermentation.

[b] HCl and NaOH are used for pH adjustment.

**Properties of the Device**

Solesta is a biocompatible gel consisting of dextranomer microspheres and stabilized sodium hyaluronate. The diameter of the dextranomer microspheres is within 80 to 250 µm which minimizes the risk for distant migration. The stabilized sodium hyaluronate accounts for the viscous properties of Solesta and acts as a carrier to facilitate the injection of the dextranomer microspheres. The dextranomer microspheres facilitate in-growth of fibroblasts and collagen in-between the microspheres thereby stabilizing the volume of the implant for a sustained, durable bulking effect. In animal studies Solesta has been seen to be durable for at least 12 months and in clinical studies Solesta has been seen to be durable for at least 24 months.

**Principle of the Device Operation**

Solesta is a bulking agent which is to be injected submucosally in the proximal part of the high pressure zone of the anal canal. For each treatment, a series of 4 equally spaced injections with 1 mL of Solesta each is performed approximately 5 mm proximal to the dentate line. The aim is to expand the submucosal layer in the proximal anal canal and thereby improve bowel control. The

efficacy of Solesta in treatment of fecal incontinence has only been studied in patients with an intact or partially functioning anorectal sphincter.

## VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the correction of fecal incontinence: surgical reconstruction (when a sphincter defect is present), biofeedback, or implantation of an artificial neosphincter (when a sphincter defect is absent). Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

## VII. MARKETING HISTORY

Solesta was approved in the European Union in November 2006 and is marketed in the following countries: Austria, Denmark, Finland, Germany, Ireland, Italy, Norway, Spain, Sweden, Switzerland and United Kingdom. Solesta was approved in Canada in April 2007 and was subsequently launched there.

Solesta has not been withdrawn from any marketplace.

## VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Below is a list of the potential adverse effects (e.g., complications) associated with the use of the device.

Abdominal discomfort, abdominal distension, abdominal pain, lower abdominal pain, abdominal rigidity, alopecia, anal abscess, anal fissure, anal hemorrhage, anal prolapse, anal pruritus, anorectal discomfort, back pain, constipation, C-reactive protein increased, chills, cold sweat, defecation urgency, dermatitis, diarrhea, device dislocation, dizziness, dyspareunia, escherichia bacteremia, fecal incontinence, feces hard, fatigue, gastrointestinal motility disorder, gastrointestinal pain, genital discharge, genital prolapse, hematochezia, hematospermia, hemorrhoids, infection, injection site abscess, injection site discomfort, injection site hemorrhage, injection site hematoma, injection site inflammation, injection site irritation, injection site nodule, injection site pain, injection site pustule, injection site swelling, injection site ulcer, intestinal mass, malaise, mucosal inflammation, musculoskeletal pain, perineal abscess, nausea, edema, pain, painful defecation, pelvic mass, perineal pain, proctalgia, proctitis, pyrexia, rectal abscess, rectal discharge, rectal hemorrhage, rectal lesion, rectal obstruction, rectal prolapse, rectal spasm, rectal tenesmus, rectovaginal septum abscess, urinary retention, vaginal discharge, vulvovaginal pain.

For details on the specific adverse events that occurred in the clinical studies, please see Section X below.

## IX. SUMMARY OF PRECLINICAL STUDIES

### A. Laboratory Studies

Bench testing was conducted to characterize the Solesta gel. Although the product has previously been approved for another indication (P000029) as described above, manufacturing changes occurred following the Solesta clinical study, and additional testing was necessary to fully characterize the material and demonstrate that no inadvertant changes to the material characteristics occurred as a result of the manufacturing modifications. This testing is summarized in Table 2.

**Table 2: Bench Studies Conducted to Characterize the Material**

| Study Objectives | Test Articles | Summary of Methods and Relevant Findings |
|---|---|---|
| **Particle Size Distribution** | | |
| To demonstrate that the particle size of the material used in the clinical study is not appreciably different from that which is marketed under this PMA. | • 4 batches of material used in the study<br>• 5 batches of material to be marketed | • A particle distribution graph was constructed showing cumulative size (vol-%) vs. particle size (μm) for all batches.<br>• The data showed that the particle size distribution does not differ between the study material and the proposed material |
| **Osmolality of Medium** | | |
| To examine the risk of hypo- or hyper-osmotic properties of the material, as excessive edema or tissue dehydration could result in these states. | • 8 batches of material to be marketed | • Measurements of the aqueous diluent were performed using an osmometer.<br>• The results were in the range between 324 to 332 mOsm/kg. |
| **Swelling Property Experiments (Three Experiments)** | | |
| To characterize the swelling properties of the injectable material, and to demonstrate that the material exhibited the same characteristics before and after a manufacturing change. | • 12 batches of material used in the study<br>• 28 batches of material to be marketed | • Method validated by manufacturer and routinely used to assess the quality of manufactured batches.<br>• Exact weighing of 1.4g gel into a 10mL measuring cylinder<br>• Cylinder was filled with 0.9% NaCl solution and rotated end-over-end at least 5 times to let the gel pieces disperse and swell<br>• The cylinder was allowed to rest for at least 4 hours to let the gel sediment to the bottom<br>• The volume of the gel phase was read.<br>• The swelling factor (SwF) was calculated as: SwF= swelled gel volume (mL)/amount gel (g).<br><br>Results showed that the average SwF for the study material was 3.1 (95% LCL* 2.7, 95% UCL** 3.6) versus 3.1 (95% LCL 2.8, 95% UCL 3.4) for the marketed material. These differences are negligible. |

| Study Objectives | Test Articles | Summary of Methods and Relevant Findings |
|---|---|---|
| | • 2 samples of material used in the study<br>• 2 samples of material to be marketed<br>• 1 sample of each manufacturing timepoint | • Conducted using osmolalities of 278 and 313 mOsm/kg<br>• The gel pieces were allowed to soak for a period of seven (7) days<br>• After more than 2 days in the measuring cylinder, there is a slight decrease in SwF, but the difference is within the recording error of the method<br>• In general, no change in swelling behavior was seen between the high and low osmolality situations, and all samples behaved similarly |
| To characterize the swelling properties of the injectable material in a dynamic (unconstrained) environment, and to demonstrate that the material exhibited the same characteristics before and after a manufacturing change. | • 12 total samples<br>• 6 batches of study material<br>• 6 batches of marketed material<br>• 3 batches of each type will be tested at osmolalities of 275 and 310 mOsm/kg | • Assesses the swelling of the gel material in a temperature controlled, non-constrained, dynamic environment<br>• The gel pieces are kept together (in a bolus) during the swelling<br>• A dialysis tube with sample was immersed in the bottom of the dissolution vessel at time point zero and additional measurements performed at 10 min and at 7 hours, on the first day<br>• Thereafter, swelling of the sample was followed by weighing of the dialysis tube containing the sample once every day.<br>• The swelling factor (g/g) was calculated by subtracting the weight of the dialysis tube without gel (blank) and dividing by the Solesta gel weight applied at time point zero.<br>• The dynamic swelling factor (DSwF) (g/g) was plotted vs time in days.<br>• Results showed no significant differences in the swelling properties of different batches of the Solesta gel over a range of osmolality.<br>• The dynamic swelling properties are the same for batches manufactured before and after the change in tests performed at the two extremes of normal osmolalities. |

*LCL = lower 95% confidence limit, ** UCL = upper 95% confidence limit

These bench studies demonstrated that the manufacturing changes that were implemented after the study material was manufactured did not appreciably alter the material characteristics of the material that will be marketed under this PMA submission.

## B. Animal Studies

Thorough biocompatibility testing, as described in the next section, was completed on Deflux, which is applicable to this PMA. However, in order to fully characterize the biocompatibility of the Solesta gel, due to the different indication of Deflux, additional long-term implantation studies in the submucosal area of the rectal wall in dogs was conducted. The intent of this testing was to establish an initial sense of durability of the material out to 12 months in the target rectal area,

and to identify the type of tissue reaction that could be expected in humans that may result from differences in rectal tissue versus ureter/bladder tissue .

**Table 3: Summary of Implantation Studies in Canines**

| Study Objectives | Study Design | Summary of Methods and Relevant Findings |
|---|---|---|
| **Preliminary Canine Study to Determine Durability and Tissue Response** | | |
| Evaluate the durability and tissue response to Solesta after implantation in the submucosal layer of the rectum of the dog | • 10 animals, all received Solesta<br>• 4 sites per dog<br>• 2 mL injected per site<br>• Follow up at 3, 6 and 12 months | • The injections inadvertently penetrated the serosa, most likely through the rectum into the peritoneal space.<br>• Most of the material was not found in the submucosa or anywhere else, but in 4 of 40 dogs it was found between the outer muscle and the serosa.<br>• Some changes in the lungs and liver were found such as swelling and vacuolation of hepatocytes and intracellular cholestasis, but the changes did not appear to be a result of the injected material.<br>• This "failed study" demonstrated the consequences of inadvertently injecting the material completely through the rectal wall, as detailed in the bullets above, since most of the injections penetrated the dog rectal wall due to anatomical differences between dogs and humans.<br>• The injection technique was refined in a second study (not detailed here) prior to the start of the main animal study. |
| **GLP Canine Study Evaluating Durability and Tissue Response to Solesta** | | |
| Evaluate the durability and tissue response to Solesta after implantation in the submucosal layer of the rectum of the dog | • 25 animals (17 animals product, 8 animals control saline)<br>• 2 sites per dog<br>• 2mL injected per site<br>• Follow-up at 3, 6, and 12 months | • Injected into perirectal submucosal layer.<br>• Gross pathology and histopathology examinations were performed to determine whether the implant was retained.<br>• The 3 month evaluation recovered 8/10 treatment injection sites, while none of the control sites were macroscopically visible at termination.<br>• At 6 months, 9/10 sites were recovered.<br>• At 12 months, 7/14 injection sites were macroscopically visible, while 11/14 sites had presence of the gel that were recovered. None of the control sites were macroscopically visible.<br>• Partial reflux *of the gel from the injection site* was sometimes observed just after injection and also may have occurred several hours afterwards which could explain the lack of recovery of some sites at necropsy.<br>• The sites showed inflammation that lessened over the 12 months with development of a fibrous capsule with activated macrophages. This appeared to be a normal response.<br>• Random checking of the lungs, lymph nodes, and liver revealed no significant changes in the final study. Laboratory values for phosphokinase (CPK) were occasionally elevated, but there did not appear to be a particular trend or significance.<br>• All animals showed presence of the gel in at least one injection site. All test articles showed evidence of a slight inflammatory reaction, an expected foreign body response. |

## C. Additional Studies

### Biocompatibility

Biocompatibility testing was conducted on Deflux, and is applicable to the evaluation of Solesta. According to the ISO 10993-1, *Biological evaluation of medical devices*, Solesta is categorized as an implant device in contact with tissue / bone where contact duration is more than 30 days. In order to evaluate the biological safety of the product, a biocompatibility program has been defined and performed as summarized in Table 4, below.

**Table 4: Summary of biocompatibility testing for Solesta**

| Title of Study | Results |
|---|---|
| 13-week toxicity study in Sprague-Dawley rats following intraperitoneal injection | Non-toxic |
| 26-week toxicity study in Fisher 344 rats following intraperitoneal injection | Non-toxic |
| In vitro cytotoxicity test (USP<87>ISO 10993-5)<br>Direct contact test | Non-toxic |
| Cytotoxicity study using the colony assay-extraction method | Non-toxic |
| Ames test | Not genotoxic |
| Mouse lymphoma assay | Not genotoxic |
| Mouse micronucleus test | Not genotoxic |
| Mouse peripheral blood micronucleus study, solution | Not genotoxic |
| In vitro mammalian chromosomal aberration test performed with human lymphocytes | Not genotoxic |
| ISO maximization sensitization study, solution | Not sensitizing |
| ISO modified intracutaneous study, solution | Score 1.6 |
| ISO modified intracutaneous study with measurements and histopathology | Score 1.3 |
| ISO muscle implantation study 4-week | Slight irritant |
| ISO muscle implantation study 26-week | Slight irritant |
| ISO muscle implantation study 52-week | Non-irritant |

**Sterilization and Shelf Life**
Solesta is provided sterile and is labeled for single use. The gel is filled in a sterile, siliconized, 1 mL glass syringe with a standard luer lock adaptor fitted with a tip cap and a plunger stopper to maintain sterility. The syringe is sealed in a pouch and sterilized using moist heat sterilization with a sterility assurance level of $10^{-6}$.

