

**Sponsor Summary for Solesta<sup>®</sup>  
P100014**

**Center for Devices and Radiological Health (CDRH) Advisory Panel**

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**Oceana Therapeutics Inc.**

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## 1 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

AE	Adverse Event is any untoward medical occurrence in a patient using a medical device.
ANCOVA	Analysis of Covariance
CCFIS	Cleveland Clinic Florida Incontinence Score
CDRH	Center for Devices and Radiological Health
DX	Dextranomer
FDA	Food and Drug Administration
FI	Fecal Incontinence
FIQL	Fecal Incontinence Quality of Life Scale
IDE	Investigational Device Exemption
ITT	Intent-To-Treat population
LOCF	Last Observation Carried Forward
LSM	Least Square Mean
LTFU	Lost to Follow-up
MedDRA	Medical Dictionary for Regulatory Activities
NASHA®	Stabilized Non-Animal Sodium Hyaluronate
NASHA/Dx Fecal	Solesta Investigational Product – Dextranomer in a gel of stabilized non-animal sodium hyaluronate
OC	Observed Case
ODE	Office of Device Evaluation
PIM	Primary Imputation Model
PMA	Premarket Approval Application
Responder <sub>x</sub>	At least “x” % improvement from baseline
SADE	Serious Adverse Device Effect – SAE related to treatment
SAE	Serious Adverse Event

## 2 INTRODUCTION

This premarket approval (PMA) application is submitted to support the safety and effectiveness of Solesta®, an injectable bulking agent for the treatment of fecal incontinence (FI) in adult patients who have failed conservative therapy. This PMA is currently under review by the Office of Device Evaluation (ODE) within the Center for Devices and Radiological Health (CDRH) of the U.S. Food and Drug Administration (FDA).

FI can disrupt the lives of people who suffer from it. Inability to control the passage of stool or flatus can produce embarrassment, and fear of such episodes may limit a person's normal daily activities. These patients frequently suffer with shame and self-imposed social isolation. FI is a complex condition that often has a multifactorial etiology including obstetric trauma, injuries to the pelvic floor and/or sphincter complex, pelvic floor weakness due to neurologic impairment, and chronic diseases that alter the stool or rectal reservoir. A recent US epidemiologic study estimates prevalence of FI at 8.3 % in the non-institutionalized adult population<sup>1</sup>.

Current treatment options for FI in the US comprise either non-invasive conservative therapies or more invasive surgical treatments. Non-invasive therapies are often tried at first, but they are not effective for many patients. These include dietary modification, anti-diarrheal agents, pelvic floor exercise and biofeedback. Depending on the etiology and severity of the FI condition, a range of surgical treatments including surgical repair of the anal sphincter or implantation of an artificial bowel sphincter device are available. Unfortunately, for those who do undergo surgical treatment, the effect of surgical repair of the anal sphincter is not durable and the implantation of the artificial bowel sphincter is associated with considerable morbidity and requires steep learning curves. Failure of surgical treatment often leaves few treatment options other than permanent end colostomy. A considerable treatment void exists for patients who fail non-invasive treatment, and who are not suitable candidates for the available surgical therapy. This void represents a need for new treatments for FI that are effective in reducing FI episodes to restore a more normal quality of life, and that are also safe and minimally invasive.

Favorable outcome following use of injectable bulking agents for the treatment of FI has been described in patients with sufficient integrity of anal structures to support injection in case series, open-label trials and single-blind randomized controlled trials<sup>2, 3, 4, 5, 6</sup>.

Solesta is an injectable bulking agent comprising dextranomer microspheres and sodium hyaluronate, both well known biosynthesized polysaccharides, and has a history of safe use. Solesta has the exact same composition as Deflux® which has been approved for the treatment of children with vesicoureteral reflux by the FDA since 2001. Solesta has been approved for treatment of FI in Europe since 2006 and Canada since 2007. Solesta is administered submucosally in the anorectal area in an outpatient setting, under direct visual control through an anoscope, and requires no anesthesia.

This PMA contains clinical data from 3 prospective trials involving 346 patients who have received a total of 566 Solesta treatments, and who were followed up for 12 to 24 months after

treatment. All three studies utilized similar eligibility criteria and used exactly the same procedure for administering Solesta. For the primary efficacy assessment, a responder analysis based on a decrease in the number of FI episodes recorded in a patient diary was used in all three studies, which constitutes a measure of clinically meaningful treatment outcome for patients.

The pivotal study is a randomized sham-controlled, evaluator and patient-blinded, multicenter clinical study of 206 patients conducted under an IDE (Pivotal IDE study). The clinical data presented constitute the highest level of valid scientific evidence. The study design and 3 pre-specified study success criteria for the primary objective were developed with interaction and feedback from the FDA. All 3 pre-specified success criteria were met: 1) Solesta was superior to Sham at 6 months after treatment; 2) the effect shown in the Solesta treatment group met a pre-defined threshold for clinical significance; and 3) durability of the effect of Solesta for up to 12 months after treatment was shown. Compared to Sham, greater improvements in quality of life and other secondary endpoints have been demonstrated, supporting clinical meaningfulness of effect of Solesta in the target FI population.

The two additional clinical studies submitted in this PMA are: 1) a prospective, multicenter, Open-Label study of 115 patients conducted outside the United States, and 2) a single center Proof-of-Concept study of 34 patients conducted at one site in Sweden. Clinical data from these three studies together present a reasonable assurance of the safety, tolerability, clinical effectiveness and durability of effect of Solesta for the treatment of patients with FI.

This sponsor summary provides details of the Study Design and Outcomes from the clinical studies and additional background information as follows for panel member review:

- Overview of FI and current treatment options([Section 3](#))
- Product Description for Solesta ([Sections 4](#))
- Product History and Development ([Section 5](#))
- Overview of Clinical Studies ([Section 6](#))
- Details on Pivotal IDE Study Design and Results ([Section 7](#))
- Summary of Supportive Studies ([Section 8](#))
- Summary of Solesta Clinical Data ([Section 9](#))
- Risk-Benefit Evaluation ([Section 10](#))
- Patient Safety Post-Approval ([Section 11](#))
- Overall Summary and Conclusions ([Section 12](#))
- Appendices ([Section 13](#))
- References ([Section 14](#))



### **3 OVERVIEW OF FECAL INCONTINENCE AND CURRENT TREATMENT OPTIONS**

#### **3.1 Fecal Incontinence – A debilitating medical condition**

The American Society of Colon and Rectal Surgeons (ASCRS) defines FI as “the impaired ability to control gas or stool, ranging in severity from mild difficulty with gas control to complete loss of control over liquid and formed stools” <sup>7</sup>.

A recent publication regarding a validated FI severity scale included in the National Health and Nutrition Examination Survey (NHANES) 2005-2006 reported the prevalence of FI in non-institutionalized US adults at 8.3 % with a prevalence of 15.3 % in participants aged 70 years or older . FI episodes occurred at least weekly in 2.7 % of the participants.

Normal control of defecation is a complex interplay of proper functioning of the colon and rectum, the anal sphincter and the pelvic floor, the neurologic system, and the amount and consistency of fecal material. The pathophysiology of FI is often multifactorial resulting from a combination of defects affecting the control of defecation, compounded by changes associated with aging.

Obstetric trauma resulting from anatomical disruption of the anal sphincter muscles or neural damage is one of the most common etiologies of FI <sup>8</sup>. Other etiologies may include spinal cord injury, surgical or other trauma, or may be idiopathic in origin <sup>9</sup>. Patients with FI frequently also suffer from urinary incontinence <sup>1, 10</sup>.

Inability to control the passage of stool or flatus can dramatically disrupt the lives of people who suffer from it and become an insidious burden on their quality of life. Patients with FI, are reluctant to disclose the problem to others, with only 5-27 % seeking help from their doctors <sup>11</sup>. Lack of disclosure may be to the result of embarrassment, the erroneous belief that FI is a normal part of aging, or the perception that no treatment is available. Validated quality of life instruments repeatedly demonstrate that patients who suffer from FI are severely limited in their ability to engage in life’s normal pleasures – activities that can be restricted include leaving the home, visiting with friends, sexual relations, and work <sup>12, 13, 14, 15</sup>. These patients frequently suffer with shame and self-imposed social isolation . Elderly patients may require early admission to a nursing home .

There is an economic effect on society as well, although not well quantified in the literature; one manuscript reports the costs of evaluating and managing an FI patient at over a half million dollars <sup>16</sup>.

#### **3.2 Treatment Options for Fecal Incontinence – The unmet need**

In the US, FI is managed with a variety of different therapeutic modalities. Non-invasive techniques for management of FI include dietary modification, antidiarrheal medication, and biofeedback. These non-invasive treatments, referred to as conservative therapy in this summary, do not provide adequate relief for some patients with FI.

Surgical approaches employed include sphincteroplasty or sphincter repair, implantation of an artificial bowel sphincter and radio-frequency ablation of the tissue of the anal canal, and ileostomy/colostomy for intractable cases of FI. Muscle transposition of the gracilis muscle around the anus in combination with the use of an electric pulse generator is no longer performed in the US.

The available surgical interventions are appropriate only in a smaller group of FI patients. For example, sphincteroplasty is performed in patients with an identifiable anatomical defect to the anal sphincter. During sphincteroplasty, the sphincter is reconstructed to form a complete ring around the anus. Overlapping sphincteroplasty has been the predominant technique of repair used by colon and rectal surgeons during the last three decades<sup>17, 18</sup>. Overlapping sphincteroplasty is reported to provide equivalent effectiveness to direct sphincter repair<sup>19, 20, 21</sup>. While anal sphincter repair often confers good-to-excellent short-term outcomes in 31 to 83 percent of patients, the benefits of sphincteroplasty tend to deteriorate with time, as reported in the practice guidelines for FI developed by the Standards Practice Task Force of the ASCRS<sup>22</sup>. Complications of surgical repair of the sphincter may include post-operative infections, poor wound healing, or post-operative pain, and constipation.

The only implantable medical device approved in the US for FI is the Acticon neosphincter, which has been approved under a PMA (P010020). The neosphincter is an implantable, fluid filled, solid silicone elastomer device, consisting of three interconnected components: an occlusive cuff, a pressure-regulating balloon and a control pump with a septum. The neosphincter has a role in the treatment of severe FI especially in patients with significant sphincter disruption; a success rate of 53 % was reported in one multi-center study<sup>23</sup>. Common adverse effects following implantation of the neosphincter are pain and discomfort, infection, erosion of the tissues surrounding the sphincter or control components. Other adverse effects include migration of implanted components, wear and failure of neosphincter components, wound problems associated with the surgical procedure, and difficulty in managing the pressure changes required for proper operation of the device<sup>24, 25, 26, 27</sup>. Rates of surgical removal have been reported to be between 20-37 % but are seen to decline with increased experience.

The SECCA<sup>®</sup> procedure utilizes a 510(k)-cleared radiofrequency ablation device. It is based on the concept that collagen deposition and subsequent scarring may increase the ability to recognize and retain stool and promote continence. The Standards Practice Task Force of the ASCRS in their review confers a level IV evidence grade with inconsistent findings for this procedure and states that it might be useful for selected patients with moderate FI. In the peer-reviewed scientific literature, evidence to support the safety and efficacy of the SECCA procedure for the treatment of FI is primarily in the form of prospective case series with small patient populations (8–50 patients). Complications of the SECCA procedure include mucosal ulceration secondary to insufficient mucosal cooling, post-operative anal pain, and delayed bleeding<sup>28, 29</sup>.

There is an unmet medical need in the treatment of FI. FI is a significant medical condition that leads to diminished quality of life. Non-invasive, conservative therapies are not effective for many patients. Surgical repair or implantation of a neosphincter medical device have been

shown to be effective in selected patients, but are associated with significant adverse effects. Long-term failure of surgical treatments is recognized. Patients who are not helped by non-invasive therapy and who either are not appropriate candidates for surgery or experience a recurrence of FI some time following the surgical procedure, have few alternative treatment options. There is a need for new treatments for FI that are effective in reducing FI episodes but are also safe and minimally invasive.

Injectable bulking agents are not currently available in the U.S., but have been reported on in the literature. Bulking agents used in clinical trial settings appear to provide a meaningful treatment effect and may serve as alternative or adjunctive therapeutics to current treatment options in FI patients with sufficient integrity of anal structures to support injection. The majority of the published reports comprise uncontrolled trials and case series, both prospective and non-prospectively defined. Only a few single-blind randomized controlled trials have been performed<sup>2,4,5,6</sup>. While these trials generally include small numbers of patients and the methodological quality of the studies varies, the available evidence lends support to the safety and effectiveness of bulking agents in treatment of FI.

Solesta is a bulking agent developed with the goal of meeting this unmet patient need. The Pivotal Solesta IDE study is the first known sham-controlled RCT study with valid scientific evidence to demonstrate and confirm the safety and effectiveness of a bulking agent in the treatment of FI. The clinical benefit of Solesta is also documented in two other prospective studies included in this PMA submission.

## **4 SOLESTA**

### **4.1 Device Description and Properties – A biocompatible gel**

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

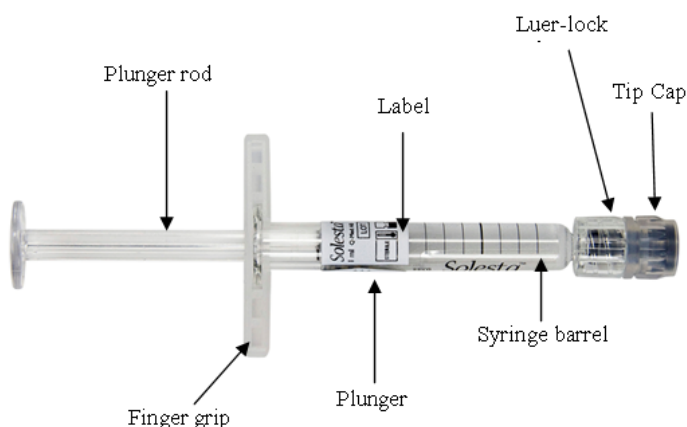
Solesta is a sterile, viscous gel contained in a disposable 1 mL assembled glass syringe with a standard luer-lock fitting. The syringe is equipped with a plunger stopper, a plunger rod and a finger grip. A transparent label with indicative volume markings, batch number and expiry date is fitted onto 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. The Sterican® needle used for injection of Solesta is 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.

Solesta consists of exactly the same composition and primary packaging as Deflux®. Deflux is indicated for treatment of children with vesicoureteral reflux (VUR) grades II-IV and was originally approved in September 2001 under PMA P000029. Deflux has been used in over 200,000 treatment procedures worldwide with proven safety.

Both Solesta and Deflux are manufactured by Q-Med AB at the same manufacturing site in Uppsala, Sweden. The manufacturing facility has been inspected by the FDA and is compliant with the FDA Quality System Regulation (21 CFR 820).

A picture of the Solesta syringe is shown in [Figure 1](#) and the composition of Solesta is provided in [Table 1](#) below.

