VALUE DOSSIER

PALETTE LIFE SCIENCES

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List of Abbreviations

ACG	American College of Gastroenterology
AE	Adverse Event
AGA	American Gastroenterological Association
AHRQ	Agency for Healthcare Research and Quality
ASCRS	American Society of Colon and Rectal Surgeons
CCFIS	Cleveland Clinic Fecal Incontinence Score
CPT	Current Procedural Terminology
IBS	Irritable Bowel Syndrome
EAS	External Anal Sphincter
FDA	U.S. Food and Drug Administration
FI	Fecal Incontinence
FIQL	Fecal Incontinence Quality of Life
GI	Gastrointestinal
GPE	Global Perceived Effect
HCPCS	Healthcare Common Procedure Coding System
IAS	Internal Anal Sphincter
ICER	Incremental Cost-Effectiveness Ratio
MCID	Minimal Clinically Important Difference
NHRIC	National Health Related Items Code
OASIS	Obstetric and Sphincter Injury
PAS	Post-Approval Study
PTQ	1, 10-phenanthroline-5,6-dione (Silicone)
QALY	Quality Adjusted Life Years
QoL	Quality of Life
SNS	Sacral Neuromodulation

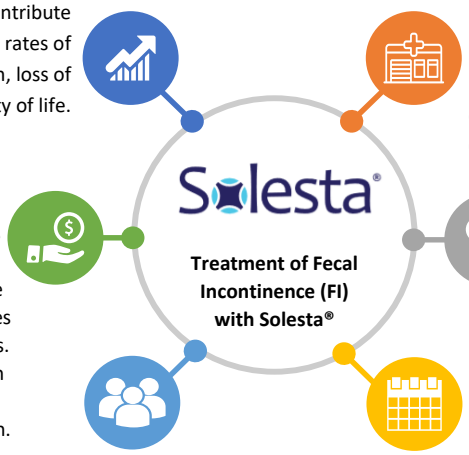
I. Executive Summary

FI causes significant socioeconomic burden

FI causes active members of society to contribute less. Patients suffering from FI have higher rates of unemployment, increased absenteeism, loss of productivity and reduced quality of life.

Solesta® fills an important gap as an effective FDA approved minimally invasive treatment

75% of FI patients will find conservative treatment options, such as dietary management and pharmacological products, inadequate. Surgical options, like SNS are expensive, invasive, contraindicated in some patients, and have high rates of re-operation. Solesta® demonstrates significant efficacy, durability and clinical improvement in a patient's QoL as a minimally invasive therapy option for FI patients.



FI costs billions to treat in the US

Healthcare costs are ~55% higher for patients with FI. This burden will continue to rise as the estimated number of FI cases rises by over 8 million in the next 40 years. When compared with SNS, the acquisition cost for one treatment of Solesta® is just 18% of the cost for a full SNS implantation.

Solesta® is safe for patients

Solesta® is an outpatient procedure with minimal recovery time and does not require anesthesia. Over multiple long-term studies, Solesta® reveals an excellent safety profile.

FI is associated with significant humanistic burden

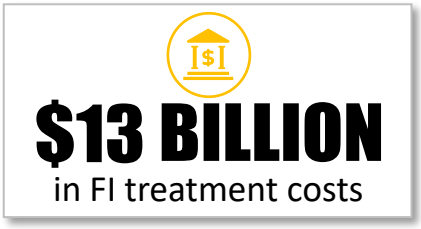
FI inhibits the ability for individuals to live alone and increases the likelihood of referral to a nursing home by

Solesta® has proven long-term efficacy

Solesta® significantly improves the number of FI episodes, FI-free days, and improved quality of life scores compared to baseline through 36 months. Solesta® prevents re-treatment intervention for >80% of FI patients.

Additional information and references can be found in the subsequent sections

Fecal Incontinence Disease Overview



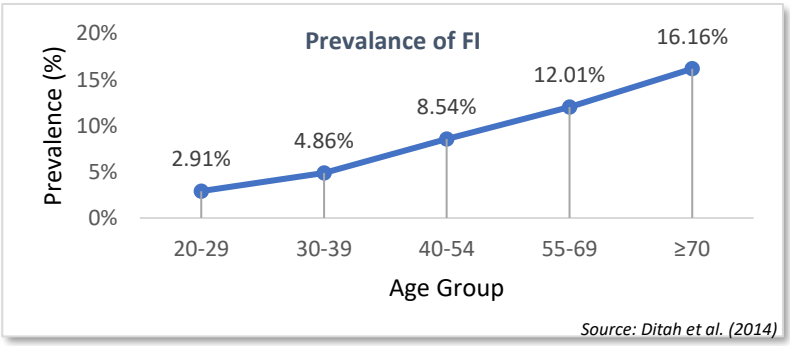
Annual FI treatment costs ~$13 billion in the US.

Fecal incontinence (FI) is defined as the involuntary discharge of gas, liquid or solid stool and is estimated to have cost the healthcare system roughly $11 billion in 2015 or ~$12.9 billion in 2020 based on Consumer Price Index (CPI) adjustments for medical care.[1]

FI is associated with substantial humanistic and quality-of-life burden for patients and caregivers.

Many patients are unwilling to report FI symptoms or seek medical treatment due to the embarrassing nature of the condition. FI severely impacts a patient's quality of life (QoL) across measures of lifestyle, coping/behavior, depression/self-perception and embarrassment. FI can lead to social isolation, disruptions in intimate relationships, problems with self-confidence and significant psychological and social impact to patients.[1]

FI affects up to ~8.3% of non-institutionalized US adults,[2,3] but it is believed the actual prevalence may be higher - ranging from 7 to 12%.[4] FI prevalence increases with age – given the aging US population, the incidence and prevalence of FI are predicted to increase in the future.[5]



Source: Ditah et al. (2014)

FI is caused by the disruption of the normal anatomy and/or physiology of the anorectal organs and occurs when mechanisms that allow continence to be maintained are disrupted. Disruptions can be both structural (as a result of injury, trauma, or childbirth) and functional in nature (involving diabetes-related neuropathy or other neurological disorders). The severity of FI varies by individual and can occur at different times, as the condition is influenced by external factors such as physical exercise, stress, concurrent illness and diet.

FI causes significant socioeconomic burden.

FI impacts the socioeconomic well-being of affected individuals. FI causes otherwise contributing members of society to become less active through increased days off, loss of productivity and higher rates of unemployment and absenteeism.[6] FI also contributes to many patients' inability to live independently, and increases the likelihood of referral to a nursing home by 10-15%.[7]

Socioeconomic Burden of FI:

- Increased unemployment
- Loss of productivity
- Inability to live independently
- Significant cost burden to the healthcare system

In addition to the socioeconomic burden of indirect FI patient costs, patients suffering from FI have substantial direct medical costs, including expenditures for incontinence products, medications and other healthcare products.[8] In one study, patients with at least 2 monthly FI episodes incurred 55% higher healthcare costs, including 77% higher gastrointestinal (GI) related healthcare costs, compared to continent patients. This cost increase is likely driven by the greater frequency of health care practitioner visits, which was significantly higher in patients with FI compared to patients without FI. On average, patients with frequent FI had 4.21 more visits per year than patients without FI.[4]

Solesta® Overview

Solesta® (non-animal stabilized hyaluronic acid/dextranomer [NASHA/Dx FI]) is a biocompatible injectable bulking agent, and is the **only** bulking agent approved by the U.S. Food and Drug Administration (FDA) for the treatment of FI.[9] Solesta® can be administered in the outpatient setting without anesthesia and is indicated for the treatment of FI in patients 18 years and older who have failed conservative therapy (e.g., diet, fiber therapy, anti-motility medication, etc.).[9]

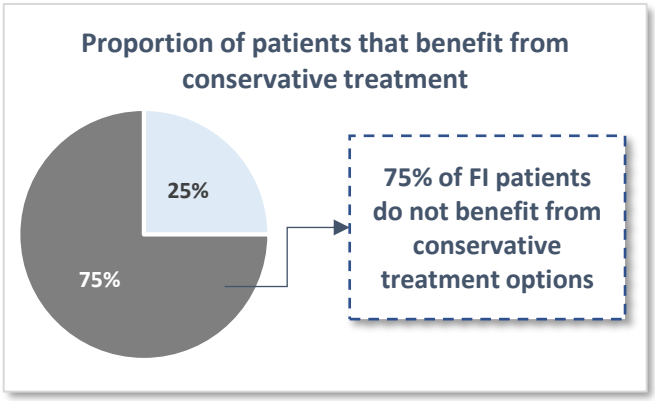
Solesta® was approved by the FDA on May 27, 2011, and has been used in over 6,500 patients and studied in ~600 patients [10–12]

The efficacy, safety, and durability of Solesta® have been reported in several large, prospective, multi-center, observational trials, including a large post-approval study (PAS) accepted by the FDA on March 17th 2020, in which 283 patients received treatment with Solesta® and were followed up for a minimum of 7 visits over 36-months following the last treatment. These trials confirm the original safety and efficacy benefits of Solesta® therapy that were the basis of FDA approval and further bolster the Product's long-term efficacy. Solesta® treatment led to both statistically and clinically significant long-term outcomes, including an improvement in all four QoL domains, disease burden and in the severity of incontinence. Over 80% of Solesta® patients remained free from re-intervention through 36 months.

Solesta® is presently available from Palette Life Sciences, whose portfolio of innovative products improve patient outcomes in colorectal, urologic, gynecologic and interventional oncology conditions.

FI Treatment Paradigm and Unmet Need

Numerous treatment options exist for managing FI; however, multiple limitations of some treatments have resulted in weak recommendation by specialty society guidelines. Limitations include inconsistent efficacy, limited long-term data, need for invasive procedures, and limited suitability to specific FI patient sub-populations. The current guidelines recommend a stepwise algorithm, with all guidelines recommending the use of conservative treatments prior to the pursuit of minimally invasive or invasive techniques, such as surgery.[13–15] Despite a universal recommendation for the initial use of conservative treatment options, only 25% of patients benefit from conservative therapy, requiring a majority of patients to seek minimally invasive or surgical treatment options as their next stage of treatment.[10]



Benefits of Solesta®

Clinical Efficacy	• In the PAS completed in 2019 (accepted as an abstract and pending publication), Solesta® was found to be efficacious in treating FI; >80% of patients did not require re-intervention through 36-months post-treatment.[12] • At 6 months, Solesta® demonstrated a ≥50% reduction in symptomatic burden for 52% of patients treated in the pivotal study.[16] • When compared to a sham arm (pivotal trial), patients receiving Solesta® experienced a significantly greater percentage of individuals who saw at least a 50% reduction in incontinence free episodes, as well as a significant increase in number of incontinence-free days from baseline through 36 months.[16] • Another important facet of Solesta®'s clinical benefit is that it offers the ability to re-treat if needed with any additional treatment options deemed appropriate for the patient; unlike invasive surgical options, such as sacral neuromodulation (SNS), which limit the additional treatment options that the patient may receive.[16]

Economic Benefit	• When compared to SNS, Solesta® offers a lower cost treatment option.
	  ○ In 2013, a 3-year cost-effectiveness model showed that the expected cost for SNS is $33,201 versus $14,962 for Solesta®.
	  ○ Solesta® may be even less costly when performed in the physician office.[17]
	• When considering the quality adjusted life-years (QALY) gained for each type of treatment, the incremental cost for Solesta® was $37,036 per QALY gained versus conservative treatment, whereas for SNS the incremental cost was $103,066 per QALY versus conservative treatment.[17]

	• When compared with SNS, the acquisition cost for the first treatment of Solesta® is only 18% of the cost for full SNS implantation. • If subsequent treatment for all patients is assumed, the costs for Solesta® are still only 36% of the direct costs for SNS treatment.[17]
Improvement in Patients' QoL	• A robust evaluation of QoL outcomes performed alongside the 36-month PAS showed that the statistically significant improvements associated with Solesta® improved patients' reported QoL and exceeded the threshold for meaningful clinical improvement through a 36-month study period.[12] o Treatment with Solesta® significantly improves a patient's overall QoL and symptom burden over the long-term. o Study results document an improvement in each sub-scale of the FIQL and a reduction in symptom burden based on the CCFIS from baseline through 36-months post-treatment.
Safety	• In the PAS, 58 device-related AEs were reported – most were GI disorders that resolved quickly, and none were assessed as serious.[12] • In the 6-months blinded phase of the pivotal study there were two serious treatment-related adverse events, one case of E. coli bacteremia and one case of rectal abscess. A third patient experienced a serious treatment-related adverse event of rectal abscess during the open phase. These events resolved following treatment without sequalae within 35 days of event onset.[9] • The frequency of serious treatment-related adverse events associated with Solesta® treatment is low and Solesta® continues to demonstrate an excellent safety profile over the long-term as evidenced by the PAS safety data.[12]
Durability	• In the PAS, data at 6- and 36-months support that the Solesta® implants remain present and, in general, do no shift from one anatomic position to another.[12]

Use of Solesta® in FI Management Guidelines

Solesta®, an injectable bulking agent, is a minimally invasive treatment option indicated for FI and is well-recognized by specialty societies.

Guidelines from the following specialty groups and quality assessment organizations uniformly recommend considering the use of bulking agents for the management of FI:

- The American College of Gastroenterology (ACG)
- The American Gastroenterological Association (AGA)
- The American Society of Colon and Rectal Surgeons (ASCRS)
- The U.S. Agency for Healthcare Research and Quality's (AHRQ) 2016 FI review

However, it is important to note that these historical recommendations are rated as "weak" but are incomplete for two critical reasons:

1. Each guideline provides one recommendation generally applied across several bulking agents. The majority of these guidelines fail to clearly document that Solesta® is the only bulking agent approved for the treatment of FI; and other bulking agents mentioned in guidelines have

generated mixed and varying evidence of efficacy and none of them have an FDA approved indication in treatment of FI.[10,13,15,18]

2. These guidelines were last updated between 2014-2017, and therefore fail to consider compelling evidence from several recent studies proving the long-term efficacy, safety, and durability of Solesta® – other bulking agents have not been approved by the FDA for FI treatment, nor do they have a comparable evidence base to Solesta® in this indication (See Figure 5.3). Furthermore, as the AHRQ review was completed in 2016, it is now labeled "archived" by the agency and should not be used for clinical decision-making.

Due to the heterogeneity in evidence of safety and efficacy for treating FI among these disparate bulking agents, the older guidelines provide a "weak" recommendation for the bulking agent category, which they considered as a whole.[13–16] These bulking agents are not all simply interchangeable for different indications. Based on these shortcomings, all guidelines recommend consideration of bulking agents, but note that evidence, at point of publication, was "weak".

> "Dextranomer FI [Solesta®] is the **only FDA approved [biocompatible bulking agent] product for FI**"
>
> - American Gastroenterological Association (AGA)[10]

Despite the fact that guidelines do not consider Solesta® publications with long-term evidence, sub-group analyses, nor any evidence from the Solesta®'s 36-month PAS, use of injectable bulking agents is the only minimally invasive treatment option recommended for consideration amongst all mentioned society guidelines, and Solesta® is the only option consistently recommend, by name, for consideration by all key FI treatment guidelines. [10,13,15,19] Within guidelines, Solesta® is documented as resulting in a clinically & statistically significant improvement in the proportion of patients who experienced:

- At least a 50% reduction in the number of incontinence episodes compared to sham treatment, and
- An increase in the number of incontinence-free days compared to sham treatment.

Additionally, recent Solesta® studies address the underlying limitations raised by previously published guidelines related to the need for additional evidence of long-term safety and efficacy associated with Solesta® treatment.[10,14,20]

Historically published guidelines fail to directly reference:

- ***Mellgren et al., 2014 Publication:*** Reports long-term efficacy of Solesta® at 12 and 36 months[16]
  - Only one FI guideline references any Solesta® data beyond 6 months, with the data not properly attributed to the Mellgren publication
- ***Franklin et al., 2016 Publication:*** Analyzed & highlighted the benefit of Solesta® vs Sham in specific key patient subgroups[21]
- ***Solesta® PAS, 2020:*** 283-patient, 36-month, multi-center PAS with robust long-term outcomes data (recently FDA approved & publication pending) demonstrates:[12]
  - Real-world safety, efficacy, and medical appropriateness of Solesta®
  - Significant improvements in objective clinical measures, re-intervention rate (>80% of patients treated do not require re-intervention through 36-months post treatment), and durability
  - Sustained statistically & clinically significant improvement in the CCFIS and FIQL scales

Limitations of Invasive Surgical Options

Amongst all recommended surgical options for FI, SNS is the most widely accepted and recommended invasive option, according to guidelines.[10,13,15,19] Although SNS has been shown to be efficacious, it is associated with a 15% failure rate and 41% surgical revision rate. There is a lack of evidence supporting the long-term management of patients with FI who do not respond to the initial SNS treatment and require retreatment.[22] Consequently, these patients have been subjected to:

1) Multiple surgeries, due to a 5-year battery replacement schedule with SNS.[23]
2) Limited long-term efficacy as the body becomes accustomed to stimulation.[23]
3) High likelihood (41%) of a surgical revision due to device-related failures such as infection, electrode displacement or breakage, system dysfunction from impedance increase and adverse stimulation resulting in pain for the patient.[23]
4) An associated infection rate ranging from 3% to 17% in patients with FI[24]
5) High costs: A typical SNS implantation generates health care costs of $29,027. ***A 3-year cost-effectiveness model showed that the expected cost for SNS is $33,201 versus $14,962 for Solesta® (in 2013 US dollars).***[17]

Given the limitations of both surgical and conservative treatment options, Solesta® fills an important gap within the FI treatment paradigm. Solesta® uniquely offers a minimally invasive, low risk, safe, and highly efficacious step-through treatment option ahead of invasive and expensive surgical options.

II. Introduction to Palette Life Sciences

Palette Life Sciences is a fully integrated life sciences company. Its products improve patient outcomes in urology and urogynecology disorders, colorectal conditions, and interventional oncology procedures. Its portfolio of products includes Solesta®, Deflux®, Lidbree® and Barrigel®.

The company serves patients often overlooked by traditional medical companies and places significant focus on improving the QoL of patients. Led by experienced healthcare executives, Palette Life Sciences is headquartered in Stockholm, Sweden, with offices in Santa Barbara, California, and Dallas, Texas.

The focus of this dossier is to document the clinical value of Solesta®, a minimally invasive, first-line interventional treatment for FI with substantial evidence documenting its efficacy, safety, and impact on QOL. Additional information can be found at MySolesta.com and palettelifesciences.com.

III. Fecal Incontinence Disease Overview

Key Takeaways	• FI is the inability to voluntarily control bowel contents. • FI can present in varying degrees of severity, ranging from gas to fecal seepage (where a patient maintains almost total control of bowel movements but experiences some leakage of stool) to passive incontinence (where a patient involuntarily defecates without awareness). • The pathological mechanisms that lead to FI are complex and often multifactorial; in women, obstetric injury is a common cause but may not develop until years after childbirth; in men, damage caused by prostate cancer radiation or brachytherapy is a common cause. • FI reportedly affects 8.3% of non-institutionalized US adults; most sufferers are aged 65 and older. • FI causes otherwise contributing members of society to become less active members through increased days off, loss of productivity and higher rates of unemployment. • FI is a common reason for inability to work among younger patients and for nursing home admission among older patients. • Patients report reduced self-esteem, shame, humiliation, depression, a need to organize life around access to a toilet and avoidance of enjoyable activities.

The clinical presentation of FI is not clearly linked to the underlying physiological or anatomical abnormality, meaning the reason for FI does not always have a clear relationship with the type or frequency of incontinence symptoms.[25] Other bowel problems, such as diarrhea, constipation, gas, and bloating, may accompany FI.[26]

Epidemiology

An estimated 22 million patients in the U.S are affected by FI each year, and FI prevalence is projected to continue growing due to population demographic changes.

FI reportedly affects ~8.3% of non-institutionalized US adults,[2,3] and ranges from 2.2% to as high as 24% with most estimates in the range of 7 to 12%.[4] It is assumed that the actual prevalence is higher, as patients are reluctant to report symptoms and seek treatment due to the embarrassing nature of this disorder. Typically, the problem must continue for at least 1 month, and the patient must be older than 4 years old, to be considered FI. Prevalence of FI showed a linear upward trend with age, from 2.91% among

individuals aged 20 to 29 to 16.16% among individuals aged 70 and older (Figure 3.1).[5] With the aging of the US population, the incidence and prevalence of FI is expected to increase in future years.[3] In 2010, the US Census Bureau projected that the population aged 65 to 84 years will more than double and the population aged 85 years and older will triple by 2050.[27] Figure 3.2 shows the projected increase in number of FI cases between 2020 and 2030, by age group.