Stability studies were conducted to validate the packaging and storage conditions. The device will be labeled as follows: a shelf life of 24 months, and storage at a temperature of up to 25°C, protected from sunlight and freezing.

Monitoring of bacterial endotoxins will be conducted, and the bioburden of each batch of product is tested. The test specification for the endotoxin testing is 0.5 EU/mL and the limit for bioburden is <100 CFU/syringe content. Two (2) validation reports were provided, using the LAL gel-clot method. The exterior of the filled syringes is also monitored through testing four (4) times per year, with an alert limit of 5000 CFU/syringe. This testing helps detect possible changes in bioburden over time.

## X. SUMMARY OF PRIMARY CLINICAL STUDY

The applicant performed a clinical study to establish a reasonable assurance of safety and effectiveness of Solesta for the treatment of fecal incontinence in adult patients who have failed conservative therapy (e.g., diet, fiber therapy, anti-motility medications). The study was conducted in the United States (US), the United Kingdom (UK), Sweden, and Germany under IDE # G050099. Data from this clinical study were the basis for the PMA approval decision. Clinical data from an additional outside United States (OUS) Open Label study and a single center proof-of-concept study were used as support and are further discussed in Section XI. A summary of the clinical study is presented below.

### A. Study Design

Patients were randomized into the study between September 7, 2006, and September 12, 2008. The database for this PMA included 206 patients and reflected 12 months efficacy data collected through December 3, 2009, and additional 18 months safety data collected through August 31, 2010. There were 13 investigational sites.

The study was a prospective, randomized, subject/evaluator blinded, sham-controlled study performed within a clinical setting in 13 sites across the US (8 sites), the UK (1 site), Germany (1 site), and Sweden (3 sites). The study was conducted in two (2) phases.

The first phase was a double-blind (evaluating investigator and patient), 2:1 randomized, parallel-group study comparing efficacy and safety of Solesta with Sham. The 206 enrolled patients were randomized to Solesta or Sham (needle stick with empty syringes, i.e., nothing injected) with 136 (66%) patients receiving treatment with Solesta and 70 (34%) patients receiving Sham treatment. Randomization was stratified by region (US or Europe) and gender. The evaluating investigator, patient, and study Sponsor personnel were blinded to study

treatment allocation until the data from the blinded phase had been cleaned and the database had been locked for each patient.

The second phase was an open-phase extending up to 12 months after randomization for the primary analysis and extending up to 36 months in total for collection of longer term safety and efficacy data. Eligible Sham-treated patients were offered an open-label injection of Solesta which was administered in connection with the 6-month study visit. These patients were followed for 24 months from the last open-label Solesta treatment received (i.e., in total 30 months from last Sham treatment in the blinded phase). Patients randomized to Sham who refused treatment with open-label Solesta were followed for another 6 months (i.e., in total 12 months from last Sham treatment in the blinded phase). Patients randomized to Solesta were followed for a total of 36 months from the last treatment received in the blinded phase of the study. Thus, the study extends to a total of 12-36 months after randomization depending on treatment arm and eligibility for open-label Solesta treatment.

The data included in the PMA comprise safety and efficacy data through the 6- and 12-month primary time points in the study and additional safety data from the extended open phase of the study through month 18 from randomization.

Patients were randomized according to a centralized system, stratified by region (US and Europe) and gender with one (1) randomization list for each gender per region, balanced within blocks of consecutive patients using a fixed block size of six (6). The evaluating investigator was different from the investigator administering treatments. Patients were unable to see the procedure.

The efficacy analyses were divided into two (2) parts; one (1) that described the blinded phase using formal comparisons of the two (2) treatment groups, and the other is the open phase where longer term data was presented over time for the Solesta treatment group. The two (2) treatment groups were not comparable in the open phase because the patients were unblinded at the 6-month follow-up visit and patients randomized to Sham treatment were offered Solesta treatment.

**Hypothesis**

The primary objective was evaluated in three (3) parts. The first two (2) parts of the primary objective were evaluated using a logistic regression model with treatment, center, gender, and baseline number of fecal incontinence episodes as covariates. The first part involved testing a null hypothesis of equal proportions $Responder_{50}$ in both treatment groups, or equivalently an odds ratio of 1, and was to be rejected if the two-sided p-value of the test was smaller than or equal to 0.05.

The null hypothesis of the second part was that the $Responder_{50}$ rate in the Solesta treatment group was equal to 35% and was to be rejected if the two-sided 95% confidence interval of $Responder_{50}$ was entirely above 35%. The third part was evaluated using a two-sided 95% confidence interval of $Responder_{25}$ at 12 months in the Solesta treatment group based on the normal approximation to the binomial distribution. The null hypothesis of proportion

$Responder_{25}$ being equal to 50% was to be rejected if the confidence interval was entirely above 50%.

**Blinded phase**

The pre-specified analyses methods for dichotomous variables, such as responder variables, were a logistic regression model whereas for continuous variables an ANCOVA model was used. Both models used treatment, center, gender, and the baseline value of the analyzed variable as covariates to adjust for baseline differences that exist between the two (2) treatment groups. The results also include the outcome from supportive analyses that focused on observed values.

**Open phase**

All continuous variables were presented using descriptive statistics by treatment for each visit. Absolute change and percentage change from baseline was presented descriptively by treatment and visit together with a p-value of a test of zero change from baseline. Continuous variables without an upper bound on outcome values (all variables concerning collection of number of incontinence episodes) were analyzed using a Wilcoxon signed-rank test (change from baseline). Continuous variables with a limit on minimum and maximum outcome (e.g., CCFIS, FIQL, number of incontinence-free days) were analyzed using a one-sample t-test (change from baseline). The categorical proportion responder variables were presented by visit with two-sided 95% confidence intervals based on the normal approximation to the binomial distribution.

**Handling of missing data**

The primary efficacy analysis was calculated for the intent-to-treat (ITT) population which comprised all 206 patients that were randomized into the study. Imputation of missing data was done using last observation carried forward (LOCF) and the Primary Imputation Model (PIM). In essence PIM is a mixture of LOCF and baseline carried forward and imputed all withdrawals as non-responders. PIM was the pre-specified primary imputation model for the primary objective while LOCF was the primary model for all other analyses.

**Sample size calculation**

A statistical sample size calculation provided that 200 patients with a 2:1 randomization to Solesta *vs.* Sham would lead to a reasonably high probability of success in all three (3) success criteria for the primary objective as described above (80-90% power), and also expand the safety database for Solesta treatment. The patient randomization was stratified by region (Europe and US) and gender.

1. Clinical Inclusion and Exclusion Criteria

Enrollment in the pivotal IDE study was limited to patients who met the following inclusion criteria:

- 18-75 years of age
- a history of fecal incontinence for at least 12 months

- a CCFIS at baseline of ≥ 10
- ≥ 4 fecal incontinence episodes over a 14 day period (no upper limit to number of FI episodes was defined)
- failed prior conservative therapy (e.g., diet, fiber therapy, anti-diarrheal medications)

Patients were not permitted to enroll in the study if they met any of the following exclusion criteria:

- flatus incontinence only
- complete external sphincter disruption at all levels of the anal canal
- significant mucosal prolapse or transanal mucosal problems
- active anorectal sepsis or proctitis
- current anorectal tumors or anal fissures
- grade IV hemorrhoids
- rectal anastomosis < 12 cm from anal verge
- anorectal stenosis or malformation
- full thickness rectal prolapse
- significant chronic anorectal or pelvic pain.
- Active Inflammatory Bowel Disease (IBD)
- history of HIV or other condition with severe compromised immune defense
- malignancies in remission for less than 2 years prior to the study (basal cell carcinoma was an exception)
- ongoing immunosuppressive therapy
- chemotherapy within 12 months
- pelvic radiotherapy
- bleeding diathesis or ongoing anticoagulant therapy.
- anorectal surgery (including sphincteroplasty and/or Secca procedure) within 12 months
- hemorrhoid treatment with rubber band within 3 months (injection or infrared coagulation permitted)
- anorectal implants and previous injection therapy
- stapled transanal rectal resection (STARR) or stapled hemorrhoidectomy
- female patients who were pregnant, breast-feeding or without adequate contraception within the first year, or within one year post partum

2. Follow-up Schedule

**Follow-up schedule and evaluations: blinded phase**

As shown below in Table 5, the assessment schedule for the blinded phase of the study consisted of a screening visit (Visit 1), a treatment visit during which the patients were randomized to Solesta or Sham (Visit 2), and clinic visits at 1, 3 and 6 months post-injection to conduct efficacy and safety assessments (Visits 3–5). Patients with persistent symptoms 1 month after initial treatment were re-treated at Visit 2Re after which the 1 month visit was repeated (Visit 3Re).

Patients were screened for baseline data and eligibility at the screening visit (Visit 1) which occurred 2-4 weeks before treatment (Visit 2). Patient eligibility, including number of fecal

incontinence episodes from the patient diary and CCFIS score, was confirmed prior to the first treatment procedure at Visit 2.

It should be noted that "last treatment" refers to the re-treatment if a second treatment has been performed, or the only treatment provided if no re-treatment has been performed.

**Table 5: Treatment schedule during blinded phase**

| Blinded phase - all patients | Visit 1 | Visit 2 / Visit 2Re | Visit 3 / Visit 3Re | Visit 4 | Visit 5 (blind) |
|---|---|---|---|---|---|
| | Baseline/ Screening | Blinded treatment | 1 month | 3 months | 6 months |
| Demography, medical history, physical examination (including endoanal ultrasound) | X | | | | |
| Patient eligibility | X | X | | | |
| CCFIS | X | | X[2)] | X | X |
| Patient diary collection | | X[1)] | | X | X |
| Solesta/Sham treatment | | X | | | |
| FIQL | X | | | | X |
| Rigid proctoscopy / flexible sigmoidoscopy | X | | X | X | X |

1) Baseline diary to confirm eligibility
2) Only performed after 1st treatment to confirm CCFIS ≥ 10 (eligibility criterion for a re-treatment)

**Follow-up schedule and evaluations: Open phase Solesta patients**

As shown in Table 6, the open phase for patients randomized to Solesta comprised clinic visits at 9, 12, 18, 24, 30 and 36 months (Visit 6 to 11) after last treatment in the blinded phase to conduct efficacy and safety assessments. Efficacy data through 12 months and safety data through 18 months have been collected and are summarized in the sections below.

**Table 6: Follow-up schedule for open-phase Solesta patients**

| Open phase – Solesta patients | Visit 6 | Visit 7 | Visit 8 | Visit 9 | Visit 10 | Visit 11 |
|---|---|---|---|---|---|---|
| | 9 months | 12 months | 18 months | 24 months | 30 months | 36 months |
| CCFIS | X | X | X | X | X | X |
| Patient diary collection | X | X | X | X | X | X |
| FIQL | | X | | X | | X |
| Proctoscopy / sigmoidoscopy | X | X | X | X | X | X |

**Follow-up schedule and evaluations: Open phase Sham patients**

As shown in Table 7, eligible patients randomized to Sham and who elected to receive treatment were injected with Solesta following completion of the blinded evaluations at visit 5. Clinic visits were thereafter conducted at up to 24 months post-injection to conduct efficacy and safety assessments (Visits 6 to 11). Eligible patients (CCFIS≥10) with persistent FI symptoms 1 month after the first open-label treatment (Visit 6), were offered a re-treatment with Solesta (Visit 5Re) after which a 1-month follow-up visit was repeated (Visit 6Re).

