FINAL CLINICAL STUDY REPORT

DATE OF REPORT: Final Report completed on Jan/20/2014

PROTOCOL TITLE:	Renew Plug Loss User Study (PLUS) To Observe Anal Insert Loss With Urination
PROTOCOL NUMBER:	200CLD
WIRB STUDY/PROTOCOL NUMBER:	1106768 / 20090416 (Protocol Number)
SPONSOR:	RENEW MEDICAL, INC. 650 Live Oak Avenue Menlo Park, CA 94025 TELEPHONE: 1-888-987-2929
INVESTIGATIONAL PRODUCT:	RENEW INSERT
INVESTIGATOR:	MARK M. SEGALL, M.D.
STUDY SITES:	MARK M. SEGALL, M.D. 15195 NATIONAL AVENUE, SUITE 202 LOS GATOS, CA 95032 SAMARITAN ENDOSCOPY CENTER 15195 NATIONAL AVENUE, SUITE 204 LOS GATOS, CA 95032
MEDICAL MONITOR:	ALFRED L. HURWITZ, M.D.
GCP STATEMENT:	THIS STUDY WAS PERFORMED IN COMPLIANCE WITH THE PRINCIPLES OF GOOD CLINICAL PRACTICE GUIDELINES.

2. Signature Page

Signed: _____ Date: ____/____/_____

Print name: Victoria Mackinnon

Position: VP, Regulatory/Clinical and Quality Assurance

Address: Renew Medical, Inc.

Signed: _____ Date: ____/____/_____

Print name: MARK M. SEGALL, M.D.

Position: INVESTIGATOR

Address: 15195 NATIONAL AVENUE, SUITE 202
LOS GATOS, CA 95032

3. SYNPOSIS

SPONSOR: RENEW MEDICAL, INC.	TEST DEVICE (PRODUCT): Renew Insert
Title of Study	Renew Plug Loss User Study (PLUS): To Observe Anal Insert Loss With Urination (Previously called Enshur PLUS)
Renew Study ID	200CLD
WIRB Study / Protocol ID	1106768 / 20090416
Principal Investigator	Mark M. Segall, M.D.
Study Center (Primary)	15195 National Ave Los Gatos, CA 95032
Study Period	From: April 6, 2009 To: August 28, 2009
First Date Subject Enrolled	April 6, 2009
Last Date Subject Enrolled	July 20, 2009
Study Objective	To better understand the frequency of Renew Insert loss with urination.
Primary Endpoints	The study had 2 primary endpoints: 1. Frequency of Renew Insert loss with urination—to measure how frequently subjects experience anal Insert loss with urination 2. Safety—as measured by the absence of serious device-related adverse events
Secondary Endpoint	The study had 1 secondary endpoint: 1. Safety—no serious irritation of the anal canal or lower rectal mucosa as a result of near-continuous use of device during the study period
Indication for Use and Main Criteria for Inclusion	Subjects suffering from accidental bowel leakage due to bowel incontinence. Subject Inclusion criteria: Females ≥ 40 years old with minimum Wexner Fecal Incontinence Score of 12 and at least weekly (score of 3 or 4) leakage of at least 2 of the 3 Wexner scale stool types (solid, liquid and gas) for the last month prior to inclusion in the study.
Study Design	The study was a prospective, open label, single-arm, non-randomized study designed to evaluate the frequency of Renew Insert loss with urination in Subjects with Accidental Bowel Leakage (ABL) due to bowel incontinence (BI) at one study site. Upon Subject enrollment: subject history was collected and a digital rectal exam, anoscopy, and sigmoidoscopy were performed. For those subjects

	who have not had a colonoscopy in the prior 36 months, a colonoscopy (to rule out other conditions) was done. During study 3-week treatment period: Daily bowel movement and insert use were recorded in subject diaries; other clinical assessments were collected (e.g. use of anti-diarrheal medications, pads, enemas), as well as insert tolerability and satisfaction using visual analog scales. Upon study completion: Anoscopy to check condition of anal canal mucosa post-treatment.
Number of Subjects:	Planned: 15-20 Enrolled: 22 Safety Cohort: 22 Intent-to-Treat Cohort: 22 Modified ITT: 19
Test product and mode of administration	The Renew Insert (test product) is a single use anal insert composed of a soft silicone and a fingertip applicator designed for self-insertion by the subject. Two sizes were used in the study: medium (or regular) and large sizes.
Duration of Treatment	3 weeks

SUMMARY CONCLUSIONS

LOSS WITH URINATION RESULTS: A marginal proportion (10%) of the Inserts used during the study were lost with urination, the majority (73%) were expelled naturally with a bowel movement.