Figure 3.1. Overall Trends in prevalence of FI by age group (years)[5]

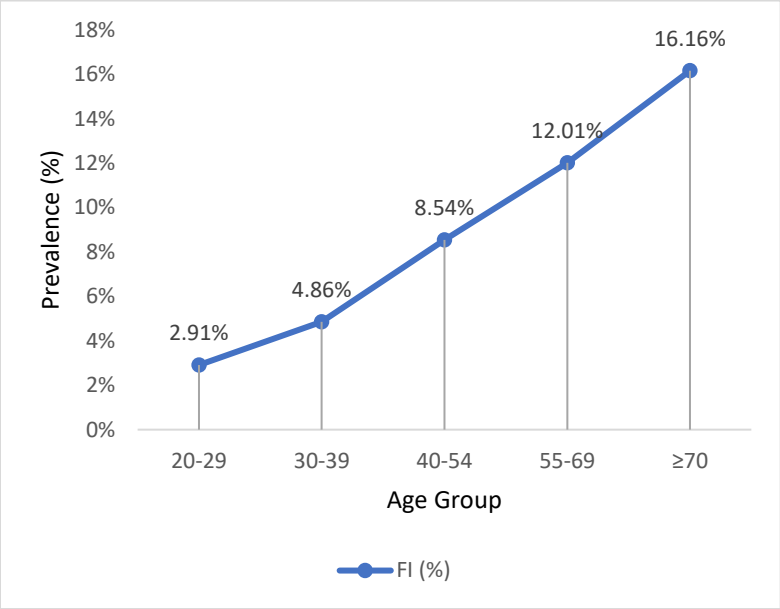
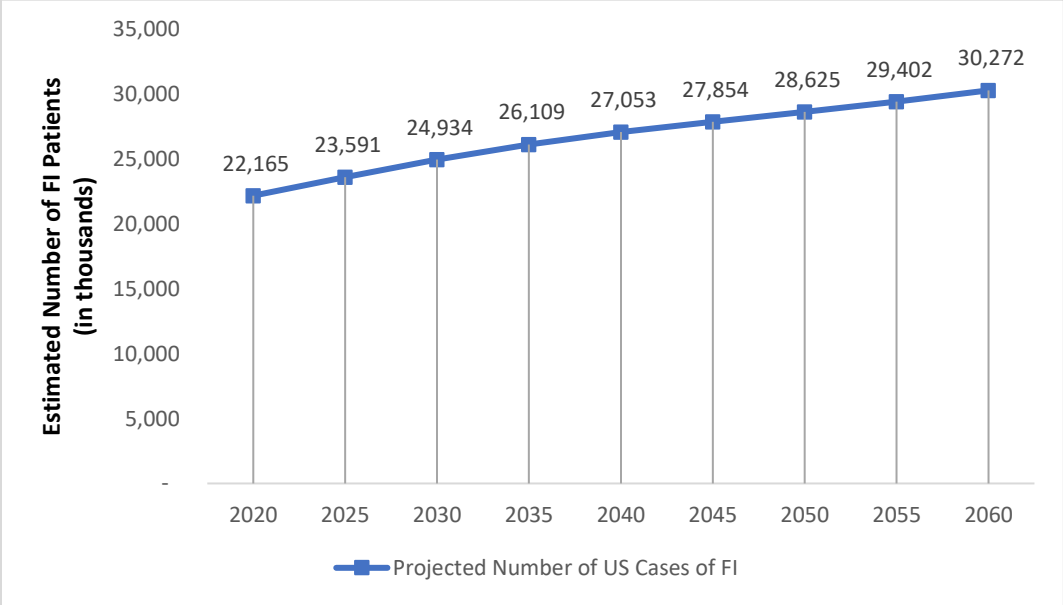


Figure 3.2. Number of Projected U.S. Individuals with FI from 2020-2060*[5,28]



*Total number of individuals with FI is based off of the population size estimates from the most recent U.S. Census data projections and the prevalence rate for the given age group as identified in the Ditah et al. paper (assuming the prevalence rate for the given age group is constant).

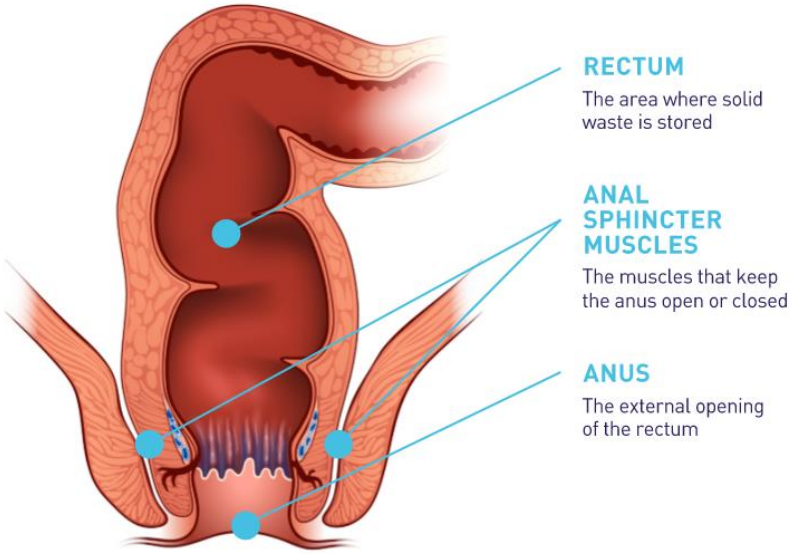
Pathophysiology

There are multiple pathological mechanisms that contribute to the development of FI.

FI is caused by disruption of the normal anatomy or physiology of the anorectal organs. It occurs when one or more mechanisms that allow continence to be maintained are disrupted to an extent that the other mechanisms cannot compensate. As a result, most cases of FI are multifactorial. In a prospective study, 80% of patients suffering from FI had multiple mechanistic abnormalities in the anorectal organs.[29]

The anorectal organs are comprised of the rectum and the anus (Figure 3.3). The following anatomical components provide functionality to the anorectal organs:

Figure 3.3. Anatomy of the Anus and Rectum[30]



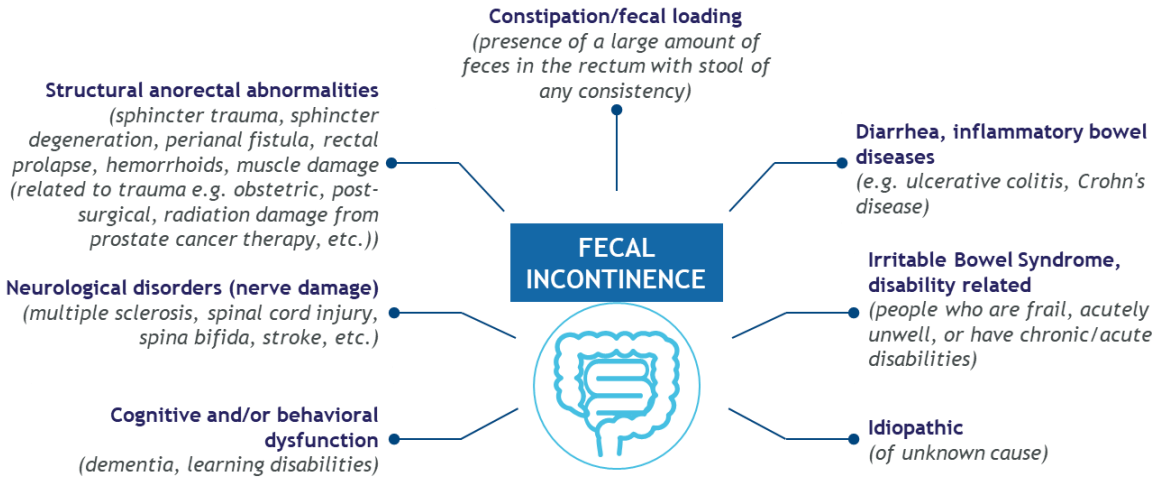
- The internal anal sphincter (IAS) and external anal sphincter (EAS) are responsible for creating and maintaining the anal pressure that allows for continence.
- Anal mucosal folds and anal vascular cushions provide a tight seal and prevent involuntary leakage. Anal vascular cushions also contribute to the anorectal sampling reflex, which allows an individual to choose whether to defecate or retain rectal contents.
- The anorectal organs also contain a multitude of sensory, motor and autonomic nerves. The pudendal nerve is the anorectal unit's principal nerve, as it innervates the EAS and serves both sensory and motor function.[29]

There are multiple pathological mechanisms that contribute to the development of FI:

- Structural in nature, as is the case with the development of sphincter muscle abnormalities due to injury or trauma, or pudendal neuropathy due to nerve damage caused by childbirth.
- Functional in nature, as is the case with loss of anorectal sensation, which can be caused by diabetes-related neuropathy or a neurological disorder like multiple sclerosis.[29]

Structural and functional abnormalities like the ones listed above can cause sphincter weakening, loss of sampling reflex, loss of anorectal angle control, sensory loss, fecal overflow, uncontrollable diarrhea, or relaxed sphincter tone. These mechanistic effects can result in loss of continence to varying degrees.[29] Figure 3.4 below summarizes the causes of FI.

Figure 3.4. Causes of FI[31–33]



Etiology and Risk Factors

As mentioned above, most FI cases occur in the elderly population. Although FI is often thought to be synonymous with loss of sphincter muscle control, this is not the only cause of FI. In fact, FI is thought to be a common final symptom of multiple independent disease etiologies.[2] Risk factors for FI include older age, diarrhea, urinary incontinence, diabetes mellitus, fecal urgency, physical disability, childbirth, and hormone therapy in postmenopausal women and radiation therapy for prostate cancer in men. [26,29,32–35]

FI can be caused by a wide variety of clinical issues. These issues include obstetric or surgical injury, trauma to the anorectal organs, spinal cord injury, nervous system damage, inflammatory bowel disease, drugs, dementia, disability, infection, excessive perineal descent, and neuropathy.[29] Women with obstetric trauma, such as obstetric and sphincter injury (OASIS), are at greater risk of FI: up to 59% of women with OASIS experience FI,[36] although it may not develop until years after childbirth. [25] Factors such as menopause and changes in the pelvic floor due to aging may explain why women who sustain obstetric injury in their 20 or 30s often do not develop FI until their 50s or later.[29]

Overall Fecal Incontinence Burden (Societal, Humanistic and Economic)

Societal Burden

Chronic FI is associated with significant burden to patients and caregivers.

Chronic FI can cause physical reactions of the perianal skin and urinary tract, including maceration (softening and whitening of skin due to continuous moisture), urinary tract infections, decubitus ulcers and anal discomfort.[26,37] For many patients, however, the larger consequence of FI is socioeconomic in nature, and contributes to patients' inability to live independently. Patients may become overwhelmed due to the financial cost of medication and incontinence products, loss of productivity, lost work and pay, medical insurers general health care costs and unemployment.[6] In fact, FI is a common reason for nursing home admission, with 26.3% of individuals admitted to nursing homes experience FI within 180 days of admission.[38] In a survey sent to American Geriatrics Society members, FI alone was associated with a 10-15% increase in likelihood of referral to a nursing home. When other risk factors, like chronic illness, immobility, and cognitive deficits were present, presence of FI added 17% to the likelihood of a nursing home referral. [7]

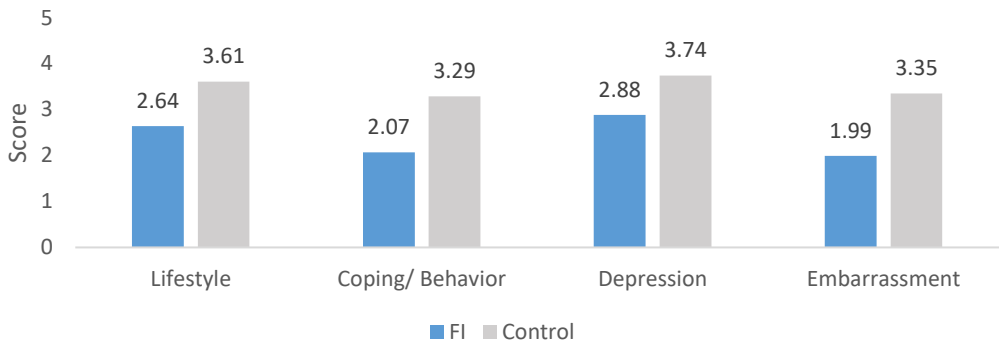
FI Impact on Quality of Life (QoL)

Numerous studies have documented that patients diagnosed with FI report significant negative impacts on their quality-of-life.

Even if a patient can still live independently, FI significantly impairs a patient's QoL. FI has been shown to lead to social isolation as well as loss of employment, intimate relationships and self-confidence.[1] Due to the subjective nature of the symptoms experienced by patients with FI, the evaluation of FI requires the consideration of two important components, severity and impact. Several instruments have been designed to measure FI impact from the patient's perspective, including the FIQL and CCFIS (also known as the Wexner Score).[39]

- The FIQL scale is a condition-specific patient-reported QoL questionnaire that consists of 29 questions and is divided into 4 domains reflecting the impact of QoL as it pertains to lifestyle, coping/behavior, depression/self-perception and embarrassment. For the FIQL scale, domain scores are calculated as the mean response to all items in the scale; the lower the score is for each domain the higher the FI impact.
    - In a cross-sectional survey conducted in the US, FIQL surveys were distributed to 118 FI patients and surveys were distributed to a control population of 72 individuals without FI, defined as patients that have been seen in clinic for a GI problem other than FI and have not been living with a person who had a diagnosis of FI. The objective of this study was to evaluate the psychometric measures of a health related QoL scale developed specifically to address patients experiencing FI. This study compared findings from those with FI and those without FI (control group) and showed that on average, patients with FI had a lower FIQL score, indicating a higher FI impact across all four FI domains (Graph 3.1.).[40]

Graph 3.1. Comparison between patients with FI and controls, for each FIQL sub-scale



- The CCFIS, also known as the Wexner Score, assesses the severity of incontinence from the patient's perspective. The CCFIS is a summed score of 5 individual parameters: frequency of incontinence to gas, liquid, solid, or need to wear an incontinence pad, and lifestyle changes. A CCFIS of zero indicates complete continence, and a score of 20 indicates severe incontinence.
    - A study of 115 FI patients across 15-centers in Europe and Canada assessed the pre-treatment impact of FI symptoms. For the 115 patients suffering from FI, the baseline CCFIS score was reported to be 13.5, before treatment, indicating that at baseline patients with FI scored on the higher end of the scale (more severe incontinence) for all 5 individual parameters.[41]

Economic Burden

The occurrence of FI is associated with significant increases in overall treatment costs for patients, caregivers, providers and insurers.

In one study that estimated the healthcare costs associated with FI, healthcare costs and utilization were calculated from medical and pharmacy claims data collected over a 5-year period. Findings from this study indicated that healthcare costs are estimated to be 55% higher for patients experiencing FI, although it is unknown how much of the excess healthcare costs are directly related to FI, or related to other co-comorbid conditions.[4] This increase in cost represents both direct costs, which includes physician and hospital fees, medication costs and incontinence supplies, and indirect costs, which includes work absenteeism, reduced work performance and changes in job status. Additionally, the average annual healthcare costs for all causes of co-morbid conditions was significantly associated with FI, with patients who had at least two monthly episodes of FI having an average of 55% higher health care costs and 77% higher gastrointestinal healthcare costs than patients without FI. This association was confirmed by multivariate analysis adjusting for Irritable Bowel Syndrome (IBS) diagnosis, loose stools, hard stools, inpatient bed days, age, race, and marital status.[10] In addition GI related health care costs were significantly related to FI in univariate analyses, but this relationship was not confirmed in multivariate testing, potentially due to sample size limitations in the study. Likewise, the frequency of health care visits was significantly higher in patients with frequent FI compared to patients without FI, with an average difference of 4.21 visits per year. This association was also confirmed by multivariate testing. Furthermore, in a different survey of over 5,000 US patients suffering from FI, 13.2% reported that they were "too sick to work or go to school", with the rate increasing to 29.4% in patients who experienced FI consisting of a large volume of stool.[8]

IV. Introduction to Solesta®

Product Summary

Solesta® (NASHA/Dx FI) is a biocompatible, non-animal stabilized hyaluronic acid/dextranomer injectable bulking agent indicated for the treatment of FI. **Solesta® is the only FDA approved device[10] (approved on May 27, 2011)[11] for use in patients with FI who are 18 years and older and have failed conservative therapy**.[9] (Conservative therapies further described in Section IV. Fecal Incontinence Current Care Paradigm and Limitations)

Indication and Usage

Solesta® is indicated for the treatment of FI in patients who are 18 years and older and have failed conservative therapy (e.g., diet, fiber therapy, anti-motility medication).[9]

Device Description

Solesta® is a sterile, viscous, biocompatible bulking agent contained in disposable 1 mL pre-assembled glass syringes. Solesta® consists of dextranomer microspheres (50 mg/mL) and stabilized sodium hyaluronate (15 mg/mL), in phosphate-buffered 0.9% sodium chloride solution. Both the dextranomer and sodium hyaluronate are made up of biosynthesized polysaccharides of non-animal origin.[9]

Dosage, Administration, and Storage

A total of 4 submucosal injections of 1 mL Solesta® are administered at each treatment session.

Administration

Solesta® is injected, as an outpatient procedure without anesthesia, into the deep submucosal layer in the proximal part of the high-pressure zone of the anal canal, about 5 mm above the dentate line. For men with an enlarged prostate, injection in the midline of the anterior wall of the rectum should be avoided. Solesta® should not be injected intravascularly. Injection of Solesta® into blood vessels may cause vascular occlusion.[9]

How Supplied and Stored

Solesta® is a sterile, viscous, biocompatible bulking agent 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. 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, four sterile needles (SteriJect®, 21G x 4 ¾ inches, 0.80 x 120 mm), patient record labels and a package insert. The product is for single use. Solesta® should be stored at up to 25°C (77°F) and used prior to the expiration data printed on the label. Solesta® should not be exposed to sunlight or frozen, as this may damage or alter the product.[9]

Benefit of Solesta®

Clinical Benefit

Solesta® offers long-term and, if necessary, repeatable relief from FI.

Several clinical trials assessing the efficacy of Solesta® have been conducted, of which, two US-based clinical trials (NCT# 00605826 and NCT# 01647906) demonstrate that patients using Solesta® see significant durable, long-term, clinical benefit sustained through 36 months.[42,43] The recently completed single-arm PAS demonstrated through use of a Bayesian probability estimate that over 80% of individuals using Solesta® remain free from FI reintervention through 36 months.[12] These long-term durability results confirmed the FDA 2011 approval of Solesta® as a well-established, durable, and effective alternative to surgery following failure of conservative treatment. The long term follow-up single-arm PAS demonstrated significant improvement in subject QoL through 36-months, as measured by mean FIQL and CCFIS scores ($p<0.001$).[12] In the multi-center, randomized control pivotal study, 52% of patients who received Solesta® sustained a ≥50% reduction in symptoms from 6 to 36 months. Additionally, the number of incontinence episodes during 2-week time periods decreased from a median of 15 at baseline to 7.0 at 36-months ($p<0.001$), and the number of incontinence-free days during 2-week time periods increased from a median of 4.7 at baseline to 8.0 at 36 months ($p<0.001$). These results indicate that there are significant and sustained improvements in severity of FI from the patient's perspective.[12]

In addition to presenting efficacy data, Solesta® has demonstrated a safe treatment profile through 36 months.

Long-term safety was confirmed through the PAS, in which no new or unexpected safety findings were identified, and only 15.2% of patients experienced a device-related adverse event, none of which were serious and most of which resolved quickly. In the 6-month blinded phase of the pivotal study, there were three serious treatment-related adverse events: one case of E. coli bacteremia and one case of rectal abscess. A third patient experienced a serious treatment-related adverse event of rectal abscess during the open phase. These events resolved following treatment without sequalae within 35 days of event onset.[9]

Another important facet of Solesta®'s clinical benefit is the ability to re-treat if needed with additional post-injection treatment options deemed appropriate for the patient, including surgical treatment

options such as SNS or rectoplasty, or an additional Solesta® treatment. Compared to more invasive clinical options like SNS, Solesta® allows patients and physicians to assess response to then initial treatment and choose additional treatment of any kind if necessary.[16]

Economic Benefit

When compared to SNS, Solesta® offers a more affordable treatment option and represents the more efficient use of healthcare resources for the treatment of FI.