**Table 7: Follow-up schedule for open phase Sham patients**

| **Open phase - Sham patients with open-label Solesta** | **Visit 5 / Visit 5Re** | **Visit 6 / Visit 6Re** | **Visit 7** | **Visit 8** | **Visit 9** | **Visit 10** | **Visit 11** |
|---|---|---|---|---|---|---|---|
| | **Open-label treatment** | **1 month** | **3 months** | **6 months** | **12 months** | **18 months** | **24 months** |
| Solesta treatment | X | | | | | | |
| CCFIS | | X[1)] | X | X | X | X | X |
| Patient diary collection | | | | X | X | | X |
| FIQL | | | | X | X | | X |
| Proctoscopy / sigmoidoscopy | | X | X | X | X | X | X |
| 1) Only performed after 1st treatment to confirm CCFIS ≥ 10 (eligibility criterion for a re-treatment) | | | | | | | |

3. Clinical Endpoints

With regards to safety, each patient was questioned about adverse events (AEs) during the study. The information could also be obtained from signs and symptoms detected during study examinations, observed by the study personnel, or spontaneous reports from the patients. Proctoscopy examinations were performed at each follow-up visit to visually identify any constrictions of the anal canal, alterations or damage to the mucosa and/or inflammation; any observed abnormalities were reported as adverse events. Adverse event reporting started at the randomization visit and was continued until the last scheduled visit in the study through 36 months. For this summary, complete data is available through 18 months. Adverse events were reported for all patients, independent of treatment assignment. All reported AEs were assessed for causality and seriousness by the study investigators. There was no hypothesis driven safety endpoint.

With regards to effectiveness, the primary objective of the study was comprised of three (3) parts which aimed to determine: 1) whether Solesta was superior to Sham treatment in patients with fecal incontinence, 2) to demonstrate a minimum level of effectiveness for Solesta, and 3) to determine the durability of the treatment response in the Solesta treatment group at 12 months. The primary endpoints were proportion responders in both treatment groups, based on change in

number of fecal incontinence episodes from baseline, measured at 6 months, and the proportion responders in the Solesta treatment group at 12 months.

The number of fecal incontinence episodes was collected from a patient incontinence diary spanning a period of 14 days prior to each of these study visits. Response to treatment at 6 months was defined as a $\geq$ 50% reduction in the number of fecal incontinence episodes compared to baseline ($Responder_{50}$). Response to treatment at 12 months was defined as a $\geq$ 25% reduction in the number of fecal incontinence episodes compared to baseline ($Responder_{25}$).

Secondary endpoints for the 6-month blinded phase included: fecal incontinence free days, change in number of fecal incontinence episodes between treatment groups, change in the composite scale Cleveland Clinic Florida Incontinence Score (CCFIS), and change in patients' quality of life based on the disease-specific Fecal Incontinence Quality of Life scale (FIQL).

The study was not powered to attain statistical significance when comparing the change from baseline in any secondary endpoint between the treatment groups. These secondary endpoints were intended only as supportive to the primary endpoints.

Secondary endpoints for the subsequent open phase included: fecal incontinence free days, change in number of fecal incontinence episodes, CCFIS score, and FIQL. These secondary endpoints were measured at each clinical study visit and will continue to be monitored through 36 months. The secondary endpoints were selected to lend longer term support and consistency to the study results.

With regards to success/failure criteria, all three (3) parts of the pre-specified primary objective had to be fulfilled to claim study success. The pre-specified success criteria were as follows:

1. statistical superiority of Solesta in $Responder_{50}$ rate (at least 50% reduction in number of incontinence episodes from baseline) compared to Sham at 6 months,

2. the lower limit of the two-sided 95% confidence interval for $Responder_{50}$ rate in the Solesta treatment group at 6 months is larger than 35%, and

3. the lower limit of the two-sided 95% confidence interval for $Responder_{25}$ rate (at least 25% reduction in number of incontinence episodes from baseline) in the Solesta treatment group at 12 months is larger than 50%.

### B. Accountability of PMA Cohort

At the time of database lock, there were 278 patients screened and of these, 206 were randomized into the PMA study – 107 (52%) US patients and 99 (48%) European patients. Of the 206 randomized patients, 92% (189 patients) are available for analysis at the completion of the study, the 12 month post-treatment visit. In addition, 90% (186 patients) of the 206 enrolled patients have contributed with safety data through the 18-month time point in the study (i.e., 12 months following open-label Solesta treatment for patients randomized to Sham).

The flowchart in Figure 2 delineates patient disposition, including number of patients completing the blinded phase and the 12-month time point in the open phase of the study, respectively.

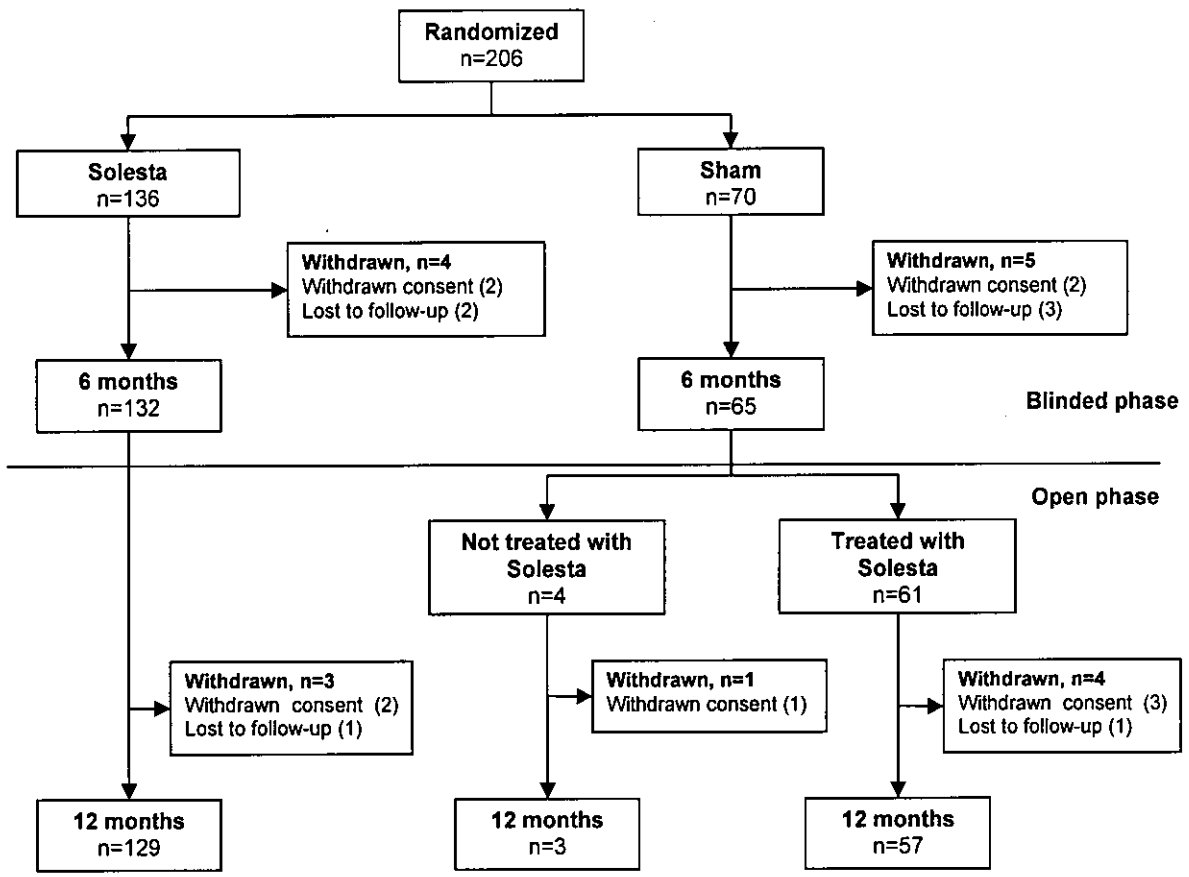


**Figure 2: Disposition of patients**

## C. Study Population Demographics and Baseline Parameters

The demographics of the study population are typical for a fecal incontinence study performed in the US. The gender and ethnicity distribution of the study population is a reflection of the patient population who actively sought medical care for treatment of refractory fecal incontinence at the selected study clinics. The pivotal study demographics and baseline demographics are shown in Tables 8 and 9, respectively.

**Table 8: Pivotal study patient demographics**

| Patient demographics | | Solesta (n=136) | Sham (n=70) | All (n=206) |
|---|---|---|---|---|
| Female | n (%) | 122 (89.7) | 61 (87.1) | 183 (88.8) |
| Male | n (%) | 14 (10.3) | 9 (12.9) | 23 (11.2) |
| Age, years | Mean (range) | 60.6 (32.8–76.0) | 59.2 (29.4–75.9) | 60.1 (29.4–76.0) |

| Patient demographics | | Solesta (n=136) | Sham (n=70) | All (n=206) |
|---|---|---|---|---|
| Body Mass Index, kg/m$^2$ | Mean (range) | 27.0 (17.2–44.8) | 27.2 (17.4–42.3) | 27.1 (17.2–44.8) |
| Caucasian | n (%) | 122 (89.7) | 59 (84.3) | 181 (87.9) |
| African-American | n (%) | 6 (4.4) | 4 (5.7) | 10 (4.9) |
| Hispanic/Latino | n (%) | 3 (2.2) | 4 (5.7) | 7 (3.4) |
| Asian | n (%) | 4 (2.9) | 2 (2.9) | 6 (2.9) |
| Other ethnic origin | n (%) | 1* (0.7) | 1† (1.4) | 2 (1.0) |
| Duration of symptoms (12 mo–5 y) | n (%) | 65 (47.8) | 35 (50.0) | 100 (48.5) |
| Duration of symptoms over 5 years | n (%) | 71 (52.2) | 35 (50.7) | 106 (51.7) |
| Obstetric cause | n (%) | 56 (41.2) | 26 (37.1) | 82 (39.8) |
| Neurogenic cause | n (%) | 27 (19.9) | 16 (22.9) | 43 (20.9) |
| Iatrogenic cause | n (%) | 30 (22.1) | 16 (22.9) | 46 (22.3) |
| Other cause (mostly idiopathic) | n (%) | 23 (16.9) | 12 (17.1) | 35 (17.0) |
| Previous anti-diarrheal drug therapy | n (%) | 82 (60.3) | 48 (68.6) | 130 (63.1) |
| Bio-feedback / Sphincter exercise | n (%) | 82 (60.3) | 35 (50.0) | 117 (56.8) |
| Previous other non-surgical therapy‡ | n (%) | 129 (94.9) | 65 (92.9) | 194 (94.2) |
| Previous surgery for FI | n (%) | 21 (15.4) | 8 (11.4) | 29 (14.1) |

* South African; † African-American / Spanish / Latino
‡ Includes: Dietary avoidance, fiber supplementation, and bowel habit training amongst others

Analysis of the entire study population without regard to the treatment group, showed no observed difference in the overall proportion responders to treatment between genders (p=0.904; Chi-square test). In addition, although there were fewer patients in the non-Caucasian group, there was no difference in overall proportion responders between ethnic groups on analyses without regard to treatment received (p=0.334; Chi-square test).