**Figure 1 Solesta syringe**



**Table 1 Composition of Solesta**

Ingredients		Each mL contains
<b>Main Ingredients:</b>		
	Dextranomer (DX)	50 mg
	Sodium hyaluronate, stabilized <sup>(a)</sup>	15 mg
<b>Other Ingredients <sup>(b)</sup>:</b>		
	Sodium Chloride	9 mg
	KH <sub>2</sub> PO <sub>4</sub>	0.03 mg
	Na <sub>2</sub> HPO <sub>4</sub> x 2H <sub>2</sub> O	0.14 mg
	Water for Injection (WFI)	Add up to 1 mL

<sup>(a)</sup> Produced from Sodium Hyaluronate Pharma Grade and BDDE.

<sup>(b)</sup> HCl and NaOH are used for pH adjustment.

The dextranomer (DX) consists of microspheres of dextran chains cross-linked into a three-dimensional network. Dextran is a polysaccharide comprising glucose units. The dextran is biosynthesized by fermentation from *Leuconostoc Mesenteroides* species of bacteria and is thereby of non-animal origin. DX is insoluble in water and organic solvents. The microspheres are hydrophilic and swell in water.

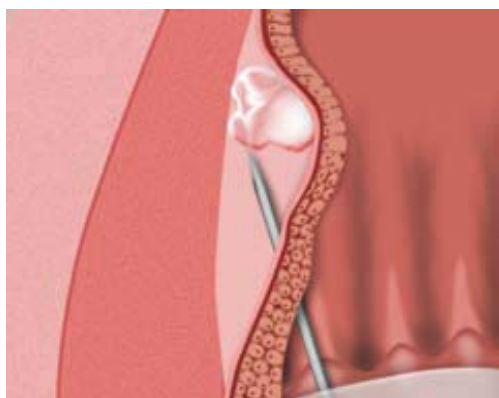
The sodium hyaluronate gel consists of sodium hyaluronate (HA) chains stabilized into a three-dimensional network and swelled in phosphate buffered 0.9 % sodium chloride solution. HA is a polysaccharide comprising of D-glucuronic acid and N-acetylglucosamine units. The HA used is biosynthesized by fermentation from *Streptococcus* species of bacteria and is thereby also of non-animal origin. The gel is insoluble in water and organic solvents. The gel is hydrophilic and swells in water.

The diameter of the dextranomer microspheres is within 80 to 250  $\mu\text{m}$  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 in the rectal tissue and in clinical studies, Solesta has been seen to offer a durable treatment effect for at least 24 months.

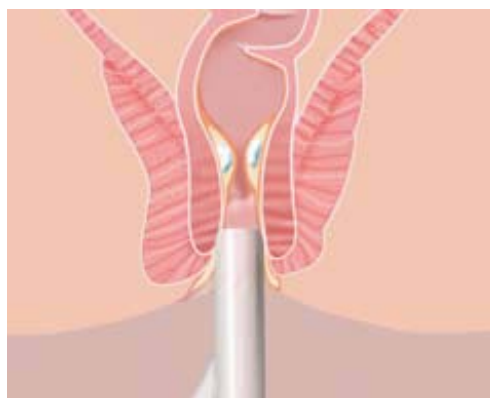
#### 4.2 Implantation of Solesta – An out-patient procedure

Solesta is a bulking agent which is to be injected into the deep submucosal layer in the proximal part of the high pressure zone of the anal canal, as illustrated in Figure 2. For each treatment, a series of 4 equally spaced injections with 1 mL of Solesta each (i.e., 4 mL in total) is performed approximately 5 mm proximal to the dentate line at the anorectal junction through an anoscope. This area lacks pain sensory innervation so the injections are relatively painless. The treatment is administered as an out-patient procedure without anesthesia following an enema evacuation of the anal canal. Prophylactic antibiotics and additional local antiseptics (such as Betadine) can be administered if clinically motivated based on the patients medical history and medical condition. If the patient remains incontinent after initial treatment a re-treatment may be performed in the same fashion.

**Figure 2 Schematic illustration of the Solesta injection in the anal canal**



a) After insertion of the needle, 1 mL of Solesta is injected underneath the lining of the anal canal.



b) The injection is repeated at the remaining three injection sites.

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 FI has only been studied in patients with an intact or partially functioning anorectal sphincter.

## 5 PRODUCT HISTORY AND DEVELOPMENT: SOLESTA

### 5.1 Regulatory History

Q-Med Scandinavia Inc. filed an IDE, on behalf of Q-Med AB, on May 16, 2005 to initiate a randomized Sham-controlled study for Solesta (known as NASHA/Dx Fecal in the study) in the treatment of FI. The IDE was assigned G050099 and was conditionally approved by the FDA on June 16, 2005. The IDE was fully approved on April 4, 2006.

In June 2009, Q-Med Scandinavia Inc. was acquired by Oceana Therapeutics LLC and Oceana Therapeutics Inc. is now the sponsor of the above referenced IDE. Q-Med AB is the manufacturer of Solesta.

Q-Med and Oceana Therapeutics have worked interactively with the FDA at every stage of development, from the pre-IDE through the IDE stage until PMA submission. The FDA review team has provided valuable feedback, which has been incorporated into the preclinical and clinical testing for Solesta whenever possible.

### 5.2 Pre-clinical Evaluation of Solesta

As previously noted, Solesta and Deflux have an identical chemical formulation and therefore, the biocompatibility tests performed on Deflux are applicable to demonstrate the biocompatibility of Solesta. The major part of the pre-clinical program for Solesta is therefore identical to the program already approved by the FDA for Deflux. In addition to the ISO 10993 biocompatibility tests, animal implantation testing in dogs and chronic toxicity testing in rodents have been performed specifically at the request of the FDA to evaluate the biological response to Solesta. The pre-clinical program for Solesta is summarized in [Table 2](#).

**Table 2 Pre-clinical program for Solesta**

Study Title	Results
<b>Toxicological studies</b>	
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) direct contact test	Non-toxic
Cytotoxicity study using the colony assay-extraction method	Non-toxic
Ames test	Not genotoxic



Study Title	Results
Mouse lymphoma assay	Not genotoxic
Mouse micronucleus test	Not genotoxic
Mouse peripheral blood micronucleus study, solution	Not genotoxic
In vitro mammalian chromosome aberration test performed with human lymphocytes	Not genotoxic
<b>Immunological studies</b>	
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
<b>Biocompatibility studies</b>	
ISO muscle implantation study, 4 week	Slight irritant
ISO muscle implantation study, 26 week	Slight irritant
ISO muscle implantation study, 52 week	Non-irritant

Long term implantation studies in the submucosal area of the rectal wall in dogs were conducted at the specific request of the FDA. No significant clinical observations were made during the studies. No major abnormalities were observed at the injection sites. The results demonstrate that when Solesta is properly implanted in the rectal submucosa, it is durable up to 12 months and the local tolerance in the perirectal sub-mucosal layer of the rectum is good. In addition distant migration of Solesta was not identified in the dog study (lymph node, liver or lung), nor was it witnessed in similar studies conducted in rabbits and rats.

The primary conclusion of all pre-clinical studies is that Solesta is composed of well tolerated materials without any signs of cytotoxicity, genotoxicity, local or systemic toxicity. The findings in the biocompatibility studies are typical of implanted materials and do not raise any safety concerns. Therefore, the preclinical evaluation has demonstrated that Solesta is safe and biocompatible when injected in the anorectal region of the intestinal submucosa for the proposed intended use.

## 6 OVERVIEW OF CLINICAL STUDIES

Clinical data supporting the safety and effectiveness of Solesta are available from three clinical studies:

1) A pivotal, prospective, multicenter, randomized, Sham-controlled double blind study of 206 patients conducted under an IDE (Pivotal IDE),

- 2) A prospective, multicenter, open-label study of 115 patients conducted outside the United States (OUS Open-Label), and
- 3) A single center Proof-of-Concept study of 34 patients conducted at one site in Sweden (Proof-of-Concept).

The Pivotal IDE study also included a cross-over option for patients initially randomized to Sham. These patients receive open-label treatment with Solesta and provide additional supporting safety and efficacy data.

The Pivotal IDE study and the OUS Open-Label study were sponsored studies while the Proof-of-Concept study was an investigator initiated study. In this summary document, an overview of each of the three clinical studies is provided first, followed by a summary of the consolidated study data. The overall analysis of the available efficacy and safety data focuses primarily on the 12-month data from the two sponsored studies because of access to the entire data sets and identical coding systems for safety information. In addition, safety data to 18-months from both of these two studies have been included and they confirm the safety of Solesta treatment.

Taken together, the clinical data provide a reasonable assurance of the safety and effectiveness of Solesta for the treatment of patients with FI. [Table 3](#) below provides an overview of the number of patients, the number of treatments and the duration of follow-up included in the clinical data for this PMA submission. All three studies utilized similar inclusion/exclusion criteria and all three studies used exactly the same procedure for administering Solesta. The study designs for the sponsored studies including treatment intervals, treatment doses and eligibility criteria were selected following the positive outcome from the prior Proof-of-Concept study.

**Table 3 Overview of three clinical studies supporting safety and effectiveness of Solesta.**

Study	Number of patients treated	Number of Solesta treatments*	Duration of observation period
<b>33DA0404</b> Pivotal IDE study – patients randomized to Solesta	136	249	12 months (18 months safety)
<b>33DA0404</b> Pivotal IDE study – Sham patients who received open-label Solesta	61	110	6 months (12 months safety)
<b>33DA0605</b> OUS Open-Label Study	115	154	12 months (18 months safety)
<b>Proof-of-Concept Study</b> Single Investigator Study	34	53	24 months
<b>Total</b>	<b>346</b>	<b>566</b>	

\* One re-treatment procedure was allowed in patients with persistent FI 1 month after initial treatment



All 3 clinical studies in the PMA were conducted in accordance with the Declaration of Helsinki and its amendments and in compliance with applicable regional and international regulations and guidelines governing the conduct of clinical trials with medical devices, and guidelines for Good Clinical Practice. The study protocols and subsequent protocol amendments were reviewed and approved by local IRBs for all sites and by regulatory authorities.

## 7 PIVOTAL IDE STUDY DESIGN AND RESULTS IN DETAIL

“33DA0404: A randomized, subject and evaluator blinded, sham-controlled, multicenter study to evaluate efficacy and safety of NASHA/Dx for the treatment of fecal incontinence.”

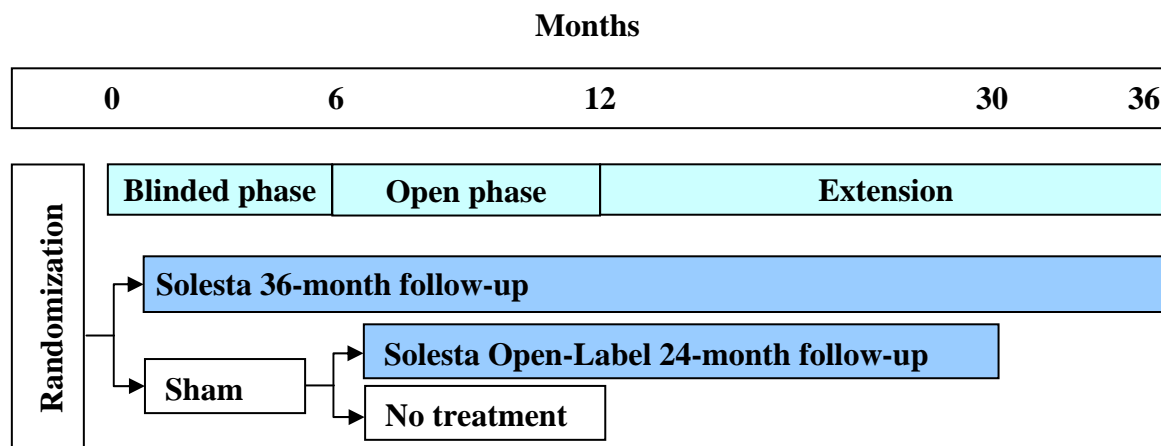
This Pivotal IDE study, representing the main body of clinical evidence in this PMA submission, is a rigorously designed and executed IDE clinical trial, which reflects the state of the art for trials of FI treatments as well as the specific recommendations of the FDA review team.

### 7.1 Investigational Plan

The study was performed within a clinical setting in 13 sites across the USA (8 sites), the UK (1), Germany (1) and Sweden (3) in 2 phases (illustrated in [Figure 3](#)):

- The first phase was a double-blind (evaluating investigator and patient), 2:1 randomized, parallel-group study comparing efficacy and safety of Solesta (denoted “NASHA/Dx Fecal” in the study) with Sham
- 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 patients previously randomized to Sham were offered open-label treatment with Solesta administered in connection with the 6-month study visits.

**Figure 3 Schematic outline of study design**



The primary objective of the study incorporated both efficacy and durability requirements for Solesta. These requirements were based on: firstly, a comparison of the results from the two treatment arms at month 6 of the blinded phase of the study, and secondly on the 12-month results for the patients randomized to Solesta. Additional, longer term data up to 36 months from randomization to further support effect durability and safety will be collected. This summary includes safety data through 18 months of follow-up.

Randomization was stratified by region and gender and the study included 206 patients. The first patient was screened on August 17, 2006 and randomized September 7, 2006. The last 12 month follow-up visit (6 months in the open phase) was performed on November 23, 2009 and the study database was locked on December 2, 2009 for the 12-month primary analysis dataset.

## **7.2 Primary Objective**

The primary objective, which was developed with interaction and feedback from the FDA, consisted of 3 parts which were pre-specified in the study protocol and all had to be fulfilled to claim success:

1. statistical superiority of Solesta in proportion Responder<sub>50</sub> (defined as the proportion of patients achieving 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 proportion Responder<sub>50</sub> 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 proportion Responder<sub>25</sub> (defined as the proportion of patients achieving at least 25 % reduction in number of incontinence episodes from baseline) in the Solesta treatment group at 12 months is larger than 50 %.

The primary endpoints (Responder<sub>25</sub> and Responder<sub>50</sub>) were based on the number of daily FI episodes recorded in a patient diary during a period of 14 days prior to the visit.

## **7.3 Secondary Objectives**

Supportive secondary objectives during the 6-month blinded phase were to determine:

- the safety of Solesta compared to Sham as measured by adverse events and
- the efficacy of Solesta compared to Sham at 3 and 6 months after last treatment as measured by diary data (i.e., change from baseline in number of FI episodes and number of incontinence-free days) and change from baseline in the Cleveland Clinic Florida Incontinence (CCFIS) score and the disease-specific Fecal Incontinence Quality of Life Scale (FIQL)

Supportive secondary objectives during the open phase were to determine, separately for each treatment group:

- the long-term safety of Solesta treatment as measured by adverse events, and

- the durability of the effect of Solesta treatment as measured by change from baseline in patient diary data (i.e., number of FI episodes, and number of incontinence-free days), FIQL and CCFIS.

### 7.3.1 FIQL

The FIQL assessment is a validated tool that is specifically designed to assess the impact of FI on a patient's quality of life. The FIQL instrument is divided into four domains reflecting the impact of quality of life as it pertains to Lifestyle, Coping/Behavior, Depression/Self perception and Embarrassment. The FIQL instrument consists of a total of 29 questions. Each response is assigned a value of 1 to 4, 5 or 6 and overall scores were calculated for each of the four domains. The more the patient is affected by FI the lower the value. A copy of the questionnaire is provided in [Appendix 3](#).