SAFETY RESULTS: No serious adverse events occurred during the trial.

SATISFACTION: Subjects reported high likability (average 5.2 out of 1-6 scale) and satisfaction (4.4 out of 1-5 scale) with the Insert. Insertion and daily use of the Insert were well tolerated (average score 9.1 out of 10 for overall insertion and average of 4.14 out of 5 for daily tolerance). The majority of subjects (94%) also reported that they would probably or definitely continue to use the device if given the opportunity.

CONCLUSION: The analysis of 22 subjects demonstrates that the Renew Insert is a safe, simple, and user-friendly device that can be easily inserted by the user. The frequency of device loss with urination was found to be minimal and does not present a concern.

NOTE: Upon the completion of the above study, the subjects in this study were offered the opportunity to continue using Renew Inserts under "Compassionate Use" program. Please see Appendix 20 for a summary of the Compassionate Use Program.

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CLINICAL STUDY REPORT

1. Introduction

Bowel incontinence ("BI"), also referred to as fecal incontinence by the medical community, can dramatically disrupt the lives of people who suffer from it. Very few benign medical situations cause as much embarrassment and impaired quality of life as the lack of control of bowel movements. Poor control of bowel movements can be a result of many conditions such as: congenital defects (such as imperforated anus), anorectal trauma, weakness of the pelvic floor muscles and nerve damage, or part of a systemic illness such as diabetes and scleroderma. However, one of the most common causes of bowel incontinence is pelvic floor weakness or anatomic damage due to obstetric trauma. During vaginal delivery, tears of the birth canal can damage the anterior portion of the circular anal sphincter muscles, which are located in the narrow septum between the anus/rectum and the vagina. In addition, pudendal nerves, which are involved in normal bowel evacuation, can be damaged in pregnancy and childbirth. Obstetric damage can remain asymptomatic for many years after childbirth due to compensation by other pelvic muscles.

It is estimated that up to 22% of woman above the age of 60 suffer from some degree of bowel incontinence (Bharucha, 2005). However, many believe that this estimation does not fully reflect true prevalence. Large portions of those suffering from bowel incontinence do not seek medical treatment, due to embarrassment or absence of knowledge of treatment options. In addition, some primary care physicians do not initiate discussions about bowel incontinence or are not fully aware of treatment modalities. Therefore, many subjects suffer this condition in silence and at great psychological expense (Norton, 2008; Kuehn, 2006).

A wide array of treatment options allows some degree of improvement in quality of life in those suffering from bowel incontinence. In mild cases, dietary changes and use of fiber supplements in combination with anti-diarrhea medications may improve quality of life. Retraining of the pelvic floor muscles, with or without biofeedback, is also a non-invasive treatment option. This is first line treatment for subjects with mild to moderate incontinence, and partially may improve control and quality of life in 65–89% of subjects. However, this treatment rarely restores continence fully without any on-going incidents of leakage (Ozturk, 2004).

Several more invasive treatment methods have been developed to treat ABL. Some interventional treatments are minimally invasive, such as the delivery of bulking agents into the sphincters that thicken the tissue around the anal canal. However, the results of injectable bulking agents suggest that although they may improve control, they rarely achieve full control and long term follow up shows gradual deterioration of any initial beneficial effect (Solesta® Package Insert, June 2011). Other approaches require surgical intervention, such as the implantation of active prosthetics around the anus or pacemakers on the sacral nerves roots such Medtronic's Interstim, (FDA approved in March 2011 ref. P080025). More invasive procedures for the treatment of incontinence, such as the implantation of prosthetic sphincters, involve major surgery, are associated with a significant risk of complications, and may not be suitable for high-risk subjects.