In a study aimed to assess the cost-effectiveness of Solesta® compared to SNS after failure of conservative therapy, a modified decision tree was used to analyze the costs and quality adjusted life-years (QALYs) for adult patients who have had FI symptoms for at least 12 months and did not adequately respond to conservative therapy options. The study incorporated findings from literature, a survey of practicing physicians, and cost data for resources consumed were derived from CMS' sources and the cost of Solesta® that was provided by the manufacturer. It is the significantly less expensive option when compared to SNS in patients who are candidates for either treatment.

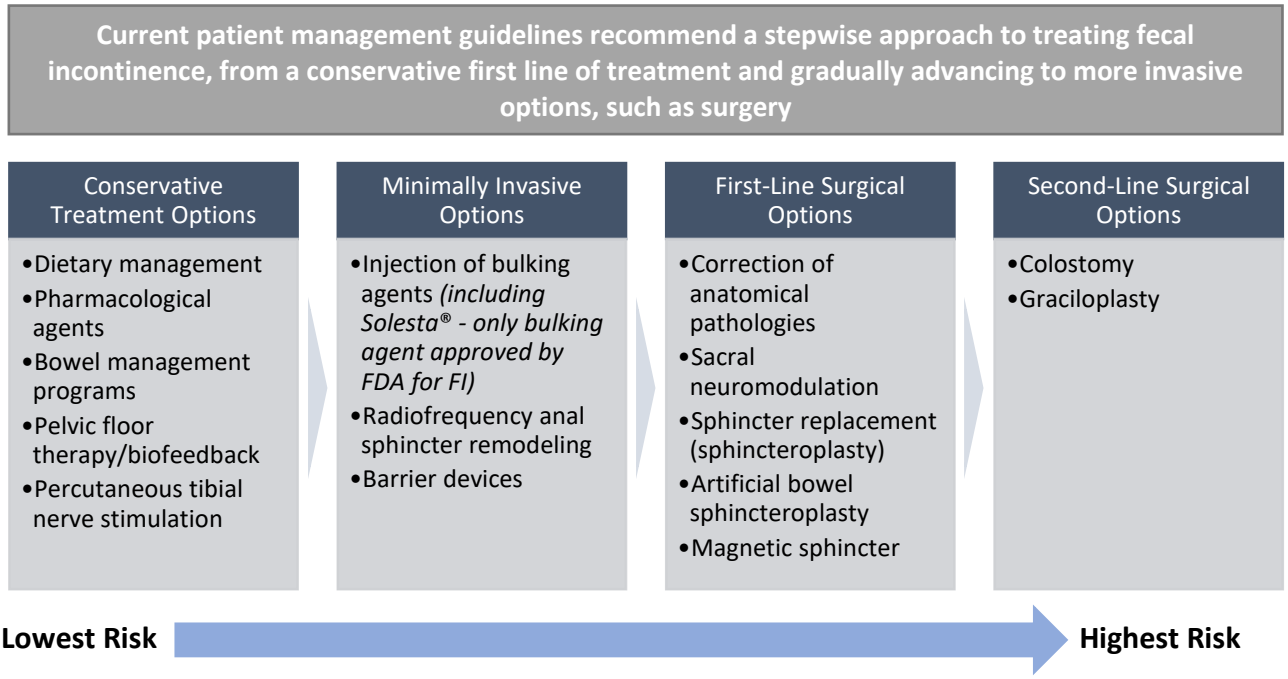
When considering the quality adjusted life-years (QALY) gained for each type of treatment, the incremental cost per QALY gained for Solesta® was $37,036 (in 2013 US dollars) versus conservative treatment, whereas for SNS the incremental cost per QALY was $103,066 versus conservative treatment. Furthermore, a budget impact analysis was performed to estimate the effect of FI treatment with Solesta® and SNS on health care plan costs, per 1 million covered lives. When compared with SNS, the acquisition cost for the first treatment of Solesta® represents only 18% of the cost for full SNS implantation. If subsequent treatment for all patients is assumed, the costs for Solesta® still only represent approximately 36% of the SNS cost.[17]

V. Current Fecal Incontinence Care Paradigm and Limitations

Previously published FI patient management guidelines recommend a stepwise approach to treating fecal incontinence, from a conservative first line of treatment and gradually advancing to more invasive options, such as surgery (Figure 5.1). However, given the inherent lag in specialty societies' guideline review and updating process, a number of important contemporary clinical studies are not reflected in past guidelines, and they should be updated (Figure 5.2).

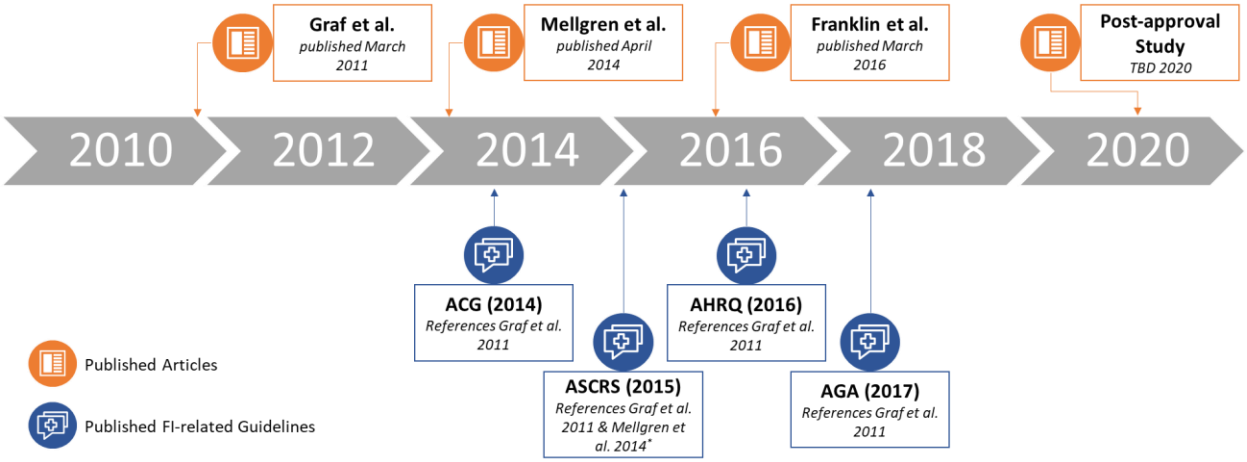
Key Takeaways	• Conservative FI treatments are recommended as a starting point, but the majority of patients do not find benefit. In fact, conservative treatments are not effective in up to 75% of patients.
	• Bulking agents are consistently recommended by guidelines as the next tier of treatment options for patients with FI who have failed conservative treatment. **Solesta® is the only FDA-approved bulking agent for FI patients proven to have long term efficacy, durability and safety.**
	• All major guidelines recommend consideration of Solesta®, if conservative treatment options prove ineffective.
	  ○ Solesta® is the only bulking agent FDA-approved for treatment of FI following unsatisfactory results with an adequate trial of conservative treatments.
	  ○ Since guidelines were published, evidence for Solesta® has been developed specifically to addresses the limitations outlined in those guidelines.
	  ○ Guideline recommendations were developed based on a limited amount of evidence from the first Solesta® pivotal study and have not been updated to include any of the contemporary evidence related to long-term efficacy and durability associated with Solesta® treatment generated and published after the last guidelines updates.
	• Society guidelines are inconsistent regarding which surgical treatment options they recommend; however, surgical treatment options have significant shortcomings:
	  ○ Sphincteroplasties are only appropriate for those with anatomic sphincter defects or sphincter injury.
	  ○ Colostomies are considered a last-option treatment due to their significant impact on patient lifestyle.
	  ○ SNS has a high reoperation rate, requiring a surgical battery replacement after 5 years, and may have limited long-term efficacy.

Figure 5.1. Approach to FI Patient Management[10,13–15]



A full list of treatment options mentioned by primary society guidelines (American Society of Colon and Rectal Surgeons (ASCRS)[14], American College of Gastroenterology (ACG)[15], American Gastroenterological Association (AGA)[10] and the Agency for Healthcare Research and Quality (AHRQ)[13], as well as their recommendations, can be found in Table 8.1.

Figure 5.2. Timeline Illustrating the Publication Dates of the FI-Management Guidelines



ASCRS = American Society of Colon and Rectal Surgeons; ACG = American College of Gastroenterology; AGA = American Gastroenterological Association; AHRQ = Agency for Healthcare Research and Quality

Conservative Treatment Options

Conservative FI treatment options, while low risk, have limited long-term efficacy for the majority of FI patients.

All society guidelines for FI, including the American Society of Colon and Rectal Surgeons (ASCRS), the American College of Gastroenterology (ACG) and the American Gastroenterological Association (AGA), as well as a review of FI by the U.S. Agency for Healthcare Research and Quality (AHRQ), recommend that conservative treatment options are used before progressing to minimally invasive or surgical treatment

options (Table 5.1).[13–15] However, guidelines indicate that conservative options are considered to improve functioning in only 25% of patients.[10] Therefore, a majority of patients will require minimally invasive or surgical treatment options as a next stage in treatment.

Table 5.1. Conservative Treatment Options for FI[13–15,44]

Treatment Option	Treatment Description	Shortfalls/ Limitations as Cited by Guidelines	Level(s) of Recommendations by Guidelines* *ASCRS/ ACG/ AGA/ AHRQ*
Dietary management	Changes in diet, including fiber, to change stool consistency	Weak evidence of efficacy, in part due to high risk of bias, short-term nature of studies, and lack of effect on QoL	↑/ ↑/ ↑/ ↔
Diarrheal and pharmacological therapies	Use of therapeutic agents to affect sense of urgency through changing the consistency of the stool, effect on the central nervous system, or other means	Compared to a placebo, studies are short-term in nature and demonstrate a lack of efficacy, particularly around the use of clonidine	↑/ ↑/ ↑/ ↓
Bowel management programs	Defecation program that schedules standard bowel evacuation or techniques such as enemas at appropriate intervals	There are limited studies evaluating the efficacy of bowel management programs and of those that do, there is variability in results and potential risk of bias	↔/ -/ ↑/ -
Pelvic floor therapy/biofeedback	Use of cognitive therapy to retrain the pelvic floor and related musculature	Results have shown variability in efficacy, and studies are often inadequately controlled	↑/ ↑/ ↑/ -
Percutaneous tibial nerve stimulation	Electrical stimulation of nerves responsible for continence and pelvic floor control	In a controlled study, percutaneous tibial nerve stimulation showed a lack of significant efficacy in improvement over the sham arm	↔/ -/ ↓/ -

*__Legend:__ ↑ = strong evidence, should be considered; ↔ = weak evidence, may be considered; ↓ = evidence considered insufficient OR recommended against; "- "= not mentioned by guidelines

Conservative treatment options are widely recommended across critical FI guidelines despite poor or mixed evidence of sustained clinical benefit.

In most cases, these treatments are recommended due to the treatment's non-invasive nature and the desire to avoid invasive, surgical treatments. Although biofeedback and other pelvic floor therapies are considered first-line treatments by ASCRS due to their non-invasive nature, the therapy methods are diverse and difficult to compare head-to-head, resulting in mixed results.[14] In fact, all clinical specialty societies with FI treatment guidelines, provide a strong recommendation for biofeedback and pelvic floor

therapy; in contrast, the AHRQ concluded that there is insufficient evidence to conclude efficacy due to variability in study results. The ACG also acknowledges the variability in evidence results for pelvic floor training and lack of controlled studies.[13,15]

There is variability amongst recommendations from key societies about the efficacy and utility of other conservative treatment options. Guidelines do not agree on whether percutaneous tibial nerve stimulation should be attempted due to a lack of significant improvement in efficacy over the control arm. In fact the ASCRS is the only society to recommend percutaneous tibial nerve stimulation (albeit weakly), while the AGA recommends against it and other societies do not provide a recommendation.[10,13–15] Bowel management programs are recommended strongly by the AGA and weakly by the ASCRS, but other society guidelines provide no recommendations.[10,14] The AHRQ notes that evidence for bowel management programs is variable, with some evidence showing worsening of symptoms, in addition to potential risk of bias.[13]

Although dietary management is strongly recommended by most guidelines, the quality of evidence regarding the impact of diet changes on FI continence is generally recognized to be poor.[13–15] While all other primary society guidelines strongly recommend use of pharmacological agents such as clonidine, the AHRQ indicates that current evidence fails to show efficacy of clonidine on FI, and recommends against use of clonidine, further stating that evidence is insufficient to make determinations for other drugs.[13] The ACG recognizes that clonidine evidence is inconclusive despite support for the therapy.[13,15] Two clonidine-specific studies are cited across society guidelines; although one study produces promising, albeit insignificant results for use of clonidine on FI symptom severity,[45] the other concludes that clonidine did not improve FI symptom severity or bowel symptoms compared to placebo.[46]

Ultimately, although conservative treatment options are largely recommended across society guidelines, this is in large part due to their non-invasive nature, not due to robustness of evidence regarding efficacy for treating FI. Therefore, even though many conservative FI treatment options exist that are widely recommended, the quality of evidence is lacking, and patients will often have to progress past these conservative treatment options.

Minimally Invasive Treatment Options

When conservative treatment options fail, society guidelines recommend that prescribing physicians consider the use of minimally invasive treatment options (Table 5.2).

These minimally invasive treatment options, which are summarized below, may help reduce the frequency and severity of FI.

Table 5.2. Minimally Invasive Treatment Options for FI[13–15,44]

Treatment Option	Treatment Description	Shortfalls/ Limitations as Cited by Guidelines	Level(s) of Recommendations by Guidelines* *ASCRS/ACG/AGA/AHRQ*
Bulking Agents	Injection that bulks the tissue of the anal canal, thereby reducing the rectal circumference	Although evidence for Solesta® shows significant reduction in FI events compared to a sham arm, CCFIS score improvement	↔/ ↔/ ↔/ ↔

		compared to sham is not significant**	
Radiofrequency of anal sphincter remodeling	Uses temperature-controlled radiofrequency to create thermal lesions at the anorectal junction	Insufficient evidence to develop a recommendation, including lack of randomized control evidence, small sample sizes, and no recent studies	↔/ -/ -/ -
Barrier Devices	Includes devices such as anal plugs and vaginal inserts, which create physical obstructions to the rectum to prevent bowel leakage	Not available in the U.S., and lead to high levels of intolerability and drop-out rates in studies	-/ -/ ↑/ -

*__Legend:__ ↑= strong evidence, should be considered; ↔ = weak evidence, may be considered, ↓ = evidence considered insufficient OR recommended against; "-" = not mentioned by guidelines ** Note additional contemporary studies address this criticism with greater long-term data

The use of injectable bulking agents is the most consistently recommended minimally invasive treatment across primary society guidelines, in which every society recommends that bulking agents should be considered, albeit they conclude that the evidence is "weak".[10,13–15] Recommendations for all bulking agents from societies are labeled "weak" for several important reasons:

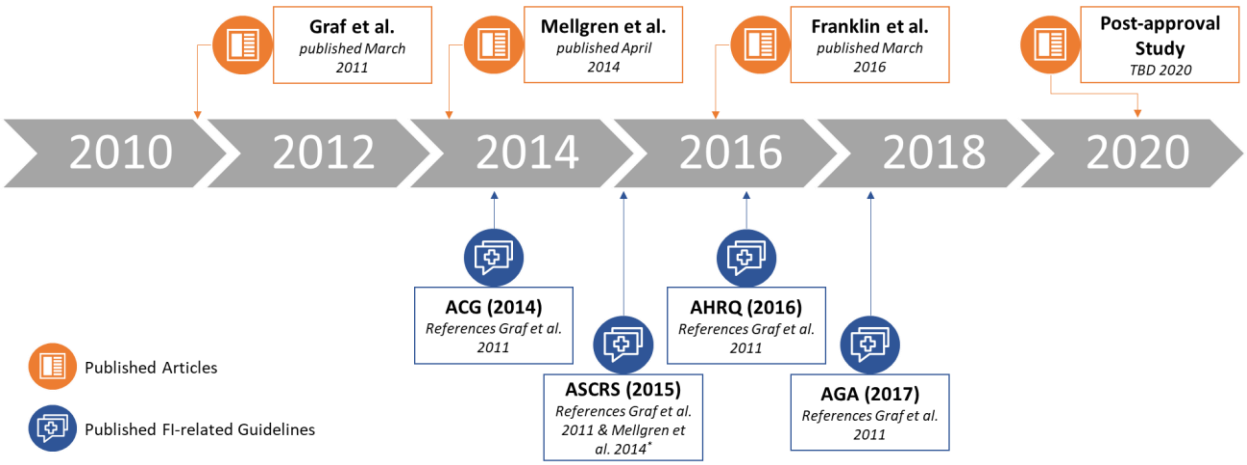
1. Each guideline for treatment of FI provides one recommendation generally applied across several bulking agents. **The majority of these guidelines fail to clearly document that Solesta® is the only bulking agent FDA approved for treatment of FI, while other bulking agents have mixed and varying evidence to demonstrate efficacy for treatment of FI.**[10,13,15,18]
2. These guidelines were last updated between 2014-2017, and therefore fail to consider important evidence from several more recent Solesta® studies that has been developed specifically to address the concerns raised by the societies and provide substantial additional long-term evidence supporting Solesta®'s efficacy, safety, and durability that other bulking agents simply do not have.

Due to the heterogeneity in evidence of safety and efficacy for treating FI among these disparate bulking agents, the older guidelines provide a "weak" recommendation for the bulking agent category, which they considered as a whole.[13–16] These bulking agents are not all simply interchangeable for different indications. Based on these shortcomings, all guidelines recommend consideration of bulking agents, but note that evidence, at point of publication, was "weak".

However, (depicted in Figure 5.3) 3 of the 4 society guidelines have not been updated to include any long-term evidence for Solesta®, and instead only include limited evidence from the first Solesta® study that assess patients through 3 to 6 months. The ASCRS is the only guideline to cite long-term evidence, and only briefly mentions the release of long-term data, without direct reference to any publications with data assessing patients past 6 months. Guidelines' review of evidence for Solesta® is additionally flawed because they combine the recommendations for Solesta® with all other bulking agents, none of which are FDA approved for treatment of FI. Despite the fact that guidelines do not take into account publications with long-term evidence, sub-group analyses, nor any evidence from the Solesta®'s single-arm study

(PAS); use of injectable bulking agents is the only minimally invasive treatment option recommended for consideration amongst all mentioned society guidelines.

Figure 5.3. Cumulation of published and unpublished evidence that has yet to be considered or reflected in guidelines



ASCRS = American Society of Colon and Rectal Surgeons; ACG = American College of Gastroenterology; AGA = American Gastroenterological Association; AHRQ = Agency for Healthcare Research and Quality

* Long-term data published in Mellgren et. al (2014) mentioned, but Mellgren article not directly cited

As mentioned previously, guidelines include other injectable bulking agents however, none are approved by the FDA for FI patients (as shown in Table 5.3).

Solesta® is cited by the ACG guidelines as "the only FDA approved bulking agent for FI treatment", and the ACG noted in 2014 that Solesta® is a promising treatment despite a "weak" recommendation level, due to a lack of baseline severity data and lack of validation studies as of the 2014 publication of the guideline.[15] AGA guidelines further note that Solesta® has demonstrated significant improvement in number of incontinence days versus a sham arm, despite lack of significant CCFIS score difference between sham and Solesta® arms at 6 months.[10,20] ASCRS similarly notes that Solesta® has shown a reduction in incontinence episodes compared to a sham arm, despite a lack of significant difference in incontinence scores compared to sham over the short-term.[14,20] While guidelines point out shortcomings with short-term Solesta® data compared to a sham treatment arm, only the ASCRS considered data extending past 6 months. Due to the significant long-term efficacy results demonstrated by Solesta® in both the randomized controlled trial and a single-arm PAS from 12 to 36 months, it is possible that significant differences were not seen between the Solesta® and sham arms at 6 months for select endpoints as a result of continuing narrowing of the anal canal past 6 months. Solesta® narrows the anal canal by encouraging tissue ingrowth and stabilization[41], a process that may take more than 6 months to reach full effect.

In the years since the publication of these guidelines, several important studies, including a PAS have demonstrated not only the significant reduction in symptom burden, but a significant improvement in QoL through 36 months. The PAS, pending publication, evidenced that Solesta® is associated with a statistically significant and clinically meaningful improvement in QoL, as measured by the CCFIS and the FIQL scale, through 36-months. Guidelines published in 2014-2017 did not take into consideration the

cumulation of published and unpublished data supporting the long-term use of Solesta®, and there is an opportunity for future guidelines to be based on a more contemporary, robust, and long-term pool of evidence, particularly when reviewing Solesta® separately from bulking agents that have not been approved by the FDA for FI treatment, which have limited and varying FI efficacy data. Additionally, Solesta® fits nicely in the stepwise progression of treatment for patients with FI because it does not preclude the potential future use of other interventions as the disorder progresses.