**Table 9: Study patient baseline characteristics**

| Baseline characteristics | Solesta (n=136) | Sham (n=70) | All (n=206) |
|---|---|---|---|
| **Baseline Patient diary data / 14 days** | | | |
| No. of fecal incontinence episodes, Median, [Range] | 15.0 (3.5-172.0)* | 12.5 (4.0-387) | 14.0 (3.5-387)* |
| Number of incontinence free days, Median, [Range] | 4.7 (0.0-11) | 4.2 (0.0-11.8) | 4.3 (0.0-11.8) |
| **Baseline CCFIS score (0-20 point scale)** | | | |
| CCFIS score, Median, [Range] | 14.0 (10.0-20.0) | 13.0 (10.0-20.0) | 14.0 (10.0-20.0) |

| Baseline characteristics | Solesta (n=136) | Sham (n=70) | All (n=206) |
|---|---|---|---|
| **Baseline FIQL score / domain (1-6 scale for Depression/Self-Perception, 1-4 scale for all others, Low L score = LowL QoL)** | | | |
| FIQL – Lifestyle score, Median, [Range] | 2.8 (1.0-4.0) | 2.7 (1.1-4.0) | 2.8 (1.0-4.0) |
| FIQL - Coping/Behavior score, Median, [Range] | 1.7 (1.0-3.8) | 1.7 (1.0-4.0) | 1.7 (1.0-4.0) |
| FIQL - Depression/Self-perception score, Median, [Range] | 2.8 (1.1-4.4) | 2.6 (1.0-4.4) | 2.8 (1.0-4.4) |
| FIQL – Embarrassment score, Median, [Range] | 1.7 (1.0-3.7) | 1.7 (1.0-4.0) | 1.7 (1.0-4.0) |
| * One patient with 3.5 episodes had only completed 6 days in the diary due to a misunderstanding. However, the investigator reported that the patient met the eligibility criteria. The diary was considered invalid and was assessed as a major deviation. | | | |

## D. Safety and Effectiveness Results

### 1. Safety Results

The analysis of safety was based on the safety cohort of all 206 patients treated in the study with either Solesta or Sham. Adverse event data was obtained on 136 patients treated with Solesta and followed for up to 18 months and on 70 patients randomized to Sham treatment in the blinded phase of the study. Of these 70 Sham patients, 61 patients subsequently received treatment with open-label Solesta and were followed for another 12 months in the open phase of the study. Safety data for Solesta are therefore available from 359 treatments in 197 patients in total followed for up to 18 months post treatment (i.e., 136 subjects from the blinded phase and 61 subjects from the open phase). Adverse effects are reported in Tables 10 to 13.

**Adverse effects that occurred in the PMA clinical study**

**Overview of all reported adverse events**

A total of 606 AEs were reported in the 206 patients included in the study through the 18 month follow up period. Of these 606 AEs, 232 events were assessed by the investigators as related to study treatment with either Sham or Solesta. Of 232 treatment-related AEs, 203 events were reported in the 197 patients treated with Solesta in the blinded or open phase of the study and followed for up to 18 months, and 29 events were reported in the 70 patients treated with Sham and followed through the 6-month blinded phase. The remaining 374 events were assessed as unrelated to study treatment. Three (3) treatment-related AEs were assessed to be serious and are discussed in more detail below. No deaths occurred amongst study patients and no patient withdrew from the study due to an adverse event.

**Adverse Events in Blinded Phase**

Through the 6-month blinded phase there were 319 AEs in 138 out of 206 subjects, as detailed in Table 10.

**Table 10: Adverse events observed in the blinded phase**

| | Solesta Group (n=136) | Sham Group (n=70) | Combined (n=206) |
|---|---|---|---|
| Total AEs | 238 events in 97 patients | 81 events in 41 patients | 319 events in 138 subjects |
| Serious | 12 events in 12 patients | 4 events in 3 patients | 16 events in 15 patients |
| Device Related AEs | 128 events in 66 patients | 29 events in 19 patients | 157 events in 85 patients |
| Serious | 2 events in 2 patients | 0 events | 2 events in 2 patients |
| Device Related AEs per Subject | 0.94 (128/136) | 0.41 (29/70) | |
| Unrelated AEs | 110 events in 71 patients | 52 events in 33 patients | 162 events in 104 patients |
| Serious | 10 events in 10 patients | 4 events in 3 patients | 14 events in 13 patients |

A comparison of all related adverse events for Solesta and Sham in the blinded phase of the study is shown in Table 11 below. Incidence of events is subgrouped by MedDRA (Medical Dictionary for Regulatory Activities) System Organ Class (SOC) and preferred terms are presented. The incidence is presented as a percentage of patients with at least one (1) event of each preferred term and percentage of events per total number of treatments in each treatment group. An incidence based on number of treatments has been added since approximately 20% of the patients had only a single injection during the study. It should be noted that in the MedDRA terminology, all events reported as bleeding are described as "hemorrhage" at the preferred term level regardless of the intensity of bleeding. However, no patients developed hypotension or required volume infusion/blood transfusion.

**Table 11: Related AEs (including serious AEs) in each treatment group in the 6-month blinded phase of the study. MedDRA System Organ Class and Preferred Term. Safety population (n=206)**

| Blinded phase MedDRA System Organ Class Preferred Term | Solesta | | | Sham | | |
|---|---|---|---|---|---|---|
| | No. of events | Incidence | | No. of events | Incidence | |
| | | % of patients n=136 | % events/ treatments (total 249) | | % of patients n=70 | % events/ treatments (total 131) |
| **Gastrointestinal disorders** | **85** | **39.7** | **34.1** | **9** | **8.6** | **6.9** |
| Abdominal distension | 1 | 0.7 | 0.4 | . | . | . |
| Abdominal pain | 1 | 0.7 | 0.4 | . | . | . |

| Blinded phase<br>MedDRA System Organ Class<br>Preferred Term | Solesta | | | Sham | | |
|---|---|---|---|---|---|---|
| | No. of events | Incidence | | No. of events | Incidence | |
| | | % of patients n=136 | % events/ treatments (total 249) | | % of patients n=70 | % events/ treatments (total 131) |
| Abdominal pain lower | 2 | 1.5 | 0.8 | . | . | . |
| Abdominal rigidity | 1 | 0.7 | 0.4 | . | . | . |
| Abdominal tenderness | . | . | . | 1 | 1.4 | 0.8 |
| Anal fissure | 1 | 0.7 | 0.4 | . | . | . |
| Anal hemorrhage* | 6 | 3.7 | 2.4 | . | . | . |
| Anal prolapse | 1 | 0.7 | 0.4 | . | . | . |
| Anal pruritus | 2 | 1.5 | 0.8 | . | . | . |
| Anorectal discomfort | 7 | 5.1 | 2.8 | . | . | . |
| Change of bowel habit | . | . | . | 1 | 1.4 | 0.8 |
| Constipation | 3 | 2.2 | 1.2 | . | . | . |
| Defecation urgency | 1 | 0.7 | 0.4 | . | . | . |
| Diarrhea | 8 | 5.1 | 3.2 | 3 | 4.3 | 2.3 |
| Fecal incontinence | 1 | 0.7 | 0.4 | . | . | . |
| Feces hard | 1 | 0.7 | 0.4 | . | . | . |
| Hemorrhoids | 1 | 0.7 | 0.4 | . | . | . |
| Nausea | 1 | 0.7 | 0.4 | . | . | . |
| Obstruction gastric | 1 | 0.7 | 0.4 | . | . | . |
| Painful defecation | 2 | 1.5 | 0.8 | . | . | . |
| Proctalgia | 23 | 14.0 | 9.2 | 2 | 2.9 | 1.5 |
| Proctitis | 4 | 2.9 | 1.6 | 1 | 1.4 | 0.8 |
| Rectal discharge | 5 | 3.7 | 2.0 | . | . | . |
| Rectal hemorrhage* | 10 | 7.4 | 4.0 | 1 | 1.4 | 0.8 |
| Rectal obstruction | 1 | 0.7 | 0.4 | . | . | . |
| Rectal spasm | 1 | 0.7 | 0.4 | . | . | . |
| **General disorders and administration site conditions** | **33** | **18.4** | **13.3** | **18** | **18.6** | **13.7** |
| Chills | 4 | 2.9 | 1.6 | . | . | . |
| Fatigue | 1 | 0.7 | 0.4 | . | . | . |
| Injection site hematoma | . | . | . | 1 | 1.4 | 0.8 |
| Injection site hemorrhage* | 7 | 5.1 | 2.8 | 16 | 17.1 | 12.2 |
| Injection site pain | 6 | 4.4 | 2.4 | 1 | 1.4 | 0.8 |
| Pain | 2 | 1.5 | 0.8 | . | . | . |
| Pelvic mass | 1 | 0.7 | 0.4 | . | . | . |
| Pyrexia | 12 | 8.1 | 4.8 | . | . | . |
| **Infections and infestations** | **2** | **1.5** | **0.8** | **.** | **.** | **.** |
| Escherichia bacteremia | 1 | 0.7 | 0.4 | . | . | . |

| Blinded phase<br>MedDRA System Organ Class<br>Preferred Term | Solesta | | | Sham | | |
|---|---|---|---|---|---|---|
| | No. of events | Incidence | | No. of events | Incidence | |
| | | % of patients n=136 | % events/ treatments (total 249) | | % of patients n=70 | % events/ treatments (total 131) |
| Rectal abscess | 1 | 0.7 | 0.4 | . | . | . |
| **Investigations** | **1** | **0.7** | **0.4** | . | . | . |
| C-reactive protein increased | 1 | 0.7 | 0.4 | . | . | . |
| **Musculoskeletal and connective tissue disorders** | . | . | . | **1** | **1.4** | **0.8** |
| Joint stiffness | . | . | . | 1 | 1.4 | 0.8 |
| **Nervous system disorders** | . | . | . | **1** | **1.4** | **0.8** |
| Dizziness | . | . | . | 1 | 1.4 | 0.8 |
| **Reproductive system and breast disorders** | **4** | **2.9** | **1.6** | . | . | . |
| Dyspareunia | 1 | 0.7 | 0.4 | . | . | . |
| Genital prolapse | 1 | 0.7 | 0.4 | . | . | . |
| Vaginal discharge | 1 | 0.7 | 0.4 | . | . | . |
| Vulvovaginal pain | 1 | 0.7 | 0.4 | . | . | . |
| **Skin and subcutaneous tissue disorders** | **3** | **2.2** | **1.2** | . | . | . |
| Alopecia | 1 | 0.7 | 0.4 | . | . | . |
| Cold sweat | 1 | 0.7 | 0.4 | . | . | . |
| Dermatitis | 1 | 0.7 | 0.4 | . | . | . |
| **ALL** | **128** | **48.5** | **51.4** | **29** | **27.1** | **22.1** |

* AEs reported as bleeding were coded as "hemorrhage" at the preferred term level in MedDRA regardless of intensity

**Adverse events related to Solesta treatment through month 18**

Integrated safety results on all 197 patients (136 patients randomized to Solesta and 61 patients originally randomized to Sham) following a total of 359 treatments with Solesta are presented in this section for the period from randomization through 18 months. All 197 patients have been followed for 12 months and the 136 patients randomized to Solesta have been followed for 18 months from last treatment.

Table 12 displays treatment-related AEs reported in the study for the 197 patients treated with Solesta in either blinded or open phase. The table displays summary information regarding number of events, incidence as percent of patients in whom an AE occurred at least once, intensity, time to onset, duration, intervention, and outcome.