Globally, outside the United States, there are anal plugs available for subjects who suffer bowel incontinence. While these plugs have been proven safe and effective, they are generally not tolerable and not used widely (Duetekom, 2005). This is because the plugs are made of porous, semi-absorbent material, similar to tampons and their diameter is significantly larger than the diameter of an empty rectum or of the anal canal even at full relaxation. As a result, the pressure applied on the rectum and

anal canal walls causes a severe urge for immediate defecation. Over a third of subjects enrolled in the clinical trials for anal plugs withdrew from the studies before study completion (Deutekom, 2005).

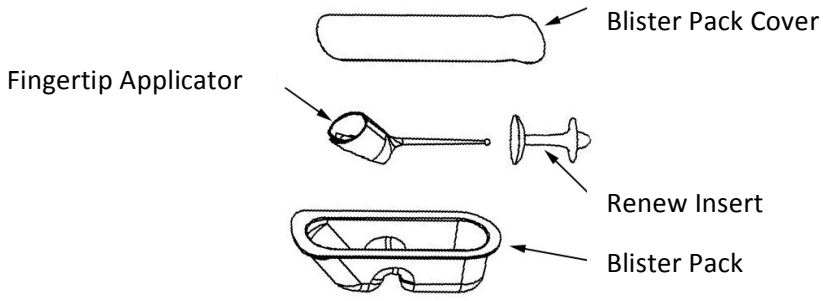
In the United States, there is also an FDA-cleared silicone bowel catheter device with a balloon cuff (ProCon2), that obstructs the lower rectum and prevents the loss of fecal material. This device is more complicated to use than an anal plug and must be manually inflated upon insertion, then deflated and removed prior to defecation. The catheter balloon is filled with 30 cc of water and may cause restricted blood flow to the surrounding capillaries, so its use beyond 8 hours is not recommended. Lastly, wearing it can also cause the constant urge to defecate.

Despite all of the options available to subjects suffering from bowel incontinence, there is general consensus that many subjects fail conservative treatments and/or do not receive long lasting control from more invasive treatments. Further, ongoing seepage of even small amounts of feces—solids and/or liquids—can cause a great deal of subject suffering. Even when this soiling is absorbed using a pad, it is frequently accompanied with odor, that causes considerable embarrassment. The continuous contact of the bowel substance with the skin around the anus can also cause infection, skin breakdown, incontinence dermatitis, itching, burning, and soreness of the perineum (Brunner et al, 2012). Many treated subjects continue to suffer the effects of bowel incontinence and there remains a large unmet clinical need for improved treatments for accidental bowel leakage (ABL) due to bowel incontinence.

2. **Device Description** - Renew Insert

The Renew Insert is a simple device intended for the management of accidental bowel leakage (ABL) due to bowel incontinence. The device is comprised of two main components: a soft silicone Insert and a plastic fingertip applicator. Both the applicator and Renew Insert are disposable, single use devices. The fingertip applicator and Renew Insert are non-sterile and preassembled in a sealed blister pack (see Figure 1). The standard box used in the study contained twenty blister packs with a copy of the Instructions for Use (IFU).

Figure 1: Components of the Renew Insert and Blister Pack



a. Principles of Operation

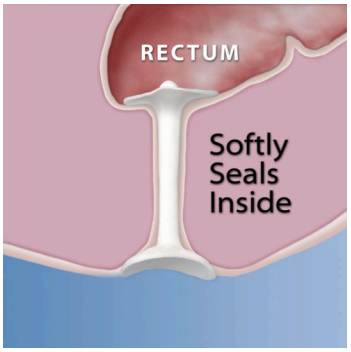
The Renew Insert is a simple-to-use device designed for self-insertion. The Renew Insert is inserted into the anus and anal canal with a motion similar to inserting a tampon.

The pre-assembled Renew Insert and applicator are removed from the blister pack, and the applicator (plus insert) is positioned on an index or middle finger (see Figure 2 for depiction).

Figure 2: Demonstration of how applicator and the Renew Insert are positioned on the fingertip for insertion.