Table 5.3: Comparing the FDA approval and Fecal Incontinence Indication of Injectable Bulking Agents Mentioned in Guidelines

Injectable Bulking Agent	FDA approved Indication	Indicated for FI	Mentioned by Relevant Specialty Guidelines*
Non-animal stabilized hyaluronic acid/dextranomer **[NASHA/Dx FI; Solesta®]**	Fecal Incontinence	Yes	Yes
Polytetrafluoroethylene paste injection (Teflon)	Maxillofacial reconstruction[47]	No	Yes
Autologous fat	Orthopedic and arthroscopic procedures[48]	No	Yes
Synthetic bovine dermal collagen	Skin/wound repair[49]	No	Yes
Stabilized hyaluronic acid	Facial wrinkle correction[50]	No	Yes
Injectable Silicone (PTQ)	*N/A*	No	Yes
Durasphere (pyrolytic carbon-coated beads)	Stress Urinary Incontinence[51]	No	Yes

Legend: ☐= Yes, ☐=Yes, but not indicated for FI, ☐= No; *Relevant guidelines include ASCRS and the AHRQ

Although barrier devices, such as anal plugs and vaginal inserts, receive a stronger recommendation from the AGA than bulking agents, anal plugs are unavailable in the United States and have demonstrated a wide range of intolerability levels across studies, resulting in non-start/drop-out rates of up to 68%.[10,15,52] Furthermore, other guidelines do not include recommendations regarding barrier device use.[13–15] Eclipse is a vaginal insert that was recently FDA-cleared for use in women with loss of bowel control.[53] Due to its recent FDA clearance in 2016, society guidelines have not reviewed use of Eclipse. Furthermore, by nature Eclipse can only be used for women with FI, and is not comfortably fitted for many women.[54] In the Eclipse LIFE clinical trial, 45% of eligible enrollees were excluded from the trial due to either unsuccessful fitting of the device or withdrawal as a result of discomfort or device displacement. Similar rates of unsuccessful fittings can be found amongst other Eclipse trials.

In general, society guidelines agree that there is insufficient evidence to conclude whether or not radiofrequency of anal sphincter remodeling should be recommended, due to lack of randomized control evidence, small sample sizes, and no recent studies.[13,14] The ASCRS, alone, weakly recommends consideration of radiofrequency, whereas other societies do not provide a recommendation due to insufficient evidence.

Surgical Treatment Options

Several types of surgical management strategies are available for the treatment of FI.

These surgical options (Table 5.4) include direct surgical repair of defects, deformities, or obstruction; sphincter modulation; or fecal diversion such as colostomy. Invasive surgical procedures are typically reserved for patients for whom conservative or less invasive options, such as Solesta®, have failed.[22] The following first-line surgical options are considered if patients fail both conservative and minimally invasive treatment options. Second-line surgical treatment options are considered a last option after first-line surgical options have also failed.

Table 5.4 Surgical Treatment Options for FI[13–15,44]

Treatment Option	Treatment Description	Shortfalls/ Limitations as Cited by Guidelines	Level(s) of Recommendations by Guidelines* *ASCRS/ACG/AGA/AHRQ*
First-Line Treatment Options			
Correction of anatomical pathologies	Surgical repair of anatomical defects in the bowel	Not relevant for patients without major anatomic defects	↑/ -/ ↑/ -
Sacral neuromodulation (SNS)	Electrical stimulation of the sacral roots that may improve bowel control through neurostimulation	Replacement of stimulator battery required every 5 years, potential of long-term non-efficaciousness, and high reoperation rates	↑/ ↑/ ↑/ -
Sphincteroplasty	Surgical reconstruction of the sphincter	Only appropriate for those with anatomic sphincter defects or sphincter injury. Success rates decrease with time following procedure	↑/ ↑/ ↑/ -
Artificial bowel sphincteroplasty	Inflatable cuff, balloon, or magnetic beads that act as a new sphincter	Full continence rarely achieved, and high rate of complications seen	↑/ -/ ↑/ -
Second-Line Treatment Options			
Colostomy	Surgical redirection of the bowel to an opening in the abdominal wall	High impact on patient's lifestyle and potential negative impact to QoL	↑/ ↑/ ↑/ -
Graciloplasty	Continuous electrical stimulation of the transposed gracilis muscle around the anal canal to create a new sphincter	High rates of morbidity, mortality and adverse events	-/ ↔/ ↔/ -

*__Legend:__ ↑ = strong evidence, should be considered; ↔ = weak evidence, may be considered, ↓ = evidence considered insufficient OR recommended against; "- "= not mentioned by guidelines

Amongst surgical treatment options, SNS has been accepted most widely as a strongly recommended first-line surgical option, due in large part to SNS's high rate of reduction in incontinence episodes over periods of long-term follow-up.[55,56] Although other guidelines view SNS as a strongly recommended FI intervention option due to high levels of efficacy demonstrated in studies,[13–15] AHRQ guidelines document a number

of limitations to SNS[13]. First, SNS requires a stimulator battery that must be surgically replaced every 5 years. Second, SNS may have limited efficacy in the long term as the body adjusts to stimulation. Third, each of the existing studies has a moderate to high risk of bias, and none replicate the same treatment-outcome combination used on a prior study to validate results. Additionally, stimulator reoperation rate for SNS is high (41%) resulting from a number of required surgical revisions, including device-related failures due to infection, electrode displacement or breakage, dysfunction from impedance increase of the system, adverse stimulation with pain, battery depletion (both spontaneous and due to MRI examinations), and loss of clinical efficacy.[23]

While the ASCRS and AGA both strongly recommend correcting anatomic pathologies for appropriate patients, this surgical option is only relevant for patients with major anatomic defects.[10,14] Similarly, sphincteroplasties are strongly recommended by the ASCRS and the ACG, but are only appropriate for those with anatomic sphincter defects or sphincter injury. The AGA provides a weak recommendation for sphincteroplasties because evidence shows decreasing success rates as time increases post-procedure, and there is little clarity to what factors lead to poorer outcomes[10]. The ASCRS provides a strong recommendation and the AGA provides a weak recommendation for artificial sphincteroplasties, the procedure is tied to a relatively high number of complications and rarely achieves full continence[14,10]. The ACG does not discuss artificial sphincteroplasties, and the AHRQ does not believe there is sufficient evidence to make a recommendation, but does recognize its corresponding rate of high adverse events.[13]

In addition to SNS, sphincteroplasties and colostomies are widely recommended treatment options. However, sphincteroplasties are reserved for those with anatomic sphincter defects or sphincter injury[10,14,15]. Colostomies are typically reserved as a last-option recourse for patients who have failed[10,14,15] other treatment options, due to the significant lifestyle changes required.[10,13–15,57]. Graciloplasty procedures are rarely used, and are tied to large morbidity and mortality rates, as well as device-related issues.[15,10] Graciloplasty is weakly recommended by the AGA and ACG, but not mentioned by the AHRQ or ASCRS.

VI. Solesta® Supporting Scientific and Clinical Evidence

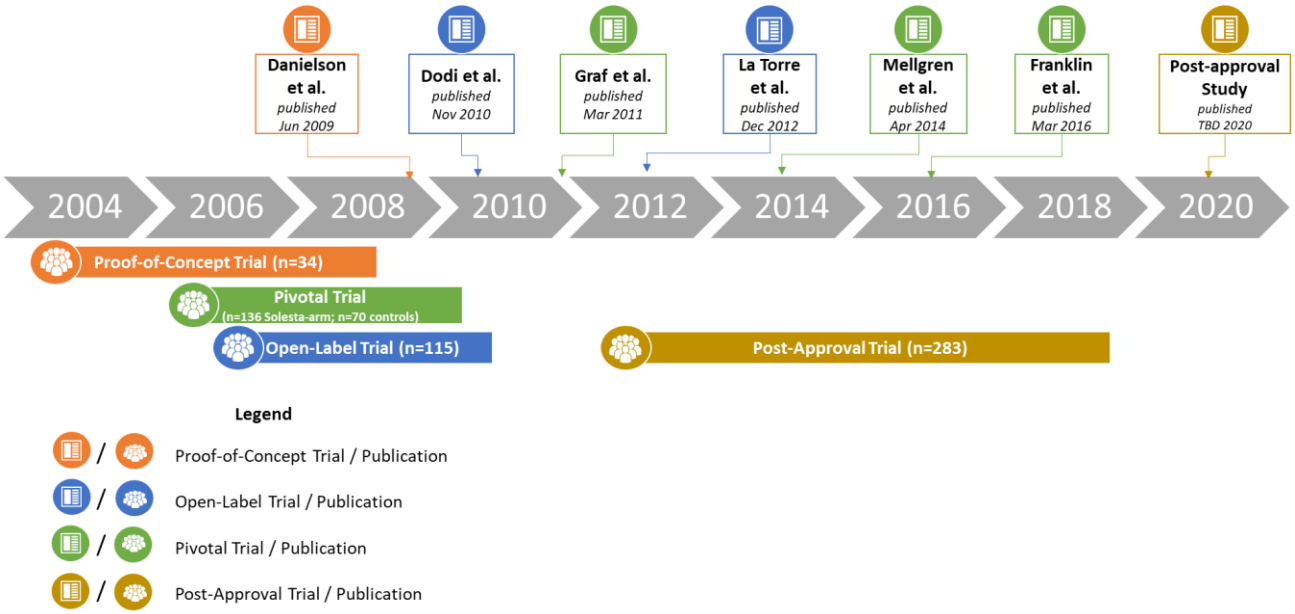
Key Takeaways	• A Bayesian posterior distribution was assessed to determine the rate of re-intervention in patients receiving Solesta® through 36 months following treatment. The posterior mean was found to be 18.9%, which was less than the primary efficacy endpoint of 50%, which indicates that >80% of patients required no FI re-intervention over a 36-month period after Solesta® treatment.
	• Re-intervention was defined as sphincteroplasty, implantation of artificial bowel sphincter, retreatment with Solesta® (considered a re-intervention if Solesta® was administered more than 3 months after initial treatment), graciloplasty, sacral neuromodulation (SN), or other surgical interventions Treatment of FI using Solesta® is associated with a statistically significant and clinically meaningful improvement in QoL from baseline to 36-months post-treatment as measured with the CCFIS and the FIQL scale.
	  ○ Significant improvement in QoL scores, including CCFIS and FIQL scores, was demonstrated for Solesta® patients from baseline to 12 months ($p<0.0001$) and long-term at 36 months ($p<0.001$)
	• Safety and efficacy of Solesta® was evaluated in a multi-center, randomized control pivotal study which yielded a significant difference in the percentage of patients who saw a reduction of incontinence episodes of ≥50%, seen in 52% of the Solesta® treatment arm, compared to the 31% in the sham-treated control arm ($p<0.0089$)
	  ○ The proportion of Solesta® patients who saw ≥50% reduction in incontinence episodes was sustained at 36 months (52%)
	  ○ Furthermore, there was a significant increase in the number of incontinence-free days over 2 weeks for individuals using Solesta® compared to the sham arm at 6 months
	• Subgroup analyses suggest specific populations that may derive the greatest benefit from Solesta®. The following populations showed a significant improved reduction from baseline in number of FI incontinence episodes of ≥50% compared to sham:
	  ○ Those with low-moderate FI severity: CCFIS score of 5-10, FI symptoms ≤5 years, patients who have not previously tried antidiarrheal medications, fiber supplements, biofeedback, bowel habit training, or surgical treatment options for FI
	  ○ Those with an obstetric etiology of FI incontinence

The efficacy of Solesta® is demonstrated by a reduction of FI incontinence episodes, lower rate of re-interventions, and an improved QoL scores that pertain to FI.

Since existing conservative treatment options are efficacious for only about 25% of patients,[10] Solesta® demonstrates meaningful efficacy and is a proven minimally-invasive treatment option before patients progress towards costly and invasive surgical options. Thus far, four clinical trials have been conducted studying 638 patients (Figure 6.1), of which two US-based multi-center, prospective studies have been conducted to assess the efficacy, safety, and long-term durability of treatment response with Solesta®; an overview of the studies are included in Table 6.1. A synopsis of additional Solesta® proof-of-concept and open-label clinical trials has been included in the supplemental Information section (Table 8.2).

In addition to three key publications (Table 8.3) and an abstract that recently has been accepted for publication, numerous other publications support the use of Solesta® in treating patients with FI, including 7 prospective studies,[18,41,58–62] 1 case report,[63] 1 review article[64] and 1 expert opinion article[65] (summarized in Table 8.4). Overall, this equates to 13 full publications and 1 abstract accepted for publication that supports the use of Solesta® in patients with FI.

Figure 6.1. Chronological Timeline of the Key Clinical Trials and their Corresponding Publications*



*List of publications above is not exhaustive

Table 6.1. Synopsis of Solesta's® Pivotal and Post-Approval Trials

Trial Title	A Randomized, Blinded, Multicenter Study to Evaluate Solesta® for the Treatment of FI	Long Term Safety and Efficacy of Solesta® Injectable Bulking Agent for the Treatment of FI (SoFI)
NCT#	00605826	01647906
Study Design	• Multi-center, randomized, double-blind sham-controlled study • At 6 months the trial was unmasked, and treatment was offered to patients in the sham arm, thereby excluding the sham arm from future analysis	• Prospective, single arm, multicenter, observational study with a 36-month follow-up
Study Participants	• 206 subjects enrolled; 136 NASHA/Dx FI patients and 70 control group patients	• 283 subjects were enrolled
Primary Objectives	• Compare the percent of patients in each arm who experienced a ≥50% reduction in FI symptoms, as recorded in patient bowel diaries	• *Effectiveness*: determine if the rate of re-intervention for FI through 36 months after last Solesta® treatment is less than 50% • *Safety*: assess device safety as measured by device-related injection, peri-injection, and long-term adverse events (AEs) with Solesta®

Secondary Objectives	• Number of incontinence-free days • Number of FI episodes • Number of adverse events and treatment-related adverse events • QoL scores that pertained to FI were also tracked, primarily the CCFIS and FIQL	• *Effectiveness*: efficacy of Solesta® measured by FIQL, CCFIS, Agency for Healthcare Research and Quality (GPE), and time to FI re-intervention • *Safety*: compare the rate of device related infectious AEs between subjects treated with or without prophylactic antibiotics prior to injection, as measured by device related infectious AEs reported • *Performance*: assess the relative anatomic stability of the Solesta®
Published Studies	• Graf et. Al (2011)[20] assessed the efficacy and safety of Solesta® compared to the sham arm through 6 months, and within the Solesta® arm through 12 months, for each endpoint measured • Mellgren et. Al (2014)[16] assessed the efficacy and safety for each endpoint measured in the Solesta® treatment arm through 36 months. • Franklin et. Al (2016)[21] performed subgroup analyses on the Solesta® treatment arm and sham arm to identify if any patient populations would benefit from Solesta® treatment. The publication assessed two primary endpoints: changes in FIQL coping/behavior subscale between sham and Solesta® arms at 6 months, and changes in a ≥50% reduction in FI symptoms between sham and Solesta® arms at 6 months, across a range of subgroups.	• Clinical Manuscript (full publication in preparation, abstract has been accepted) assessing the efficacy and safety of Solesta®, including several subgroup analyses; per protocol population and those that received 1 vs. 2 Solesta® treatments • Quality-of Life focused Manuscript (In preparation) demonstrated the relationship between the efficacy of Solesta® and patient reported QoL measures that are both statistically and clinically meaningful

Clinical Efficacy

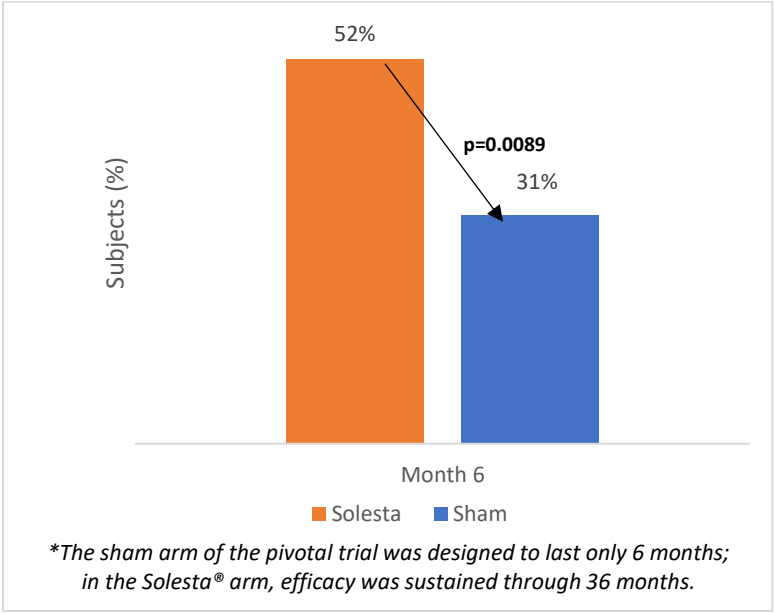
Data from the single-arm PAS further validated the long-term clinical efficacy of Solesta®. At 36 months, 152 patients were free from FI re-intervention and 40 were not. A Bayesian posterior distribution was assessed for the rate of re-intervention through 36 months and was found to have a posterior mean of 18.9%, which was less than the primary efficacy endpoint of 50%, indicating that >80% of patients required no re-intervention over a 36-month period. Several sensitivity analyses were run to assess whether there were any potential bias or distortion of the primary effectiveness endpoint. Results show that the study was robust and that there was a high improbability that the missing data could change the study conclusion.[12] Time to re-intervention was calculated as the date of last treatment with Solesta® to the date of first FI re-intervention. Using the Kaplan-Meier method, freedom from FI-reintervention was estimated to be 82% at 36 months.[12]

Other important results in the randomized, controlled study include:

- At 6 months, the primary endpoint of reduction of incontinence episodes by ≥50% compared with baseline was met in 52% of the treatment group compared with 31% in the sham arm (p=0.0089) (shown in Figure 6.1).
- The mean increase in incontinence-free days from baseline, measured over a 2-week recall period at baseline and 6 months, was 3.1 in the Solesta® group versus 1.7 in the sham arm (p=0.0156).

- When compared to baseline assessment, patients in the Solesta® arm had a significant increase in incontinence-free days, nearly doubling the number of incontinence free-days reported compared to baseline, with a median of 4.7 at baseline vs. 9.0 incontinence free days at month 12 (p<0.001).
- Patients in the Solesta® arm experienced fewer FI episodes at 6 months compared to the sham arm, measured over a 2-week time period, and although the results were not significant (p=0.09) at 6 months, patients in the Solesta® arm showed significant reduction in FI episodes at 12 months compared to baseline (p<0.001).[16] These improvements in the Solesta® treatment arm were sustained at 36 months, as 52% of patients in the Solesta® arm sustained a decrease of ≥50% in symptoms. (A response to treatment was defined as a reduction in number of episodes by 50% or more)
- The number of incontinence episodes during a 2-week time period decreased from a median of 15 at baseline to 7.0 at 36-months (p<0.001). The number of incontinence-free days during a 2-week time period increased from a median of 4.7 at baseline to 8.0 at 36 months (p<0.001).[16] The percentage of subjects in the treatment arm that saw at least a 50% reduction in FI events remained consistent at 52.2% at both 6 and 36 months.

Figure 6.1. Reduction of Incontinence Episode of ≥50% Compared to the Sham Arm at Month 6*



**The sham arm of the pivotal trial was designed to last only 6 months; in the Solesta® arm, efficacy was sustained through 36 months.*

Solesta's® demonstrated efficacy is broadly experienced by numerous patient demographics, regardless of disease duration, etiology, severity, or past treatments.

As evidenced by the significant improvement in reduction of FI incontinence episodes of ≥50% with NASHA/Dx FI compared to sham treatment in the following patient subgroups:

- Patients with FI symptoms of ≤5 years duration (p=0.0026),
- Patients with a CCFIS score of 10-15 (mild to moderate FI) (p=0.0169),
- Patients with obstetric causes of FI (p=0.0191),
- Patients who did not have a treatment history of the following treatment modalities: fiber supplementation (p=0.0002), antidiarrheal medication (p=0.0205), biofeedback (p=0.0206), bowel habit training (p=0.0115), or surgery for FI (p=0.0054).

