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ORIGINAL CONTRIBUTION

Efficacy and Safety of a Nonanimal Stabilized Hyaluronic Acid/Dextranomer in Improving Fecal Incontinence: A Prospective, Single-Arm, Multicenter, Clinical Study With 36-Month Follow-up

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BACKGROUND: Fecal incontinence affects 7% to 12% of the US adult population, causing social, financial, and quality of life burdens.

OBJECTIVE: The primary aim of this study was to evaluate the efficacy and safety of nonanimal stabilized hyaluronic acid/dextranomer through 36 months as a condition of postmarket approval application.

DESIGN: This was a prospective, single-arm, multicenter, observational Food and Drug Administration–mandated postapproval clinical study.

SETTINGS: This study was designed and executed by participating centers in 18 hospitals and colorectal health clinics in coordination with the Food and Drug Administration and the study sponsor.

PATIENTS: A total of 283 subjects who previously failed conservative therapy were enrolled across 18 US sites.

INTERVENTIONS: Participants received 1 to 2 nonanimal stabilized hyaluronic acid/dextranomer treatments. The first treatment occurred within 30 days of baseline, and a second treatment was administered 1 to 3 months

Funding/Support: This Food and Drug Administration (FDA)–required postapproval study was sponsored by Salix Pharmaceuticals (Bridgewater Township, NJ) at the time of patient study enrollment and development and distributed the product to the study sites. Following the completion of the data capture, Palette Life Sciences, Inc (Stockholm, Sweden), purchased the rights to the product, assumed the role as the current sponsor, and completed the FDA commitment. Palette Life Sciences funded M-Squared Associates (New York, NY), a clinical research organization and consultancy, to complete all statistical and data analyses. Palette Life Sciences provided funding to Boston Healthcare Associates (Boston, MA), a global health care research and consulting firm, to develop the analysis plan for the analysis and interpretation of the quality of life data collected in the postmarketing study, which was submitted to the FDA as part of the postmarketing study commitment. The coauthors from Boston Healthcare did not receive any direct payment from Palette Life Sciences, the sponsor. Each author participated in the preparation of the manuscript per International Council of Medical Journal Editors guidelines.

Financial Disclosure: M-Squared Associates provided statistical support. Boston Healthcare Associates provided quality of life data analysis, abstract, and presentation support. Cook Cellebrate and Renovia were responsible for research grants for Dr Quiroz's institution. Boston Healthcare Associates received research funding from Palette Life Sciences. Dr Quiroz receives royalties from UpToDate. Dr Quiroz is a consultant for BK Medical. Dr Quiroz, Dr da Silva, and Dr Galliano were investigators for the Solesta postapproval trial but did not receive additional payments or support for the submitted work.

Poster presented at the virtual meeting of PFD (Pelvic Floor Disorders) Week, October 8 to October 10, 2020. Published in abstract form in Female Pelvic Med Reconstr Surg;26(10S):S43-S44.

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Dis Colon Rectum 2023; 66: 278–287
DOI: 10.1097/DCR.0000000000002348

after initial treatment if determined necessary by the physician. Subjects were followed through 7 visits over 36 months after last treatment.

MAIN OUTCOME MEASURES: Efficacy (as specified by the Food and Drug Administration) was measured as a fecal incontinence reintervention rate of <50% at 36 months. Reintervention included nonanimal stabilized hyaluronic acid/dextranomer re-treatment, surgical interventions, and physical therapy. Safety was measured by device-related adverse events. Secondary end points included Fecal Incontinence Quality of Life Scale and Cleveland Clinic Florida Fecal Incontinence Score.

RESULTS: Using a Bayesian estimate, the reintervention rate of the intention-to-treat population (n = 283) was 18.9% (95% CI, 14.0–24.4) at 36 months. At 36 months, the reintervention rate for subjects with complete data (n = 192) was 20.8% (95% CI, 15.1–26.6). Significant improvement ($p < 0.0001$) was noted across the Cleveland Clinic Florida Fecal Incontinence Score and Fecal Incontinence Quality of Life subscales at 36 months. Ninety-two device-related adverse events were reported by 15.2% of enrolled patients; most were GI disorders and resolved quickly. There were no serious adverse events.

LIMITATIONS: Limitations of the study included a 32% attrition rate and homogeneous patient population (91.8% white; 85.5% female), possibly limiting generalizability.

CONCLUSIONS: Nonanimal stabilized hyaluronic acid/dextranomer demonstrated clinically significant, sustained improvement in symptoms and quality of life for fecal incontinence patients without the occurrence of any serious adverse events. See **Video Abstract** at http://links.lww.com/DCR/B890.

REGISTRATION: ClinicalTrials.gov; Unique identifier: NCT01647906.

EFICACIA Y SEGURIDAD DE UN ÁCIDO HIALURÓNICO/ DEXTRANÓMERO ESTABILIZADO DE ORÍGEN NO ANIMAL PARA MEJORAR LA INCONTINENCIA FECAL: UN ESTUDIO CLÍNICO PROSPECTIVO, MULTICÉNTRICO Y DE UN SOLO BRAZO CON SEGUIMIENTO DE 36 MESES

ANTECEDENTES: La incontinencia fecal afecta entre el 7 y el 12% de la población adulta de los EE. UU. Y genera cargas sociales, económicas y de calidad de vida.