### 7.3.2 CCFIS

The CCFIS is a composite score based on a patient's recall using standardized questions regarding incidence and type of incontinence (solid, liquid or gas), pad usage and lifestyle alterations during the past 3 months. The score ranges from 0 (perfect) to 20 (complete incontinence). A CCFIS score of 10 or higher was required for eligibility in the study and for re-treatment. A score of 10 or higher in the CCFIS has been shown to correlate to a significant poorer quality of life compared to healthy individuals<sup>30</sup>. A copy of the questionnaire is provided in [Appendix 4](#).

## 7.4 Statistical Design and Sample Size

The statistical analyses including the success criteria for the primary efficacy objective were developed with interaction and feedback from the FDA prior to study start and were prospectively defined in the statistical analysis plan (SAP) prior to database lock and unblinding.

A statistical sample size calculation provided that 200 patients with a 2:1 randomization to Solesta vs. Sham would lead to a reasonable high probability of success in all three success criteria for the primary objective (80-90 % power) and also expand the safety database for the Solesta treatment.

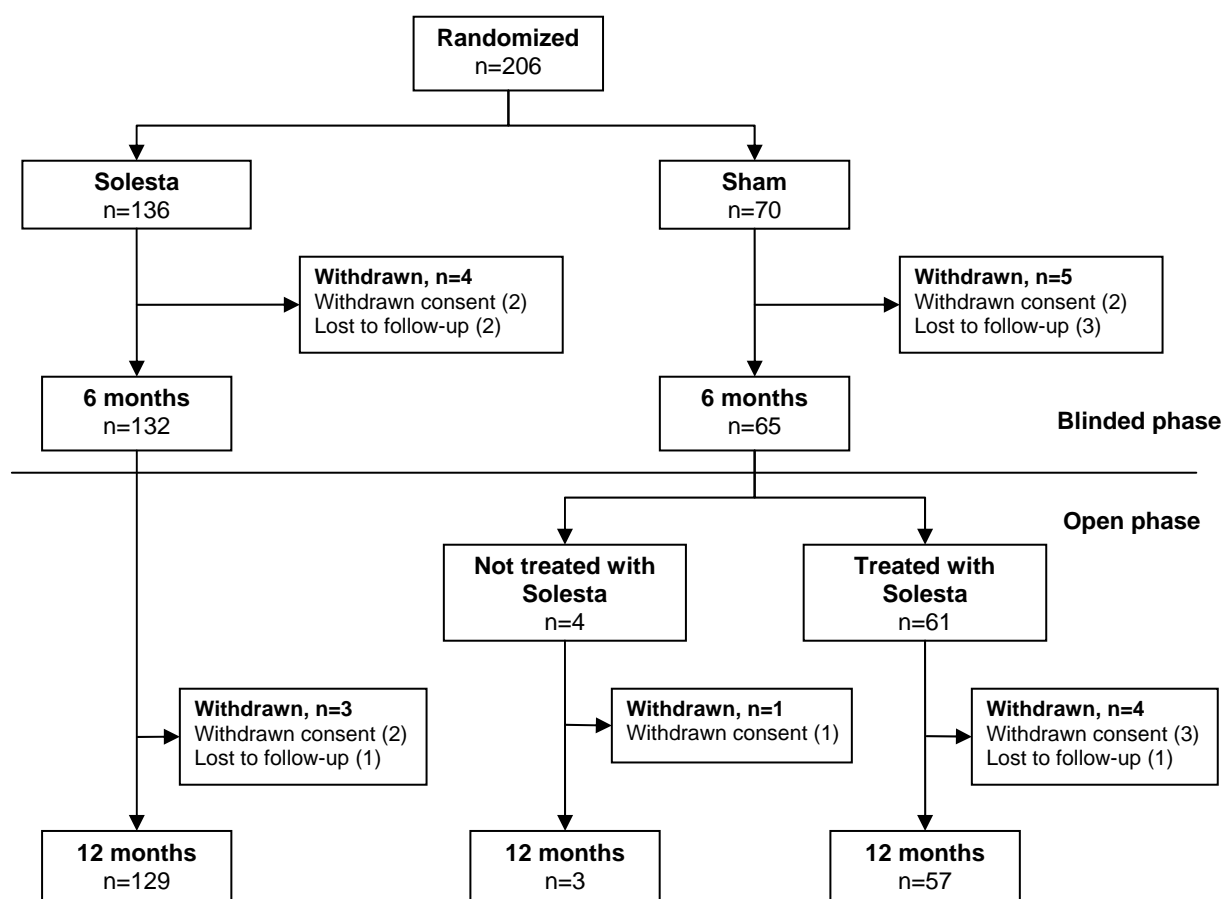
## 7.5 Patient Inclusion

The study included 206 patients of both genders 18-75 years of age, with a history of FI for at least 12 months, a CCFIS at baseline of  $\geq 10$ , and  $\geq 4$  FI episodes over a 14 day period. Furthermore, the patients had failed prior conservative treatment.

Patient exclusion criteria included: Incontinence to flatus only; complete external sphincter disruption; significant mucosal prolapse or transanal mucosal problems or full thickness rectal prolapse; current anorectal sepsis, tumors, fissures, proctitis, stenosis, grade IV hemorrhoids, or significant chronic anorectal pain; active IBD; prior anorectal surgery within 12 months;

There were 278 patients screened and of these, 206 were randomized into the study – 107 (52 %) US patients and 99 (48 %) European patients. Patient disposition is illustrated in Figure 4.

**Figure 4 Disposition of patients**



In total, 96 % of the patients completed the 6-month blinded phase of the study and 92 %, (including patients with and without open-label treatment) completed the 6-month visit in the open phase of the study. The reasons for premature study termination included consent withdrawal (n=10) and patient lost to follow-up (n=7). No deaths occurred in the study and no patient was withdrawn due to an AE

## 7.6 Randomization and Blinding

Eligible patients were randomized in a 2:1 ratio to Solesta or Sham according to a centralized web-based system administered by an independent vendor. The randomization was stratified by region (i.e., US and Europe) and gender balanced within blocks of consecutive patients using a fixed block size of six. There was no pre-defined minimum or maximum number of patients for each gender.

Blinding of the evaluating investigator was accomplished by using a separate investigator to administer the treatments. A blinded evaluator performed all efficacy evaluations or assessments during the blinded phase of the study. The patients were kept blind since the treatment was performed with the patient in the left lateral or prone position and they were therefore unable to see the injection procedure. All sponsor personnel remained blinded to the patients' treatment allocation until all decisions with respect to the classification of patients for the various analyses had been taken and the patients' dataset was locked for the blinded phase of the study.

### **7.7 Intervention**

Study treatment consisted of injections of four 1 mL injections of Solesta (i.e., 4 mL in total) or four Sham injections (needle sticks only). The injections were made into the submucosal layer of the anal canal at 4 positions, approximately 5 mm above the dentate line at the anorectal junction, through an anoscope. The injection procedure for Sham mimicked the active treatment procedure as closely as possible. As the Sham syringes were empty, the 4 separate syringes with mounted needles were used to pierce the mucosa without injecting anything and held in place for a period of time similar to the Solesta injections. The treatment was administered as an out-patient procedure without anesthesia following a Fleet enema evacuation of the anal canal. Prophylactic antibiotics were to be used at the investigators' discretion and were administered to 15 patients at 3 sites in the US. Additional local antiseptics (Betadine) could also be used at the investigators' discretion and were administered at one site. If the patient remained incontinent with a CCFIS score  $\geq 10$  one month after initial treatment a re-treatment with Solesta or Sham, respectively, was allowed. The re-treatment was to be given in the same fashion.

In total, 249 treatments with Solesta in 136 patients and 131 treatments with Sham in 70 patients were given during the blinded phase of the study. Sixty-one (61) of the 70 patients randomized to Sham were eligible for and received 110 treatments with Solesta in the open phase of the study. The number of treatments administered during the blinded phase was similar for both study products with 83 % and 87 % of the Solesta and Sham patient populations receiving a re-treatment. Likewise, during the open phase of the study the re-treatment rate for the Solesta open-label group was 80 %.

All but one randomized patient received the correct treatment in the blinded phase of the study. At the second treatment in the blinded phase, one patient who was randomized to Solesta erroneously received a Sham treatment instead. The patient did not receive another treatment with Solesta to compensate for this error. This patient has been analyzed as a Solesta patient for both safety and ITT efficacy.

### **7.8 Follow-up Schedule**

Patients had follow-up visits scheduled at 1, 3 and 6 months after randomization during the blinded phase. During the open phase, patients randomized to Solesta had follow-up visits at 9 and 12 months for the primary analysis, and thereafter were to have follow-up visits at 18, 24, 30 and 36 months from last treatment in the blinded phase. Patients randomized to Sham were

offered open-label treatment at month 6 and thereafter were to have follow-up visits 1, 3, 6, 12, 18 and 24 months after the last open-label treatment.

## 7.9 Demographics and Baseline Data

Demography and baseline characteristics were largely similar for patients in both treatment groups and by region. There were no clinically meaningful differences between treatment groups in any baseline or demographic parameter (Table 4).

**Table 4 Pivotal IDE study: Demographics – ITT population**

		<b>Solesta (n=136)</b>	<b>Sham (n=70)</b>	<b>ALL (n=206)</b>
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)
Body Mass Index, kg/m <sup>2</sup>	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)
Non-Caucasian	n (%)	14 (10.3)	11 (15.7)	25 (12.1)

As shown in Table 5, approximately, half of the patients had been symptomatic for over 5 years and the most common underlying cause of the condition (seen in 40 % of the patients) was attributed to obstetric injuries. All patients had tried at least one form of non-invasive treatment prior to inclusion in the study. Fourteen percent (14 %) of the patients had received a previous surgical intervention for their condition and 41 % of the study patients had ongoing urinary incontinence symptoms at baseline.

**Table 5 Pivotal IDE study: History of Fecal Incontinence – ITT population**

<b>History of fecal incontinence</b>		<b>Solesta (n=136)</b>	<b>Sham (n=70)</b>	<b>ALL (n=206)</b>
Duration of symptoms (12 months–5 years)	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)

History of fecal incontinence		Solesta (n=136)	Sham (n=70)	ALL (n=206)
Previous surgery for FI	n (%)	21 (15.4)	8 (11.4)	29 (14.1)

\* Includes: Dietary avoidance, fiber supplementation, and bowel habit training amongst others

Baseline characteristics for the 2 treatment groups are summarized in [Table 6](#). For both treatment groups at baseline, there was a wide range in number of leakage episodes over the 2-week diary period. The number of FI episodes ranged up to 172.0 in the Solesta group and up to 387.0 in the Sham group. Both groups had patients with high baseline numbers of FI episodes because there was no upper limit to number of FI episodes recorded in the patient diary at study inclusion.

**Table 6 Pivotal IDE study: Baseline characteristics – ITT population**

Baseline characteristics, Median [Range]	Solesta (n=136)	Sham (n=70)
<b>Baseline Patient diary data / 14 days</b>		
Number of FI episodes	15.0 (3.5-172.0)	12.5 (4.0-387.0)
Number of incontinence-free days	4.7 (0.0-11.0)	4.2(0.0-11.8)
<b>Baseline CCFIS score (0-20 point scale; 0 = continent, 20 = incontinent)</b>		
CCFIS score	14.0 (10.0-20.0)	13.0 (10.0-20.0)
<b>Baseline FIQL score / domain (low score = low QoL)</b>		
FIQL – Lifestyle score	2.8 (1.0-4.0)	2.7 (1.1-4.0)
FIQL – Coping/Behavior score	1.7 (1.0-3.8)	1.7 (1.0-4.0)
FIQL – Depression/Self-perception score	2.8 (1.1-4.4)	2.6 (1.0-4.4)
FIQL – Embarrassment score	1.7 (1.0-3.7)	1.7 (1.0-4.0)

## 7.10 Summary of Efficacy Analysis Plan

The efficacy objectives were chosen to provide clinically meaningful assessment of treatment response using reduction in FI episodes from baseline (from 14-day patient diary) and impact of treatment on quality of life (FIQL, CCFIS). The efficacy analyses were divided into two parts; one that described the blinded phase or the first 6 months following last treatment using formal comparisons of the two treatment groups, and the other the open phase where longer term data was presented over time for the Solesta group. The two 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.



### 7.10.1 Hypothesis

The first two parts of the primary objective were evaluated using a logistic regression model with treatment, center, gender, and baseline number of FI episodes as covariates. The first part involved testing a null hypothesis of equal proportions Responder<sub>50</sub> 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.

- An odds ratio of 1 indicates that a positive response is equally likely in both groups.
- An odds ratio greater than 1 indicates that a positive response is more likely in the Solesta group and an odds ratio less than 1 indicates that a positive response is more likely in the Sham group.

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

### 7.10.2 Blinded phase

The pre-specified analyses methods for the dichotomous responder variables, were a logistic regression model whereas for continuous variables, such as CCFIS and FIQL, 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 treatment groups. Least square means (LSM) estimates were obtained from the models. Apart from the outcome of these pre-specified statistical models, the study also includes supportive analyses of observed outcome rather than model estimates.

### 7.10.3 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 one-sample test (signed-rank test). Continuous variables with a limit on minimum and maximum outcome (such as CCFIS, FIQL, and number of incontinence-free days) were analyzed using a one-sample t-test (paired t-test). The dichotomous responder variables were presented by visit together with two-sided 95 % confidence intervals based on the normal approximation to the binomial distribution.

### 7.10.4 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. Methods for imputation of



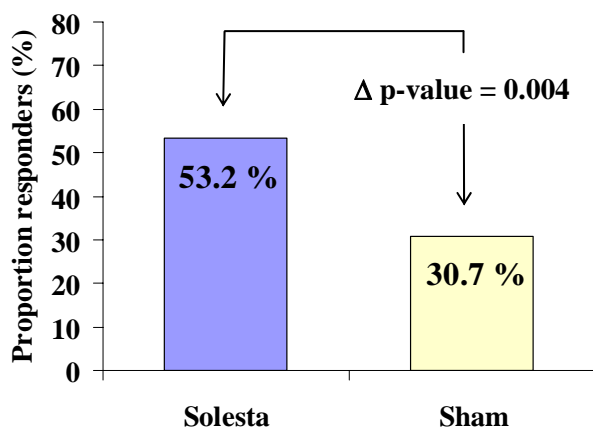
missing data were pre-specified in the study protocol and statistical analysis plan. Imputation of missing data was done using last observation carried forward (LOCF) and the Primary Imputation Model (PIM). In essence PIM is a mixture of LOCF and baseline carried forward and imputed all withdrawals as non-responders. PIM was the primary imputation model for the primary objective while LOCF was the primary model for all other analyses.

### 7.11 Primary Efficacy Results – Primary objective was achieved

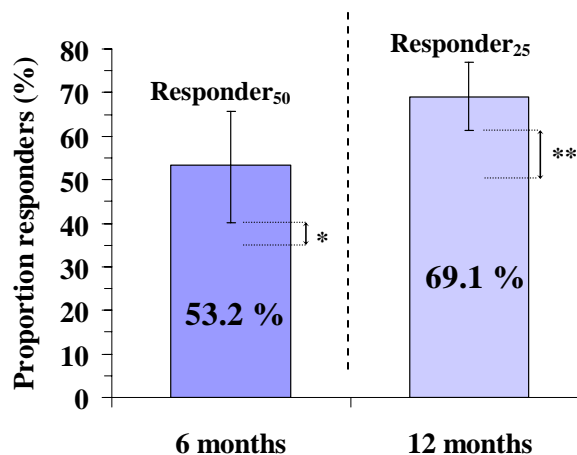
The study achieved the primary objective stated in the study protocol based on the pre-specified analyses in the statistical analysis plan. As illustrated below, superiority to Sham at 6 months was demonstrated (Figure 5) and treatment efficacy and durability achieved the predefined levels at 6 and 12 months (Figure 6).