Findings from the Franklin et al. paper indicated that several patient populations (e.g., patients with mild-to-moderate FI) derived a clinical benefit from Solesta®, which may translate into meaningful enhancements in some FI-related QoL measures before the patient undergoes more invasive treatment options such as surgery.[21] The treatment benefit observed with Solesta® in patients who had an obstetric FI etiology is particularly notable and may be related to the nature of the trauma incurred during childbirth. As a neurologic etiology of FI following childbirth (e.g. pudendal neuropathy) is different than a sphincter tear during childbirth. Maintenance of anal pressure in the anal canal is important for continence,[66] as anal pressure has been shown to decrease in many patients following vaginal delivery for at least 6 to 10 weeks compared with anal pressure before childbirth.[67] The benefit observed in patients with obstetric damage may be related, at least in part, to the mechanism of action of Solesta®. The dextranomer microspheres establish a scaffold for fibroblasts, smooth muscle cells, and collagen to grow around, stabilizing the tissue near the injection sites, and narrowing the anal canal [9,18,41,68] thus restoring anal pressure.[66,69] Obstetric trauma and injury is a risk factor for FI[70] and these findings suggest that this patient population may benefit from treatment with Solesta®.

Quality of Life Impact (CCFIS and FIQL)

Solesta® therapy is associated with clinically significant improvements in patients' QoL.

In the more recent PAS that included a larger sample size (n=283), patients showed an improvement in each sub-scale of the FIQL and a reduction in symptom burden as measured by the CCFIS from baseline to 36 months post-treatment. This study went on to assess whether the change in scores were clinically relevant. Clinical relevance refers to the benefits the patient derives from a clinically meaningful treatment, this requires an assessment of the minimal clinically important difference (MCID): a magnitude change in a scale score that is associated with a meaningful clinical change as evaluated by the ordinal assessment of improvement. Therefore, by definition, any change in score that exceeds the MCID is considered to be clinically relevant. For both the CCFIS and each FIQL sub-scale, the mean change from baseline to 36-months post-treatment exceeds the MCID and is therefore both clinically and statistically significant.[12]

For the randomized-controlled trial, while the CCFIS score at 6 months did not significantly differ between the sham and treatment arms, FIQL scores for coping and behavior showed significant improvement (p=0.0016). Mean CCFIS scores and all FIQL domain scores significantly improved from baseline to 36 months (p<0.001). A summary of FIQL domain results through 36 months in the Solesta® treatment arm can be found in Table 6.2 below.[16] Lack of significant short-term improvement in CCFIS scores and select FIQL domains between Solesta® and sham patients may be a result of Solesta® effects not yet being fully realized at 6 months. The dextranomer of Solesta® encourages ingrowth and stabilizes of tissue, thus narrowing the anal canal.[41] It is possible that this narrowing of the anal canal takes more than 6 months, and this interpretation is supported by the fact that CCFIS scores all FIQL domains continued to increase after 6 months in the Solesta® RCT.

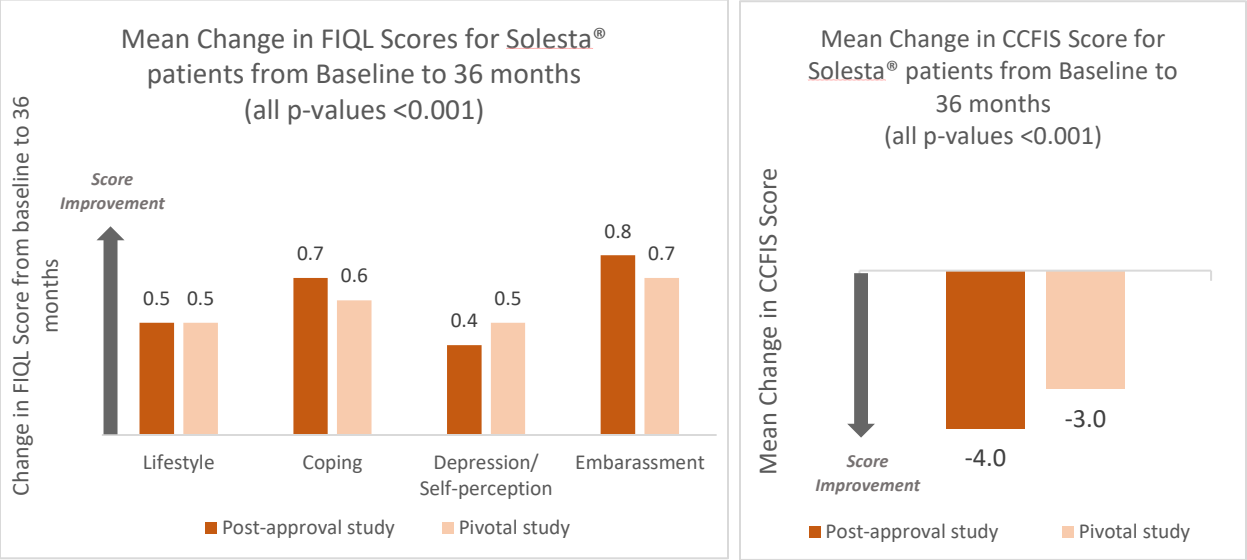
Table 6.2. Summary of Mean FIQL Score Improvement in the Solesta® Treatment Arm

Time Point	Lifestyle	Coping	Depression/Self-perception	Embarrassment	p-value*
Baseline	2.7	1.9	2.8	1.8	<0.001
6 months	3.0	2.3	3.1	2.2	<0.001
12 months	3.2	2.5	3.3	2.5	<0.001
36 months	3.2	2.5	3.3	2.5	<0.001

*For each domain at each time point. Last observation carried forward, n=136

The previously discussed PAS was conducted to validate that Solesta® patients continue to see increasing improvement in CCFIS and FIQL domains past 6 months. The PAS demonstrated similar improvement in FIQL and CCFIS scores as compared to the RCT (pivotal study). As seen in the pivotal study, all CCFIS and FIQL scores saw a significant improvement ($p<0.001$) from baseline to 36 months, demonstrating that Solesta® provides consistent and long-term QoL improvement. Change in FIQL and CCFIS scores within the pivotal and PAS are summarized in Figure 6.2 below.

Figure 6.2. Mean Change in FIQL and CCFIS Scores for Solesta® Patients from Baseline to 36 Months



The efficacy of Solesta® in improving patient QoL is consistent across various subgroups.

When compared to clinical efficacy outcomes, a similar profile of subgroup responsiveness was observed for the FIQL coping/behavior subscale, where patients with mild-to-moderate FI at baseline (CCFIS ≤15, duration of FI ≤5 years, exposure to few prior FI treatment modalities) and an obstetric etiology of FI had a significant change in the FIQL coping/behavior subscale score at 6 months.

Cost-effectiveness

Solesta® has been shown to be cost-effective at willingness-to-pay thresholds well below widely accepted industry and government standards.

A 3-year cost effectiveness model compared Solesta® to SNS after conservative therapy for the management of FI.[17] The model captured all direct costs (in 2013 US dollars) and outcomes during a 3-year period from the view of a US third party payer. Costs of devices medical and surgical care, and hospitalization were included. Outcomes included quality adjusted life-years (QALYs) and incontinence-free days.

Results from the model illustrated that, when compared to SNS, Solesta® is the more cost-effective treatment and offers more efficient use of resources for the treatment of FI.

- In a probabilistic sensitivity analysis, 59% of simulations found Solesta® to be the most cost-effective treatment option at a willingness-to-pay threshold of $50,000, compared to 3% of simulations that favored SNS. Solesta® was also more likely to be cost-effective than either conservative therapy or SNS even at a willingness-to-pay threshold of $40,000 (Figure 6.3).[17]
- When considering the quality adjusted life-years (QALY) gained for each type of treatment, the incremental cost per QALY gained for Solesta® was $37,036 versus conservative treatment,

whereas for SNS the incremental cost per QALY was $103,066 versus conservative treatment and $244,509 when compared to Solesta® (Table 6.4).[17]

- A budget impact analysis was performed to estimate the effect of FI treatment with Solesta® and SNS on health care plan costs, per 1 million covered lives. When compared with SNS, the acquisition cost for the first treatment of Solesta® represents only 18% of the cost for full SNS implantation. If subsequent treatment for all patients is assumed, the costs for Solesta® still only represent approximately 36% of the SNS cost.[17]

Figure 6.3. Cost-effectiveness Acceptability Curve

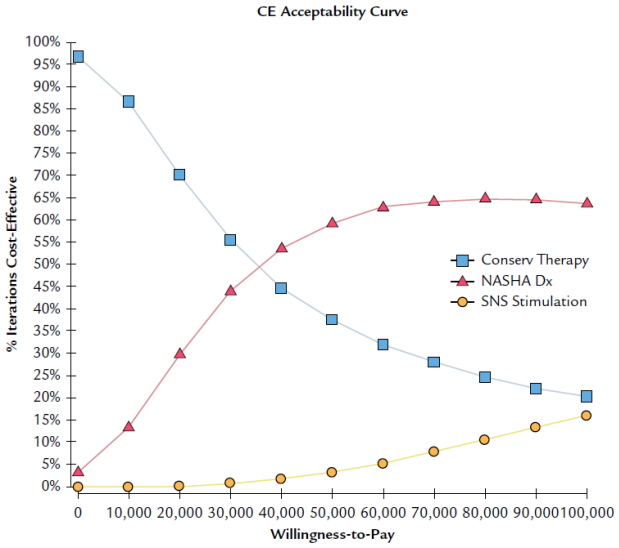


Table 6.4. Results of the cost-effectiveness base case analysis

Treatment	Expected Cost, $	Incremental Cost, $	Effectiveness, QALY*	Incremental Effectiveness, QALY*	ICER** (Δ Cost/ Δ Effect)
Conservative therapy	$9,053	-	1.769	-	-
NASHA/Dx (Solesta®)	$14,968	$5,915	1.929	0.160	$37,036
Sacral nerve stimulation	$33,201	$18,233	2.004	0.075	$244,509

*QALY = Quality-adjusted life year

**ICER = Incremental cost-effectiveness ratio

Safety

At 36 months, for the PAS, 15.2% of subjects (43/283) reported device-related AEs, resulting in a total of 92 device-related AEs; 43 during the injection interval (≤ 2 days post-first Solesta® injection), 11 during the peri-injection interval (> 2 days and ≥ 2 weeks post-first Solesta® injection), and 38 during the long-term interval (> 2 weeks post-first Solesta® injection). This is an expected number of device-related adverse events no higher than that seen in the original pivotal trial. Out of the 283 total Solesta® patients enrolled in the study, zero experienced a serious unexpected device or treatment-related safety event, and no new safety findings were identified that differed from the established safety profile of Solesta®. Most of the events were gastrointestinal disorders that resolved quickly, and none were assessed as serious. Furthermore, there was only 1 subject (0.4%) that experienced 1 peri-injection device-related infectious AE (vaginitis bacterial), which was mild and resolved with additional treatment.[12]

For the pivotal trial, 128 treatment-related adverse events were recorded in the treatment group and 29 in the sham group. Three of the treatment-related adverse events were assessed as serious. In the 6-months blinded phase there was one case of E. coli bacteremia and one case of rectal abscess. In the open phase, a third patient experienced a serious treatment-related adverse event of rectal abscess during the open phase. These events resolved following treatment without sequalae within 35 days of event onset.[9]

The frequency of serious treatment-related adverse events associated with Solesta® treatment is low and Solesta® continues to demonstrate an excellent safety profile over the long-term as evidenced by the PAS safety data.[12]

Conclusion

In conclusion, FI is a complex clinical condition that may be associated with a number of other pathological diseases; Given the broad association of FI with numerous underlying causes, there is not one treatment proven to successfully treat FI across the broad array of underlying causes. However, given its known efficacy as a bulking agent, **Solesta® has been proven in multiple studies to be an efficacious, safe, and durable treatment options for patients suffering from FI, and is the only FDA approved bulking agent indicated for FI patients**. The long-term safety and efficacy of Solesta® has been demonstrated in numerous clinical trials and published studies. In addition, a recently completed PAS with 36-month follow up demonstrating the safety and efficacy of Solesta® has been filed and accepted by the FDA, and an abstract has been accepted for publication (with a full manuscript to follow). The accumulation of this clinical data confirms that Solesta® is a medically appropriate therapeutic option for patients who have failed conservative treatment options before attempting more invasive surgical options. As the only FDA-approved bulking agent for treatment of FI, Solesta® has demonstrated that it is broadly efficacious in multiple patient populations, regardless of disease duration, etiology, severity, or past treatment, and has proven to be a cost-effective and lower cost treatment option when compared to more invasive treatment options (e.g., SNS).

VII. Reimbursement Information

In order to facilitate in established automated payment, Table 7.1 describes coding information for the reimbursement of Solesta®.[71]

Table 7.1 Summary of Coding for Solesta®[71]

Indication	Diagnosis Code(s)	HCPCS Code	NHRIC	CPT Code
FI	R15, R15.0, R15.1, R15.2, R15.9	L8605	89114-0850-03	46999

HCPCS: Healthcare Common Procedure Coding System; NHRIC: National Health Related Items Code; CPT: Current Procedural Terminology

VIII. Supplemental Information

Additional Information on Guideline Recommendations

Table 8.1. Standard of Care FI Treatments and Society Guideline Recommendations[13–16]

	American Society of Colon and Rectal Surgeons (ASCRS)*	American College of Gastroenterology (ACG)**	American Gastroenterological Association (AGA)***	Agency for Healthcare Research and Quality (AHRQ)****
Conservative Treatment Options				
Dietary management	✓ (1C)	✓ (Strong)	✓ (Should be tried)	✓ (Low)
Diarrheal and other pharmacological therapies	✓ (1C)	✓ (Strong)	✓ (Should be tried)	X (Low evidence against clonidine), insufficient evidence for other drugs
Bowel management program	✓ (2C)	-	✓ (Should be tried)	Insufficient evidence
Pelvic floor therapy/biofeedback	✓ (1B)	✓ (Strong)	✓ (Should be tried)	Insufficient evidence
Percutaneous tibial nerve stimulation	✓ (2C)	-	X (Should not be used)	Insufficient evidence
Minimally Invasive Options				
Injection of bulking agents (recommendation groups together bulking agents that have not been approved by the FDA for FI treatment and Solesta® - *only FDA approved bulking agent*)	✓ (2C)	✓ (Weak)	✓ (May be tried)	✓ (Low)
Radiofrequency anal sphincter remodeling	✓ (2B)	No recommendation- Insufficient evidence	No recommendation	Insufficient evidence
Barrier devices	-	-	✓ (Should be offered)	-
First-Line Surgical Options				
Correction of anatomical pathologies	✓ (1C)	-	✓ (Should be corrected)	-
Sacral neuromodulation	✓ (1B)	✓ (Strong)	✓ (Should be tried)	Insufficient evidence
Sphincter replacement (sphincteroplasty)	✓ (1B)	✓ (Strong)	✓ (May be considered)	Insufficient evidence
Sphincter replacement of	✓ (1C)	-	✓ (May be considered)	Insufficient evidence

artificial bowel Sphincter				
Second-Line Surgical Options				
Colostomy	✓ (1C)	✓ (Strong)	✓ (Should be considered)	-
Graciloplasty	-	✓ (Weak)	✓ (May be considered)	-

~Recommendation for bulking agents is "weak" across all guidelines due to the variability in bulking agent products considered. "Weak" recommendations take into consideration all bulking agents, including bulking agents that have not been FDA-approved for FI, and Solesta®, the only FDA approved bulking agent for FI. Evidence for these other products have mixed evidence of efficacy for usage in FI. Additionally, while guidelines consider Solesta® evidence, guidelines were published prior to additional Solesta® evidence, resulting in only one guideline that considers any data past 6 months. This guideline only considers long-term evidence in a limited capacity.

*Recommendations marked with a 1 are those that are strongly recommended by the ASCRS, those marked with a 2 have a weak recommendation by the ASCRS. Letters A-C signify the perceived strength of evidence for the treatment, with A representing the highest quality evidence. Treatments that are supported by the ASCRS with a strong recommendation (1) have been marked green, those indicated as a weak recommendation (2) have been marked as yellow. Treatments that are not supported by the ASCRC are marked as red, whether the recommendation is strong or weak.

**Recommendations for the ACG were marked either as strong, or weak. Supported treatment options that have a weak recommendation are labeled yellow, and those with a strong recommendation are labeled as green. Treatment options that are unsupported are marked as red, whether the recommendation is strong or weak.

***The AGA does not label any of their best practices as strong or weak, but the AGA does write that some treatments "should" be considered, whereas others "may" be considered. Supported therapies that are marked as "should" are labeled green, those labeled "may" are marked as yellow. Treatments that the AGA doesn't support are labeled red. AGA guidelines state that a sphincteroplasty typically "may" be considered, buy "should" be considered for in postpartum women/patients with recent sphincter injuries.

****The AHRQ concluded that for the majority of treatment options there is insufficient evidence to provide a recommendation. For treatments for which the AHRQ was supportive, but believed there was low strength evidence, the treatment was marked with yellow. For those that the AHRQ was not supportive of, treatments were marked in red. The AHRQ did not believe any treatment had high strength evidence.

Table 8.2. Summary of Clinical Evidence for Solesta's® Proof of Concept and Open-Label Studies

Trial Title	Safety and Efficacy of Anorectal Application of Dx-gel for Treatment of Anal Incontinence (Solesta® Proof of Concept Trial)	An Open, Non-comparative, Post-marketing, Multi-center Study to Evaluate Efficacy and Safety of Solesta™ for the Treatment of Fecal Incontinence (Solesta® Open-Label Trial)
NCT#	**01380132**	**01110681**
Study Design	• Prospective, single-arm, single-site, observational study with a 12-month follow-up	• Prospective, single arm, multicenter, observational study with a 12-month follow-up (with extension phase up to 24 months post-treatment)
Study Participants	• 34 subjects enrolled	• 115 subjects enrolled; 86 completed the study
Primary Objectives	• Number of FI episodes, with individuals considered to be responders if they experienced a ≥50% reduction in FI episodes	• Assess the percent of patients who experienced a ≥50% reduction in FI episodes at 12 months, as recorded in patient bowel diaries during a 28-day period

Secondary Objectives	Measured at 12 months post-treatment: • Change in FI episodes • QoL as measured by a bowel function questionnaire (Miller's Incontinence Score) • Global assessment rating (excellent, good, fair or poor) • Number of adverse events	Measured at 12 and 24 months: • QoL efficacy of Solesta® measured by FIQL and CCFIS • Number of incontinence-free days • Number of FI episodes • Number of adverse events and treatment-related adverse events Measured at 24 months: • The percent of patients who experienced a ≥50% reduction in FI episodes at 12 months

Table 8.3. Summary of Clinical Evidence for Solesta®; Randomized, Double-blind, Sham-controlled Study

Title	**Efficacy of dextranomer in stabilized hyaluronic acid for treatment of feacal incontinence: a randomized sham-controlled trial**	**Long-term efficacy of NASHA/Dx FI injection therapy for treatment of FI**	**Identifying factors associated with clinical success in patients treated with NASHA/Dx FI injection for FI**
First Author	Graf et al.	Mellgren et al.	Franklin et al.
Year	2011	2014	2016
Key Findings	**Treatment vs. Sham arms (up to 6 months):** • Reduction of incontinence episodes by 50% or more compared with baseline was 52% in the treatment group compared with 31% in the sham arm (p=0.0089) • Mean increase of incontinence free days during 2 weeks at 6 months was 3.1 in the treatment group versus 1.7 in the sham arm (p=.0156), with no significant difference at 3 months • There was no significant difference between arms of number of fecal incontinence episodes during 2 weeks at 3 months (p=0.14) or 6 months (p=0.09) • CCFIS scores at 3 and 6 months did not significantly differ between sham and treatment arms • FIQL scores for coping and behavior at 6 months were better in the treatment group compared to the sham arm (p=0.0016), but showed no significant difference in other FIQL domains	**Treatment-only (through 36-months):** • Treatment with NASHA/Dx FI resulted in decreased symptoms in 52.2% of patients in the treatment arm at 6 months, and this was sustained at 36 months (52.2%) • A limited number of patients experienced an increase of FI episodes of ≥25%: 6% at 12 months, 12% at 12 months and 15% at 36 months • The number of incontinence episodes during 2 weeks decreased from a median of 15 at baseline to 7.2 at 6-months (p<0.001) and stayed fairly consistent: 6.2 at 12 months (p<0.001)	**Treatment-only Sub-group analyses (at 6 months):** • Patients with FI symptoms of ≤5 years duration had a significantly improved reduction from baseline in number of FI incontinence episodes of ≥50% with NASHA/Dx FI compared to sham treatment (p=0.0026) • A significantly greater percentage of patients with obstetric causes of FI had an improved reduction from baseline in number of FI incontinence episodes of ≥50% compared to sham (p=0.0191) • A significantly greater percentage of patients with a CCFIS of 10-15 had a significantly improved reduction from baseline in number of FI incontinence episodes of ≥50% compared to sham (p=0.0169)