OBJETIVO: Los objetivos principales de este estudio fueron evaluar la eficacia y seguridad del ácido hialurónico/ dextranómero estabilizado de origen no animal durante 36 meses como condición para la solicitud de aprobación posterior a la comercialización.

DISEÑO: Este fue un estudio clínico prospectivo, observacional, de un solo brazo, multicéntrico, ordenado por la FDA después de la aprobación.

AJUSTES: Este estudio fue diseñado por los investigadores participantes, la FDA y el patrocinador del estudio que gestionó la recopilación de datos.

PACIENTES: Un total de 283 sujetos en quienes previamente falló la terapia conservadora se inscribieron en el estudio prospectivo de un solo brazo en 18 sedes de EE. UU. (NCT01647906).

INTERVENCIONES: Los participantes recibieron 1-2 tratamientos con ácido hialurónico/ dextranómero estabilizado no animal. El primer tratamiento se dio dentro de los 30 días posteriores al inicio, mientras que un segundo tratamiento se administró 1-3 meses después del tratamiento inicial si el médico lo determinaba necesario. Los sujetos fueron seguidos durante 7 visitas durante 36 meses después del último tratamiento.

PRINCIPALES MEDIDAS DE RESULTADO: La eficacia (según especificado por la FDA) se midió como una tasa de reintervención de incontinencia fecal de <50% a los 36 meses. La reintervención incluyó retratamiento con ácido hialurónico/ dextranómero estabilizado no animal, intervenciones quirúrgicas y fisioterapia. La seguridad se midió mediante los eventos adversos relacionados con tratamiento. Los criterios de valoración secundarios incluyeron la escala de calidad de vida de incontinencia fecal y la puntuación de incontinencia fecal de Cleveland Clinic Florida.

RESULTADOS: Utilizando una estimación bayesiana, la tasa de reintervención de la población por intención de tratar (n = 283) fue del 18.9% (IC del 95%: 14.0%, 24.4%) a los 36 meses. A los 36 meses, la tasa de reintervención para los sujetos con datos completos (n = 192) fue del 20.8% (IC del 95%: 15.1%, 26.6%). Se observó una mejora significativa (p <0.0001) en las subescalas de la puntuación de incontinencia fecal de la Cleveland Clinic Florida y de la calidad de vida de la incontinencia fecal a los 36 meses. El 15.2% de los pacientes inscritos informaron 92 eventos adversos relacionados con el tratmiento; la mayoría eran trastornos gastrointestinales y se resolvieron rápidamente. No hubo eventos adversos graves.

LIMITACIONES: Las limitaciones incluyen una tasa de deserción del 32% y una población de pacientes homogénea (91.8% blancos, 85.5% mujeres), lo que posiblemente limite la generalización.

CONCLUSIÓNES: El ácido hialurónico/ dextranómero estabilizado de origen no animal demostró una mejora sostenida y clínicamente significativa de los síntomas y la calidad de vida de los pacientes con incontinencia fecal, sin que se produjeran efectos adversos graves. Consulte el **Video Resumen** en http://links.lww.com/DCR/B890. (*Traducción—Dr. Jorge Silva Velazco*)

Registro: ClinicalTrials.gov número NCT01647906

KEY WORDS: Bulking agent; Fecal incontinence; Nonanimal stabilized hyaluronic acid/dextranomer; Quality of life; Solesta; Treatment efficacy.

Fecal incontinence (FI) is characterized by the inability to control bowel movements, leading to the involuntary passage of feces. Although some patients with FI experience abnormal gas or fecal leakage, others experience more severe disease characterized by involuntary defecation.[1]

The prevalence of FI ranges from 7% to 12% and increases with age; approximately 16% of adults older than 70 years report FI compared to 3% between ages 20 and 29, suggesting that the physiologic changes and common comorbidities associated with aging are also associated with FI.[2–4] Because the proportion of adults aged ≥65 years is projected to increase across Africa, Asia, Latin America, Europe, and the United States by 2050, the prevalence of FI is likely to rise.[3,5]

The inability to control bowel movements creates social and financial challenges, leading to lower quality of life (QoL), and affects individuals' ability to maintain a consistent work schedule.[6–9] The rising prevalence of FI and the associated decline in patients' QoL underscore the need for effective treatments.

Although guidelines recommend conservative treatment as a first-line therapy for FI, conservative treatment limitations are recognized.[10–13] The American Gastroenterological Association indicates that most patients will not report symptom improvement following conservative treatments including dietary, bowel management programs, pharmacological intervention, and biofeedback therapy.[10] The Agency for Healthcare Research and Quality provides a weak recommendation for dietary management.[11] Surgical interventions, including sacral neuromodulation (SNM), are available to patients who do not respond to conservative treatment. However, surgical intervention carries a higher risk of complications. SNM is associated with failure rates ranging from 19% to 41%, with higher reoperation rates reported in patients with longer follow-up.[14]

Nonanimal stabilized hyaluronic acid/dextranomer (NASHA/Dx; Solesta, Palette Life Sciences (Palette), Stockholm, Sweden) is a bulking agent approved by the US Food and Drug Administration (FDA). It is the only FDA-approved bulking agent for the treatment of FI and offers patients a minimally invasive treatment option. The safety and efficacy of NASHA/Dx were evaluated in a registered multicenter randomized controlled trial (RCT) for FDA approval. A significant increase in the number of incontinence-free days was seen with NASHA/Dx versus sham treatment at 6 months ($p = 0.02$); however, the decrease in number of FI episodes was not significant ($p = 0.09$).[15]

The present prospective, single-arm study was conducted to meet FDA NASHA/Dx postmarket approval order requirements to confirm long-term results from the RCT. The primary aim was to determine treatment efficacy measured by FI reintervention rate at 36 months.