Collectively, all three parts of the primary objective were fulfilled and the study success criteria were achieved. The results of the primary efficacy analyses are detailed in the sections below.

**Figure 5 Comparison of proportion Responder<sub>50</sub> at 6 months**



**Figure 6 Solesta – proportion responders at 6 and 12 months**



\* Responder<sub>50</sub> LCL = 40.2 % > 35 %

\*\* Responder<sub>25</sub> LCL = 61.4 % > 50 %

#### 7.11.1 Primary objective

The first part of the primary objective was a test of the null hypothesis of no difference between the treatment groups in proportion Responder<sub>50</sub> at 6 months; i.e., the success criterion was that the odds ratio (odds for Solesta divided by odds for Sham) was to be greater than 1 with 95 % confidence. The outcome is illustrated in Figure 5 above and shown in Table 7 below. The proportion Responder<sub>50</sub> was 53.2 % for the Solesta treatment group and 30.7 % for the Sham treatment group at 6 months. Since the odds ratio is statistically significantly larger

than 1 ( $p=0.004$ ) the first part of the primary objective to show superiority to Sham treatment was met at 6 months.

**Table 7 Primary efficacy: Odds ratio Solesta against Sham at 6 months – ITT population. PIM.**

Treatment	n	Odds ratio	LCL	UCL	p-value
Difference Solesta-Sham	206	2.56	1.34	4.90	0.004*

\* Test of  $H_0$ : odds ratio = 1; LCL/UCL = lower and upper confidence limit

The second part of the primary objective was to demonstrate a clinically relevant degree of efficacy at 6 months post treatment in the Solesta treatment group. The success criterion required that the lower limit of a two-sided 95 % confidence interval for Responder<sub>50</sub> was above 35 %. The outcome is illustrated in [Figure 6](#) above and shown in [Table 8](#) below. Since the lower limit of the confidence interval for Responder<sub>50</sub> for the Solesta group (LCL=40.2 %) was above the pre-defined success criterion of 35 % ( $p=0.005$ ) the second part of the primary objective (i.e., to demonstrate adequate efficacy at 6 months post treatment) was met.

**Table 8 Primary efficacy: Proportion Solesta Responder<sub>50</sub> at 6 months – ITT population. PIM.**

Treatment	n	Responder <sub>50</sub> LSM estimate (%)	LCL (%)	UCL (%)	p-value
Solesta	136	53.2	40.2	65.8	0.005*
Sham	70	30.7	19.0	45.6	

\* Test of  $H_0$ : proportion = 35 %; LSM = least square mean; LCL/UCL = lower and upper confidence limit

The third part of the primary objective was to demonstrate durability of the treatment effect at 12 months post treatment in the Solesta treatment group. The success criterion required that the lower limit of a two-sided 95 % confidence interval for Responder<sub>25</sub> was above 50 %. The outcome is displayed in [Table 9](#). The Responder<sub>25</sub> estimate at 12 months was 69.1 % and since the lower limit of the confidence interval (LCL=61.4 %) was above 50 % ( $p\text{-value}<0.001$ ), the third part of the primary objective (i.e., to show adequate efficacy at 12 months post treatment) was met.

**Table 9 Primary efficacy: Observed proportion Responder<sub>25</sub> at 12 months – ITT population. PIM.**

Treatment	n	Responder <sub>25</sub> point estimate (%)	LCL (%)	UCL (%)	p-value
Solesta	136	69.1	61.4	76.9	<0.001*

\* Test of  $H_0$ : proportion = 50 %; LCL/UCL = lower and upper confidence limit

With this, all three parts of the primary objective were met, demonstrating that Solesta is effective in the treatment of patients with FI.

#### 7.11.2 Supportive analyses

As a supportive analysis, the proportion Responder<sub>50</sub> based on change in number of incontinence episodes from baseline to 12 months in the Solesta group was determined. As displayed in Table 10 below, the observed proportion Responder<sub>50</sub> 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, which provides further evidence for the durability of a clinically meaningful treatment effect.

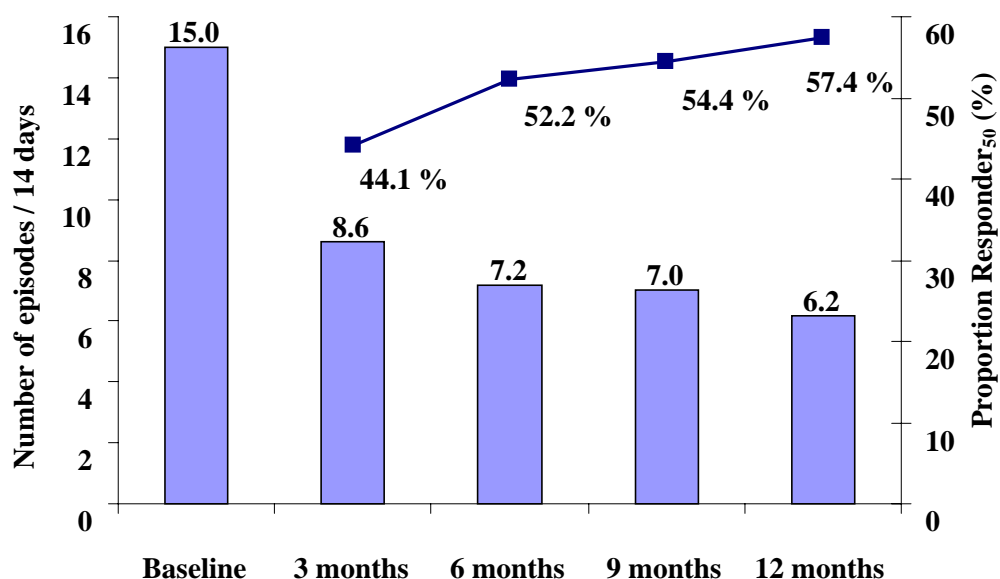
**Table 10 Supportive efficacy: Observed proportion Responder<sub>50</sub> at 12 months – ITT population. PIM.**

Treatment	n	Responder <sub>50</sub> point estimate (%)	LCL (%)	UCL (%)	P-value
Solesta	136	57.4	49.0	65.7	<0.001*

\* Test of  $H_0$ : proportion = 35 %; LCL/UCL = lower and upper confidence limit

The stable long term durability of Solesta in the treatment of FI for up to 12 months post treatment is further supported by the secondary efficacy analysis of change in number of incontinence episodes over time as illustrated in Figure 7.

**Figure 7 Median number of incontinence episodes and proportion (%) Responder<sub>50</sub> at each follow-up time point in the study – Solesta ITT population. LOCF.**



A positive treatment effect measured as decrease in number of incontinence episodes and proportion Responder<sub>50</sub> was observed 3 months after treatment. The treatment effect was seen to be improved further at 6 months and was durable through month 12. The Solesta group at baseline had a median of 15.0 incontinence episodes over 14 days which had decreased to 7.2 at 6 months and 6.2 at 12 months ( $p < 0.001$  at both time points). A stable proportion Responder<sub>50</sub> was seen during the study; 52.2 % at 6 months and 57.4 % at 12 months.

## **7.12 Secondary Efficacy Analyses – Provide support to primary efficacy results**

### **7.12.1 Analysis of FI episode data**

The secondary analyses included an investigation of the difference in change from baseline in number of incontinence episodes between the treatment groups. At 6 months from last treatment, there was a small difference in favor of Solesta in the mean reduction in number of FI episodes from baseline, see [Table 11](#) below. Both treatment groups however, had a number of patients who were outliers who affected the estimate of the mean values in each group at baseline because of high number of FI episodes. For example there were 7 patients (4 patients in the Solesta and 3 in the Sham group) who had over 100 episodes, during the 14-day diary period (Note that there was no upper limit for the number of incontinence episodes in the patient diary for inclusion into the study). Furthermore, these “outlier” patients influence the pre-specified statistical test for treatment comparison which is based on the difference in mean change from baseline. Due to the influence of the outliers, the results for the change in FI episodes are also presented using the median values along with a supportive non-parametric statistical test for treatment comparison, referred to as Wilcoxon rank-sum test, which is not sensitive to extreme values, see [Table 12](#), below.

### **7.12.2 Results of secondary efficacy analyses – Blinded phase**

The results of the analyses of the secondary objectives at month 6 in the blinded phase (primary time point) are summarized in [Table 11](#). The study was not powered to attain statistical significance when comparing the change from baseline in the secondary variables between the treatment groups. The secondary objectives in the study were intended only as supportive to the primary objective. As demonstrated in [Table 11](#), such support was achieved since the results trended in the same direction as the outcome of the primary analysis (i.e., the estimated treatment difference showed greater improvement in the Solesta group even if not statistically significant).

**Table 11 Secondary efficacy: Difference in change from baseline between Solesta and Sham in blinded phase. Pre-specified analyses of difference – ITT population. LOCF.**

Solesta - Sham Variable	Estimate of change from baseline		Estimate of difference (95 % CI)	p-value
	Solesta	Sham		
FI episodes (during 14-day diary period)				
Number of FI episodes*	-5.41	-5.37	-0.04 (-5.05:4.97)	0.988
Number of incontinence-free days <sup>†</sup>	3.08	1.96	1.11 (0.00:2.22)	0.049
Cleveland Clinic Florida Incontinence Score (CCFIS) (0 = continent; 20 = total incontinence)				
CCFIS score*	-3.06	-2.85	-0.21 (-1.15:0.72)	0.657
Fecal Incontinence Quality of Life (FIQL) scale (higher score = increased QoL)				
Coping/Behavior <sup>†</sup>	0.44	0.19	0.25 (0.08:0.43)	0.005
Lifestyle <sup>†</sup>	0.33	0.11	0.22 (0.04:0.40)	0.014
Depression/Self perception <sup>†</sup>	0.27	0.18	0.09 (-0.08:0.26)	0.287
Embarrassment <sup>†</sup>	0.53	0.38	0.16 (-0.05:0.36)	0.132

\* Negative value indicate improvement in change from baseline

<sup>†</sup> Positive value indicate improvement in change from baseline

As discussed in section 7.12.1 above, both treatment groups had a number of outliers that affected the estimate of the mean change from baseline in number of incontinence episodes in each group and thereby influenced the pre-specified statistical comparison between the two treatment-groups based on these mean values. Therefore, the change in number of incontinence episodes from baseline has also been presented with focus on the observed median values and has been compared between the treatment groups using a non-parametric statistical test. The results are displayed in Table 12, below.

**Table 12 Secondary efficacy: Difference in change from baseline between Solesta and Sham at 6 months in the blinded phase. Supportive analyses of difference – ITT population. LOCF**

Solesta - Sham Variable	Median change from baseline		Median difference	p-value <sup>‡</sup>
	Solesta	Sham		
Number of FI episodes	-6.0	-3.0	-3.00	0.090

<sup>‡</sup> Wilcoxon rank-sum test

### 7.12.3 Results of secondary efficacy analyses – Open phase

The 12-month efficacy analysis for Solesta is a secondary objective in the study aiming to show durability of the treatment effect. The outcomes from the analyses of the selected secondary objectives through month 12 in the study (primary time point) are summarized in [Table 13](#).

A stable long term effect of Solesta in the treatment of FI for up to 12 months post treatment was demonstrated. As displayed in [Table 13](#) and previously illustrated in [Figure 7](#), a positive treatment effect measured as decrease in number of incontinence episodes and in proportion Responder<sub>50</sub> was observed 3 months after treatment. The treatment effect was seen to be improved further at 6 months and was durable 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 ( $p < 0.001$ ). A stable proportion Responder<sub>50</sub> was seen during the study; 52.2 % at 6 months and 57.4 % at 12 months.

A similar durable effect was observed as an increase in number of incontinence-free days, and improvement in patient quality of life (FIQL) and CCFIS score. Significant improvement compared to baseline was observed at both 6 and 12 months in all four domains of the FIQL evaluation. There was an observed improvement in number of incontinence-free days from baseline to 3 months and through 12 months; improved from a mean of 4.4 days at baseline to 7.9 at 12 months. Mean CCFIS score decreased from 14.3 at baseline to 10.9 at 12 months.

**Table 13 Secondary efficacy: Observed change from baseline in the Solesta group through month 12 – ITT population. LOCF.**

Variable	3 months		6 months		9 months		12 months	
	Estimate	p-value	Estimate	p-value	Estimate	p-value	Estimate	p-value
<b>FI episodes (during 14-day diary period)</b>								
<u>Absolute change from baseline</u>								
Number of FI episodes, median	-4.8	<0.001	-6.0	<0.001	-6.3	<0.001	-7.0	<0.001
Number of incontinence-free days, mean	2.61	<0.001	3.13	<0.001	3.44	<0.001	3.44	<0.001

Variable	3 months		6 months		9 months		12 months	
	Estimate	p-value	Estimate	p-value	Estimate	p-value	Estimate	p-value
<b>Proportion responders</b>								
Responder <sub>25</sub> , <i>proportion</i>	57.4 %		66.2 %		65.4 %		69.1 %	
Responder <sub>50</sub> , <i>proportion</i>	44.1 %		52.2 %		54.4 %		57.4 %	
<b>Cleveland Clinic Florida Incontinence Score (CCFIS) (0 = continent; 20 = total incontinence)</b>								
Absolute change from baseline, <i>mean</i>	-2.59	<0.001	-2.45	<0.001	-3.25	<0.001	-3.47	<0.001
<b>Fecal Incontinence Quality of Life (FIQL) scale (higher score = increased QoL)</b>								
<u>Absolute change from baseline</u>								
Coping/Behavior, <i>mean</i>			0.42	<0.001			0.65	<0.001
Lifestyle, <i>mean</i>			0.29	<0.001			0.45	<0.001
Depression/Self perception, <i>mean</i>			0.30	<0.001			0.49	<0.001
Embarrassment, <i>mean</i>			0.45	<0.001			0.78	<0.001

\* 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)

### 7.13 Additional Subgroup Efficacy Analyses

In addition to the pre-specified secondary analysis, other subgroup analyses of treatment efficacy for Solesta have been performed. These subgroup analyses have been based on gender, ethnicity, primary etiology, baseline FI-episode frequency, and use of concomitant anti-diarrheal medication. The outcomes for these analyses, presented in the sections below, were supportive of the pre-specified analyses.

#### 7.13.1 Subgroup analysis by gender

When comparing outcome in the 23 males versus 183 females, the effect of Solesta treatment in males showed a tendency to be larger than in females and the Sham effect to be lower (see [Table 14](#) below). However, the overall proportion Responder<sub>50</sub>, when not considering treatment administered, was similar for both genders (p=0.904; Chi-square test).