**Table 12: Related adverse events (including serious AEs) for patients with blinded or open-label treatment with Solesta through month 18 in the study. MedDRA Preferred Term. Safety population, (n=197)**

| MedDRA Preferred Term | Number and (%) of patients | Number of events | Maximum intensity | | | Median (days) | | Intervention | | | % of events resolved |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mild | Moderate | Severe | Time to onset | Duration | None | Medical treatment | Other* | |
| Abdominal discomfort | 1 (0.5) | 1 | . | 1 | . | 1.0 | 6.0 | . | . | 1 | 100% |
| Abdominal distension | 1 (0.5) | 1 | . | 1 | . | 0.0 | 3.0 | 1 | . | . | 100% |
| Abdominal pain | 1 (0.5) | 1 | . | 1 | . | 68.0 | 52.0 | . | 1 | . | 100% |
| Abdominal pain lower | 2 (1.0) | 2 | 2 | . | . | 30.5 | 60.0 | 2 | . | . | 100% |
| Abdominal rigidity | 1 (0.5) | 1 | . | 1 | . | 196.0 | . | . | 1 | . | 0% † |
| Alopecia | 1 (0.5) | 1 | . | . | 1 | 6.0 | 189.0 | 1 | . | . | 100% |
| Anal abscess | 1 (0.5) | 1 | . | 1 | . | 139.0 | 44.0 | . | . | 1 | 100% |
| Anal fissure | 2 (1.0) | 2 | 1 | 1 | . | 90.5 | 228.0 | . | 2 | . | 100% |
| Anal hemorrhage‡ | 8 (4.1) | 9 | 7 | 2 | . | 1.0 | 4.0 | 7 | . | 2 | 100% |
| Anal prolapse | 3 (1.5) | 3 | 2 | 1 | . | 287.0 | 2.0 | 1 | . | 2 | 100% |
| Anal pruritus | 3 (1.5) | 4 | 4 | . | . | 49.0 | 72.0 | 3 | 1 | . | 100% |
| Anorectal discomfort | 8 (4.1) | 8 | 7 | 1 | . | 2.0 | 21.0 | 3 | 5 | . | 100% |
| Back pain | 1 (0.5) | 1 | 1 | . | . | 70.0 | 113.0 | . | . | 1 | 100% |
| C-reactive protein increased | 1 (0.5) | 1 | . | 1 | . | 11.0 | 18.0 | . | 1 | . | 100% |
| Chills | 4 (2.0) | 4 | 1 | 2 | 1 | 0.5 | 4.5 | 4 | . | . | 100% |
| Cold sweat | 1 (0.5) | 1 | . | 1 | . | 0.0 | 3.0 | 1 | . | . | 100% |
| Constipation | 3 (1.5) | 3 | 3 | . | . | 3.0 | 2.0 | 1 | 2 | . | 100% |
| Defecation urgency | 2 (1.0) | 2 | 2 | . | . | 2.5 | 4.5 | 1 | 1 | . | 100% |
| Dermatitis | 1 (0.5) | 1 | 1 | . | . | 90.0 | 79.0 | . | . | 1 | 100% |
| Device dislocation | 1 (0.5) | 1 | 1 | . | . | 260.0 | 14.0 | . | . | 1 | 100% |
| Diarrhea | 8 (4.1) | 10 | 9 | 1 | . | 2.5 | 5.0 | 4 | 6 | . | 100% |
| Dyspareunia | 2 (1.0) | 2 | 2 | . | . | 65.0 | 60.5 | 2 | . | . | 100% |
| Escherichia bacteremia | 1 (0.5) | 1 | . | 1 | . | 0.0 | 36.0 | . | 1 | . | 100% |
| Fecal incontinence | 1 (0.5) | 1 | . | 1 | . | 0.0 | 64.0 | 1 | . | . | 100% |

| MedDRA Preferred Term | Number and (%) of patients | Number of events | Maximum intensity | | | Median (days) | | Intervention | | | % of events resolved |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mild | Moderate | Severe | Time to onset | Duration | None | Medical treatment | Other* | |
| Feces hard | 1 (0.5) | 1 | 1 | . | . | 15.0 | 63.0 | 1 | . | . | 100% |
| Fatigue | 1 (0.5) | 1 | . | 1 | . | 0.0 | 3.0 | 1 | . | . | 100% |
| Gastrointestinal motility disorder | 1 (0.5) | 1 | 1 | . | . | 226.0 | 117.0 | 1 | . | . | 100% |
| Gastrointestinal pain | 1 (0.5) | 1 | . | 1 | . | 0.0 | 8.0 | 1 | . | . | 100% |
| Genital prolapse | 1 (0.5) | 1 | . | 1 | . | 1.0 | 10.0 | . | . | 1 | 100% |
| Hemorrhoids | 1 (0.5) | 1 | . | 1 | . | 0.0 | 6.0 | . | . | 1 | 100% |
| Injection site hemorrhage‡ | 16 (8.1) | 18 | 18 | . | . | 0.0 | 1.0 | 17 | . | 1 | 100% |
| Injection site inflammation | 1 (0.5) | 1 | 1 | . | . | 0.0 | 5.0 | . | 1 | . | 100% |
| Injection site irritation | 1 (0.5) | 1 | 1 | . | . | 28.0 | 8.0 | 1 | . | . | 100% |
| Injection site nodule | 1 (0.5) | 1 | 1 | . | . | 294.0 | 99.0 | 1 | . | . | 100% |
| Injection site pain | 10 (5.1) | 10 | 7 | 3 | . | 0.0 | 1.5 | 9 | 1 | . | 100% |
| Injection site pustule | 1 (0.5) | 1 | 1 | . | . | 0.0 | 22.0 | . | 1 | . | 100% |
| Injection site swelling | 1 (0.5) | 1 | 1 | . | . | 0.0 | 78.0 | 1 | . | . | 100% |
| Intestinal mass | 1 (0.5) | 1 | 1 | . | . | 196.0 | 14.0 | . | . | 1 | 100% |
| Mucosal inflammation | 1 (0.5) | 1 | 1 | . | . | 27.0 | 74.0 | 1 | | | 100% |
| Musculoskeletal pain | 1 (0.5) | 1 | 1 | . | . | 358.0 | 183.0 | 1 | . | . | 100% |
| Nausea | 1 (0.5) | 1 | 1 | . | . | 0.0 | 3.0 | 1 | . | . | 100% |
| Pain ("body aches") | 2 (1.0) | 2 | . | 1 | 1 | 1.5 | 5.0 | 2 | . | . | 100% |
| Painful defecation | 2 (1.0) | 2 | 2 | . | . | 1.5 | 132.5 | 1 | . | 1 | 100% |
| Pelvic mass | 1 (0.5) | 1 | . | 1 | . | 2.0 | 27.0 | . | 1 | . | 100% |
| Perineal pain | 1 (0.5) | 1 | . | 1 | . | 0.0 | 5.0 | 1 | . | . | 100% |
| Proctalgia | 34 (17.3) | 41 | 20 | 21 | . | 1.0 | 8.0 | 14 | 19 | 8 | 97.6% § |
| Proctitis | 5 (2.5) | 5 | 2 | 2 | 1 | 5.0 | 16.0 | 2 | 3 | . | 100% |
| Pyrexia | 13 (6.6) | 14 | 12 | 1 | 1 | 1.0 | 6.0 | 5 | 8 | 1 | 100% |
| Rectal abscess | 3 (1.5) | 3 | . | 1 | 2 | 2.0 | 6.0 | . | 1 | 2 | 100% |

| MedDRA Preferred Term | Number and (%) of patients | Number of events | Maximum intensity | | | Median (days) | | Intervention | | | % of events resolved |
|---|---|---|---|---|---|---|---|---|---|---|---|
| | | | Mild | Moderate | Severe | Time to onset | Duration | None | Medical treatment | Other* | |
| Rectal discharge | 7 (3.5) | 7 | 6 | 1 | . | 2.0 | 4.0 | 4 | 2 | 1 | 100% |
| Rectal hemorrhage‡ | 15 (7.6) | 15 | 11 | 4 | . | 7.0 | 3.0 | 13 | 1 | 1 | 100% |
| Rectal lesion | 1 (0.5) | 1 | . | 1 | . | 5.0 | 179.0 | . | . | 1 | 100% |
| Rectal obstruction | 2 (1.0) | 2 | 2 | . | . | 75.5 | 66.0 | 2 | . | . | 100% |
| Rectal spasm | 1 (0.5) | 1 | . | 1 | . | 133.0 | 50.0 | 1 | . | . | 100% |
| Urinary retention | 1 (0.5) | 1 | 1 | . | . | 8.0 | 20.0 | 1 | . | . | 100% |
| Vaginal discharge | 1 (0.5) | 1 | 1 | . | . | 0.0 | 5.0 | 1 | . | . | 100% |
| Vulvovaginal pain | 1 (0.5) | 1 | . | 1 | . | 0.0 | 6.0 | . | 1 | . | 100% |
| **Totals** | **103 (52.3)** | **203** | **136** | **60** | **7** | **1.0** | **6.0** | **115** | **60** | **28** | **99.0%** |

* Other intervention included: follow up Ultrasound, I & D of rectal abscess, Kenalog injection to anal area scar, rubber band ligation, observation, extra check-up at clinic, Silicone or Xylocaine ointment, examinations, blood tests, feces-Hb screen, outpatient visit to gynecologist, irrigation with water, lanced hemorrhoid, pressure, irrigation-dissection of abscess, flexible sigmoidoscopy, pelvic v/s scan, warm baths, drainage of anal abscess

† Outcome for one event pending at time of this summary report (patient withdrawn and event currently recorded as not recovered)

§ Outcome for one event pending at time of this summary report

‡ AEs reported as bleeding were coded as "hemorrhage" at the preferred term level in MedDRA regardless of intensity

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**Treatment-related serious adverse events**

Three (3) case reports of treatment-related serious adverse events (SAEs) were received from three (3) patients in the study through 18 months of follow-up. Two (2) events occurred in the blinded phase of the study and comprised one (1) case of *Escherichia coli* bacteremia and one (1) case of rectal abscess, in 2 patients in the Solesta treatment group. The third event was a rectal abscess which occurred in the open phase of the study following treatment with open-label Solesta. No treatment-related SAEs were reported following Sham treatment. See summary information regarding the 3 Solesta-related SAEs in Table 13 below.

All three (3) treatment-related SAEs had an early onset suggestive of a possible peri-operative infection. None of the patients had received prophylactic antibiotics prior to treatment. The events were assessed as serious because they required surgical intervention and/or hospitalization. All three (3) events were assessed as resolved without sequelae following intervention.

**Table 13: Summary listing of treatment-related adverse events assessed as serious through 18 months in the study. Safety population (n=206)**

| Treatment | Adverse Event MedDRA PT | Time to onset (days) | Duration (days) | Culture results | Intervention | Concurrent symptoms |
|---|---|---|---|---|---|---|
| Solesta | Escherichia bacteremia | 0 | 36 | *Klebsiella pneumoniae* in urine<br>*Escherichia Coli* in blood and urine | Antipyretic<br>Antibiotics<br>Fluids<br>Flomax | Prostatitis<br>Fever (101.3 °F)<br>Urinary urgency<br>Frequency<br>Urine flow decr. |
| Solesta | Rectal abscess | 2 | 6 | Not done on aspirate | Per anal I&D of abscess<br>Antibiotics<br>Analgesics | Fever (38 °C) |
| Solesta | Rectal abscess | 2 | 6 | Gram negative bacilli and beta-hemolytic streptococci in aspirate | Per anal I&D of abscess<br>Antibiotics<br>Hot baths | Fever (38-39 °C)<br>Diarrhea |

Approximately 95% (192/203 events) of the related AEs were reported within a 6-month period following treatment (i.e., prior to month 6 for patients randomized to Solesta and within the first 6 months in the open phase for Sham patients receiving open-label Solesta). Eleven (11) Solesta treatment-related events had an onset more than 6 months after treatment. These events comprised three (3) cases of proctalgia, two (2) cases of anal prolapse, and one (1) case each of possible device dislocation (located 2 cm above level of mid-internal sphincter), diarrhea, rectal emptying problems, pain in buttocks, minor rectal bleeding, and tender nodule at injection site. All but two (2) Solesta-related events had resolved as of the time of data cut-off for this summary report. One (1) of these two (2) events was a case of abdominal spasms (abdominal

rigidity) reported by a patient who approximately 6 months later withdrew consent to further participate in the study without providing a final outcome for the event. The other case concerns a report of anal pain (proctalgia) in an active patient with onset 493 days post treatment and without a reported final outcome at the time of the 18 months visit, 426 days from onset.