MATERIALS AND METHODS

Study Design

This multicenter, open-label, single-arm prospective study was conducted using a standardized protocol across 18 US sites (https://www.clinicaltrials.gov; NCT01647906). The protocol was approved by the institutional review board at each participating center using the Declaration of Helsinki guidelines for good clinical trial practice, and participants provided written informed consent. Baseline measurements were recorded during the initial visit. Patients received a NASHA/Dx intervention at visit 2 (within 3 months of baseline); select patients received a second NASHA/Dx intervention at visit 3a, per physician discretion. The study product was administered in a real-world, outpatient setting without anesthesia following an enema to ensure evacuation of the anorectum. NASHA/Dx was injected into the deep submucosal layer in the proximal part of the high-pressure zone of the anal canal approximately 5 mm above the dentate line. Four submucosal injections of 1 mL NASHA/Dx were administered at each treatment session. Approximately 3 months later, patients were evaluated at visit 3a to determine the need for repeat NASHA/Dx treatment if response to the first was deemed inadequate by the treating physician. Patients who received a second NASHA/Dx intervention attended an extra follow-up visit 3 months later at visit 3b. Visits 4 to 7 occurred 6, 12, 24, and 36 months after the last NASHA/Dx intervention, respectively. Subjects were followed for 36 months after NASHA/Dx intervention at visit 2 (or visit 3a, if an additional intervention injection was given).

Eligible patients were ≥18 years old, spoke English, and underwent previous conservative FI treatment that had failed. Primary exclusion criteria included pregnancy, active irritable bowel syndrome, or surgical FI intervention within 12 months before enrollment. Baseline demographic and clinical information, including parity and cause of FI, was collected via self-report.

Role of Funding Source

This study was designed by participating investigators, the FDA, and the study sponsor, Salix Pharmaceuticals, who managed the data collection. Palette acquired NASHA/Dx and data from the completed study in 2018, supported data analysis, prepared and filed the FDA postapproval study report, and supported manuscript development. M-Squared is a consultancy that received funding from Palette to perform independent statistical analysis and verify study results. Boston Healthcare Associates, a consulting firm with expertise in health outcomes research,

including QoL research, received funding from Palette to independently develop the QoL data analysis plan and draft the associated manuscript. All third-party work was based on the statistical analysis plan approved a priori, and all results were accepted by the FDA as part of the post-marketing study (PMS) requirement.

Study End Points

Study end points and statistical methods were negotiated with and authorized by the FDA as part of a PMS design for NASHA/Dx injection. When Palette acquired NASHA/Dx, they also assumed the responsibility to analyze and submit the associated study data as part of the PMS commitment. Neither Palette and Boston Healthcare Associates nor M-Squared had direct input on the protocol end points. The primary end point was to determine whether the rate of reintervention for FI after NASHA/Dx intervention was <50% at 36 months. Initial intervention allowed for up to 2 NASHA/Dx injections: one at visit 2 and a second injection at visit 3a per physician discretion. Any other NASHA/Dx injections were considered reintervention, as were any of the following treatments: sphincteroplasties, implantations of artificial bowel sphincter, graciloplasties, SNM, other surgical interventions, or physical therapy.

Secondary end points included patient-reported global assessment of perceived improvement relative to pretreatment, measured at 36 months (measured via Global Perceived Effect [GPE] Score, a subjective score ranging from "significantly relieved" [a score of 1] to "significantly worse" [a score of 7]); QoL, measured by the Fecal Incontinence Quality of Life (FIQL) Scale, a 29-item validated scale where higher scores indicate better QoL; and symptom severity, measured by the Cleveland Clinic Florida Fecal Incontinence Score (CCFIS), a validated 5-parameter scale, where each parameter ranges from 0 to 4 and higher scores indicate higher symptom burden.[16] Improvements in symptoms and QoL were assessed at baseline and 36 months to assess durability of NASHA/Dx efficacy and to provide additional NASHA/Dx clinical evidence.[17] In addition to these prespecified analyses, exploratory subgroup analyses were conducted to assess whether statistically relevant differences in results were observed based on baseline characteristics.

Device-related adverse events (DAEs) were recorded by treating physicians using a MedDRA, version 15.0 or later, coding dictionary. DAEs were considered injection related if they occurred ≤2 days post-injection, peri-injection if they occurred >2 days but ≤2 weeks postinjection, and long term if they occurred >2 weeks postinjection.