**Table 14 Proportion Responder<sub>50</sub> at 6 months by gender – ITT population. PIM.**

Gender	Solesta		Sham	
	n	Responder <sub>50</sub> (%)	n	Responder <sub>50</sub> (%)
Male	14	64.3	9	11.1
Female	122	50.8	61	32.8

### 7.13.2 Subgroup analysis by ethnicity

As displayed in [Table 15](#) below, the results for the Solesta treatment group are consistent in showing an improvement for Solesta given the expected responder variation due to the lower number of patients in the non-Caucasian groups. While the result in the Caucasian group can be observed to be similar to that for the study ITT population, the small number of patients in the non-Caucasian groups does not make a comparison between Solesta and Sham meaningful in these groups.

**Table 15 Proportion Responder<sub>50</sub> at 6 months by ethnicity – ITT population. PIM.**

Ethnicity group	Solesta		Sham	
	n	Responder <sub>50</sub> (%)	n	Responder <sub>50</sub> (%)
Caucasian	122	53.3	59	33.9
African American	6	50.0	4	25.0
Hispanic/Latino	3	33.3	4	0.0
Asian	4	50.0	2	0.0
Other	1	0.0	1	0.0

### 7.13.3 Subgroup analysis by FI etiology

In this study, the investigators were asked to assign a single, primary etiology for the patient's FI based on past medical history; despite the fact that the patient's FI etiology could have been multifactorial. Therefore, comparisons based on different etiologies must be interpreted in the context of this limitation.

The Responder<sub>50</sub> results for the Solesta treatment group is similar for the obstetric, neurogenic and iatrogenic etiology categories while it is somewhat lower for the "other" category, which mainly consists of patients with an idiopathic etiology, see [Table 16](#). There are variations in the Sham response, but the Solesta response is consistently higher than the Sham response for each category.

**Table 16 Proportion Responder<sub>50</sub> at 6 months by etiology as reported by investigator – ITT population. PIM.**

Etiology	Solesta		Sham	
	n	Responder <sub>50</sub> (%)	n	Responder <sub>50</sub> (%)
Obstetric	56	53.6	26	23.1
Neurogenic	27	55.6	16	43.8
Iatrogenic	30	53.3	16	31.3
Other	23	43.5	12	25.0



#### 7.13.4 Subgroup analysis by FI frequency

A Responder<sub>50</sub> analysis was performed by stratifying patients by baseline FI-episode in multiples of 7. This analysis was requested by the FDA. The results are displayed in [Table 17](#). Because the diary spans 14 days, categorizing patients by FI episodes in multiples of 7 allows for a simplified interpretation of the frequency categories over the 14-day diary period. As the distribution is skewed with relatively few observations above 42, all patients above 42 were included in a single group. As shown in [Table 17](#), the proportion Responder<sub>50</sub> is consistently higher in the Solesta treatment group; although, the difference between the treatment groups is smaller in the highest category of FI episodes (those over 42 episodes).

**Table 17 Proportion Responder<sub>50</sub> at 6 months by baseline FI frequency categories – ITT population. PIM.**

FI frequency category (No. of episodes/14 days)	Solesta		Sham	
	n	Responder <sub>50</sub> (%)	n	Responder <sub>50</sub> (%)
0-7 episodes	23	43.5	13	30.8
7-14 episodes	40	52.5	28	25.0
14-28 episodes	41	51.2	12	25.0
28-42 episodes	19	68.4	8	37.5
Over 42 episodes	13	46.2	9	44.4

#### 7.13.5 Primary efficacy analyses for subjects not taking anti-diarrheals

Intake of anti-diarrheal medications might be considered confounders in the interpretation of the efficacy results. At the request of the FDA, the 3 parts of the primary efficacy analyses have been repeated for the subpopulation of subjects not taking any anti-diarrheals (WHO Drug ATC code A07D) during the diary periods prior to each of the evaluation visits. As detailed below, all 3 parts of the primary objective were met also in this subpopulation not taking A07D.

When evaluating the potential impact of A07D on the treatment effect at 6 and 12 months, patients that took A07D in connection with the baseline and 6 or 12 months diary periods, respectively, during which time incontinence data was recorded, were excluded. The diary period is the most relevant time period since the diary data are used to calculate the efficacy results.

Ninety-two (92) subjects in the Solesta treatment group and 35 subjects in the Sham treatment group did not take A07D either during the baseline or the 6-month diary period. At 12 months, 74 subjects in the Solesta treatment group had not taken any A07D during the baseline or 12-month diary period.

The difference in the proportion of Responder<sub>50</sub> for Solesta (60.3 %) and Sham (38.8 %) patients not taking A07D was found to be statistically significant, with  $p = 0.049$  (test of odds

ratio), at 6 months. The lower bound of the 95 % confidence limit for the Solesta group was 42.6 %, which exceeds the pre-specified limit of 35.0 % for the proportion Responder<sub>50</sub> at 6 months. At 12 months, the lower confidence limit for the proportion Responder<sub>25</sub> (70.3 %) was 59.9 % which exceeded 50.0 %, the pre-specified limit for proportion Responder<sub>25</sub>.

## 7.14 Safety Results

Each patient was questioned about adverse events 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 and any observed abnormalities were reported as adverse events. Adverse event reporting started at the randomization visit and continued until the last scheduled visit in the study. Adverse events were reported for all patients, independent of treatment assignment. All reported AEs were assessed for causality and seriousness by the study investigators.

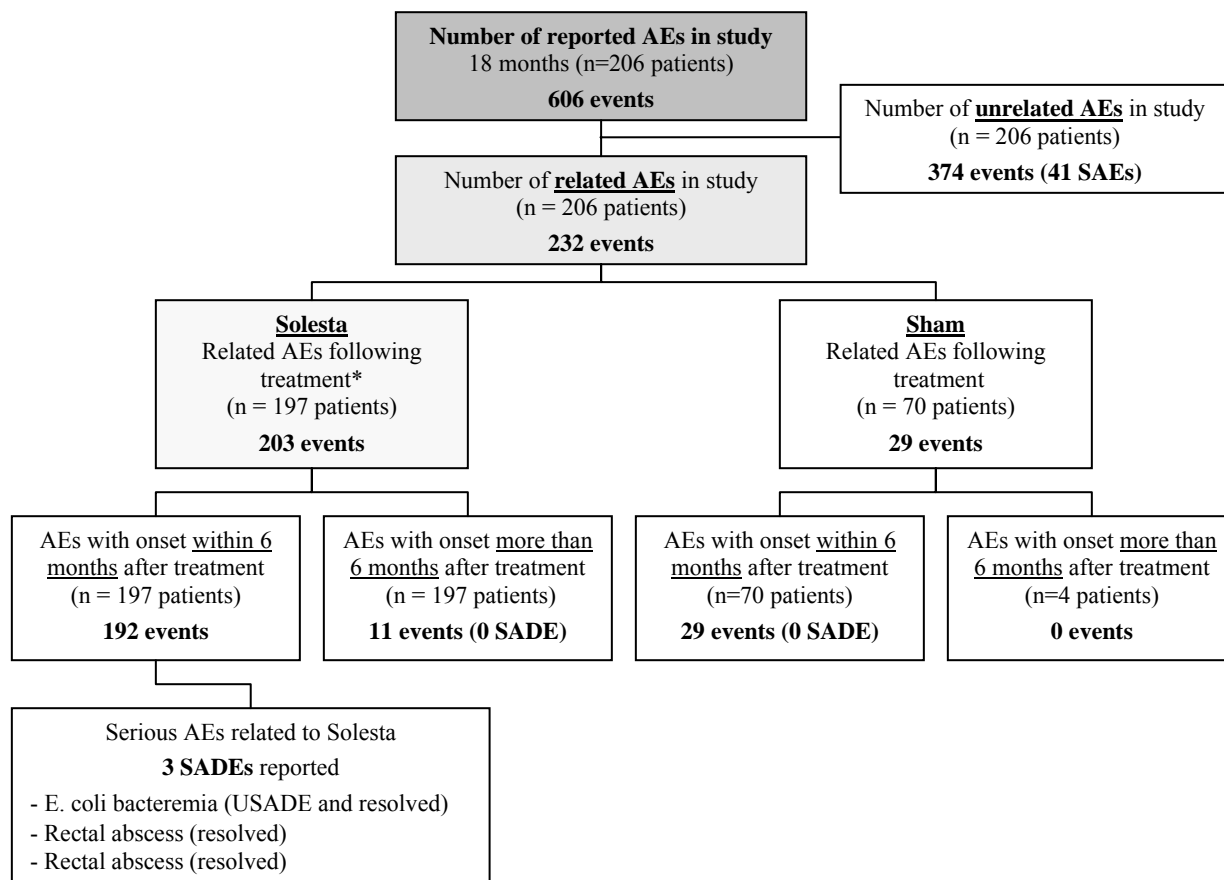
The analysis of safety was based on the safety cohort of all 206 patients treated in the study with either Solesta or Sham. Adverse event (AE) data was obtained on 136 patients treated with Solesta and followed for up to 18 months and on 70 patients randomized to Sham treatment and followed for 6 months 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 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).

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.

No deaths occurred amongst study patients and no patient withdrew from the study due to an adverse event.

Figure 8 below gives a schematic overview of all reported AEs in the study. Treatment-related AEs are discussed more in Sections 7.14.1 to 7.14.4, to follow. First, reported SAEs are discussed. Secondly, the AE data for the 197 patients who received Solesta in either the blinded or open phases of the study are presented. Next, the treatment-related adverse events for Solesta observed during the 6-month blinded phase are compared to those observed for Sham. Finally, more in depth discussion is provided for specific adverse events of interest that occurred during the blinded and open phases of the study for both Solesta and Sham.

**Figure 8 Schematic overview of study adverse events from randomization to month 18**



\* NB! Includes all 197 subjects treated with Solesta (i.e., the 136 patients randomized to Solesta treatment in the blinded phase and the 61 patients who received Solesta in the open phase)

#### 7.14.1 Adverse events assessed as serious and related to treatment

Three (3) case reports of adverse device effects assessed to be serious adverse device effects (SADE) were received from 3 patients in the study through 18 months of follow-up. Two events occurred in the blinded phase of the study and comprised one case of *Escherichia coli* bacteremia which was an unanticipated adverse effect and one case each 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 SADEs were reported following Sham treatment. See summary information in [Table 18](#), below.

Two of the SADEs concerned rectal abscesses subsequent to treatment and 1 SADE was a post-treatment bacteremia. All 3 events had an early onset suggestive of a possible peri-operative infection. None of the patients had received prophylactic antibiotics prior to treatment; however, 2 of the patients had a Betadine swab of the injection area (Case number [REDACTED]) or perianal swab with alcohol (Case number [REDACTED]). The events were

assessed as serious because they required surgical intervention and/or hospitalization. All 3 events were assessed as resolved without sequelae following intervention.

**Table 18 Solesta-related adverse device effects assessed as serious (SADE) through 12 months in the study – Safety population**

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

**Abbreviations:** MedDRA = Medical Dictionary for Regulatory Activities; PT = preferred term

A complete listing of all SAEs deemed to be unrelated to treatment, is provided in [Appendix 1](#) of this document.

#### 7.14.2 Adverse events related to Solesta treatment through month 18

Integrated safety results on all 197 patients 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.

Through the 18-month follow up period, 203 treatment-related AEs were reported by 103 (52.3 %) patients who received Solesta treatment in the study. The incidence for treatment-related adverse event was thus 56.5 % based on total number of Solesta treatments administered (203 events/359 treatments).

[Table 19](#) provides a summary of the most common groups of adverse events reported in the study following treatment with Solesta.

**Table 19 Most common Solesta treatment-related adverse events through 18 months for the Pivotal IDE study. Groups of adverse events reported in more than 2 % of 197 treated patients.**

Group of adverse events	No. of patients (%)	No. of events	Intensity of AE			Intervention to treat AE			
			Mild	Moderate	Severe	None	Medical	Surgical	Other
Post-treatment proctalgia	34 (17.3)	41	20	21	0	14	19	1*	7
Anal or rectal bleeding	22 (11.2)	24	18	6	0	20	1	0	3
Injection site bleeding	16 (8.1)	18	18	0	0	17	0	0	1
Post-treatment fever	13 (6.6)	14	12	1	1	5	8	0	1
Constipation or diarrhea	11 (5.6)	13	12	1	0	5	8	0	0
Injection site pain or irritation	11 (5.6)	11	8	3	0	10	1	0	0
Injection site reaction	9 (4.6)	10	7	2	1	5	5	0	0
Post-treatment anorectal discomfort	8 (4.1)	8	7	1	0	3	5	0	0
Rectal discharge	7 (3.6)	7	6	1	0	4	2	0	1
Post-treatment infection	5 (2.5)	6	1	3	2	0	3	3†	0
Abdominal pain or discomfort	5 (2.5)	5	2	3	0	3	1	0	1

\* Incision and drainage of a suspected abscess. No aspirate was obtained and infection was not confirmed.

† Per anal incision and drainage of an abscess in all 3 cases

The majority (96.6 %) of the Solesta treatment-related events were of mild to moderate intensity. Median time to onset was 1 day and duration was less than a week. Approximately, 95 % (192/203 events) of the 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) events had an onset more than 6 months after treatment. These events comprised 3 cases of proctalgia, 2 cases of anal prolapse, and one 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.

The majority of the Solesta-related events required no intervention (57 %; 115/203 adverse events), or required medical or simple non-invasive intervention (40 %; 81/203 adverse events). Examples of medical intervention included treatment with analgesics, antipyretics, antibiotics and bowel medication, etc. Other simple procedures included silicone ointment, irrigation with water and local pressure to control bleeding. Seven (7) events required other anorectal procedures including: per anal drainage of abscesses (4 events), one case of rubber band ligation of an anal prolapse, one case of lancing of a hemorrhoid, and one case of a Kenalog injection in a pre-existing anal scar.

All but two Solesta-related events had resolved as of the time of data cut-off for this summary report. The outcome was pending for one case of proctalgia and there was also one unresolved case of abdominal rigidity. This latter patient was randomized to Solesta and withdrew consent to participation in the study after the 9-month visit.

Additional information on Solesta treatment-related adverse events is provided in [Table 26](#) (Section 9 of this document) which lists the most common treatment-related AEs for the pivotal IDE study and OUS Open-Label study combined. In addition, a list of all Solesta treatment-related events occurring in both the pivotal IDE and the OUS Open-Label studies is provided in [Appendix 2](#) of this document.

#### 7.14.3 Related adverse events in blinded phase

A comparison of all related adverse events for Solesta and Sham is shown in [Table 20](#). Incidence of events sub-grouped by MedDRA system organ class and preferred term is presented. The incidence is presented as a percentage of patients with at least one 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 only had a single injection in 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.

During the blinded phase of the study, the most frequent adverse events following Solesta treatment pertained to minor bleeding and pain or discomfort at the injection site, post treatment fever, diarrhea, rectal discharge and a few cases of proctitis. The most frequent treatment-related adverse events in the Sham group were rectal or injection site bleeding, proctalgia or injection site pain, and diarrhea. There were overall fewer adverse events in the Sham group and only one case of proctitis, which could be indicative of a possible post-treatment infection. Also, as would be expected, the majority of the events in the Sham group had an onset within a day from the treatment procedure.