	• 128 treatment-related adverse events were recorded in the active group and 29 in the sham group **Treatment-only arm (through 12 months):** • The median number of incontinence episodes during 2 weeks in the treatment arm decreased from 15.0 to 6.2 at 12 months (p<0.001) • The mean number of incontinence-free days during 2 weeks increased from 4.4 at baseline to 7.9 at 12 months (p<0.0001) • Mean CCFIS score decreased from 14.3 at baseline to 10.9 at 12 months (p<0.0001) • Mean FIQL scores for all four items improved significantly between baseline and month 12 (p<0.0001)	and 7.0 at 36-months (p<0.001) • The number of incontinence-free days during 2 weeks increased from a median of 4.7 at baseline to 8.3 at 6 months (p<0.001), and stayed relatively consistent: 9.0 at 12 months (p<0.001) and 8.0 at 36 months (p<0.001) • Mean CCFIS decreased from 14 at baseline to 11 at 36 months (p<0.001) • All four FIQL domain scores improved between baseline and 36 months follow-up (p<0.001)	• A significantly greater percentage of patients who had not previously tried biofeedback (p=0.0206), bowel habit training (p=0.0115) or surgery for FI (p=0.0054) had a significantly improved reduction from baseline in number of FI incontinence episodes of ≥50% compared to sham • A significantly greater percentage of patients who did not have a treatment history of antidiarrheal medications (p=0.0205) or fiber supplementation (p=0.0002) had a significantly improved reduction from baseline in number of FI incontinence episodes of ≥50% compared to sham

Table 8.4. Summary of Additional Studies Published to Support the Use of Solesta® in FI

Prospective Studies	
Study Title	Injectable bulking treatment of persistent fecal incontinence in adult patients after anorectal malformations.
Full Citation	Danielson J, Karlbom U, Wester T, Graf W. Injectable bulking treatment of persistent fecal incontinence in adult patients after anorectal malformations. J Pediatr Surg. 2020;55(3):397-402. doi: 10.1016/j.jpedsurg.2019.06.026
Abstract	OBJECTIVE: Injectable bulking therapy has emerged as a treatment for fecal incontinence (FI), however there are no studies including adult patients with anorectal malformations (ARM). This study aimed to evaluate non-animal stabilized hyaluronic acid with dextranomer (NASHA/Dx) for the treatment of adult ARM patients with persistent FI. METHODS: Seven adults with ARM and incontinence to loose stool at least once weekly and without rectal or mucosal prolapse were treated with anal NASHA/Dx injection. They were evaluated preoperatively, at 6 and 18 months with a bowel function questionnaire and a 2-week bowel diary as well as FIQL and SF-36 quality of life questionnaires. RESULTS: Before treatment, the mean number of incontinence episodes over 2 weeks was 20.7 (median 16, range 8-52). At 6 months, the corresponding figures were 5.3 (median 4, range 0-19, p = 0.018), and at 18 months the figures were 4.3 (median 2, range 1-20, p = 0.018). An improved physical function in SF-36 from 74.3 at baseline to 86.4 at 6 months was noted (p = 0.04). No serious adverse events occurred. CONCLUSIONS: NASHA/Dx is a promising treatment option for selected adult patients with persistent FI after ARM. Longer follow up of larger patient series and studies on patients in adolescence is needed.
Study Title	Persistent fecal incontinence into adulthood after repair of anorectal malformations.
Full Citation	Danielson J, Karlbom U, Graf W, Wester T. Persistent fecal incontinence into adulthood after repair of anorectal malformations. Int J Colorectal Dis. 2019;34(3):551-554. doi:10.1007/s00384-018-3220-6

Abstract	OBJECTIVE: Persistent fecal incontinence beyond childhood is common in ARM patients. The aim of this study was to analyze a consecutive series of adult patients with persistent incontinence, establish the causes, and evaluate whether further treatment could be offered. METHODS: Forty-four adult ARM patients with reported incontinence were invited. Eighteen patients (11 males, median age 40.5 years, range 18-50 years) accepted and underwent clinical examination, rectoscopy, and 3D-ultrasound. Five had previously been treated with secondary surgery to improve continence. RESULTS: Seventeen of the 18 patients had abnormal findings at examination. Eight patients had obstruction of the reconstructed anus. Eleven patients had sacral deformities. Nine patients had a defect in the external anal sphincter and nine patients could not contract the sphincter on demand. Five patients had significant prolapse of mucosa. In one patient, the neoanus was totally misplaced, one patient had a rectovaginal fistula, and one patient had short bowel syndrome due to several small bowel resections. Ten patients were offered conservative and five surgical treatment. CONCLUSIONS: This case series of adults shows that a majority of the patients can be offered further treatment. This indicates a need for structured follow-up of ARM patients into adulthood.
Study Title	Effectiveness of Bulking Agent (Solesta) Therapy in Fecal Incontinence in Patients Refractory to Conventional Therapies.
Full Citation	Al-Bayati I, Saadi M, Elhanafi S, McCallum RW. Effectiveness of Bulking Agent (Solesta) Therapy in Fecal Incontinence in Patients Refractory to Conventional Therapies. Am J Med Sci. 2017;354(5):476-479. doi: 10.1016/j.amjms.2017.09.001
Abstract	Fecal incontinence is a problem that imposes considerable socioeconomic consequences. Despite many medical therapies, unmet needs remain. A new treatment option is a biocompatible bulking agent (Solesta) administered by submucosal injection in the distal rectum. The aims of this study are as follows: (1) To evaluate the efficacy and safety of this bulking agent in decreasing the severity of fecal incontinence (FI) and improving quality of life. (2) To obtain objective evidence of changes in anorectal physiology by high-resolution anorectal manometry pretreatment and posttreatment. From January 2014 to June 2015, 17 patients who had failed medical therapy for FI received stabilized hyaluronate injected submucosally into the rectum under direct anoscopic visualization. The treatment was considered successful if patients achieved >50% reduction in FI events during monitoring for up to 12 months. After the first treatment session, 14 patients (82.3%) had a successful outcome. The remaining 3 patients received a second therapy 3 months later to achieve this result. At last follow-up, 7 of the 17 patients (41%) were having no FI events. The remaining patients had reduction in fecal accidents from a mean of 6.4/week baseline to 2.8/week during follow-up. Intrarectal injection of stabilized hyaluronate is effective for treating FI in patients who had failed standard medical treatments and is technically easy and safely performed as an outpatient procedure.
Study Title	Efficacy and quality of life 2 years after treatment for faecal incontinence with injectable bulking agents.
Full Citation	Danielson J, Karlbom U, Wester T, Graf W. Efficacy and quality of life 2 years after treatment for faecal incontinence with injectable bulking agents. Tech Coloproctol. 2013;17(4):389-395. doi:10.1007/s10151-012-0949-8
Abstract	BACKGROUND: Stabilized non-animal hyaluronic acid/dextranomer (NASHA Dx) gel as injectable bulking therapy has been shown to decrease symptoms of faecal incontinence, but the durability of treatment and effects and influence on quality of life (QoL) is not known. The aim of this study was to assess the effects on continence and QoL and to evaluate the relationship between QoL and efficacy up to 2 years after treatment. METHODS: Thirty-four patients (5 males, mean age 61, range 34-80) were injected with 4 × 1 ml NASHA Dx in the submucosal layer. The patients were followed for 2 years with registration of incontinence episodes, bowel function and QoL questionnaires. RESULTS: Twenty-six patients reported sustained improvement after 24 months. The median number of incontinence episodes before treatment was 22 and decreased to 10 at 12 months (P = 0.0004) and to 7 at 24 months (P = 0.0026). The corresponding Miller incontinence scores were 14, 11 (P = 0.0078) and 10.5 (P =

	0.0003), respectively. There was a clear correlation between the decrease in the number of leak episodes and the increase in the SF-36 Physical Function score but only patients with more than 75 % improvement in the number of incontinence episodes had a significant improvement in QoL at 24 months. CONCLUSIONS: Anorectal injection of NASHA Dx gel induces improvement of incontinence symptoms for at least 2 years. The treatment has a potential to improve QoL. A 75 % decrease in incontinence episodes may be a more accurate threshold to indicate a successful incontinence treatment than the more commonly used 50 %.
Study Title	Long-term efficacy of dextranomer in stabilized hyaluronic acid (NASHA/Dx) for treatment of faecal incontinence
Full Citation	La Torre F, de la Portilla F. Long-term efficacy of dextranomer in stabilized hyaluronic acid (NASHA/Dx) for treatment of faecal incontinence. Color Dis Off J Assoc Coloproctology Gt Britain Irel. 2013;15(5):569-574. doi:10.1111/codi.12155
Abstract	Aim: Randomized, controlled trials have demonstrated the efficacy and safety of injectable bulking agents for the treatment of faecal incontinence (FI), although the long-term outcome has not been assessed. NASHA/Dx gel, a biocompatible, nonallergenic bulking agent consisting of nonanimal stabilized hyaluronic acid and dextranomer microspheres, has demonstrated efficacy and safety for up to 12 months after treatment. The objective of this study was to evaluate the long-term efficacy and safety of NASHA/Dx, assessed 24 months after treatment. Method: This study was a 24-month follow-up assessment of patients treated with NASHA/Dx under open-label conditions. Data on FI episodes and quality of life measures were collected from diaries over the 28-day period immediately preceding the 24-month assessment. Adverse events were collected. Results: Eighty-three of 115 patients completed the 24-month follow-up assessment. At 24 months, 62.7% of patients were considered responders and experienced a ≥ 50% reduction in the total number of FI episodes. The median number of FI episodes declined by 68.8% ($P < 0.001$). Episodes of both solid and liquid stool incontinence decreased. The mean number of incontinence-free days increased from 14.6 at baseline to 21.7 at 24 months ($P < 0.001$). Incontinence scores and FI quality of life scores also showed significant improvements. The most common adverse events (AEs) were proctalgia (13.3%) and pyrexia (9.6%). The majority of AEs were mild to moderate, self-limited and resolved within 1 month of the injection. Conclusion: NASHA/Dx is safe, effective and durable over a 24-month period with a majority of patients experiencing significant improvement in multiple symptoms associated with FI.
Study Title	An Open-Label, Noncomparative, Multicenter Study to Evaluate Efficacy and Safety of NASHA/Dx Gel as a Bulking Agent for the Treatment of Fecal Incontinence.
Full Citation	Giuseppe Dodi, Johannes Jongen, Fernando de la Portilla, Manoj Raval, Donato F. Altomare, Paul-Antoine Lehur. An Open-Label, Noncomparative, Multicenter Study to Evaluate Efficacy and Safety of NASHA/Dx Gel as a Bulking Agent for the Treatment of Fecal Incontinence. Gastroenterol Res Pr. 2010.
Abstract	Fecal incontinence (FI) is the involuntary loss of rectal contents through the anal canal. Reports of its prevalence vary from 1–21%. Studies have demonstrated a positive effect on FI symptoms with injectable bulking agents. This study evaluated the safety and efficacy of NASHA/Dx gel in the treatment of FI. One hundred fifteen eligible patients suffering from FI received 4 injections of 1 mL NASHA/Dx gel. Primary efficacy was based on data from 86 patients that completed the study. This study demonstrated a ≥50% reduction from baseline in the number of FI episodes in 57.1% of patients at 6 months, and 64.0% at 12 months. Significant improvements ($P < .001$) were also noted in total number of both solid and loose FI episodes, FI free days, CCFIS, and FIQL scores in all 4 domains. The majority of the treatment related AEs (94.9%) were mild or moderate intensity, and (98.7%) of AEs resolved spontaneously, or following treatment, without sequelae. Results of this study indicate NASHA/Dx gel was efficacious in the treatment of FI. Treatment effect was significant both in reduction of number of FI episodes and disease specific quality of life at 6 months and lasted up to 12 months after treatment.

Study Title	Submucosal injection of stabilized nonanimal hyaluronic acid with dextranomer: a new treatment option for fecal incontinence.
Full Citation	Danielson J, Karlbom U, Sonesson AC, Wester T, Graf W. Submucosal injection of stabilized nonanimal hyaluronic acid with dextranomer: A new treatment option for fecal incontinence. Dis Colon Rectum. 2009;52(6):1101-1106. doi: 10.1007/DCR.0b013e31819f5cbf
Abstract	OBJECTIVE: NASHA Dx gel has been used extensively for treatments in the field of urology. This study was performed to evaluate NASHA Dx gel as an injectable anal canal implant for the treatment of fecal incontinence. METHODS: Thirty-four patients (5 males, 29 females; median age, 61 years; range, 34 to 80) were injected with 4 x 1 ml of NASHA Dx gel, just above the dentate line in the submucosal layer. The primary end point was change in the number of incontinence episodes and a treatment response was defined as a 50 percent reduction compared with pretreatment. All patients were followed up at 3, 6, and 12 months. RESULTS: The median number of incontinence episodes during four weeks was 22 (range, 2 to 77) before treatment, at 6 months it was 9 (range, 0 to 46), and at 12 months it was 10 (range, 0 to 70, P = 0.004). Fifteen patients (44 percent) were responders at 6 months, compared with 19 (56 percent) at 12 months. No long-term side effects or serious adverse events were reported. CONCLUSIONS: Submucosal injection of NASHA Dx gel is an effective treatment for fecal incontinence. The effect is sustained for at least 12 months. The treatment is associated with low morbidity.
Case Report	
Study Title	Endoscopic, Ultrasonographic, and Histologic Descriptions of Dextranomer/Hyaluronic Acid in a Case of Fecal Incontinence.
Full Citation	Irwin T, Snow AR, Orton TS, Elliott C. Endoscopic, Ultrasonographic, and Histologic Descriptions of Dextranomer/Hyaluronic Acid in a Case of Fecal Incontinence. Case Rep Pathol. 2018; 2018:1-5. doi:10.1155/2018/5873094
Abstract	To present a case of fecal incontinence treated with dextranomer/hyaluronic acid (Solesta®) injections, which later caused clinical confusion and avoidable interventions. The endoscopic, ultrasonographic, and histologic appearances of dextranomer/hyaluronic acid will also be reported. A middle-aged Hispanic male who failed conservative management of his fecal incontinence was injected with dextranomer/hyaluronic acid in an attempt to alleviate symptoms. An unrelated screening colonoscopy was performed soon after, revealing a submucosal rectal lesion. Flexible sigmoidoscopy and endoscopic rectal ultrasound with FNA were scheduled for patient for further evaluation. An unknown foreign material was noted under microscopy and, upon attaining additional history, the gastroenterologist uncovered the patient's recent injections of dextranomer/hyaluronic acid. Dextranomer/hyaluronic acid for the treatment of fecal incontinence has become more common in recent years. Though the imaging and histologic appearance of this gel-like material is seen in other areas of medicine, equivalent descriptions are limited in the anorectal region. To curb misdiagnoses and prevent unnecessary interventions, it is important to expound on the endoscopic, imaging, and histopathologic features of this tissue-bulking agent in the setting of fecal incontinence and to encourage communication, proper documentation, and easy accessibility to patient health information by all medical staff.
Review Article	
Study Title	Fecal Incontinence: Etiology, Diagnosis, and Management.
Full Citation	Alavi K, Chan S, Wise P, Kaiser AM, Sudan R, Bordeianou L. Fecal Incontinence: Etiology, Diagnosis, and Management. J Gastrointest Surg. 2015;19(10):1910-1921. doi:10.1007/s11605-015-2905-1
Abstract	BACKGROUND: Fecal incontinence is a debilitating condition affecting primarily the elderly. Many patients suffer in silence resulting in both underdiagnosis and undertreatment often culminating in an overall poor quality of life. METHODS: We sought to review the etiology, diagnosis, and treatment of fecal incontinence based on current literature. Additionally, newer treatment methods such as Solesta will be evaluated. RESULTS: There are many diagnostic

	modalities available to assess the degree and severity of the patient's incontinence; however, a thorough history and physical exam is critical. Initial attempts at treatment focus on medical management primarily through stool texture modification with the aid of bulking agents. Failure of medical therapy is often followed by a graded increase in the complexity and invasiveness of the available treatment options. The selection of the most appropriate surgical option, such as overlapping sphincteroplasty and neuromodulation, is multifactorial involving both surgeon and patient-related factors. Neuromodulation has received increased attention in the last decade due to its documented therapeutic success, and newer office-based procedures, such as the Solesta injection, are showing promising results in properly selected patients. Finally, diversion remains an option for select patients who have failed all other therapies. CONCLUSIONS: The etiology of fecal incontinence is multifactorial, involving a complex interplay between stool consistency and anatomic integrity. The diagnosis and treatment of fecal incontinence continue to evolve and are showing promising results.
Expert Opinion Article	
Study Title	Dextranomer in stabilized sodium hyaluronate (Solesta®): in adults with faecal incontinence.
Full Citation	Hoy SM. Dextranomer in Stabilized Sodium Hyaluronate (Solesta®). Drugs. 2012;72(12):1671-1678. doi:10.2165/11209030-000000000-00000
Abstract	Dextranomer in stabilized sodium hyaluronate, hereafter referred to as dextranomer/hyaluronic acid, is a biocompatible bulking agent administered by submucosal injection. It is hypothesized to expand the submucosal layer of the proximal anal canal, thereby augmenting bowel control. Treatment with dextranomer/hyaluronic acid was associated with symptomatic improvements in adult patients with faecal incontinence participating in a randomized, double-blind, sham-controlled, multinational study and a noncomparative, multinational study. In the double-blind study, patients in the dextranomer/hyaluronic acid group met the primary efficacy objective in that a significantly higher proportion of patients responded to treatment (≥50% reduction from baseline in the number of incontinence episodes) at the 6-month post-treatment timepoint than in the sham group (two of three primary response criteria), with the durability of the treatment response (≥25% reduction from baseline in the number of incontinence episodes) confirmed at the 12-month post-treatment timepoint (third primary response criterion). For the most part, dextranomer/hyaluronic acid did not significantly differ from the sham treatment in terms of quality of life and various other symptomatic endpoints at 6 months post-treatment in the double-blind study, although there were significant improvements from baseline in various parameters, such as the mean number of incontinence-free days, the median number of incontinence episodes and mean Faecal Incontinence Quality of Life domain scores, at 12 months post-treatment. In general, dextranomer/hyaluronic acid was well tolerated for up to 18 months post-treatment, with the majority of treatment-related adverse events considered mild or moderate in intensity.

Package Insert

Solesta® Injectable Gel

CAUTION: Federal Law restricts this device to sale by or on the order of a physician.

INDICATION FOR USE

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

DEVICE DESCRIPTION

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

Solesta is a sterile, viscous, biocompatible bulking agent 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. 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, four sterile needles (Sterifine®, 21G x 4 ½ inches, 0.80 x 120 mm), patient record labels and a package insert. The product is for single use.

Both the dextranomer and sodium hyaluronate are made up of biosynthesized polysaccharides of non-animal origin. The dextranomer component consists of microspheres of dextran chains cross-linked into a three-dimensional network. The stabilized sodium hyaluronate accounts for the viscous properties of Solesta and acts as a carrier that facilitates the injection of the dextranomer microspheres.

Solesta is injected in the deep submucosal layer in the proximal part of the high pressure zone of the anal canal about 5 mm above the dentate line. A total of 4 submucosal injections of 1 mL Solesta are administered at each treatment session.

CONTRAINDICATIONS

Solesta is contraindicated in patients with the following conditions:

- Active inflammatory bowel disease
- Immunodeficiency disorders or ongoing immunosuppressive therapy
- Previous radiation treatment to the pelvic area
- Significant mucosal or full thickness rectal prolapse
- Active anorectal conditions including abscess, fissures, sepsis, bleeding, proctitis, or other infections
- Anorectal stenosis, tumors, stenosis or malformation
- Rectocele
- Rectal varices
- Presence of existing implant (other than Solesta) in anorectal region
- Allergy to hyaluronic acid based products

WARNINGS

- Do not inject Solesta intravascularly. Injection of Solesta into blood vessels may cause vascular occlusion.
- Injection in the midline of the anterior wall of the rectum should be avoided in men with enlarged prostate.