The majority (97%) of the Solesta-related events required no intervention, or required medical or simple non-invasive intervention, including application of local pressure, silicon ointment, water irrigation and warm baths. Seven (7) events required more invasive procedures including: perianal drainage of abscesses (4 events), one (1) case of rubber band ligation of an anal prolapse, one (1) case of lancing of a hemorrhoid, and one (1) case of a Kenalog injection in a pre-existing anal scar.

2. Effectiveness Results

The analysis of effectiveness was based on the 206 evaluable patients at the 6-month time point. Key effectiveness outcomes are presented in Tables 14 to 19.

**Primary Efficacy Analyses – Blinded Phase**

The primary objectives (and some secondary endpoints) were to be evaluated using information obtained from patient diaries. Patients were to record fecal incontinence (FI) episodes in a patient diary, over several 14-day periods: baseline, 3 months, 6 months (primary time point), and 12 months (unblinded phase). Some patients only had partial records, and their information was extrapolated from available information (as per the sponsor's pre-specified imputation method described below). Seventy-four percent (74%) of treatment patients and 73% of Sham patients had complete diary data for the primary endpoint at both baseline and six (6) months.

Many patients had complete 14 day diaries; however, for those that did not, data was imputed, and patients withdrawn or lost to follow up were treated as non-responders. In total, 6 Solesta (4.4% of Solesta patients) and 6 Sham patients (8.6% of Sham subjects) did not have diary data at 6 months due to premature withdrawal (5), lost to follow up (5), or not completing the diary prior to the visit (2). The 10 patients withdrawn or lost to follow up were imputed as failures while the 2 patients who had failed to complete their diaries had their month 3 diary data imputed.

The following results were calculated after fitting a logistic regression model with $Responder_{50}$ at 6 months as the dependent variable, with covariates of treatment group, baseline number of fecal incontinence episodes, gender, and center.

*First part of primary objective:* A patient was defined as a responder if the decrease in number of FI episodes from baseline was ≥ 50%. Statistical superiority based on the proportion $Responder_{50}$ (≥ 50% improvement from baseline) was shown for Solesta (53.2%) against Sham (30.7%) at 6 months (p=0.004; logistic regression), as seen in Figure 3.

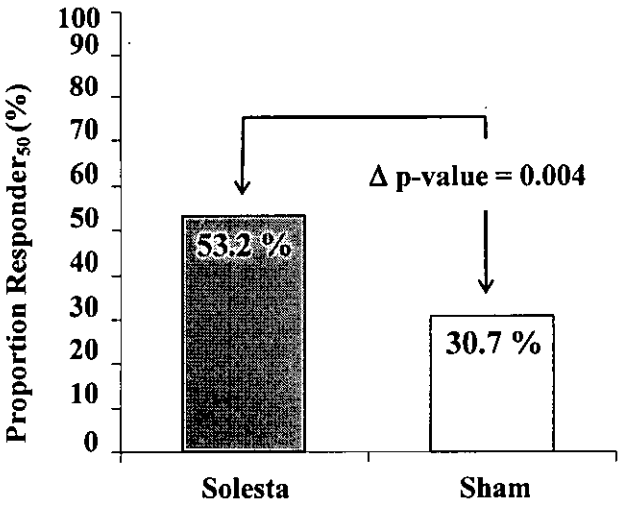


**Figure 3: Comparison of proportion Responder$_{50}$ at 6 months**

*Second part of primary objective:* The lower limit of a two-sided 95% CI (LCL) for Responder$_{50}$ in the Solesta group at 6 months was above 35%. As can be seen in Table 14 below, the lower bound of the 95% CI for the active group was 40.2%, satisfying this second component.

**Table 14: Comparison of Responder$_{50}$ between Solesta and Sham at 6 months**

| Treatment | Statistic | Estimate (%) | LCL (%) | UCL (%) | p-value* |
|---|---|---|---|---|---|
| Solesta | Proportion | 53.2 | 40.2 | 65.8 | 0.005 |
| Sham | Proportion | 30.7 | 19.0 | 45.6 | |

* test of $H_0$: proportion = 35%

*Third part of primary objective:* The LCL for Responder$_{25}$ of the Solesta group at 12 months was above 50%. The table below shows that this criterion was satisfied (LCL = 61.4%). As a supportive analysis (not pre-specified as part of primary objective), the proportion Responder$_{50}$ based on change in number of incontinence episodes from baseline to 12 months in the Solesta treatment group was performed. As displayed in Table 15 below, the observed proportion Responder$_{50}$ at 12 months was 57.4%. The lower limit of the confidence interval was higher than 35% ($p<0.001$), similar to what was observed at 6 months.

**Table 15: Observed proportion Responder$_{25}$ and Responder$_{50}$ at 12 months (open phase) for patients randomized to Solesta. ITT population (n = 136 patients). PIM.**

| Solesta treatment | Timepoint | Estimate (%) | LCL (%) | UCL (%) | p-value |
|---|---|---|---|---|---|
| Proportion Responder$_{25}$ | 12 months | 69.1 | 61.4 | 76.9 | <0.001* |
| Proportion Responder$_{50}$ | 12 months | 57.4 | 49.0 | 65.7 | <0.001** |

* Test of $H_0$: proportion = 50%
** Test of $H_0$: proportion = 35%

The device met all 3 components of the pre-defined primary endpoint for effectiveness.

**Secondary Efficacy Analyses in the Blinded Phase**

The primary analyses all used a responder variable, where a subject was considered a responder if they met a certain percentage reduction in FI episodes from baseline. The secondary endpoints dealt with the actual changes in number of episodes (or number of incontinence-free days).

The statistical analyses plan pre-specified that missing data in these analyses were to be imputed using last observation carried forward (LOCF). Because of outliers in baseline number of incontinence episodes in both groups, the sponsor evaluated median values in certain circumstances.

**Number of incontinence episodes**

The secondary analysis of change in number of incontinence episodes from baseline has been done with focus on the observed median value. The results are displayed in Table 16.

**Table 16: Median number of fecal incontinence episodes/14 days for each treatment group and change from baseline 6 months. As observed. Last Observation Carried Forward (LOCF). ITT population (n=206 patients: Pivotal study)**

| Number of episodes | Solesta (n=136) | Sham (n=70) | Difference in median changes between groups (Solesta-Sham) |
|---|---|---|---|
| | Median | Median | |
| **Baseline** | 15.0 | 12.5 | |
| **6 months** | 7.2 | 10.0 | |
| Δ from baseline | -6.0 | -3.0 | -3.0 |
| % Δ from baseline | -50.6 | -22.6 | -28.0 |

**Number of incontinence-free days**

At baseline, the observed mean number of incontinence-free days was 4.4 days in the Solesta group and 4.8 days in the Sham group. At 3 months, both groups had increases in the absolute number of fecal incontinence-free days compared to baseline and the difference between groups was approximately half a day. Both treatment groups also experienced an increase in number of incontinence free days at 6 months; for the Solesta group it had increased by 3.1 days and by 2.0 days in the Sham group. The difference in change from baseline was greater in the Solesta group, Table 17.



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**Table 17: Absolute change from baseline in number of incontinence-free days**

| Treatment group | 3 months | | 6 months | |
|---|---|---|---|---|
| | LSM estimate | ΔSolesta vs. Sham (95% CI) | LSM estimate | ΔSolesta vs. Sham (95% CI) |
| Solesta (n=136) | 2.4 | 0.45 [-0.66:1.57] | 3.1 | 1.11 [0.00:2.22] |
| Sham (n=70) | 1.9 | | 2.0 | |

**Fecal Incontinence Quality of Life (FIQL) and Cleveland Clinic Florida Incontinence Score (CCFIS)**

Missing values were imputed using the LOCF approach (8 Solesta and 6 Sham patients had missing observations at 6 months).

Changes in CCFIS Scores for the 2 groups are summarized in Table 18 below. Partially missing data in one (1) of the five (5) domains in CCFIS was left missing. For evaluation of CCFIS, the calculated sum as entered by the blinded evaluator/investigator was used.

For the FIQL, as seen in Table 18 below, the change from baseline at 6 months was greater in the Solesta group than Sham in all four (4) domains of the FIQL. The largest difference was ¼ of a point on a 1-4 scale.

**Table 18: Secondary efficacy evaluations of difference in change from baseline between Solesta and Sham at 6 months. ITT population (n=206). LOCF.**

| Secondary Endpoints | Score/Scale Range | Estimate of mean change from baseline | | Estimate of difference (95% CI) |
|---|---|---|---|---|
| | | Solesta | Sham | |
| **Cleveland Clinic Florida Incontinence Score (CCFIS)** | | | | |
| CCFIS score† | (0 = continent; 20 = total incontinence) | -3.06 | -2.85 | -0.21 (-1.15:0.72) |
| **Fecal Incontinence Quality of Life (FIQL) scale (higher score = increased QoL)** | | | | |
| Coping/Behavior* | 1-4 | 0.44 | 0.19 | 0.25 (0.08:0.43) |
| Lifestyle* | 1-4 | 0.33 | 0.11 | 0.22 (0.04:0.40) |
| Depression/Self perception* | 1-6 | 0.27 | 0.18 | 0.09 (-0.08:0.26) |
| Embarrassment* | 1-4 | 0.53 | 0.38 | 0.16 (-0.05:0.36) |
| * Positive values indicate improvement; † Negative values indicate improvement | | | | |

**Secondary 12-month efficacy analyses for Solesta**

The 12-month efficacy analysis (including the period from baseline through month 12 for the patients randomized to Solesta) in the study aimed to show durability of the Solesta treatment effect. A total of 121 patients had completed diaries at 12 months, with 95 subjects having both baseline and 12 month diaries complete with 14 days of data (70%). The analyses were performed on the ITT population for all variables. Sham patients were not followed for 12 months.

As illustrated in Figure 4 below, a decrease in number of incontinence episodes and increase in proportion Responder$_{50}$ was observed through month 12. The Solesta group at baseline had a median of 15.0 incontinence episodes which had decreased to 6.2 at 12 months. A stable proportion Responder$_{50}$ was seen during the open phase of the study; 52.2% at 6 months and 57.4% at 12 months.