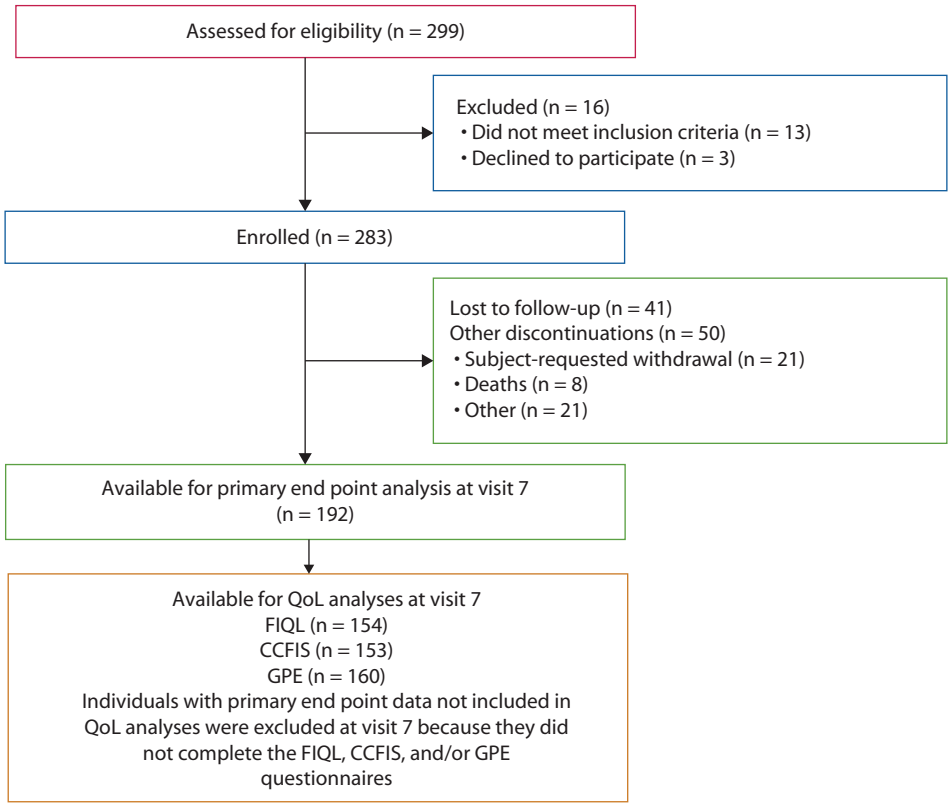

FIGURE 1. Summary of subject enrollment. CCFIS = Cleveland Clinic Florida Fecal Incontinence Score; FIQL = Fecal Incontinence Quality of Life Scale; GPE = global perceived effect; QoL = quality of life.

TABLE 1. Demographic and baseline characteristics

Variable	*ITT*
Age at first Solesta treatment, mean (SD) (N = 283)	64.6 (12.99)
Sex, n (%) (N = 283)	
Female	242 (85.5)
Male	41 (14.5)
Age group, n (%) (N = 283)	
<65 y	129 (45.6)
≥65 y	154 (54.4)
BMI (kg/m^2), mean (SD) (N = 279)	27.6 (8.03)
Ethnicity, n (%) (N = 283)	
Hispanic or Latino	15 (5.3)
Not Hispanic or Latino	268 (94.7)
Race, n (%) (N = 282)	
American Indian or Alaskan	3 (1.1)
Asian	4 (1.4)
Black	16 (5.7)
White	259 (91.8)
Diabetes, n (%) (N = 283)	
Yes	26 (9.2)
No	257 (90.8)
High blood pressure, n (%) (N = 283)	
Yes	176 (62.2)
No	107 (37.8)
Prior biofeedback therapy, n (%) (N = 283)	
Yes	163 (57.6)
No	120 (42.4)
Urinary incontinence, n (%) (N = 283)	
Yes	114 (40.3)
No	169 (59.7)
No. of NASHA/Dx treatments (N = 283)	
1	66 (23.3)
>1	217 (76.7)
FI duration, n (%) (N = 283)	
<12 mo	21 (7.4)
12 mo to 5 y	135 (47.7)
>5 y	127 (44.9)
Cause, n (%) (N = 283)	
Obstetric	154 (54.4)
Other	129 (45.6)
CCFIS liquid stool leakage, n (%) (N = 281)	
Never	20 (7.1)
Rarely	14 (5.0)
Sometimes	60 (21.4)
Usually	110 (39.1)
Always	77 (27.4)
CCFIS solid stool leakage, n (%) (N = 281)	
Never	28 (10.0)
Rarely	22 (7.8)
Sometimes	54 (19.2)
Usually	107 (38.1)
Always	70 (24.9)
CCFIS, mean (SD) (N = 281)	13.5 (3.52)
FIQL total score, mean (SD) (N = 281)	2.3 (0.67)
Lifestyle, mean (SD) (N = 283)	2.6 (0.85)
Coping/behavior, mean (SD) (N = 283)	1.9 (0.71)
Depression/self-perception, mean (SD) (N = 281)	2.6 (0.75)
Embarrassment, mean (SD) (N = 281)	1.9 (0.73)

CCFIS = Cleveland Clinic Florida Fecal Incontinence Score; FI = fecal incontinence; FIQL = Fecal Incontinence Quality of Life Scale; ITT = intention-to-treat; NASHA/Dx = nonanimal stabilized hyaluronic acid/dextranomer.

DAEs were categorized as serious or nonserious, where serious adverse events were events that led to death or a serious deterioration in patient health.