PRECAUTIONS

General precautions

- Solesta should only be administered by physicians experienced in performing anorectal procedures and who have successfully completed a comprehensive training and certification program in the Solesta injection procedure.
- The safety and effectiveness of Solesta have not been investigated in patients with complete external sphincter disruption or significant chronic anorectal pain.
- The safety and effectiveness of Solesta have not been investigated in patients with previous procedures involving the anorectal region: rectal sweatsomas >12 cm from anal verge, anorectal surgery within previous 12 months, hemorrhoid treatment with rubber band within 3 months, anorectal implants and previous injection therapy. Stapled Transanal Rectal Resection (STARR) or stapled hemorrhoidectomy.
- The safety and effectiveness of Solesta have not been studied in patients under the age of 18 years.
- The safety and effectiveness of Solesta have not been studied in pregnant or breastfeeding women.
- The durability of Solesta has not been studied past 36 months.
- The safety and effectiveness of Solesta have been studied in patients who received one or two treatments. In the Pivotal study, the majority of patients received two treatments, four weeks apart.

Patient related precautions

- Patients with bleeding diathesis or patients using anticoagulant or antiplatelet agents, as with any injections, may experience increased bleeding at injection sites.
- Patients should be counseled that a repeated Solesta injection procedure may be required to achieve a satisfactory level of improvement in incontinence.

Procedure related precautions

- Adequate bowel preparation of the rectum using enema is required prior to injection. The enema should be given immediately prior to the procedure to ensure evacuation of the anorectum. It is recommended that additional cleansing of the injection area with an antiseptic be performed prior to injection. Use of prophylactic antibiotics is recommended.
- Solesta should be injected slowly to avoid undue stress on the Luer-lock connection which could cause leakage of the gel.
- After injection of Solesta, hold the needle at the injection site for an additional 15-30 seconds to minimize leakage of Solesta.
- Injections too close to the dentate line or too deep in the tissue might cause excessive pain.
- Injection should be stopped if excessive bleeding or pain occurs.
- One sterile needle should be used per syringe and injection.

Device related precautions

- The use of needles other than those supplied may impede injection of Solesta due to the properties of the gel and may cause device malfunction.
- Solesta is supplied ready to use in a prefilled syringe with a Luer-lock fitting. Carefully examine the unit to verify that neither the contents nor the package has been damaged in shipment. Do not use if damaged.
- Solesta is supplied sterile and is intended for single use only. Do not re-sterilize, as this may damage or alter the product.
- In the event of accidental contamination of a needle, discard the needle.
- Never mix Solesta with other products.
- Solesta is to be stored at up to 25°C (77°F), and used prior to the expiration date printed on the label. Do not expose Solesta to either sunlight or freezing, as this may damage or alter the product.
- Care should be taken when handling the glass syringe and disposing of broken glass to avoid laceration or other injury.
- After use, syringes and needles should be handled as potential biohazards. Disposal should be in accordance with accepted medical practice and applicable local, state and federal requirements.

ADVERSE EVENTS

The adverse event profile of Solesta was investigated up to 36 months post injection. Adverse events considered possibly or probably related to Solesta treatment include the following events that were experienced by at least 2 patients in the Pivotal study (Table 5 in the Clinical Studies section): proctalgia, injection site hemorrhage, pyrexia, diarrhea, injection site pain, anorectal discomfort, anal hemorrhage, rectal discharge, proctitis, anal prolapse, constipation, anal pruritus, lower abdominal pain, defecation urgency, painful defecation, rectal obstruction, chills, injection site nodule, pain, rectal abscess, rectovaginal septum abscess, dyspareunia, and alopecia. Adverse events considered possibly or probably related to Solesta treatment and reported for only 1 patient each are listed in the footnote to Table 5.

The observed adverse events are discussed in the Clinical Studies section below.

CLINICAL STUDIES

Introduction

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 306 patients conducted under an Investigational Device Exemption (IDE; Pivotal study), 2) a prospective, multicenter, open-label study of 115 patients conducted outside the United States (Open-Label study), and 3) a single center study of 34 patients conducted at one site in Sweden (Proof-of-Concept study). The Pivotal study also included a cross-over option for patients initially randomized to Sham. The majority of patients (over 84%) in all three studies were female.

Table 1 provides an overview of the design of the three studies.

Table 1: Comparison of the three clinical studies supporting safety and effectiveness of Solesta

	Pivotal study	Open-Label study	Proof-of-Concept study
Study Design	Randomized double-blind comparative study of Solesta versus Sham in 2:1 ratio	Open study	Open study
Primary Efficacy Endpoints	Effectiveness: (1) Superiority in proportion Responder$_{50}$ compared with Sham at 6 months (2) Durability of response based on proportion responders at 12 months Durability of response was also evaluated up to 36 months following last injection	Effectiveness: Proportion Responder$_{50}$ at 12 months Durability of response was also evaluated up to 24 months following last injection	Effectiveness: Proportion Responder$_{50}$ at 12 and 24 months
Secondary Efficacy Variables	Fecal Incontinence Quality of Life (FIQL) Scale	FIQL	SF-36 European Organization for Research and Treatment of Cancer (EORTC) QLQ-C30
	Cleveland Clinic Florida Incontinence Score (CCFIS)	CCFIS	Miller Score
	Fecal Incontinence (FI) free days	FI free days	FI free days
	Fecal Incontinence (FI) episodes, controlled bowel emptying, medications	FI episodes, controlled bowel emptying, medications	FI episodes, global evaluation by patient, patient subjective judgment of treatment effect
Investigational Centers	8 centers in US and 5 centers in Europe	14 centers in Europe and 1 center in Canada	1 center in Sweden
Sample Size	136 patients randomized to Solesta, and 70 patients randomized to Sham	115 patients	34 patients
Inclusion Criteria	Age 18-75 years	Age 18-80 years	Age 18-80 years
	≥4 FI episodes over 14 days in patient diary	≥4 FI episodes over 28 days in patient diary	At least one FI episode weekly
	CCFIS≥10	CCFIS≥5	Miller score ≥6
	Solid or liquid FI episodes	Solid or liquid FI episodes	Solid or liquid FI episodes
	Failed conservative treatment	Failed conservative treatment	Failed conservative treatment
Exclusion Criteria	Complete external sphincter disruption, Significant mucosal prolapse	Complete external sphincter disruption, Significant mucosal prolapse	Complete external sphincter disruption, Significant mucosal prolapse
Retreatment Criteria	Incontinent at one month after initial treatment and CCFIS ≥10	Incontinent at one month after initial treatment	Some subjective improvement but less than 50 % reduction in FI episodes

The Pivotal Study is the primary data set that demonstrates the safety and effectiveness of Solesta. The Open-Label and Proof-of-Concept studies provide supporting evidence of safety and effectiveness.

Treatment Information

Pre-operative Bowel Preparation

Pre-treatment evacuation of the rectum was done with an enema in the majority of the patients in all 3 studies. A small number of patients received topical antiseptic cleansing at the discretion of the treating physician. Prophylactic antibiotics were administered to individual patients in the Pivotal study at the treating investigator and only 15 patients at 3 sites received prophylactic antibiotics in this study. No patients in the Open-Label study received prophylactic antibiotics.

Treatment Procedure

The Solesta injection procedure was the same in all 3 studies. Treatment was administered in an out-patient setting without anesthesia. Four equally spaced injections were administered through an anoscope and placed about 5 mm proximal to the dentate line. Treatment volume was generally 4 x 1 mL per treatment session. A single re-treatment procedure was offered to patients with persistent fecal incontinence after approximately 1 month. If a patient received retreatment, the maximum total treatment dose was 8 mL (4 mL per treatment x 2 treatments). In the Pivotal study, the sham injection procedure consisted of using 4 separate syringes to pierce the mucosa. The syringes were held in place for the same amount of time as Solesta injection; however, nothing was injected.

Table 5: Related Adverse Events (Including Serious AEs) by Time Interval of Event Onset Experienced by at Least 2 Patients Following Blinded or Open-Label Treatment with Solesta through Month 36 in the Pivotal Study. MedDRA Preferred Term. Safety Population (n=197)

	☐ 1st Solesta injection		☐ 2nd Solesta injection (at 1 month)				
MedDRA Preferred Term	**1st Solesta injection All hours (N = 197) n (%)**	**>48 hours - 7 days (N = 197) n (%)**	**>7 days - 1 month (N = 197) n (%)**	**>1 month - 2 months (N = 197) n (%)**	**>2 months - 4 months (N = 197) n (%)**	**>4 months - 36 months (N = 196) n (%)**	**>24 months (N = 117) n (%)**
Proctalgia	17 (8.6%)	2 (1.0%)	7 (3.6%)	12 (6.1%) † (0.5%)	3 (1.5%)	0	0
Injection site hemorrhage	5 (2.5%)	0	3 (1.5%)	6 (3.0%)	3 (1.5%)	0	0
Rectal hemorrhage	3 (1.0%)	† (0.5%)	2 (1.0%)	6 (3.0%)	2 (1.0%)	2 (1.0%)	0
Pyrexia	7 (3.6%)	0	2 (1.0%)	5 (2.5%)	0	0	0
Diarrhea	0	† (0.5%)	2 (1.5%)	3 (1.5%) † (0.5%)		2 (1.0%)	0
Injection site pain	6 (3.0%)	0	† (0.5%)	† (0.5%)	† (0.5%)	† (0.5%)	0
Anorectal discomfort	3 (1.5%)	0	2 (1.0%)	2 (1.0%)	2 (1.0%)	0	0
Anal hemorrhage	4 (2.0%)	0	† (0.5%)	3 (1.5%)	† (0.5%)	0	0
Rectal discharge	2 (1.0%)	0	† (0.5%)	4 (2.0%)	0	0	0
Proctitis	† (0.5%)	† (0.5%)	† (0.5%)	† (0.5%)	2 (1.0%)	0	0
Anal prolapse	0	0	0	0	† (0.5%)	2 (1.0%)	0
Constipation	0	0	0	2 (1.0%)	† (0.5%)	0	0
Anal pruritus	0	0	† (0.5%)	† (0.5%)	0	† (0.5%)	0
Abdominal pain lower	† (0.5%)	0	0	0	† (0.5%)	0	0
Defecation urgency	0	0	0	2 (1.0%)	0	0	0
Painful defecation	† (0.5%)	0	0	† (0.5%)	0	0	0
Rectal obstruction	† (0.5%)	0	0	0	† (0.5%)	0	0
Chills	3 (1.5%)	0	† (0.5%)	0	0	0	0
Injection site nodule	0	0	0	0	0	3 (1.5%)	0
Pain	† (0.5%)	0	† (0.5%)	0	0	0	0
Rectal abscess	† (0.5%)	0	† (0.5%)	† (0.5%)	0	0	0
Anal fissure	0	0	0	† (0.5%)	0	† (0.5%)	0
Rectovaginal septum abscess	0	0	0	0	0	† (0.5%)	† (0.9%)
Dyspareunia	0	0	0	0	2 (1.0%)	0	0
Alopecia	0	0	0	† (0.5%)	† (0.5%)	0	0

Notes: The following treatment-related adverse events were reported for 1 patient each: abdominal discomfort, abdominal distension, abdominal pain, abdominal rigidity, fecal incontinence, hard feces, gastrointestinal motility disorder, gastrointestinal pain, hemorrhoids, intestinal mass, nausea, rectal spasm, device dislocation, fatigue, implant site cyst, injection site inflammation, injection site irritation, injection site swelling, pelvic mass, anal abscess, Escherichia coli bacteremia, injection site pustule, mucosal excoriation, c-reactive protein increased, back pain, musculoskeletal pain, urinary retention, genital prolapse, perineal pain, vaginal discharge, vulvovaginal pain, cold sweat, and dermatitis.
The down arrow symbol (☐) indicates the timing of Solesta injections. Greater than 80% of subjects had 2 injections with Solesta (initial treatment and re-treatment approximately 1 month later).

Effectiveness

Primary Efficacy Objective - Pivotal Study

The Pivotal study included a primary efficacy objective composed of 3 parts. All 3 parts of the primary objective were met. The study was only powered for the primary endpoint and was not designed or powered to demonstrate a statistical difference between Solesta and Sham for the secondary efficacy endpoints.

Superiority was shown for Solesta (53.2%) versus Sham (30.7%) at 6 months (p=0.004; logistic regression), as illustrated in Figure 1, based on analysis of proportion Responder$_{50}$. Responder$_{50}$ defined as proportion of patients with a ≥ 50% reduction in number of incontinence episodes compared to baseline, has been used to objectively evaluate response to treatments for FI in other studies.

The second success criterion required that the results achieve a pre-specified minimum level of responders in the treatment group as defined by a lower confidence limit (LCL) of at least 35%. The LCL of the 95% confidence interval of the proportion Responder$_{50}$ at 6 months was 40.2%, as illustrated in Figure 2.

Patient Demographics

Both of the multicenter studies enrolled patients with a broad range of age and body mass index. The majority of patients enrolled in both studies were females. Over 10% of patients enrolled in the Pivotal study were African-Americans, Hispanics or Asians. The causes of FI in both studies were attributed mainly to obstetric cause, neurogenic cause, and iatrogenic cause based on available medical history.

Table 2 provides an overview of the patient demographics in the Pivotal study. The Open-Label study and the Proof-of-Concept study enrolled patients with similar demographics.

Table 2: Demographics in the Pivotal Study

Subject Demographics		**Pivotal study (n=206)**
Female	n (%)	183 (88.8)
Age, years	Mean (range)	60.1 (29.4–76.0)
Body Mass Index (BMI), kg/m^2	Mean (range)	27.1 (17.2–44.8)
Caucasian origin	n (%)	181 (87.9)
Duration of symptoms over 5 years	n (%)	106 (51.7)
Obstetric cause	n (%)	82 (39.8)
Neurogenic cause	n (%)	43 (20.9)
Iatrogenic cause	n (%)	46 (22.3)
Other cause (mostly idiopathic)	n (%)	35 (17.0)

Safety Data

The safety evaluation of Solesta in the treatment of fecal incontinence (FI) is based on the results from the Pivotal clinical study, and is supported by the Open-Label multicenter clinical study and one single site Proof-of-Concept study. The analyses of safety was based on the safety cohort of all 206 patients treated in the Pivotal study with either Solesta or Sham. During the 6-month blinded phase (n = 136 in the Solesta group and n = 70 in the Sham group), treatment-emergent adverse events were experienced by 72% of the Solesta-treated patients and 60% of Sham-treated patients. Table 3 provides an overview of treatment-emergent adverse events during the 6-month blinded phase.

Table 3: Overview of Adverse Events during the 6-Month Blinded Phase of the Pivotal Study

	Solesta (n = 136) n (%)	**Sham (n = 70) n (%)**
Any treatment-emergent adverse event	98 (72.1)	42 (60.0)
Severe treatment-emergent adverse events	6 (4.4)	1 (1.4)
Serious treatment-emergent adverse events	7 (5.1)	2 (2.9)
Treatment-emergent adverse events considered related to study treatment by the investigator (treatment-related adverse events)	66 (48.5)	19 (27.1)
Serious treatment-related adverse events*	2 (1.5)	0

* Serious treatment-related adverse events were one case of E. coli bacteremia and one case of rectal abscess. A third patient experienced a serious treatment-related adverse event of rectal abscess during the open phase.

Safety data for Solesta are available from 359 treatments in 197 total patients followed for up to 36 months post treatment during the blinded and open phases of the Pivotal study (ie, the long-term population, including 136 patients who received Solesta during the blinded phase and an additional 61 patients who received Solesta during the open phase). Greater than 80% of subjects had 2 injections with Solesta (initial treatment and re-treatment approximately 1 month later); 113 of 136 patients (83.1%) received 2 Solesta injections during the blinded phase and 49 of 61 patients (80.3%) received 2 Solesta injections during the open phase. At least 1 treatment-emergent adverse event was experienced by 87% of patients in the long-term population. Severe treatment-emergent adverse events were reported for 12% of patients. For the subgroup of 61 patients who received Solesta at the start of the open phase, treatment-emergent AEs were experienced by 85% of patients and severe treatment-emergent adverse events were reported for 12% of patients.

In the long-term population, treatment-related adverse events (ie, treatment-emergent adverse events considered by the investigator to be related to Solesta injection) were experienced by 104 of 197 patients (53%) up to 36 months after treatment. For the subgroup of 61 patients who received Solesta at the start of the open phase, 31 of 61 (51%) had treatment-related adverse events during follow-up. Three (3) of 197 patients (1.5%) had treatment-related adverse events that were deemed serious by the investigators. These serious treatment-related adverse events include: one subject with *E. coli* bacteremia who was presented with an ongoing urinary tract infection, prostatic hypertrophy, and possible upper respiratory tract infection, and 2 subjects with rectal abscess. The event of *E. coli* bacteremia and one event of rectal abscess occurred during the blinded phase; the other event of rectal abscess occurred during the open phase. These serious treatment-related adverse events resolved following treatment without sequelae within 35 days of event onset. The times from injection to event onset and other details of the 3 serious treatment-related adverse events are shown in Table 4.

Table 4: Serious Treatment-Related Adverse Events during the Blinded or Open Phases (up to 36 months post treatment)

Event	**Treatment group**	**Intensity**	**Time from injection to event onset**	**Event Duration**	**Outcome**
Escherichia coli bacteremia*	Solesta treatment - blinded phase	Moderate	0.5 days post first injection	35 days	Recovered
Rectal abscess†	Solesta treatment - blinded phase	Mild	2 days post second injection	5 days	Recovered
Rectal abscess‡	Solesta treatment - open phase	Severe	4.5 months post second injection	5 days	Recovered

* These events occurred during the blinded phase.
† This event occurred during the open phase.

The third success criterion concerned durability of the treatment effect and required a minimum level of proportion Responder$_{50}$ (≥ 25% improvement from baseline) for Solesta at 12 months, as defined by a lower confidence limit of 50%. The LCL for proportion Responder$_{50}$ at 12 months was 61.4%, as illustrated in Figure 2.

As an additional supporting analysis, the proportion Responder$_{50}$ at 12 months after last treatment was also calculated and it was 57.4%, similar to the results at 6 months. Analyses were performed to determine whether there was any association between baseline or demographic characteristics and treatment response. No such relationship was found.

Figure 1. Comparison of Proportion Responder$_{50}$ at 6 Months

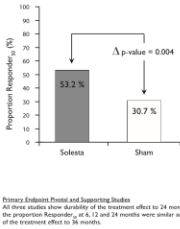
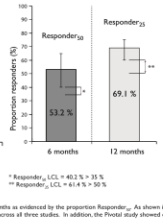


Figure 2. Solesta Proportion Responders at 6 and 12 Months



* Responder$_{50}$ LCL = 40.2 % > 35 %
** Responder$_{25}$ LCL = 61.4 % > 50 %

Primary Endpoint Pivotal and Supporting Studies

All three studies show durability of the treatment effect to 24 months as evidenced by the proportion Responder$_{50}$. As shown in Table 6 the proportion Responder$_{50}$ at 6, 12 and 24 months were similar across all three studies. In addition, the Pivotal study showed durability of the treatment effect to 36 months.

Table 6: Summary of Proportion of Responder$_{50}$ at 6,12, 24 and 36 Months with Solesta Treatment.

Proportion Responder$_{50}$ [95% CI][a]	**Pivotal study (ITT, PIM [6 month time point]; ITT, LOCF [12, 24, and 36 month time points])[b]**	**Open-Label Study (ITT, OC)**	**Proof-of-Concept Study (OC)**
6 months	53.2% [40.2–65.8] n= 136	57.1% [47.3–66.9] n=98	44.1% [27.4–60.8] n=34
12 months	57.4% [49.0–65.7] n=136	64.4% [54.3–74.4] n=87	55.9% [39.2–72.6] n=34
24 months	54.4% [46.0-62.8] n = 136	62.7% [51.7-73.6] n=75	59.4% [42.4–76.4] n=32
36 months	53.2% [43.8-60.6] (n=136	N/A	N/A

a The responder$_{50}$ proportion at 6 months in the ITT population was determined from the primary imputation model and is the same as shown in Figure 1. The responder$_{50}$ proportions at 12, 24, and 36 months in the ITT population were determined by the LOCF method. The responder$_{50}$ proportion at 6 months by the LOCF method was 53.2% [43.8-60.6].
CI = confidence interval; ITT = intent-to-treat; LOCF = last observation carried forward; PIM = primary imputation model.
OC = observed cases; n = number of patients

Combined with the supportive studies, a total of 346 patients received 566 treatments with Solesta. All three studies utilized similar inclusion/exclusion criteria and all three studies used exactly the same procedure for administering Solesta. The multi-center Open-Label study demonstrated similar safety results as the Pivotal study. A total of 163 AEs were reported by 71 of the 115 patients treated with Solesta in the Open-Label study. Of these AEs, 79 AEs reported by 44 patients (38%) were assessed by the investigators to be related to the study treatment. Thus, the incidence of treatment-related AEs per total number of performed treatments was 31.3% (79 events/154 treatments). Similar to the Pivotal study, the 5 most frequently reported types of treatment-related AEs were proctalgia, pyrexia, constipation, diarrhea and injection site pain. Six (6) treatment-related AEs reported in 4 patients were classified as serious in the study. Three (3) of these serious and treatment-related adverse events were cases of abscess reported by 3 patients and the remaining 3 were reported by a single patient who had a rectal prolapse with concurrent rectal bleeding and pain. In this latter case, tissues surrounding a Solesta bulge had prolapsed downward in the anal canal and the Solesta bulge was excised in surgery.