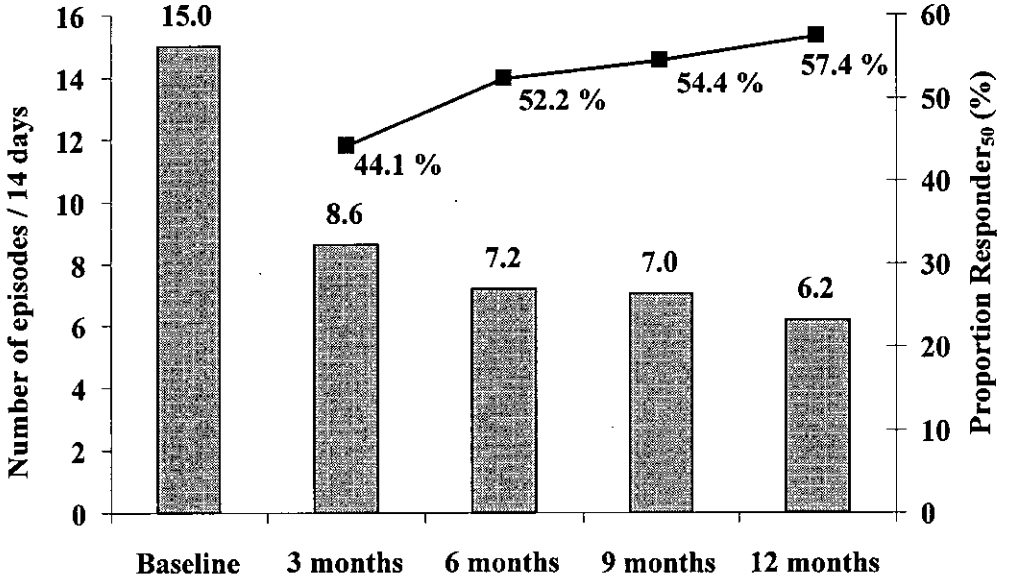


**Figure 4: Median number of FI episodes and proportion Responder$_{50}$ at each follow up time point in the Pivotal study. Solesta ITT population (n=136)**

A similar effect was observed as an increase in number of incontinence-free days (increase of 0.31 from 6 months), and improvement in patient quality of life (FIQL) and CCFIS score. A summary of the outcome from the analyses through month 12 is displayed in Table 19, below.

**Table 19: Efficacy data from the patients randomized to** Solesta **from study start through month 12. Observed change from baseline and 95% CI. ITT. LOCF (n=136)**

| Variable | 6 months | 12 months | Δ month 12 – month 6 |
|---|---|---|---|
| | Estimate | Estimate | Estimate |
| **Fecal incontinence episodes (during 14-day diary period)** | | | |
| Absolute change from baseline | | | |
| Total number of FI episodes, *median* | -6.0 (-8.0:-4.0) | -7.0 (-9.0:-5.0) | 0.0 (-1.0:0.0) |
| Number of incontinence-free days, *mean* | 3.13 (2.44:3.81) | 3.44 (2.71:4.17) | 0.31 (-0.29:0.92) |
| Proportion Responders | | | |
| $Responder_{25}$, *proportion* | 66.2% (58.2:74.1) | 69.1% (61.4:76.9) | 2.9% |
| $Responder_{50}$, *proportion* | 52.2% (43.8:60.6) | 57.4% (49.0:65.7) | 5.2% |
| **Cleveland Clinic Florida Incontinence Score (CCFIS) (0 = continent; 20 = total incontinence)** | | | |
| Absolute change from baseline, *mean* | -2.45 (-3.06:-1.83) | -3.47 (-4.22:-2.72) | -1.02 (-1.63:-0.42) |
| **Fecal Incontinence Quality of Life (FIQL) scale (higher score = increased QoL)** | | | |
| Absolute change from baseline | | | |
| Coping/Behavior, *mean* | 0.42 (0.32:0.52) | 0.65 (0.53:0.77) | 0.22 (0.13:0.32) |
| Lifestyle, *mean* | 0.29 (0.18:0.39) | 0.45 (0.31:0.58) | 0.16 (0.07:0.25) |
| Depression/Self perception, *mean* | 0.30 (0.20:0.40) | 0.49 (0.37:0.62) | 0.19 (0.09:0.30) |
| Embarrassment, *mean* | 0.45 (0.34:0.57) | 0.78 (0.64:0.92) | 0.32 (0.20:0.44) |

3. Subgroup Analyses

Analyses were performed to evaluate whether response to treatment was associated with any baseline or demographic factors. No such relationship was observed.

4. Combined Safety Analyses

As discussed in depth in Section XI below, safety data was leveraged from two supplemental clinical studies: an OUS Open-Label study and an OUS Proof-of-Concept study. The efficacy data

from these supplemental studies was also supportive of the Pivotal Study data, and is briefly discussed below.

## XI. SUMMARY OF SUPPLEMENTAL CLINICAL INFORMATION

Clinical data supporting the safety of Solesta are available from two (2) outside the United States clinical studies: 1) OUS Open-Label study, and 2) Proof-of-Concept study. The results from these 2 studies are summarized below.

### OUS Open-Label Study

An open-label multicenter study was performed at one (1) site in Canada and 14 sites in Europe. Patients were treated with Solesta up to two (2) times and followed for 12 months after last treatment. The study also includes an extension phase up to 24 months following last treatment. Examinations included proctoscopy at follow up. A 28-day patient incontinence diary was completed before visits and CCFIS and FIQL were completed at the visits. Data from the 12-month primary time point and 18-month safety data from the extension phase have been collected and are included in this summary.

### Objectives

The primary objective of the study was to evaluate the efficacy of Solesta, defined as proportion of $Responder_{50}$ at 12 months after treatment. The proportion $Responder_{50}$ was based on the change in the number of fecal incontinence episodes from baseline, collected over a 28-day diary period.

Secondary objectives included: safety of Solesta treatment, change in number of fecal incontinence episodes and incontinence-free days, change in CCFIS, and change in FIQL.

### Study Population

The study included 115 patients of both genders, 18-80 years of age, with a history of fecal incontinence for at least 12 months, a CCFIS at baseline of $\geq 5$ and $\geq 4$ fecal incontinence episodes over a 28 day period. Furthermore, patients had failed prior conservative therapy (e.g., diet, fiber therapy, anti-diarrheal medications).

Patient exclusion criteria included: Incontinence to flatus only; complete external sphincter disruption; significant mucosal prolapse, transanal mucosal problems, or full thickness rectal prolapse; anorectal tumors, fissures, sepsis, proctitis, stenosis, or grade III-IV hemorrhoids; significant chronic anorectal or pelvic pain; active IBD; prior anorectal surgery within 12 months; rectal anastomosis < 10 cm from anal verge; idiopathic anorectal bleeding, rectal varices or vascular malformation; and anorectal implants and previous injection therapy.

**Demographics and baseline parameters**

The study population consisted of 87% females and 13% males. Mean patient age at enrollment was 62 years and the mean BMI was 26 kg/m$^2$. Ninety-five percent (95%) of women had delivered at least one (1) child. All patients were Caucasian except for one (1) patient who was Hispanic/Latino. Approximately two-thirds of the patients had been symptomatic for FI for less than 5 years.

For the ITT population, the median number of FI episodes over 28 days was 16.0 at baseline as recorded in the patient diary. The mean number of incontinence free-days was 13.5. All patients had a CCFIS of at least 5 at baseline and the mean CCFIS was 13.7. A total of 99 patients (85.2%) in the ITT population had a CCFIS at baseline of 10 or higher.

**Safety Results**

Safety data are available from 115 patients followed for up to 18 months after treatment in this study. In total, 154 treatments with Solesta were performed in the 115 included patients. A majority (67%) of the patients in the study were only treated once with Solesta.

A total of 163 AEs were reported by 71 of the 115 patients treated with Solesta in the study. Of these AEs, 79 AEs reported by 44 patients (38%) were assessed by the investigators to be related to the study treatment. Thus, the incidence of treatment-related AEs per total number of performed treatments was 51.3% (79 events/154 treatments).

The five (5) most frequently reported types of treatment-related AEs were proctalgia, pyrexia, constipation, diarrhea and injection site pain. A listing of all treatment-related AEs and incidence of events grouped by MedDRA SOC and preferred term is presented in Table 13 above (data combined with AE data from Pivotal IDE study).

Twenty-one (21) AEs reported by 15 patients were classified as serious. Of these 21 SAEs, 6 SAEs were assessed by the investigators to be related to the study treatment. These related SAE are described in more detail below.

One (1) patient died from cardiac failure which was assessed by the investigator to be unrelated to the study treatment. This patient had been receiving treatment for an earlier cardiac failure of New York Heart Association class III severity. With exception for this unrelated fatal case of cardiac failure no adverse events led to patient withdrawals.

**Treatment-related adverse events assessed as serious**

Six (6) treatment-related AEs reported in 4 patients were classified as serious in the study. Three (3) of these serious and treatment-related adverse events were cases of abscess reported by three (3) patients and the remaining three (3) were reported by a single patient who had a rectal prolapse with concurrent rectal bleeding and pain. In this latter case, tissues surrounding a Solesta bulge had prolapsed downwards in the anal canal and the Solesta bulge was excised in surgery. See summary information for all cases in Table 20 below.

**Table 20: Summary listing of treatment-related adverse events classified as serious through 18 months in the study. Safety population (n=115 patients)**

| Event Number | Adverse Event (MedDRA Preferred term) | Time to onset (days) | Duration (days) | Culture results | Intervention | Concurrent symptoms /AEs |
|---|---|---|---|---|---|---|
| 1 | Rectal abscess | 4 | 72 | Not done | Per anal I&D of abscess. Antibiotics. | None |
| 2 | Rectovaginal septum abscess | 1 | 14 | Not done | Antibiotics | Anal pain. Fever (max 38°C). Painful mass in rectovaginal septum. |
| 3 | Perineal abscess | 18 | 18 | *Bacteroides fragilis* | Per anal I&D of abscess. Antibiotics. NSAIDs. | Perineal pain |
| 4 | Rectal prolapse | 308 | 168 | Not done | Surgical excision of Solesta bulge | None |
| | Rectal hemorrhage | 308 | 168 | | | |
| | Proctalgia | 308 | 168 | | | |

**Efficacy Results**

The primary and secondary variables were primarily analyzed for observed cases (OC) in the intent-to-treat (ITT) population (i.e., no imputation of missing data).

The primary efficacy analysis produced a proportion $Responder_{50}$ of 64.0% at 12 months after last treatment. Secondary analyses provided a proportion $Responder_{50}$ of 57.1% at 6 months. See Table 21 for a summary tabulation of the results for the individual secondary efficacy endpoints.

**Table 21: Baseline, 6 and 12 months results after last treatment. OUS Open-label study. (ITT, OC)**

| Variable | 6 months | | | 12 months | | |
|---|---|---|---|---|---|---|
| | n | Baseline estimate | 6-month estimate | n | Baseline estimate | 12-month estimate |
| **Fecal incontinence episodes (during 28-day diary period)** | | | | | | |
| Total number of FI episodes, *median* | 99 | 16.0 | 5.6 | 87 | 15.0 | 4.0 |
| Number of incontinence-free days, *mean* | 99 | 14.0 | 20.9 | 87 | 14.1 | 21.2 |
| **Cleveland Clinic Florida Incontinence Score (CCFIS) (0 = continent; 20 = total incontinence)** | | | | | | |
| CCFIS, *mean* | 99 | 13.5 | 9.2 | 90 | 13.4 | 8.7 |

| Variable | 6 months | | | 12 months | | |
|---|---|---|---|---|---|---|
| | n | Baseline estimate | 6-month estimate | n | Baseline estimate | 12-month estimate |
| **Fecal Incontinence Quality of Life (FIQL) scale (higher score = increased QoL)** | | | | | | |
| Lifestyle, *mean* | 78 | 2.41 | 2.95 | 74 | 2.42 | 2.93 |
| Coping/Behavior, *mean* | 79 | 1.75 | 2.33 | 75 | 1.74 | 2.42 |
| Depression/Self perception, *mean* | 78 | 2.60 | 3.07 | 72 | 2.67 | 3.20 |
| Embarrassment, *mean* | 77 | 1.83 | 2.47 | 71 | 1.81 | 2.59 |
| * p-value: Test of change from baseline = 0. Test used: Wilcoxon one-sample test (Number of episodes), One-sample t-test (Number of incontinence-free days, CCFIS and FIQL) | | | | | | |

**Conclusions Drawn from OUS Open-Label Study**

This OUS Open Label study supports the findings of the Pivotal IDE study. Specifically:

- The safety of Solesta in the treatment of patients with fecal incontinence was based on adverse event data from 115 patients followed for up to 18 months after treatment. The adverse event profile was similar to that observed for the pivotal study.