Statistical Analysis

Based on an exact binomial test ($\alpha = 0.05$), it was determined that 150 subjects would provide ≥80% power to determine whether the FI reintervention rate was below 50%, if the observed FI reintervention rate at 3 years is 39.5% or less. Primary statistical analysis was calculated via Bayesian imputation with a uniform prior distribution to estimate whether reintervention would have been required in patients withdrawn, lost to follow-up, or with missing data at 36 months. A frequentist calculation was also performed among patients with 36-month primary end point data. A tipping point analysis was conducted to determine the number of subjects with missing data that would need to have had an FI reintervention for the end point objective to exceed 50%.

All analyses were conducted using SAS, version 9.4, using $\alpha = 0.05$. Unless otherwise stated, statistical significance for continuous variables was assessed using a 2-sided unpaired Student *t* test. A χ^2 test was used for categorical variables.

RESULTS

Patient Population

A total of 283 patients were enrolled and received either 1 (23.3%; 66 subjects) or 2 (76.7%; 217 subjects) NASHA/Dx treatments at visits 2 to 3a. Enrollment began in May 2012; last follow-up was completed by June 2019. The number of FI reinterventions were similar across the 18 study sites, ranging from 1 to 5 patients.

The number of individuals who had complete results at 36 months ranged from 153 to 192 patients across end points due to loss to follow-up and other discontinuations (Fig. 1). Therefore, different subsets of the intention-to-treat (ITT) population were assessed for efficacy results:

Reintervention population (n = 192)
CCFIS population (n = 153)
FIQL population (n = 154)
GPE population (n = 160)

Demographic and baseline characteristics of the ITT population are reported in Table 1. Individuals with 36-month reintervention data available had significantly higher scores across select FIQL measures at baseline and had a significantly different makeup than those with Latino ethnicity but were otherwise similar (Table 2).

Efficacy Results

Within the reintervention population (n = 192), 152 subjects did not require reintervention at 36 months

TABLE 2. Demographic and baseline characteristics across individuals with complete end point data at 36 months

Variable	*Reintervention completers (reintervention population)*	*Reintervention noncompleters*	*p*
Age at first Solesta treatment, y, mean (SD)	64.7 (12.79), N = 192	64.3 (13.47), N = 91	0.80
Sex, n (%)	N = 192	N = 91	0.95
Female	164 (85.4)	78 (85.7)	
Male	28 (14.6)	13 (14.3)	
Age group, n (%)	N = 192	N = 91	0.37
<65 y	84 (43.8)	45 (49.5)	
≥65 y	108 (56.3)	46 (50.5)	
BMI (kg/m^2), mean (SD)	27.7 (8.32), N = 189	28.0 (6.32), N = 90	0.78
Ethnicity, n (%)	N = 192	N = 91	0.003
Hispanic or Latino	5 (2.6)	10 (11.0)	
Not Hispanic or Latino	187 (97.4)	81 (89.0)	
Race, n (%)	N = 192	N = 90	0.83
American Indian or Alaska Native	2 (1.0)	1 (1.1)	
Asian	2 (1.0)	2 (2.2)	
Black	10 (5.2)	6 (6.7)	
White	178 (92.7)	81 (90.0)	
Diabetes, n (%)	N = 192	N = 91	0.55
Yes	19 (9.9)	7 (7.7)	
No	173 (90.1)	84 (92.3)	
High blood pressure, n (%)	N = 192	N = 91	0.25
Yes	115 (59.9)	61 (67.0)	
No	77 (40.1)	30 (33.0)	
Prior biofeedback therapy, n (%)	N = 192	N = 91	0.38
Yes	114 (59.4)	49 (53.8)	
No	78 (40.6)	42 (46.2)	
Urinary incontinence, n (%)	N = 192	N = 91	0.73
Yes	76 (39.6)	38 (41.8)	
No	116 (60.4)	53 (58.2)	
No. of NASHA/Dx treatments, n (%)	N = 192	N = 91	0.08
1	39 (20.3)	27 (29.7)	
2	153 (79.7)	64 (70.3)	
FI duration, n (%)	N = 192	N = 91	0.07
<12 mo	18 (9.4)	3 (3.3)	
12 mo to 5 y	95 (49.5)	40 (44.0)	
>5 y	79 (41.1%)	48 (52.7%)	
Cause, n (%)	N = 192	N = 91	0.53
Obstetric	102 (53.1)	52 (57.1)	
Other	90 (46.9)	39 (42.9)	
CCFIS liquid stool leakage, n (%)	N = 190	N = 91	0.91
Never	13 (6.8)	7 (7.7)	
Rarely	10 (5.3)	4 (4.4)	
Sometimes	42 (22.1)	18 (19.8)	
Usually	76 (40.0)	34 (37.4)	
Always	49 (25.8)	28 (30.8)	
CCFIS solid stool leakage, n (%)	N = 190	N = 91	0.21
Never	20 (10.5)	8 (8.8)	
Rarely	15 (7.9)	7 (7.7)	
Sometimes	43 (22.6)	11 (12.1)	
Usually	70 (36.8)	37 (40.7)	
Always	42 (22.1)	28 (30.8)	
CCFIS, mean (SD)	13.3 (3.42), N = 192	13.9 (3.70), N = 91	0.20
FIQL total score, mean (SD)	2.4 (0.66), N = 191	2.2 (0.67), N = 90	0.013
Lifestyle, mean (SD)	2.7 (0.83), N = 192	2.5 (0.89), N = 91	0.03
Coping/behavior, mean (SD)	2.0 (0.70), N = 192	1.8 (0.71), N = 91	0.01
Depression/self-perception, mean (SD)	2.7 (0.75), N = 191	2.5 (0.73), N = 90	0.07
Embarrassment, mean (SD)	1.9 (0.72), N = 191	1.7 (0.75), N = 90	0.051

CCFIS = Cleveland Clinic Florida Fecal Incontinence Score; FI = fecal incontinence; FIQL = Fecal Incontinence Quality of Life Scale; NASHA/Dx = nonanimal stabilized hyaluronic acid/dextranomer.