**Table 20 Related AEs (including serious AEs) in each treatment group in the 6-month blinded phase of the study - Safety population**

<b>Blinded phase</b> <b>MedDRA System Organ Class</b> <b>Preferred Term</b>	<b>Solesta</b>			<b>Sham</b>		
	<b>No. of events</b>	<b>Incidence</b>		<b>No. of events</b>	<b>Incidence</b>	
		<b>% of patients n=136</b>	<b>% events/ treatments (total 249)</b>		<b>% of patients n=70</b>	<b>% events/ treatments (total 131)</b>
<b>Gastrointestinal disorders</b>	<b>85</b>	<b>39.7</b>	<b>34.1</b>	<b>9</b>	<b>8.6</b>	<b>6.9</b>
Abdominal distension	1	0.7	0.4	.	.	.
Abdominal pain	1	0.7	0.4	.	.	.
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	.	.	.
<b>General disorders and administration site conditions</b>	<b>33</b>	<b>18.4</b>	<b>13.3</b>	<b>18</b>	<b>18.6</b>	<b>13.7</b>
Chills	4	2.9	1.6	.	.	.
Fatigue	1	0.7	0.4	.	.	.
Injection site hematoma	.	.	.	1	1.4	0.8



<b>Blinded phase</b> <b>MedDRA System Organ Class</b> <b>Preferred Term</b>	<b>Solesta</b>			<b>Sham</b>		
	<b>No. of events</b>	<b>Incidence</b>		<b>No. of events</b>	<b>Incidence</b>	
		<b>% of patients n=136</b>	<b>% events/ treatments (total 249)</b>		<b>% of patients n=70</b>	<b>% events/ treatments (total 131)</b>
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	.	.	.
<b>Infections and infestations</b>	<b>2</b>	<b>1.5</b>	<b>0.8</b>	.	.	.
Escherichia bacteremia	1	0.7	0.4	.	.	.
Rectal abscess	1	0.7	0.4	.	.	.
<b>Investigations</b>	<b>1</b>	<b>0.7</b>	<b>0.4</b>	.	.	.
C-reactive protein increased	1	0.7	0.4	.	.	.
<b>Musculoskeletal and connective tissue disorders</b>	.	.	.	<b>1</b>	<b>1.4</b>	<b>0.8</b>
Joint stiffness	.	.	.	1	1.4	0.8
<b>Nervous system disorders</b>	.	.	.	<b>1</b>	<b>1.4</b>	<b>0.8</b>
Dizziness	.	.	.	1	1.4	0.8
<b>Reproductive system and breast disorders</b>	<b>4</b>	<b>2.9</b>	<b>1.6</b>	.	.	.
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	.	.	.
<b>Skin and subcutaneous tissue disorders</b>	<b>3</b>	<b>2.2</b>	<b>1.2</b>	.	.	.
Alopecia	1	0.7	0.4	.	.	.
Cold sweat	1	0.7	0.4	.	.	.
Dermatitis	1	0.7	0.4	.	.	.
<b>ALL</b>	<b>128</b>	<b>48.5</b>	<b>51.4</b>	<b>29</b>	<b>27.1</b>	<b>22.1</b>

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

#### 7.14.4 Analysis of specific treatment-related adverse events

Treatment-related adverse events of interest that occurred during both the blinded and open phases of the study are described in more detail below.



### Post-treatment proctalgia and injection site pain

There were 54 events of post-operative pain coded as proctalgia or injection site pain and assessed as related to treatment by the investigators. 51 events occurred in the Solesta group and 3 occurred in the sham group.

Of the 51 events assessed as related to Solesta, 65 % (33/51 events) occurred within 24 hours and 84 % (43/51) within the first 7 days. The median duration for these events was 7 days. All events were assessed as mild or moderate in approximately equal proportions. No treatment or observation was used in 45 % (23/51) of the events, and analgesics were prescribed in 29 % (15/51). Additional treatment was required where there was underlying pathology for the pain, for example, one patient had an abscess and it was drained via the mucosa. All but one event resolved without sequelae. One unresolved event of proctalgia, treated with Xylocaine ointment, is pending final outcome.

The 3 events assessed as related to Sham occurred after 0, 17, and 97 days, respectively, and the duration was 1, 39 and 85 days, respectively. All 3 events were mild and resolved without sequelae. No medical intervention was required for any of the 3 events.

### Anorectal bleeding

There were 79 events of post-operative anorectal bleeding events assessed as related to treatment by the investigators. 42 events occurred in the Solesta group and 17 occurred in the Sham group. No patient in the study experienced “hemorrhage” in the true clinical sense (i.e., demonstrating hemodynamic instability or requiring volume replacement, transfusion or pressor support).

The 42 events assessed as related to Solesta were coded as injection site hemorrhage (18 events), rectal hemorrhage (15) or anal hemorrhage (9), based on AE descriptions provided by the investigators, regardless of severity. The majority of these events 64 % (27/42 events) occurred within 24 hours and 76 % (32/42) within the first 7 days. The median duration of these bleeding events was 2 days. Eighty-six percent (86 %) of the events were mild and 14 % were moderate. No intervention was required in 88 % (37/42) of the events and no surgical intervention was required in any case.

The 17 events assessed as related to Sham were coded as injection site hemorrhage (16 events) and rectal hemorrhage (1). All events of injection site hemorrhage were mild, occurred within 24 hours and resolved without sequelae within a day. Intervention involved local pressure and topical epinephrine in one case. The single case of rectal hemorrhage occurred 17 days after treatment concurrent with proctalgia; both events resolved without intervention after 39 days.

### Post-treatment fever

There were a total of 14 reports of pyrexia in the Solesta treatment group and none in the Sham group. Fever was documented by elevated body temperature in 50 % of the 14 reported cases, while the remaining concerned reports of feverishness without documentation of elevated body temperature. The onset of event was within 24 hours in 79 % (11/14 events) while the remaining came on within 5 days. The median duration was 6 days. Eighty-six

percent (86 %) of events were assessed as mild. Antibiotics were prescribed in 9/14. Infection was confirmed in one patient who had a rectal abscess that was drained via the mucosa. All cases of fever resolved without any sequelae.

#### Anorectal abscesses or injection site infection

There were a total of 5 reports of anorectal abscesses in 4 subjects. All cases occurred following Solesta treatment. One case was described as pus noted during the re-treatment procedure (coded as “injection site pustule”) and was treated with antibiotics. Four other events required incision and drainage via the mucosal route. All but one event had onset within 2 days while one event was a recurrence 4 months after recovery from the first episode of abscess. Microbiological investigation was performed on the aspirated material in 2 cases, gram negative bacilli on gram stain and heavy growth of beta-hemolytic streptococci was grown in one, while the other (the recurrent abscess) was culture negative. All subjects made full recovery without sequelae.

#### Proctitis

Proctitis was reported following both Solesta (5 events) and Sham (1 event) treatment in 6 subjects. The clinical picture was usually erythema or inflammation on proctoscopy, some cases were associated with pain or fever. No diarrhea was reported in any of the affected subjects and no biopsies were performed. All cases were visually confirmed to have resolved, either spontaneously or following antibiotics treatment.

#### Anal prolapse

Anal prolapse was reported in 3 Solesta subjects and none after Sham treatment. One patient was treated with rubber band ligation and the other two did not require any treatment. One event resolved spontaneously after one day and the other event resolved after discharge of a “gel-like” material after 3 months. All 3 cases resolved without sequelae.

### **7.15 Conclusions from Pivotal IDE Study**

The results from the pivotal IDE study demonstrated that treatment with Solesta is safe and effective for the treatment of patients with FI who have failed conservative therapy.

Specifically:

- The 3 success criteria of the pre-specified primary objective of the study were met. Superiority for Solesta against Sham at 6 months was demonstrated and treatment efficacy and durability achieved a predefined minimum level at 6 and 12 months.
- Solesta provides a clinically meaningful improvement in patients suffering from FI for up to 12 months after treatment. There was an observed reduction in the number of incontinence episodes and a positive improvement in the number of incontinence-free days, CCFIS score and in quality of life.
- The safety of Solesta in the treatment of patients with FI was demonstrated in this study based on adverse event data from 197 patients followed for up to 18 months

post-treatment. Treatment with Solesta was well tolerated; 97 % of the treatment-related events were of mild to moderate intensity and 97 % of the events required no intervention or required medical or simple non-invasive intervention. The majority of the events were anticipated, occurred shortly after treatment with a median duration less than a week and resolved without sequelae.

## 8 SUPPORTIVE STUDIES

### 8.1 OUS Open Label Study

“33DA0605: An open, non-comparative, post marketing, multi-center study to evaluate efficacy and safety of Solesta for the treatment of fecal incontinence”

An open-label multicenter study was performed in the European Union and Canada, in order to obtain additional information on the safety and efficacy of Solesta as a bulking agent in the treatment of FI. The study was performed within a clinical setting at 1 site in Canada and 14 sites in Europe. After a 4 - 6 week run-in period, patients were treated with Solesta up to 2 times and followed for 12 months after last treatment. A 28-day patient incontinence diary was completed before visits and CCFIS and FIQL were completed at the visits. Examinations included proctoscopy at each follow up visit. The study also includes an extension phase up to 24 months following last treatment. 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.

#### 8.1.1 Objectives

The primary objective of the study was to evaluate the efficacy of Solesta, defined as proportion of responders at 12 months after treatment, where response was defined as having  $\geq 50$  % reduction in number of FI episodes from baseline (based on the 28-day diary period).

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

#### 8.1.2 Study population

The study included 115 patients of both genders 18-80 years of age, with a history of FI for at least 12 months, a CCFIS at baseline of  $\geq 5$  and  $\geq 4$  FI episodes over a 28 day period. Furthermore, the patients had failed prior conservative treatment.

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.

The sample size of the study was not based on a power calculation. By including 100 patients there was approximately 99 % probability to observe at least one occurrence of an adverse event with a hypothetical prevalence of 4.5 %, and approximately 63 % probability when the hypothetical prevalence was 1 %.

### 8.1.3 Study results

#### Demographics and baseline characteristics

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<sup>2</sup>. Ninety-five (95 %) of females had delivered at least one child. All patients were Caucasian except for one patient who was Hispanic/Latino.

Approximately two-thirds of the patients had been symptomatic for FI for less than 5 years. The most common underlying cause for the FI was attributed to obstetric injuries, reported in 32 % of patients; closely followed by neurogenic cause affecting 30 % of patients. All patients had tried at least one form of non-invasive treatment for FI prior to inclusion and 13 % of patients had undergone surgical intervention for the condition.

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.

#### 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), but analyses using last observation-carried-forward (LOCF) in the ITT population were performed as well.

The primary efficacy analysis showed a proportion Responder<sub>50</sub> of 57.1 % at 6 months and 64.0 % at 12 months based on an OC approach, and 49.1 % and 51.8 %, respectively, based on an LOCF approach.

Secondary analyses were supportive of the primary efficacy results and are detailed in [Table 21](#).

**Table 21 Summary of secondary efficacy results at 6 and 12 months after last treatment. P-values represent tests for difference from baseline – ITT population. OC.**

Variable	6 months				12 months			
	n	Baseline estimate	6-month estimate	p-value*	n	Baseline estimate	12-month estimate	p-value*
<b>Fecal incontinence episodes (during 28-day diary period)</b>								
Total number of FI episodes, <i>median</i>	99	16.0	5.6	<0.001	87	15.0	4.0	<0.001
Number of incontinence-free days, <i>mean</i>	99	14.0	20.9	<0.001	87	14.1	21.2	<0.001

Variable	6 months				12 months			
	n	Baseline estimate	6-month estimate	p-value*	n	Baseline estimate	12-month estimate	p-value*
<b>Cleveland Clinic Florida Incontinence Score (CCFIS) (0 = continent; 20 = total incontinence)</b>								
CCFIS, <i>mean</i>	99	13.5	9.2	<0.001	90	13.4	8.7	<0.001
<b>Fecal Incontinence Quality of Life (FIQL) scale (higher score = increased QoL)</b>								
Lifestyle, <i>mean</i>	78	2.41	2.95	<0.001	74	2.42	2.93	<0.001
Coping/Behavior, <i>mean</i>	79	1.75	2.33	<0.001	75	1.74	2.42	<0.001
Depression/Self perception, <i>mean</i>	78	2.60	3.07	<0.001	72	2.67	3.20	<0.001
Embarrassment, <i>mean</i>	77	1.83	2.47	<0.001	71	1.81	2.59	<0.001

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)

### Summary of safety results

The safety of Solesta in treatment of FI was demonstrated in 115 patients followed for up to 18 months after last treatment in the study. In total, 154 treatments with Solesta were performed in the 115 included patients. A majority (67 %) of the patients in the study only received one treatment with Solesta.

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

More than half (57 %) of all related AEs belonged to the MedDRA system organ class gastrointestinal disorders. The 5 most frequently reported types of treatment-related AEs were proctalgia, pyrexia, constipation, diarrhea and injection site pain. [Table 26](#) in [Section 9](#) below, summarizes the most common related AEs from the OUS study together with the Solesta related AEs from the Pivotal IDE study. In addition, a listing with further details on these relates adverse events is provided in [Appendix 2](#).

A majority (95 %) of related AEs were of mild to moderate intensity. Most related AEs (91 %) commenced within 2 weeks following Solesta treatment and a majority (86 %) resolved within 2 weeks. The median time to onset was 1 day and the median duration was 5 days. Forty-six percent (46 %) of the treatment-related AEs did not require intervention. When intervention was required it was usually analgesics, antipyretics, anti-inflammatory agents or antibiotics. A case of rectal prolapse (reported as an SAE) with concomitant events of rectal bleeding and pain in one patient was surgically treated. In this case, tissues surrounding a Solesta bulge had prolapsed downwards the anal canal and the Solesta bulge was excised in surgery. With one exception, all treatment-related events had resolved at the time of database closure.

Twenty-one (21) AEs were classified as serious by the investigators and 6 of these were assessed to be related to study treatment. These 6 related SAEs occurred in four patients. Three of the related SAEs comprised on case each of perineal abscess, rectovaginal septum abscess and rectal abscess in three patients. The remaining three events were reported by a single patient who had a rectal prolapse with concurrent rectal bleeding (coded as “rectal hemorrhage” and proctalgia. All 6 related SAEs resolved without sequelae following intervention with antibiotics alone, per-anal incision and drainage of the rectal and perineal abscesses, and surgical excision of the prolapsed bulge.

One patient died from cardiac failure but the event was not related to the study treatment. Other than this case of fatal cardiac failure no adverse events led to premature withdrawal of any study patient.

#### 8.1.4 Conclusion drawn from study

The results from this OUS Open Label study are consistent with the findings of the Pivotal IDE study and demonstrate that Solesta is safe and effective for the treatment of patients with FI who have failed conservative therapy. The safety of Solesta in the treatment of patients with FI was demonstrated based on adverse event data from 115 patients followed for up to 18 months after treatment.

Treatment with Solesta was well tolerated. The majority of the treatment-related events occurred shortly after treatment and were of mild to moderate intensity. Few events required invasive intervention. With the exception of one event of mild persistent abdominal discomfort, all treatment-related adverse events resolved without sequelae.

The primary efficacy analysis showed that the proportion of patients meeting the Responder<sub>50</sub> criterion was 57.1% at 6 months and 64.0 % at 12 months in an observed case analysis. At both 6 and 12 months after Solesta treatment, the mean CCFIS and the mean scores in all four FIQL domains were significantly improved compared to baseline.