- The primary efficacy analysis showed that the proportion of patients meeting the $Responder_{50}$ criterion was 57.1% at 6 months and 64.0% at 12 months in an observed case analysis. In addition, at both 6 and 12 months after Solesta treatment, the mean CCFIS and the mean scores in all four FIQL domains were improved compared to baseline.

In comparison to the main study supporting the PMA, there were substantial differences in eligibility criteria, baseline disease parameters, and number of treatment sessions given. As such, the safety results are relevant, but the effectiveness results cannot be combined with or compared to those of the PMA study.

**Proof-of-Concept Study**

This open, single center investigator-initiated study was undertaken to evaluate the safety and efficacy of Solesta for treatment of fecal incontinence. The study was conducted at a single site in Sweden.

Patients were given up to two (2) treatments and were followed for 24 months. The follow-up visits were scheduled at months 3, 6, 12, 18 and 24 (including one telephone contact at 1 month). Examinations included rectoscopy, anorectal manometry, and anorectal ultrasound at screening and proctoscopy at follow up. A 4-week patient diary, which is routinely used at the clinic, was completed before visits and a bowel function questionnaire was completed at the visits.

**Study objectives**

The primary objective of the study was to evaluate the efficacy of Solesta as an injectable bulking agent in patients with fecal incontinence as measured by proportion of $Responder_{50}$ up to 24 months after treatment.

Secondary objectives included safety assessment, change in number of incontinence episodes and days, change in "Miller incontinence score," patient global assessments of their FI condition and judgment of treatment effect, and quality of life.

**Study Population**

The study included 34 patients of both genders, 18-80 years of age and with fecal incontinence to loose or solid stool at least once weekly (Miller score 6 or higher), and who had failed prior conservative therapy.

Patient exclusion criteria included: total sphincter defect visible on anal ultrasound; pregnancy; rectal prolapse; inflammatory bowel disease; recent anorectal surgery except hemorrhoids (within the last 6 months); anticoagulant medication or bleeding diathesis; or presence of anorectal sepsis.

**Patient Demographics**

Twenty-nine (29, 85%) evaluable patients in the study were females and five (5, 15%) were males. Mean patient age at enrollment was approximately 66 years. At baseline, the mean number of leakage episodes was 25 over a 4-week period as recorded in the patient diary and the mean Miller score was 13.

**Safety Results**

Thirty-four (34) patients were treated in the study and 33 patients were followed for 24 months. One (1) patient withdrew consent after completing the 18 month follow-up visit. In total, 53 treatments with Solesta were administered in the study. Seventeen (17) of 34 patients received one (1) retreatment with 2-4 mL, and one (1) patient was retreated twice with 4 mL each time. The mean total volume given was $6 \pm 2$ mL (range 4 to 12 mL).

In total, 86 treatment-related adverse events have been reported by 29 patients. No treatment-related adverse event was reported as serious. The duration was 1-4 days for most events and all events were resolved within 1 week. No adverse events occurred after month 12. One (1) patient gave birth to a healthy child approximately 18 months after treatment and the delivery was a normal vaginal delivery.

Total number of treatment-related adverse events reported during the study and incidence in relation to total number of treatments performed in the study is presented in Table 22, below.

**Table 22: Related adverse events and incidence based on total number of treatment procedures performed in the study.**

| Adverse Event | Number of patients n=34 | | Total number of events | Incidence % events/ treatments (53 treatments) |
|---|---|---|---|---|
| | n | % | | |
| Bleeding | 9 | 26 | 9 | 17 |
| Constipation | 2 | 6 | 2 | 4 |
| Fatigue | 2 | 6 | 2 | 4 |
| Fever | 2 | 6 | 2 | 4 |
| Hematoma | 1 | 3 | 1 | 2 |
| Hot flush 1 day | 1 | 3 | 1 | 2 |
| Leakage of gel | 3 | 9 | 3 | 6 |
| Mucus secretion | 15 | 44 | 20 | 38 |
| Pain at injection | 12 | 35 | 14 | 26 |
| Pain post-treatment | 19 | 56 | 28 | 53 |
| Proctitis | 1 | 3 | 1 | 2 |
| Tenesmus | 1 | 3 | 1 | 2 |
| Urgency | 2 | 6 | 2 | 4 |

**Efficacy Results**

Treatment success was defined as a reduction in number of incontinence episodes from baseline by more than 50% ($Responder_{50}$). The proportion $Responder_{50}$ was 44% (15 of 34 patients) at 6 months, 56% (19 of 34 patients) at 12 months, and 59% (19 of 32 patients) at 24 months.

In addition, the Miller Score was shown to have a decrease (improvement) at 6, 12 and 24 months and patient global assessment of improvement showed that 77%, 74%, and 79% considered themselves improved at 6, 12, and 24 months, respectively.

**Conclusions Drawn from Study**

The safety and efficacy results are similar to those observed in the Pivotal IDE study. The proportion $Responder_{50}$ at 12 months was 55.9%, which was shown to be maintained through 24 months. The safety profile was similar to that observed in the Pivotal IDE study.

## XII. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on December 2, 2010, the Gastroenterology and Urology Devices Advisory Panel indicated to CDRH that Solesta provided adequate assurance of safety, effectiveness, and a favorable risk/benefit ratio. The meeting transcript may be accessed at the following webpage:

http://www.fda.gov/downloads/AdvisoryCommittees/CommitteesMeetingMaterials/MedicalDevices/MedicalDevicesAdvisoryCommittee/Gastroenterology-UrologyDevicesPanel/UCM242373.pdf

B. FDA's Post-Panel Action

The panel recommended that there be additional post-approval study to further assess durability of the product. There was some sentiment that a post-approval study should include an investigation via imaging of the location of the injections over time. Both of these recommendations have been incorporated into the proposed design of a post-approval study. The panel also recommended that "conservative" be better defined in the indications for use, since it can have different meaning to different disease conditions. Although not unanimous, there was a recommendation to more strongly encourage the use of prophylactic antibiotics. These recommendations were incorporated into the final labeling.

## XIII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

### A. Safety Conclusions

- Solesta is composed of the same materials as Deflux (P000029), which has been approved for the treatment of children with vesicoureteral reflux (VUR) grades II-IV. The data established from this approval adds to the safety profile of the product, although it is used in a different area of the body. Preclinical testing has also been performed with the material to evaluate the biocompatibility and 12 month durability of Solesta in a canine model, demonstrating its appropriateness for the study of the material for the proposed intended use.

- The adverse effects of the device are based on data collected in clinical studies conducted to support PMA approval as described above. In total, from the three (3) studies described above, clinical safety data are available from 346 patients who had received a total of 566 treatments and followed for 18 to 24 months after last treatment. In the Pivotal IDE (primary) study, the most common adverse events were proctalgia, minor anal or rectal bleeding, and pyrexia. The majority (97%) of the treatment-related events were of mild to moderate intensity and required no intervention, medical intervention, or other simple intervention (e.g., application of pressure, silicon ointment, water irrigation, warm baths) and resolved without sequelae. The median time to resolution of Solesta-related AEs was 6 days (range 1 to 725 days) after occurrence. As discussed by the FDA advisory panel, the types of adverse events reported were similar to those that could be expected for a procedure performed in the anorectal region.

- There were no deaths associated with Solesta treatment. There were a total of nine (9) serious treatment-related adverse events reported in seven (7) patients, all of which resolved without sequelae following intervention. The majority of events resolved within 36 days (range 6 to 168 days) after occurrence.

### B. Effectiveness Conclusions

- The 3-part success criteria of the pre-specified primary objective of the study were met. Statistical superiority for Solesta against Sham was demonstrated and treatment efficacy and durability achieved a pre-defined minimum level at 6 months. Lastly, open-label treatment efficacy and durability achieved a pre-defined minimum level at 12 months.

- Although the study was not powered to demonstrate a statistical difference, the results of the secondary efficacy analyses showed benefit over Sham in number of incontinence-free days. Patients treated with Solesta also had improvements in quality of life, although the Sham group also showed improvement. In the quality of life assessment, all of the four (4) elements demonstrated improvement over sham at 6 months, although the clinical significance of these improvements is unclear.

### C. Overall Conclusions

- The data in this application support the reasonable assurance of safety and effectiveness of this device when used in accordance with the indications for use. Solesta provides improvement in some patients suffering from FI for up to 12 months after treatment. At 6 months, there was a statistically significantly larger proportion of responders in the Solesta group compared to the sham group (primary endpoint), and an observed reduction in the number of incontinence episodes in both the Solesta and the Sham group. A positive improvement in the number of incontinence-free days, CCFIS score, and in quality of life was also observed in both groups, and the Solesta group showed greater observed changes in each of these secondary endpoints. The observed Solesta treatment effect was sustained for up to 12 months.

- There is a significant unmet need for patients who suffer from fecal incontinence. The benefits of treatment with Solesta for a portion of these patients outweigh the associated risks. Based on the pivotal study data, a number of patients demonstrated clinical improvement with Solesta, although it is difficult to predict which patients may respond to Solesta treatment.

## XIV. CDRH DECISION

CDRH issued an approval order on May 27, 2011. The final conditions of approval cited in the approval order are described below. As a condition of approval, Oceana must conduct the following post-approval study:

*Assessment of Long Term Safety and Durability of Solesta*: This will be a single-arm, multi-center observational study to address the following questions: (a) What is the safety and durability of the Solesta Injectable Bulking Agent in the treatment of fecal incontinence (FI) when the product is used in a real world setting through 36 months? (b) What is the device-related injection, peri-injection and long-term complications with Solesta Injectable Bulking Agent through 36 months? (c) What is the rate of device-related adverse events in subjects

treated with or without prophylactic antibiotics prior to injection?; and (d) What is the relative anatomic stability of the Solesta Injectable Bulking Agent?

The study will include patients age 18-75 who have failed conservative treatment and meet the specified inclusion criteria. A total of 293 subjects will be enrolled to achieve 150 evaluable subjects at 36 months. Subjects will be enrolled in at least 10-15 sites. The total length of follow-up will be 36 months from the last Solesta treatment. Patients will be evaluated at 3, 6, 12, 24 and 36 months. The Fecal Incontinence Quality of Life (FIQL) score and Cleveland Clinic Florida Incontinence Score (CCFIS) will be collected at baseline and 12 and 36 months after last treatment. A patient global assessment of improvement will be performed at 12 and 36 months after last treatment. An additional FIQL score, CCFIS score and patient global assessment of improvement will also be performed prior to a patient receiving additional FI interventions.

Primary effectiveness endpoint is treatment durability as defined by re-intervention for fecal incontinence including any of the following FI treatments: sphincteroplasty, implantation of artificial bowel sphincter, retreatment with Solesta, graciloplasty, Sacral Nerve Stimulation (SNS), or other surgical interventions. Retreatment with Solesta can occur within the first 3 months, and will not be considered a re-intervention.

Safety endpoints include all adverse events, which will be collected at each visit will be evaluated for device-relatedness. Patients will be specifically queried to the presence of rectal abscess, post-treatment fever, and proctitis.

The main study hypothesis is that the re-intervention rate within 3-years is less than 50%. You will perform an exact binomial test and time to first and any subsequent re-intervention for fecal incontinence using Kaplan-Meier curves with 95% confidence intervals. The mean, median, and range in number of interventions in patients with 1, 2, and 3-years of follow-up will be reported.

A sub-study will be conducted at 3 to 4 sites aimed at providing 30 evaluable subjects to evaluate the anatomic stability of Solesta by comparing anatomical positioning via transrectal ultrasound at time of injection to positioning at 6- and 36-months.

The applicant's manufacturing facility was inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

## XV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.