TABLE 3. Fecal incontinence reintervention rate: frequentist estimation

Population characteristics	*Frequentist estimation: rate of reintervention*	*One-proportion Z test (95% CI)*	*p*
Reintervention population (n = 192)	20.8%	(15.1%–26.6%)	
Age, y			
<65 (n = 84)	21.4%	(12.7%–30.2%)	
≥65 (n = 108)	20.4%	(12.8%–28.0%)	
Sex			0.67
Male (n = 28)	17.9%	(3.7%–32.0%)	
Female (n = 164)	21.3%	(15.1%–27.6%)	
Cause			0.53
Obstetric trauma (n = 102)	22.5%	(14.4%–30.7%)	
Other than obstetric (n = 90)	18.9%	(10.8%–27.0%)	
No prior biofeedback therapy			0.53
Yes (n = 114)	19.3%	(12.1%–26.5%)	
No (n = 78)	23.1%	(13.7%–32.4%)	
No. of treatments			0.17
1 (n = 39)	12.8%	(2.3%–23.3%)	
>1 (n = 153)	22.9%	(16.2%–29.5%)	

(reintervention rate, 20.8% [95% CI, 15.1–26.6]), well below the predefined success rate of <50% (Table 3). A total of 51 FI reinterventions were reported across 40 subjects, including 29 SNM or SNM revision treatments, 8 additional NASHA/Dx treatments, 9 physical therapy treatments, 3 colostomies, 1 magnetic sphincter stimulation, and 1 vaginal insert system. Reintervention rate did not differ by sex, age, cause, prior biofeedback therapy, or number of NASHA/Dx treatments.

When Bayesian imputation was used to estimate reintervention rates for the entire ITT population (n = 283) through imputation of data for individuals with visit 7 data missing, reintervention rate remained well below the 50% cutoff (18.9% [95% CI, 14.0–24.4]; Table 4). A tipping point analysis, which imputed all missing data as reinterventions, was conducted as a sensitivity analysis to determine how many of the patients with an unknown status would have to have received a reintervention before the primary effectiveness end point finding of success would "tip" to failure. The study would fail when at least 85 of 91 (93.4%) patients with an unknown status are imputed as reinterventions; these results show the improbability that the missing data would have changed the study conclusion.

CCFIS and FIQL scores improved between baseline and visit 7 (36 months; $p < 0.0001$; Table 5). Mean FIQL and mean CCFIS scores at visit 7 significantly improved from baseline (95% CI; Table 6). FIQL results showed improvements in all 4 subscales ($p < 0.0001$). The mean change from baseline in CCFIS was −4.0 (95% CI, −4.8 to −3.2), whereas the mean change from baseline in FIQL was 0.6 (95% CI, 0.5–0.7). Mean change in FIQL and CCFIS did not differ by age, cause, or number of NASHA/Dx treatments. Individuals with prior biofeedback had greater

TABLE 4. Fecal incontinence reintervention rate: Bayesian imputation

Population characteristics	*Bayesian estimation: rate of reintervention*	*95% CI*
ITT population (n = 283)	18.9%	14.0%–24.4%
Age, y		
<65 (n = 127)	19.8%	12.4%–28.3%
≥65 (n = 156)	18.7%	12.3%–26.2%
Sex		
Male (n = 41)	17.4%	6.8%–31.6%
Female (n = 242)	19.5%	14.1%–25.6%
Cause		
Obstetric trauma (n = 41)	20.5%	13.7%–28.4%
Other than obstetric (n = 242)	17.7%	10.9%–25.7%
No prior biofeedback therapy		
Male (n = 163)	18.0%	11.8%–25.2%
Female (n = 120)	20.9%	13.1%–30.0%
No. of treatments		
1 (n = 66)	12.0%	4.6%–22.6%
>1 (n = 217)	21.0%	15.2%–27.6%

ITT = intention to treat.