In the Proof-of-Concept study, 34 patients were treated in the study and 33 patients were followed for 24 months. In total, 53 treatments with Solesta were administered in the study. These patients experienced a total of 86 treatment-related adverse events that were reported by 29 patients. No treatment-related adverse event was reported as serious. The duration was 1-4 days for most events and all events were resolved within 1 week. No adverse events occurred after month 12. One (1) patient gave birth to a healthy child approximately 18 months after treatment and the delivery was a normal vaginal delivery. The observed adverse events were similar to those seen in the Pivotal study.

Secondary Endpoints for Pivotal and Supporting Studies

The following secondary endpoints were evaluated in the three clinical studies:

- Fecal incontinence episodes
- Fecal incontinence-free days
- Fecal Incontinence Quality of Life (FIQL) assessment
- Cleveland Clinic Florida Incontinence Score (CCFIS) or Miller Score

Fecal Incontinence Episodes

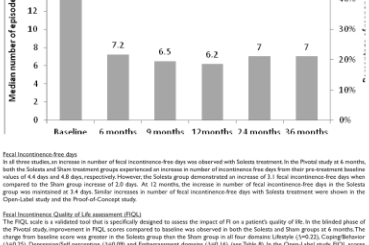
In the Pivotal study, reductions in number of FI episodes from baseline at both 3 and 6 months were observed in both the Solesta and Sham treatment groups. For the Solesta group the median FI episodes were shown to decrease from 15 episodes at baseline to 7.2 episodes at 6 months and 6.2 episodes at 12 months. For the Sham group the median FI episodes were shown to decrease from 12.5 episodes at baseline to 10.0 episodes at 6 months (see Table 7). Both the Solesta and Sham groups showed a change from baseline at 6 months, and the change from baseline in the Solesta group was larger than that observed for the Sham group. Similar reductions from baseline with Solesta treatment were observed in the Open-Label study and the Proof-of-Concept study.

Figure 3 shows the sustained improvement in Responder$_{50}$ analysis and reduction in fecal incontinence episodes over 36 months in the Pivotal study for the Solesta group only.

Table 7: Median Number of Fecal Incontinence Episodes/14 Days for Each Treatment Group and Change from Baseline to 6 Months. As Observed. Last Observation Carried Forward (LOCF). ITT population (n=206 patients: Pivotal Study)

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

Figure 3. Median Number of FI Episodes and Proportion Responder$_{50}$ at Each Follow Up Time Point in the Pivotal Study. Solesta ITT Population (n=136)



Fecal Incontinence-free days

In all three studies, an increase in number of fecal incontinence-free days was observed with Solesta treatment. In the Pivotal study at 6 months, both the Solesta and Sham treatment groups experienced an increase in number of incontinence-free days from their pre-treatment baseline values of 4.4 days and 4.8 days, respectively. However, the Solesta group demonstrated an increase of 3.1 fecal incontinence-free days when compared to the Sham group increase of 2.0 days. At 12 months, the increase in number of fecal incontinence-free days in the Solesta group was maintained at 3.4 days. Similar increases in number of fecal incontinence-free days with Solesta treatment were shown in the Open-Label study and the Proof-of-Concept study.

Fecal Incontinence Quality of Life assessment (FIQL)

The FIQL scale is a validated tool that is specifically designed to assess the impact of FI on a patient's quality of life. In the blinded phase of the Pivotal study, improvement in FIQL scores compared to baseline was observed in both the Solesta and Sham groups at 6 months. The change from baseline score was greater in the Solesta group than the Sham group in all four domains: Lifestyle (↑=0.22), Coping/Behavior (↑=0.25), Depression/Self perception (↑=0.09) and Embarrassment domains (↑=0.16), (see Table 8). In the Open-Label study, FIQL scores showed a similar improvement. The Proof-of-Concept study did not evaluate FIQL.

Cleveland Clinic Florida Incontinence Score (CCFIS)

The CCFIS is a validated measure of the impact of FI on patients. In the pivotal study, in both the Solesta and Sham groups, the CCFIS was improved as compared to baseline at 6 months. The difference at 6 months in mean change from baseline between the Solesta group and the Sham group was small (see Table 8). Solesta showed improvements from baseline at 12 months in both the Pivotal study and the Open-Label study.

The Proof-of-Concept study did not incorporate CCFIS but instead used the Miller Score, another assessment tool for FI. The Miller Score is based on a subject interview using standardized questions regarding incidence and type of incontinence (solid, liquid or gas). Improvements from baseline and sustained improvements were shown at 6, 12, and 24 months.

Table 8: Secondary Efficacy Evaluations of Difference in Change from Baseline Between Solesta and Sham at 6 Months. LOCF, ITT Population (n=206 Patients: Pivotal Study)

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

* Positive value indicates improvement; † Negative value indicates improvement

PATIENT COUNSELING INFORMATION

The patient should be advised that Solesta treatment is not effective for all patients with fecal incontinence and that repeat treatment might be required for treatment effect. It should also be made clear to the patient that the available clinical study data are not sufficient to predict in whom Solesta treatment will be effective. The patient should be informed about post-treatment care and potential adverse events. The patient should also be made aware that the implants might be detected during future anorectal examinations and radiographic imaging of the pelvis. Patients should be instructed to inform all future treating physicians about the presence of Solesta gel.

If there should be a need for future surgery (e.g., hemorrhoidectomy) the Solesta implant can be resected.

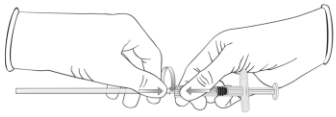
DIRECTIONS FOR USE

Solesta should be administered by qualified physicians with experience in the treatment of anorectal conditions and who have successfully completed a comprehensive training and certification program in the Solesta injection procedure. Solesta should only be used after a thorough physical evaluation of the patient to exclude treatable underlying disorders.

For the safe use of Solesta it is important that a new sterile needle is properly assembled and tightly fastened to each syringe.

Please note that the Luer-lock adapter is snapped onto the syringe and held in place with friction only. It can rotate freely or be pulled off should enough force be applied. Because of this it is recommended that the thumb and forefinger be held firmly around the Luer-lock adapter on the glass syringe while attaching the needle to the syringe. DO NOT attach the needle by holding onto the glass barrel of the syringe. To facilitate proper threading/fastening of the needle hub and Luer-lock adapter, please firmly push and rotate the needle hub into the Luer-lock adapter as illustrated in Figure 4.

Figure 4: Proper threading/fastening of the needle hub and Luer-lock adapter



To avoid any interruption in patient treatment or the need to repeat a procedure because of leakage, or accidental contamination or damage of a syringe or needle, it is recommended that extra Solesta cartons be kept in inventory.

Method of Administration

1. The treatment is administered as an outpatient procedure without anesthesia.
2. Prior to treatment, the rectum should be evacuated with an enema. The enema should be given immediately prior to the procedure to ensure evacuation of the anorectum. Additional cleansing of the injection area with an antiseptic may be performed prior to injection.
3. Use of prophylactic antibiotics is recommended.
4. Four Solesta syringes should be made ready with mounted needles under aseptic conditions. Have small swabs and suction prepared and ready for use.
5. The patient is placed in the left lateral position, and a lubricated anoscope is inserted. The obturator is removed and the anoscope withdrawn so that the dentate line is identified.
6. There is a triangular mark on the needle hub that provides the orientation of the needle bevel to ensure the bevel is facing the lumen when the needle is inserted (Figure 5).

Figure 5: Mark Indicating Needle Bevel Orientation

7. The four injections are to be given in the following order: posterior, left lateral, anterior, and right lateral.
8. The injections should be performed slowly to avoid stress on the Luer-lock connection and allow the tissue to adapt to the injected gel.
9. Under direct vision, the mucosa is penetrated, approximately 5 mm proximal to the dentate line. The needle is advanced a further 5 mm at approximately 30° to the axis of the rectum. If the patient indicates pain at the puncture, the injection site should be adjusted a few mm in the cephalic direction. If the puncture is painless, 1 mL of Solesta is injected in the deep submucosal layer. After injection, the needle should be kept in position for 15-30 seconds to minimize leakage of Solesta.
10. The injection is to be repeated at the remaining three injection sites. A new needle should be used for each syringe and injection site.
11. After completion of the 4 injections, the anoscope is extracted and the patient may rise. The patient should be instructed to rest at the clinic for approximately 60 minutes.
12. If no bleeding or other treatment related symptoms are observed during this time, the patient can be allowed to leave the clinic.
13. Confirming placement of Solesta gel by imaging may be of benefit.

Post-treatment care

1. The patient should be instructed to avoid taking hot baths during the first 24 hours post-treatment.
2. The patient should be informed of the risk of infections and bleeding.
3. The patient should be instructed to contact the clinic or physician's office immediately if symptoms of rectal bleeding, bloody diarrhea, fever, tenesmus or problems with urinating occur.
4. Anti-diarrheal drugs should not be used for one week after treatment.
5. Stool softeners may be used until the first defecation occurs.
6. Analgesics other than Non-steroidal Anti-inflammatory Drugs (NSAIDs) may be prescribed, if needed.
7. The patient should be instructed to:
   - Avoid physical activity for 24 hours
   - Avoid sexual intercourse and strenuous physical activity for one week (e.g., horse back riding, bicycling and jogging, etc.)
   - Avoid anal manipulation for one month (e.g., insertion of suppositories or enemas and rectal temperature recording)

Re-treatment procedure

1. If the patient does not have an adequate response to Solesta after the first injection, a re-injection with a maximum of 4 mL Solesta can be performed, no sooner than 4 weeks after the first injection.
2. The re-treatment procedure and all pretreatment preparations are performed the same way as the initial treatment procedure. All pretreatment preparations and injection procedures should be performed as described in "Methods of Administration" above. However, the point of injection should be made in between the initial injections, shifted one-eighth of a turn (e.g., left posterolateral, left anterolateral, right anterolateral, and right posterolateral).

HOW SUPPLIED

Solesta is supplied in a glass syringe with a standard Luer-lock fitting containing 1 mL gel. Each syringe is terminally moist heat sterilized in a pouch. Four pouches, each containing one syringe are packed in a carton together with four StorIject® needles (21G x 4½ inches, 0.80 mm x 120 mm), patient record labels and a package insert. The needles are sterilized by gamma irradiation.

STORAGE

Store at a temperature up to 25°C (77°F) and protect from sunlight and freezing.

Manufactured for:
Salix Pharmaceuticals, a subsidiary of Valeant Pharmaceuticals International,
Rochester, NY 14609 USA

For product information, adverse event reports, and product complaint reports, please contact:

Salix Product Information Call Center
Phone: 1-800-508-0024
Fax: 1-510-595-8183
E-mail: Salix@medcomsol.com

Manufactured by:
Q-Med AB
Seminariegatan 21
SE-752 28 Uppsala
Sweden

Made in Sweden

Rev. 04/2016
9509000

FDA Approval Letter

March 17, 2020

Palette Life Sciences
Cliff Kline
Head of Regulatory
27 East Cota Street
Suite 402
Santa Barbara, CA 93101

Re: P100014/R018
Trade/Device Name: Solesta Injectable Gel
Study Name: Solesta - Long Term Study
Received: December 23, 2019

Dear Cliff Kline:

The Center for Devices and Radiological Health of the Food and Drug Administration (FDA) has completed the review of your final Post-Approval Study (PAS) Report P100014/R018 for the Solesta Injectable Gel. This PAS requirement was described in the approval order dated May 27, 2011 for premarket approval application (PMA) P100014. FDA is pleased to inform you that you have fulfilled your post-approval study requirement for the study referenced above.

Please submit a PMA supplement, within 30 days from the date of our letter, which modifies the labeling to reflect the findings of the study. This supplement should include a new section of the label that reflects long-term data from the Post-Approval Study. The labeling supplement should include a summary of the post-approval study design, results, and study strengths and limitations.

The format below is recommended.

Post-Approval Study

Summary of the Post-Approval Study Methods

Study Objective

Study Design

Study Population

Data Source

Key Study Endpoints

U.S. Food & Drug Administration
10903 New Hampshire Avenue
Silver Spring, MD 20993
www.fda.gov

Total number of Enrolled Study Sites and Subjects, Follow-up Rate

Study visits and length of follow-up

Summary of the Post-Approval Study Results

Final safety findings (key endpoints)

Final effectiveness findings (key endpoints)

Study Strength and Weaknesses

For review purposes, CDRH has categorized the submission as a no user fee 180-day supplement. The required copy of your PMA supplement should include the FDA reference number to facilitate processing, be identified as a "PMA Post-Approval Study Labeling Update" and should be submitted to the following address:

U.S. Food and Drug Administration
Center for Devices and Radiological Health
Document Control Center - WO66-G609
10903 New Hampshire Avenue
Silver Spring, MD 20993-0002

Please be advised that once you have submitted this supplement, you should also submit an amendment to this post-approval study final report that notifies us of the date you submitted the labeling supplement and the supplement number assigned by FDA. **Your post-approval study report will remain open until we receive this amendment.**

Please be advised that your study status will be marked as "Progress Adequate" on the Post-Approval Studies webpage until we receive your amended report (https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfPMA/pma_pas.cfm).

If you have any questions concerning this letter, please contact Manuel Bayona at 301-796-6096 or Manuel.Bayona@fda.hhs.gov.

Sincerely,

Daniel G. Walter Jr -S

Daniel G. Walter, Jr.
Assistant Director
DHT3A: Division of Renal, Gastrointestinal,
Obesity and Transplant Devices
OHT3: Office of GastroRenal, ObGyn,
General Hospital and Urology Devices
Office of Product Evaluation and Quality
Center for Devices and Radiological Health

Billing Guide

Solesta®

CODE FORM 1500

Coding and Billing Instructions

FOR CMS 1500 FORM

While all coding decisions should be made by the physician based on independent review of the patient's condition, below is a list of codes you may find helpful.

BOX 21 - DIAGNOSIS CODES

Enter the appropriate ICD-10-CM code in Box 21

→ **Box 21**	R15	Fecal incontinence
	R15.0	Incomplete defecation
	R15.1	Fecal smearing
	R15.2	Fecal urgency
	R15.9	Full incontinence of feces

COLUMN 24D AND BOX 19 - MEDICATION INFORMATION

The below codes may be used:

→ **Column 24D**	HCPCS L8605	Injectable bulking agent, dextranomer/ hyaluronic acid copolymer implant, anal canal, 1 mL, includes shipping and necessary supplies
→ **Box 19**	NHRIC 89114-0850-03	Solesta Injectable Gel – 1 carton of four 1 mL prefilled syringes

COLUMN 24D - ADMINISTRATION CODE

Since Solesta does not have a unique CPT code for administration, physicians may file for reimbursement for the injection of Solesta using:

→ **Column 24D**	CPT 46999	Unlisted procedure, anus

Please note: for guidance and additional information regarding billing and administration of Solesta, check with your local Medicare carrier.

COLUMN 24G - MEDICATION QUANTITY

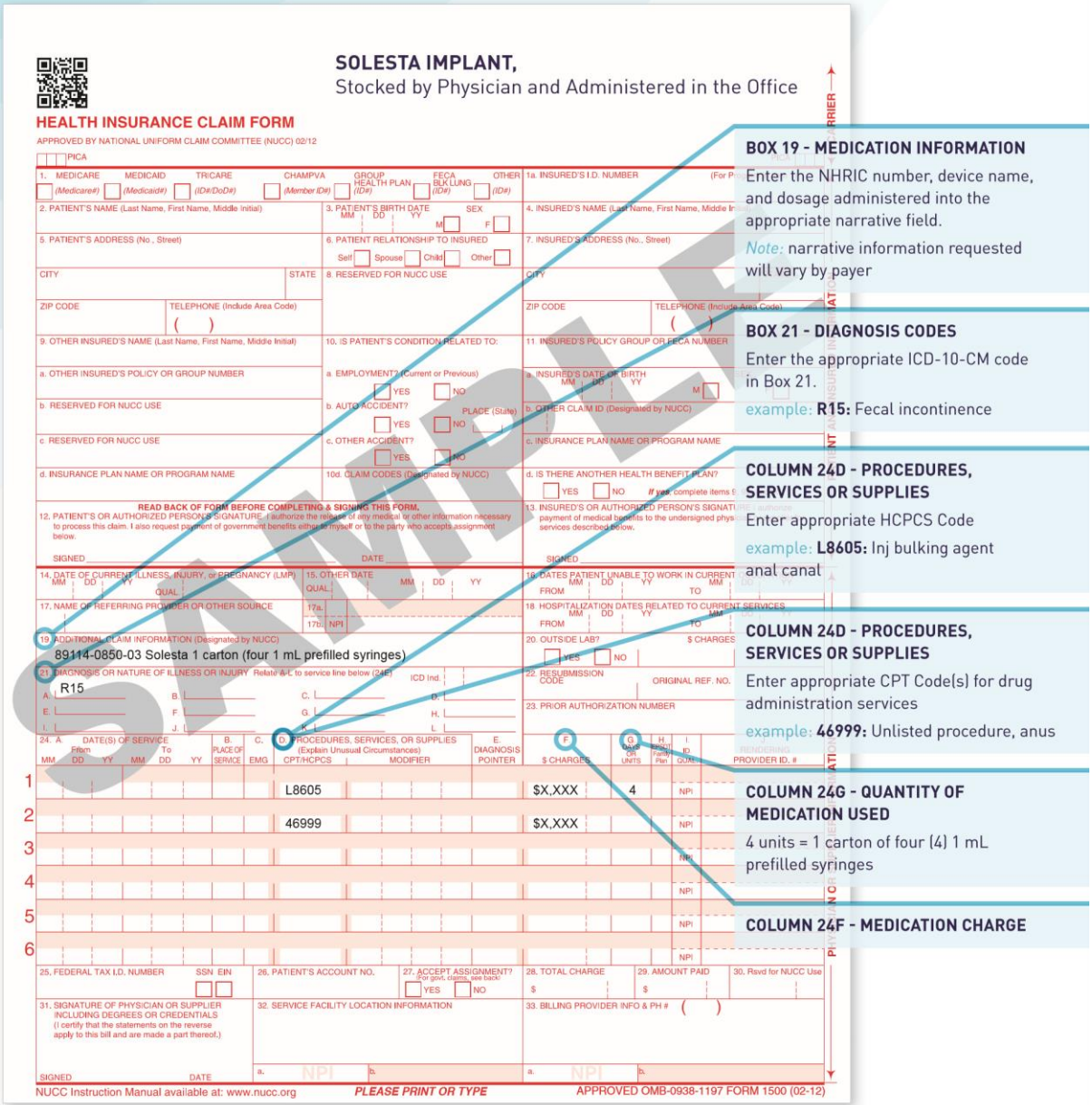
→ **Column 24G**	Indicate the quantity of medication administered Enter the number of units as "4" 4 units = 1 carton of four (4) 1 mL prefilled syringes

Palette LIFE SCIENCES

Solesta®

CODE FORM 1500

CODING AND BILLING INSTRUCTIONS FOR CMS 1500 FORM



BOX 19 - MEDICATION INFORMATION

Enter the NHRIC number, device name, and dosage administered into the appropriate narrative field.

Note: narrative information requested will vary by payer

BOX 21 - DIAGNOSIS CODES

Enter the appropriate ICD-10-CM code in Box 21.

example: **R15:** Fecal incontinence

COLUMN 24D - PROCEDURES, SERVICES OR SUPPLIES

Enter appropriate HCPCS Code

example: **L8605:** Inj bulking agent anal canal

COLUMN 24D - PROCEDURES, SERVICES OR SUPPLIES

Enter appropriate CPT Code(s) for drug administration services

example: **46999:** Unlisted procedure, anus

COLUMN 24G - QUANTITY OF MEDICATION USED

4 units = 1 carton of four (4) 1 mL prefilled syringes

COLUMN 24F - MEDICATION CHARGE

For product information, adverse event reports, and product complaint reports, contact:
Palette Life Sciences – Medical Information Department Tel: 844.350.9656 Fax: 510.595.8183 Email: palettemci@dlss.com

Palette LIFE SCIENCES

IX. References

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