## 8.2 Proof-of-Concept Study

This open, single center investigator-initiated study supported by Q-Med AB was undertaken to evaluate the safety and efficacy of Solesta for treatment of FI. The study was conducted at one site in Sweden. Patients were given up to 2 treatments and were followed for 24 months. 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.

### 8.2.1 Study objectives

The primary objective of the study was to evaluate the efficacy of Solesta as an injectable bulking agent in patients with FI as measured by proportion of responders 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 and judgment of treatment effect, and quality of life.

#### 8.2.2 Study population

The study included 34 patients of both genders, 18-80 years of age and with FI to loose or solid stool at least once weekly (Miller score 6 or higher). The patients 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.

#### 8.2.3 Study results

##### Demographics and baseline characteristics

Twenty-nine (85 %) evaluable patients in the study were females and 5 (15 %) were males. Mean patient age at enrolment was approximately 66 years. The most common underlying cause of the FI condition (seen in 74 % of the patients) was attributed to neurogenic causes. 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.

In total, 53 treatments with Solesta were administered in the study. Seventeen (17) of 34 patients received one retreatment with 2-4 mL, and one patient was retreated twice with 4 mL each time. The mean total volume given was  $6 \pm 2$  mL (range 4 to 12 mL).

##### Efficacy results

Treatment success was defined as a reduction in number of incontinence episodes from baseline by more than 50 % (Responder<sub>50</sub>). The proportion Responder<sub>50</sub> 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.

The secondary efficacy results are summarized in [Table 22](#) and [Table 23](#). Significant improvements in number of incontinence episodes, in number of incontinence-free days and in Miller incontinence score were achieved and sustained for up to 24 months from last treatment with Solesta. In addition, patient assessments showed that a majority of patients considered their condition improved up to 24 months from last treatment with Solesta.



**Table 22 Diary data and Miller score at baseline, 6, 12 and 24 months after last treatment – ITT population. OC.**

Variable	Baseline estimate	6-month estimate	p-value*	12-month estimate	p-value*	24-month estimate	p-value*
<b>Fecal incontinence episodes (during 4-week diary period)</b>							
	n=34	n=34		n=34		n=32	
Number of FI episodes, <i>median</i>	22	9	<0.001	10	0.001	8.5	0.002
Number of incontinence-free days, <i>mean</i>	11	17	<0.001	17	0.004	18	0.002
<b>Miller incontinence score (0 = total continence; 18 = total incontinence)</b>							
	n=34	n=34		n=34		n=33	
Miller score, <i>mean</i>	13	11	0.006	10	<0.001	10	<0.001

\* Wilcoxon signed rank test (change from baseline)

**Table 23 Patient global assessment of treatment effect at 6, 12 and 24 months – ITT population. OC.**

Variable	6 months		12 months		24 months	
	n	Value	n	Value	n	Value
Patient global assessment (% improved)	34	79 %	34	77 %	33	79 %
Patient assessment of treatment effect (% acceptable – excellent)	34	91 %	34	82 %	33	91 %

There was no significant change of SF-36 scores for the whole study group through 24 months.

### Safety results

In total, 86 treatment-related adverse events have been reported by 29 patients. The intensity of the majority of the events was mild. 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. All adverse events except two events occurred within 6 months. These 2 events comprised one case each of mucus secretion and of constipation and occurred prior to month 12. No treatment-related adverse events occurred after month 12. One 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 24](#) below.

**Table 24 Related adverse events and incidence based on total number of treatment procedures in the Proof-of-Concept study through 24 months of follow up.**

Adverse Event	Number of patients	% of patients	Total number of events	Incidence % events/ treatments (total 53 treatments)
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

#### Conclusions Drawn from Study

The safety and efficacy results are similar to those observed in the Pivotal IDE study. Similar efficacy was observed at 12 months, with a proportion Responder<sub>50</sub> of 55.9 %. In addition, the study data demonstrate the durability of the treatment effect out to 24 months after treatment. The safety profile was similar to that observed in the Pivotal IDE study. The intensity of the majority of the events was mild. No treatment-related adverse events were reported as serious.

## 9 SUMMARY OF SOLESTA CLINICAL DATA

The Pivotal IDE study, representing the main body of clinical evidence in this PMA submission, is a rigorously designed and executed IDE clinical trial, which reflects the state of the art for trials of FI treatments as well as the specific recommendations of the FDA review team. Because FI is a condition with some subjectivity and variability in its assessment, the study incorporated a sham control and was double-blinded – neither the patient nor the evaluating investigator had knowledge of the treatment assignment.

All three studies of Solesta described in this PMA submission incorporated, as the primary efficacy assessment, the number of FI episodes over a 14-day or 28-day period, which reflects a clinically meaningful measure of a patient's condition. The study utilized a responder analysis as the primary efficacy variable. A responder was defined as a patient who experienced a 50 % reduction in the number of FI episodes from baseline (Responder<sub>50</sub>).

Therefore, by definition, the primary endpoint reflects a treatment outcome that is clinically meaningful to patients. The studies also investigated the impact of treatment on patient quality of life using validated disease specific assessments. Retreatment was offered in all three studies if incontinence persisted at one month.

The Pivotal IDE study incorporated a stringent three part primary efficacy objective and all three parts of the objective had to be met for success to be declared. As discussed in the preceding sections, the Pivotal IDE study was shown to meet all parts of the primary objective, demonstrating superiority to Sham and a clinically significant treatment effect that was shown to be durable through 12 months of follow-up. The positive results from the Pivotal IDE study are supported by the available results for the prospective, multicenter, open-label study of Solesta conducted outside the United States. This study was conducted on 115 subjects who received Solesta for the treatment of FI (using nearly the same inclusion/exclusion criteria as the Pivotal IDE study). The effectiveness results mirror those observed in the Pivotal IDE study, and therefore provide strong supporting evidence for the effectiveness of Solesta for the treatment of FI. Finally, supporting clinical data are also available from a Proof-of-Concept study of 34 subjects treated with Solesta, conducted at a single site in Sweden. This study shows the same safety and effectiveness results as the Pivotal IDE study and the OUS Open Label study, with the additional finding of continued safety and effectiveness through 24 months.

The results of the Pivotal IDE, Proof-of-Concept and the OUS Open-Label studies are summarized in [Table 25](#).

**Table 25 Proportion Responder<sub>50</sub> for Solesta in all three clinical studies at 6 and 12 months and at 24 months for Proof-of-Concept study.**

Proportion Responder <sub>50</sub> [95% CI]	Pivotal IDE study (ITT, PIM)	OUS Open-Label Study (ITT, LOCF)	Proof-of-Concept Study (OC)
6 months	53.2 % [40.2–65.8] n= 136	49.1 % [39.9–58.3] n=114	44.1 % [27.4–60.8] n=34
12 months	57.4 % [49.0–65.7] n=136	51.8 % [42.6–60.9] n=114	55.9 % [39.2–72.6] n=34
24 months	N/A	N/A	59.4 % [42.4–76.4] n=32

PIM = primary imputation model; LOCF = last observation carried forward; OC = observed cases; n = number of patients

As shown in [Table 25](#), the treatment effect measured by the primary endpoint proportion Responder<sub>50</sub>, has been reproducible in three clinical studies and has been demonstrated to be superior to placebo (sham) in the Pivotal IDE study. All three studies, therefore, collectively provide strong evidence for the effectiveness of Solesta in the treatment of patients with FI.

Analyses of the secondary endpoints from all three studies provide supportive evidence for the effectiveness of Solesta. Although no study was designed to demonstrate a statistically significant effect for the secondary endpoints, all secondary endpoints show a significant improvement from baseline or trend in favor of Solesta.

FIQL is a validated, tool that is specifically designed to assess the impact of FI on a patient's quality of life<sup>31</sup>. In the Pivotal IDE and OUS Open-Label studies overall, significant improvement compared to baseline was observed at both 6 and 12 months in all four domains of the FIQL. The FIQL results demonstrate that the reductions in FI episodes observed following treatment with Solesta are associated with a measurable improvement in quality of life for FI patients.

The CCFIS is a validated measure of the impact of FI on patients. It is based on patient's recall using standardized questions regarding incidence and type of incontinence (solid, liquid or gas), pad usage and lifestyle alterations during the past 3 months. Treatment with Solesta was shown to improve CCFIS as compared to baseline at 6 and 12 months in the Pivotal IDE and OUS Open-Label studies. The Proof-of-Concept study did not incorporate CCFIS but instead used the Miller score, another common assessment tool for FI. The Miller score is based on a patient interview using standardized questions regarding incidence and type of incontinence (solid, liquid or gas) only. Significant improvements from baseline and sustained improvements were shown at 6, 12 and 24 months.

Collectively, the data for FIQL, CCFIS and Miller score analyses support the findings of the primary assessments, i.e., that Solesta is effective in reducing the number of FI episodes and that treatment with Solesta has a positive impact on the patients' quality of life.

Extensive data are available to support the safety of Solesta for the treatment of FI. As described in [Table 3](#) above, this PMA submission provides data on 346 patients who have received 566 treatments with Solesta. The data comprise 18 months of follow-up for the Pivotal IDE and OUS Open Label studies, and 24 months of follow-up for the Proof-of-Concept study. Collectively, the data in this PMA demonstrate that treatment with Solesta is safe and well tolerated. The majority of the events was of mild to moderate intensity and required no intervention or required medical or simple non-invasive interventions. No treatment-related deaths occurred amongst study patients and no patient withdrew from the studies due to a related adverse event.

[Table 26](#) provides a summary of the adverse events through 18 months for the Pivotal IDE and OUS Open-Label studies combined. A total of 282 events were assessed by the investigators as related to Solesta in the two sponsored studies. The table includes related adverse events, or groups of adverse events, that were reported in more than 2 % of the 312 patients who received a total of 513 treatments with Solesta in the two studies. A more detailed summary of the collated adverse event data for the two sponsored studies is available in [Appendix 2](#).

**Table 26 Solesta treatment-related adverse events through 18 months for the sponsored Pivotal IDE and OUS Open-Label studies combined. Groups of adverse events reported in more than 2 % of patients.**

Group of adverse events	Patients (n=312)		Events	
	Number of patients affected by the event	Percentage of patients affected by the event (%)	Number of events	Incidence % events / 513 Solesta treatments
<b>Abdominal pain or discomfort</b>	9	2.9	9	1.8
<b>Other abdominal complaints - including constipation, diarrhea</b>	19	6.1	23	4.5
<b>Injection site discomfort, pain or irritation</b>	16	5.1	16	3.1
<b>Post-treatment anorectal discomfort</b>	9	2.9	9	1.8
<b>Post-treatment proctalgia</b>	49	15.7	56	10.9
<b>Injection site bleeding</b>	18	5.8	20	3.9
<b>Anal or rectal bleeding</b>	28	9.0	30	5.8
<b>Post-treatment fever</b>	21	6.7	22	4.3
<b>Post-treatment infection</b> - including Anal and rectal abscess, Escherichia bacteremia, Injection site abscess/pustule, Perineal abscess, Rectovaginal septum abscess	12	3.8	13	2.5
<b>Injection site reaction</b> - including anal pruritus, inflammation, ulcer, proctitis	10	3.2	11	2.1
<b>Rectal discharge</b>	9	2.9	9	1.8

The safety results from the Proof-of-Concept study are similar to those observed in the Pivotal IDE and OUS Open-Label studies. In addition, this study provides evidence that through 24 months of follow-up, no new safety concerns arose.

Taken together, this PMA presents a strong and comprehensive package of clinical data to support the safety and effectiveness of Solesta. The data demonstrate that Solesta is safe and effective in treating patients with FI (a condition with limited treatment options and a devastating impact on patient's quality of life).

## 10 RISK-BENEFIT EVALUATION

The positive benefit risk of Solesta for treatment of FI refractory to conservative therapy can be concluded based on the safety and efficacy data from 346 patients who had received a total of 566 treatments and followed up for up to 24 months after last treatment.

Solesta is an injectable bulking agent that is comprised of well-known materials that have been in safe clinical use for nearly 10 years. The injection procedure is performed as an office procedure without need for anesthesia.

Adverse events associated with the treatment procedure were reported in 48.5 % of patients following Solesta treatment in the Pivotal IDE study and the majority of these adverse events were related to the injection procedure. Ninety-seven percent (97 %) of these treatment-related adverse events were mild to moderate in severity and 97 % required no or simple non-invasive interventions. Few treatment-related adverse events had onset more than 6 months after treatment. The incidence of adverse events is comparable to that reported following other common procedures performed in the anorectum, such as sclerosing therapy or infrared coagulation of hemorrhoids <sup>32, 33</sup>.

There were no deaths associated with Solesta treatment. There were a total of nine serious treatment-related adverse events reported in seven patients from both multicenter studies and all of which resolved without sequelae following treatment. These serious treatment-related adverse events predominantly concerned peri-operative infection. Peri-operative infection requiring submucosal incision and drainage of abscess at the injection site was reported in 2.6 % of all treatments. All events of infection resolved without sequelae following treatment with either antibiotics alone or in combination with drainage.

Efficacy and durability of Solesta for treatment of FI has been shown in the Pivotal IDE study and all pre-specified success criteria were met. Improvements in disease severity, number of incontinence-free days and quality of life were shown and were sustained over the 12-month study period following last treatment. Results from two open-label studies add further support to the findings from the Pivotal IDE study.

There is an unmet need for patients with FI refractory to conservative treatment. The benefits of treatment with Solesta for these patients outweigh the associated risks. Serious adverse events are uncommon. The spectrum of Solesta treatment-related adverse events has also been described for procedures performed in the anorectal region, so colorectal surgeons are already skilled with the treatment of these adverse events <sup>34, 35, 36</sup>. Unlike surgical procedures, there was no wound complication or fistula formation reported following Solesta treatment.

The injection procedure is performed under direct visual control and can be performed by colorectal surgeons who are already familiar with performance of anorectal procedures. The risk associated with the injection procedure can be minimized by education including information provided in the Package Insert and a dedicated training program. In comparison to alternative surgical treatments of FI that are more invasive procedures with significant adverse events and known risk of long-term failure, injectable Solesta offers an alternative treatment with favorable benefit risk.

## 11 PATIENT SAFETY POST-APPROVAL

Oceana Therapeutics has given careful consideration to maximizing correct and safe use of Solesta after PMA approval.

Solesta is intended to be administered by physicians experienced in performing anorectal procedures. Also, post approval vigilance that includes adverse event and device malfunction reporting will be implemented.

To further ensure that Solesta is administered safely, Oceana Therapeutics intends to also institute a training program for new users. This comprehensive program will serve to optimize outcomes and minimize adverse events. The overall program is planned to commence with a screening process which will delineate physicians/surgeons as either “expert” or “non-expert”. Once identified, the physician will proceed to an appropriately tailored training program. The physician will not be allowed to administer Solesta until this training program has been completed. Two ancillary elements to this program are a “Training Advisory Panel” and the “Centers of Excellence”.