TABLE 5. Change in FIQL and CCFIS scores from baseline to visit 7

Population characteristics	Total FIQL, mean (95% CI)	FIQL subscales				Total CCFIS, mean (95% CI)
		Lifestyle, mean (95% CI)	Coping/behavior, mean (95% CI)	Depression/self-perception, mean (95% CI)	Embarrassment, mean (95% CI)	
FIQL/CCFIS population (n = 154)[a]	0.6 (0.5 to 0.7)	0.5 (0.4 to 0.6)	0.7 (0.6 to 0.9)	0.4 (0.2 to 0.5)	0.8 (0.6 to 0.9)	−4.0 (−4.8 to −3.2)
Paired *t* test from baseline	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001	<0.0001
Age, y						
<65 (n = 129)	0.6 (0.4 to 0.8)	0.6 (0.4 to 0.7)	0.8 (0.6 to 0.9)	0.4 (0.2 to 0.5)	0.7 (0.5 to 1.0)	−4.0 (−5.1 to −2.8)
≥65 (n = 154)	0.5 (0.4 to 0.7)	0.4 (0.3 to 0.6)	0.7 (0.5 to 0.9)	0.3 (0.2 to 0.5)	0.8 (0.6 to 1.0)	−4.0 (−5.1 to −2.9)
Pooled *t* test	0.59	0.27	0.82	0.66	0.61	0.92
Sex						
Male (n = 41)	0.5 (0.2 to 0.8)	0.4 (0.1 to 0.8)	0.7 (0.6 to 0.9)	0.1 (−0.2 to 0.4)	0.9 (0.5 to 1.4)	−5.5 (−7.4 to −3.6)
Female (n = 242)	0.6 (0.5 to 0.7)	0.5 (0.4 to 0.6)	0.7 (0.3 to 1.1)	0.4 (0.3 to 0.5)	0.8 (0.6 to 0.9)	−3.7 (−4.6 to −2.8)
Pooled *t* test	0.59	0.75	0.77	0.07	0.46	0.10
Cause						
Obstetric trauma (n = 154)	0.6 (0.5 to 0.8)	0.6 (0.4 to 0.8)	0.8 (0.6 to 1.0)	0.4 (0.3 to 0.6)	0.8 (0.6 to 1.0)	−4.0 (−5.2 to −2.9)
Other than obstetric (n = 129)	0.5 (0.3 to 0.6)	0.4 (0.2 to 0.6)	0.6 (0.5 to 0.8)	0.3 (0.1 to 0.4)	0.8 (0.6 to 1.0)	−4.0 (−5.1 to −2.8)
Pooled *t* test	0.14	0.09	0.21	0.13	0.90	0.95
Prior biofeedback therapy						
Yes (n = 163)	0.7 (0.5 to 0.8)	0.6 (0.4 to 0.7)	0.8 (0.7 to 1.0)	0.5 (0.3 to 0.6)	0.9 (0.7 to 1.0)	−4.1 (−5.2 to −3.0)
No (n = 120)	0.4 (0.2 to 0.6)	0.3 (0.2 to 0.5)	0.6 (0.4 to 0.8)	0.2 (0.0 to 0.4)	0.7 (0.5 to 0.9)	−3.8 (−4.9 to −2.7)
Pooled *t* test	0.03	0.0498	0.047	0.03	0.27	0.71
No. of treatments						
1 (n = 66)	0.6 (0.3 to 0.8)	0.5 (0.2 to 0.8)	0.8 (0.5 to 1.1)	0.3 (0.1 to 0.5)	0.7 (0.2 to 1.1)	−3.9 (−5.9 to −1.9)
>1 (n = 217)	0.6 (0.4 to 0.7)	0.5 (0.4 to 0.6)	0.7 (0.6 to 0.9)	0.4 (0.2 to 0.5)	0.8 (0.7 to 1.0)	−4.0 (−4.9 to −3.2)
Pooled *t* test	0.93	0.85	0.65	0.71	0.53	0.90

CCFIS = Cleveland Clinic Florida Fecal Incontinence Score; FIQL = Fecal Incontinence Quality of Life Scale.
[a]n = 153.

improvements in FIQL subscales: lifestyle (p = 0.0498), coping/behavior (p = 0.047), depression/self-perception (p = 0.03), and total FIQL (p = 0.03) compared to individuals without prior biofeedback. GPE results indicate that 72.5% of patients experienced some degree of relief from FI at visit 7 (32.5% reported significant relief, 21.3% reported moderate relief, and 18.8% reported feeling a little bit relieved; Table 7).

Safety Results

Of the patients, 15.2% had 92 DAEs reported during the study; 31 individuals experienced mild, 13 experienced moderate, and 6 experienced severe DAEs. Most DAEs resolved quickly, no adverse events that were characterized by the study investigator as "severe" met the FDA-defined intensity criteria to be classified as serious, and no deaths were reported. The most common DAEs were reported as "gastrointestinal disorders" (57/92) and "general disorders and administration site conditions" (9/92). Most common GI-related DAEs include anorectal discomfort (13 events) and proctalgia (18 events; Table 8).

DISCUSSION

This study provides efficacy and safety information for use of NASHA/Dx in patients with FI through 36 months.

TABLE 6. Mean FIQL and CCFIS scores at baseline and visit 7

Population characteristics	Baseline, mean (95% CI); ITT population	Visit 7, mean (95% CI); CCFIS/FIQL population	Change in score p
CCFIS	13.5 (n = 281)	9.2 (n = 153)	<0.0001
FIQL scale 1: lifestyle	2.6 (n = 283)	3.2 (n = 154)	<0.0001
FIQL scale 2: coping/behavior	1.9 (n = 283)	2.7 (n = 154)	<0.0001
FIQL scale 3: depression/self-perception	2.6 (n = 281)	3.1 (n = 154)	<0.0001
FIQL scale 4: embarrassment	1.9 (n = 281)	2.7 (n = 154)	<0.0001

CCFIS = Cleveland Clinic Florida Fecal Incontinence Score; FIQL = Fecal Incontinence Quality of Life Scale; ITT = intention to treat.

TABLE 7. Patient perceived change in degree of FI at visit 7

GPE score	*n (% of GPE population), n = 160*
Significant relief (GPE 1)	52 (32.5)
Moderate relief (GPE 2)	34 (21.3)
A little relief (GPE 3)	30 (18.8)
No change (GPE 4)	32 (20.0)
A little worsening (GPE 5)	5 (3.1)
Moderate worsening (GPE 6)	3 (1.9)
Significant worsening (GPE 7)	4 (2.5)

GPE = global perceived effect; FI = fecal incontinence.

The Bayesian estimate of the 36-month reintervention rate among patients treated with NASHA/Dx (18.9% [95% CI, 14.0–24.4]) demonstrated success for the primary end point as it did not exceed the predetermined threshold of 50%. FIQL and CCFIS results showed sustained significant improvement during the 36-month follow-up period.

Current FI management guidelines recommend a stepwise approach, where bulking agents are the only minimally invasive option recommended between conservative and surgical treatments.[10–13] Given the mixed results of conservative treatments, many patients with FI will proceed to more invasive options.[10–13]

Before this study, the primary clinical data documenting NASHA/Dx efficacy were limited to results from the preapproval RCT where data from a 6-month comparison to placebo were inconclusive.[15] Although the RCT demonstrated significant improvements of FIQL score for coping and behavior (p = 0.002), CCFIS scores at 6 months did not differ between sham and treatment arms.[15] Continued improvement of CCFIS and all FIQL domain scores after 6 months in the prior RCT and significant score improvements through 36 months in the present study may suggest that narrowing of the anal canal via NASHA/Dx may take more than 6 months.[17] Individuals with prior biofeedback therapy in the present study reported significantly greater improvement in FIQL at 36 months. This contrasts results from the RCT, which indicated that individuals who did not receive prior biofeedback were significantly more likely to respond to NASHA/Dx compared to sham treatment (measured as a reduction in FI episodes by at least 50%) at 6 months.[18]

TABLE 8. Summary of device-related adverse events during 36 months

Time interval	*Type of adverse event*	*n (% of ITT population)*
No. of subjects with DAEs by type		
Injection	GI disorders[a]	24/283 (8.5)
	Other	9/283 (3.2)
Peri-injection	GI disorders[a]	17/283 (6.0)
	Other	9/283 (3.2)
Long term	GI disorders[a]	6/283 (2.1)
	Other	4/283 (1.4)
No. of subjects with serious vs nonserious device-related adverse events		
Nonserious adverse events		
Mild		31/283 (11.0)
Moderate		13/283 (4.6)
Severe		6/283 (2.1)
Serious adverse events		0 (0)
Deaths		0 (0)

DAE = device-related adverse event; ITT = intention to treat.
[a]Leading GI disorders were proctalgia (n = 18), anorectal discomfort (n = 13), and rectal hemorrhage (n = 8).

NASHA/Dx was well tolerated in this study, and DAEs were similar to those identified in the prior RCT, in which the most common adverse events were proctalgia (14.0%), pyrexia (8.1%), and rectal hemorrhage (6.6%).[15,17] In the present study, no patients experienced a serious adverse event, and there were no safety findings that differed from the established safety profile of NASHA/Dx. Neither rate of reintervention nor improvements in FIQL and CCFIS differed by age, sex, or FI cause, demonstrating efficacy across a range of populations.

Several limitations should be considered when interpreting these results. The primary end point of reintervention may not reflect the rate of treatment success, because patients may avoid invasive options even in situations where symptoms do not improve. GPE results may provide better insight into patients' perceptions; by this measure, 32.5% of patients reported "significant relief," 21.3% reported "moderate relief," and 18.8% reported "feeling a little bit relieved" after NASHA/Dx intervention. Generalizability may be limited because 91.8% of subjects were white and 85% were female and the cause of FI was self-reported by the participants.

The study experienced approximately 32% attrition by 36 months. However, sufficient follow-up data were obtained to maintain >80% statistical power. Furthermore, the tipping point analysis showed that at least 85 of 91 subjects without 36-month reintervention data would have been required to have a reintervention to change the study outcome. Individuals who had reintervention data available at 36 months had significantly better FIQL lifestyle (p = 0.03), coping/behavior (p = 0.01), and total scores at baseline compared to those without (p = 0.013); if patients with poorer baseline QoL exited the study due to lack of efficacy, these findings may overestimate effectiveness. Strengths of the present study include long follow-up duration and assessment of NASHA/Dx in a real-world setting. Because anesthesia was not required, results are expected to be generalizable to outpatient clinic settings.

CONCLUSION

This postapproval study supports prior safety and efficacy results demonstrated in the previous RCT for NASHA/Dx. The primary effectiveness end point of freedom from FI reintervention was met, indicating treatment success with NASHA/Dx. Results demonstrate sustained QoL

improvement through 36 months across a range of patient populations, irrespective of age, sex, or cause.

ACKNOWLEDGMENTS

Protocol summary available on https://www.clinicaltrials.gov. Complete protocol may be available on written request to Medical Affairs at Palette Life Sciences, Inc.

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