- The “Training Advisory Panel” will likely comprise physicians who were involved in the clinical studies and other established experts in the field of FI and anorectal pathology. This panel is intended to provide general advice on issues regarding training, and assist in establishing an appropriate screening process.
- The “Centers of Excellence” will be established throughout the country for physicians who request or require witness of administration by injectors with a robust experience in administering Solesta. Centers of Excellence are preferred places of education and will be selected based on good outcomes, the finest operational standings and the best patient care. Most importantly these centers will demonstrate a commitment to training and education and will not only instruct physicians about Solesta, but will detail the comprehensive management of FI.

The screening process will identify the level of training necessary for each individual physician prior to gaining certification of competency to administer Solesta. The screening process will enquire into the physicians prior experience operating and/or manipulating the anorectal canal, history of using injection techniques – for example to sclerose hemorrhoids, professional training, licensure status and board status.

- “Experts”, most likely colorectal surgeons and proctologists, will have demonstrated an interest in the treatment of FI in the past. They will also be expected to have a deep understanding of the anatomy and physiology surrounding the anorectal area as well as the pathophysiology of FI. General surgeons and gastroenterologists with a special interest in gastrointestinal motility disorders may be deemed “experts” as well. The training track for “experts” will encompass specific reading materials.
- “Non-experts”, will need to complete a more intensive training program. This will include the basic curricula that the “experts” had to read, as well as web-based training and visits to the Centers of Excellence for hands-on training.



Both “experts” and “non-experts” will be required to pass a written exam to gain certification from Oceana Therapeutics to administer Solesta.

## **12 OVERALL SUMMARY AND CONCLUSIONS**

FI is a serious medical condition which has a significant negative impact on well-being and quality of life for sufferers. For patients who are not helped by non-invasive conservative therapies or surgery, the existing treatment options are limited.

This PMA has been submitted to support the safety and effectiveness of Solesta, an injectable bulking agent for the treatment of FI in adult patients who have failed conservative therapy. Solesta is administered locally to the anorectal area in an outpatient setting and requires no anesthesia.

Solesta is composed of well-known materials that have a history of safe use for similar applications. Extensive preclinical testing has been performed to evaluate the biocompatibility and long term durability of Solesta, demonstrating its appropriateness for the proposed intended use.

The data in this PMA submission provide strong evidence that treatment with Solesta is effective. The data show a clinically meaningful reduction in FI episodes which is sustained through at least 12 months following treatment. This reduction in the number of FI episodes is accompanied by a statistically significant improvement in quality of life and other supportive assessments. The data also show that treatment with Solesta remains safe 24 months after treatment. In the overwhelming majority of cases reported adverse events are of mild to moderate intensity, have an onset shortly after treatment, are of short duration and are generally shown to resolve without sequelae.

In keeping with the FDA’s criteria for premarket approval, we believe that the preclinical and clinical evaluations described in this PMA meet FDA’s criteria for valid scientific evidence to establish reasonable assurance of safety and effectiveness of Solesta according to 21 CFR 860.7(d)(1) and 21 CFR 860.7(e)(1).

## **13 APPENDICES**

**Appendix 1** Pivotal IDE study: Serious adverse events

**Appendix 2** Collated Solesta Safety Data

**Appendix 3** Fecal Incontinence Quality of Life (FIQL) questionnaire

**Appendix 4** Cleveland Clinic Florida Incontinence Score (CCFIS)

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## Appendix 1 Pivotal IDE study: Serious adverse events

**Table 27 List of SAEs in the pivotal IDE study assessed as unrelated to treatment by the study investigators.**

MedDRA Preferred Term	Solesta (blinded and open phase)		Sham (blinded phase only)	
	Number of events	Number of subjects	Number of events	Number of subjects
Abdominal pain	1	1	-	-
Anemia	1	1	-	-
Arrhythmia	1	1	-	-
Arterial stenosis limb	1	1	-	-
Arthralgia	4	3	-	-
Artrial fibrillation	1	1	-	-
Back pain	2	2	-	-
Benign ovarian tumor	1	1	-	-
Bladder cancer	1	1	-	-
Carotid artery stenosis	-	-	1	1
Cerebrovascular accident	1	1	-	-
Chest pain	2	2	1	1
Cholecystectomy	1	1	-	-
Cholelithiasis	1	1	-	-
Concussion	1	1	-	-
Enterocoele	1	1	-	-
Gastroenteritis	2	2	-	-
Gastric bypass	1	1	-	-
Hemorrhoids	1	1	-	-
Hydronephrosis	1	1	-	-
Incisional hernia	1	1	-	-
Intervertebral disc protrusion	1	1	1	1
Multiple endocrine adenomatosis Type II	1	1	-	-

<b>MedDRA Preferred Term</b>	<b>Solesta (blinded and open phase)</b>		<b>Sham (blinded phase only)</b>	
	<b>Number of events</b>	<b>Number of subjects</b>	<b>Number of events</b>	<b>Number of subjects</b>
Spinal stenosis	1	1	-	-
Nausea	1	1	-	-
Pneumonia	-	-	1	1
Post-procedural hematoma	1	1	-	-
Rectal prolapse	1	1	-	-
Spinal column stenosis	1	1	-	-
Thyroid adenoma	1	1	-	-
Thyroid neoplasm	-	-	1	1
Urinary tract infection	2	2	-	-
Wound decomposition (sp. removal of benign ovarian tumor)	1	1	-	-

## Appendix 2 Collated Solesta Safety Data

Table 28 includes AEs or groups of AEs that occurred in more than 2 % of the patients and that were assessed as related to treatment in the sponsored Pivotal IDE and OUS Open Label studies. A total of 282 events were assessed by the investigators as related to Solesta in the 2 studies which together included 312 patients, who received a total of 513 treatments with Solesta. The majority (96.1 %) of these 282 events were of mild to moderate intensity. The median time to onset was 1 day and duration was less than a week for these treatment-related adverse events. All adverse events were coded according to the standardized MedDRA terminology.

**Table 28 Solesta treatment-related adverse events through 18 months for the sponsored Pivotal IDE and OUS Open-Label studies combined. Groups of adverse events reported in more than 2 % of patients.**

Group of adverse events - MedDRA Preferred Term	Patients		Events		Intensity of AE			Intervention to treat AE			
	n	%	Number of events	Incidence/ treatment*	Mild	Moderate	Severe	None	Medical	Other	Both†
<b>Abdominal pain or discomfort</b>	<b>9</b>	<b>2.9</b>	<b>9</b>	<b>1.8</b>							
- Abdominal discomfort	2	0.6	2	0.4	0	2	0	0	0	1	1
- Abdominal pain	4	1.3	4	0.8	1	3	0	1	3	0	0
- Abdominal pain lower	2	0.6	2	0.4	2	0	0	2	0	0	0
- Gastrointestinal pain	1	0.3	1	0.2	0	1	0	1	0	0	0
<b>Other abdominal complaints</b>	<b>19</b>	<b>6.1</b>	<b>23</b>	<b>4.5</b>							
- Constipation	7	2.2	8	1.6	7	1	0	2	6	0	0
- Diarrhea	13	4.2	15	2.9	11	4	0	7	8	0	0
<b>Injection site discomfort or pain</b>	<b>16</b>	<b>5.1</b>	<b>16</b>	<b>3.1</b>							
- Injection site discomfort	1	0.3	1	0.2	0	1	0	1	0	0	0

Group of adverse events - MedDRA Preferred Term	Patients		Events		Intensity of AE			Intervention to treat AE			
	n	%	Number of events	Incidence/treatment*	Mild	Moderate	Severe	None	Medical	Other	Both†
- Injection site irritation	1	0.3	1	0.2	1	0	0	1	0	0	0
- Injection site pain	14	4.5	14	2.7	9	5	0	9	5	0	0
<b>Post-treatment anorectal discomfort</b>	<b>9</b>	<b>2.9</b>	<b>9</b>	<b>1.8</b>							
- Anorectal discomfort	9	2.9	9	1.8	7	2	0	3	6	0	0
<b>Post-treatment proctalgia</b>	<b>49</b>	<b>15.7</b>	<b>56</b>	<b>10.9</b>							
- Proctalgia	49	15.7	56	10.9	27	28	1	23	23	9	1
<b>Injection site bleeding</b>	<b>18</b>	<b>5.8</b>	<b>20</b>	<b>3.9</b>							
- Injection site hemorrhage	17	5.4	19	3.7	19	0	0	18	0	1	0
- Injection site hematoma	1	0.3	1	0.2	1	0	0	1	0	0	0
<b>Anal or rectal bleeding</b>	<b>28</b>	<b>9.0</b>	<b>30</b>	<b>5.8</b>							
- Anal hemorrhage	10	3.2	11	2.1	9	2	0	8	0	3	0
- Rectal hemorrhage	18	5.8	18	3.5	13	5	0	15	1	2	0
- Hematochezia	1	0.3	1	0.2	1	0	0	1	0	0	0
<b>Post-treatment fever</b>	<b>21</b>	<b>6.7</b>	<b>22</b>	<b>4.3</b>							
- Pyrexia	21	6.7	22	4.3	15	5	2	7	13	1	1
<b>Post-treatment infection</b>	<b>12</b>	<b>3.8</b>	<b>13</b>	<b>2.5</b>							
- Anal abscess	3	1.0	3	0.6	0	3	0	0	1	1	1
- Escherichia bacteremia	1	0.3	1	0.2	0	1	0	0	1	0	0
- Infection	1	0.3	1	0.2	0	1	0	0	1	0	0



Group of adverse events - MedDRA Preferred Term	Patients		Events		Intensity of AE			Intervention to treat AE			
	n	%	Number of events	Incidence/treatment*	Mild	Moderate	Severe	None	Medical	Other	Both†
- Injection site abscess	1	0.3	1	0.2	1	0	0	0	1	0	0
- Injection site pustule	1	0.3	1	0.2	1	0	0	0	1	0	0
- Perineal abscess	1	0.3	1	0.2	0	1	0	0	0	0	1
- Rectal abscess	4	1.3	4	0.8	0	1	3	0	1	2	1
- Rectovaginal septum abscess	1	0.3	1	0.2	0	0	1	0	1	0	0
<b>Injection site reaction</b>	<b>10</b>	<b>3.2</b>	<b>11</b>	<b>2.1</b>							
- Anal pruritus	3	1.0	4	0.8	4	0	0	3	1	0	0
- Injection site inflammation	1	0.3	1	0.2	1	0	0	0	1	0	0
- Injection site ulcer	1	0.3	1	0.2	1	0	0	0	0	0	1
- Proctitis	5	1.6	5	1.0	2	2	1	2	3	0	0
<b>Other</b>	<b>9</b>	<b>2.9</b>	<b>9</b>	<b>1.8</b>							
- Rectal discharge	9	2.9	9	1.8	7	2	0	5	3	1	0

\* 513 treatments with Solesta

† Both refers to a combination of medical and another intervention (e.g., incision and drainage of abscesses and concurrent treatment with antibiotics)

Other events reported include the following MedDRA preferred terms: abdominal distension, abdominal rigidity, alopecia, anal fissure, anal prolapse, anal pruritus, back pain, C-reactive protein increased, chills, cold sweat, defecation urgency, dermatitis, device dislocation, dizziness, dyspareunia, fecal incontinence, feces hard, fatigue, gastrointestinal motility disorder, gastrointestinal pain, genital discharge, genital prolapse, hematochezia, hematospermia, hemorrhoids, injection site nodule, injection site swelling, intestinal mass, malaise, mucosal inflammation, musculoskeletal pain, nausea, edema, pain, painful defecation, pelvic mass, perineal pain, rectal lesion, rectal obstruction, rectal prolapse, rectal spasm, rectal tenesmus, urinary retention, vaginal discharge, vulvovaginal pain.

### Appendix 3 Fecal Incontinence Quality of Life (FIQL) questionnaire

#### QUALITY OF LIFE SCALE FOR FECAL INCONTINENCE (Dis Colon Rectum, January 2000)<sup>31</sup>

**Q1:** In general, would you say your health is:

- 1 ☐ Excellent  
2 ☐ Very Good  
3 ☐ Good  
4 ☐ Fair  
5 ☐ Poor

**Q2:** For each of the items, please indicate how much of the time the issue is a concern for you due to accidental bowel leakage.

Q2. Due to accidental bowel leakage:	Most of the Time	Some of The Time	A Little of the Time	None of the Time
a. I am afraid to go out	1	2	3	4
b. I avoid visiting friends	1	2	3	4
c. I avoid staying overnight away from home	1	2	3	4
d. It is difficult for me to get out and do things like going to a movie or to church	1	2	3	4
e. I cut down on how much I eat before I go out	1	2	3	4
f. Whenever I am away from home, I try to stay near a restroom as much as possible	1	2	3	4
g. It is important to plan my schedule (daily activities) around my bowel pattern	1	2	3	4
h. I avoid traveling	1	2	3	4
i. I worry about not being able to get to the toilet in time	1	2	3	4
j. I feel I have no control over my bowels	1	2	3	4
k. I can't hold my bowel movement long enough to get to the bathroom	1	2	3	4
l. I leak stool without even knowing it	1	2	3	4
m. I try to prevent bowel accidents by staying very near a bathroom	1	2	3	4

**Q3:** Due to accidental bowel leakage, indicate the extent to which you AGREE or DISAGREE with each of the following items.

Q3. Due to accidental bowel leakage:	Strongly Agree	Somewhat Agree	Somewhat Disagree	Strongly Disagree
a. I feel ashamed	1	2	3	4
b. I can not do many things I want to do	1	2	3	4
c. I worry about bowel accidents	1	2	3	4
d. I feel depressed	1	2	3	4
e. I worry about others smelling stool on me	1	2	3	4
f. I feel like I am not a healthy person	1	2	3	4
g. I enjoy life less	1	2	3	4
h. I have sex less often than I would like to	1	2	3	4
i. I feel different from other people	1	2	3	4
j. The possibility of bowel accidents is always on my mind	1	2	3	4
k. I am afraid to have sex	1	2	3	4
l. I avoid traveling by plane or train	1	2	3	4
m. I avoid going out to eat	1	2	3	4
n. Whenever I go someplace new, I specifically locate where the bathrooms are	1	2	3	4

**Q4:** During the past month, have you felt so sad, discouraged, hopeless, or had so many problems that you wondered if anything was worthwhile?

- 1 ☐ Extremely So – To the point that I have just about given up
- 2 ☐ Very Much So
- 3 ☐ Quite a Bit
- 4 ☐ Some – Enough to bother me
- 5 ☐ A Little Bit
- 6 ☐ Not At All

#### Appendix 4 Cleveland Clinic Florida Incontinence Score (CCFIS)

The CCFIS score is based on a patient interview using standardized questions regarding incidence and type of incontinence (solid, liquid or gas), pad usage and lifestyle alterations during the past month. The score ranged from 0 (perfect) to 20 (complete incontinence). A score of 10 or higher in the CCFIS has been shown to correlate to a significant poorer quality of life compared to healthy individuals .

The CCFIS questionnaire is shown below:

Type of incontinence	Frequency				
	Never	Rarely	Sometimes	Usually	Always
<b>Solid</b>	0	1	2	3	4
<b>Liquid</b>	0	1	2	3	4
<b>Gas</b>	0	1	2	3	4
<b>Wears pad</b>	0	1	2	3	4
<b>Lifestyle alteration</b>	0	1	2	3	4

Never	0 episodes / 3 months
Rarely	<1/month
Sometimes	<1/week, ≥1/month
Usually	<1/day, ≥1/week
Always	≥1/day