Once properly positioned on the finger, the pre-lubricated Insert is then gently pushed into the anus until the fingertip applicator touches the entrance of the anus. Once the subject feels the fingertip applicator at the entrance to the anus, the subject gently withdraws their finger with the applicator, thus properly positioning the Renew Insert in the lower rectum and anal canal as shown in Figure 3 below.

Figure 3: Diagram of Insert in the Rectum



The bottom disk of the Renew Insert remains outside the anus to keep the device positioned in the anal canal. The fingertip applicator is discarded and the Renew Insert remains in position until it is evacuated naturally during the subject's next bowel movement. If subjects wanted to remove a Renew Insert at any time, the subjects were advised to pull on the Renew Insert's external bottom disc, positioned just outside the anus.

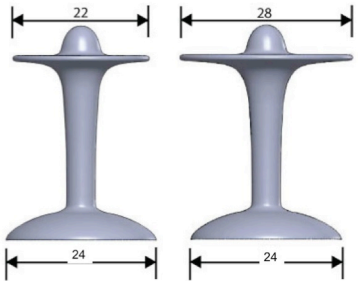
b. <u>Insert Design and Sizes</u>

The Renew Insert is designed as a stem with two disks: an upper disk that sits in the lower rectum and bottom disk that sits outside the anus. The insert was provided in two sizes: medium (also referred to as 'regular') and large (as depicted in Figure 4). The differences in size are primarily the diameter of the upper portion of the Renew Insert. The two sizes are designed to accommodate a variety of lower rectum anatomies.

The design of the insert changed slightly during the course study in three aspects: there was a slight reduction in the size of the upper disk's nose cone, the overall length of the inserts was reduced from approximately 40mm to 35-36mm and the diameter of the bottom disk in the large size was reduced by 2mm (from 26 to 24mm). The diameters of the top disks (for both sizes) did not change. The upper disc diameters of the Renew Insert are 22 and 28 mm and the external lower disc diameter were initially 24 and 26 mm and later changed to 24mm for both sizes. The length of the Renew Insert, regardless of size, is 40 mm.

The manufacturing lot numbers for the Inserts used in the study were 90211601, 9021611, 9021371 and 9021381.

Figure 4: Renew Insert Sizes (mm)

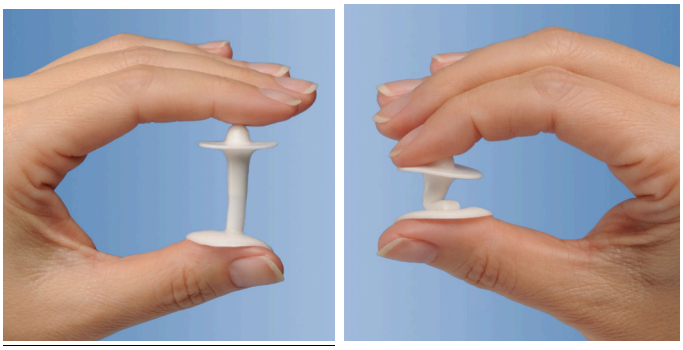


Medium **Large**

c. Materials:

The Insert is composed of a soft silicone that allows easy insertion and comfortable wear (see Figure 5 for demonstration of the Insert's pliability). The fingertip applicator of the Renew Insert is made of polycarbonate. A very small amount of glycerine lubricant inside the insert stem is included during manufacturing to facilitate smooth Insert release upon withdrawal of the applicator. This applicator is highly flexible and the insert top disk has a reinforced tip so as to prevent damage upon insertion in the anal canal.

Figure 5 - Demonstration of the softness and deformability of the Renew Insert



3. Ethics

This study was performed at a single site in Los Gatos, California. The study and participating site received approval from an Ethical Committee to conduct the study (Western Institutional Review Board – WIRB

Submission Number W830377311 and protocol #20090416). Informed consent was obtained from all subjects prior to using the Insert.

4. Study Objectives

The subjects were monitored regarding their Insert use and the safety of the Renew Inserts throughout the 3-week study period.

The primary objective of this study was to better understand the frequency of Renew Insert loss (or expulsion) with urination. Data on the loss of the Insert with gas and anticipated expulsion with bowel movements was also collected.

There were two safety endpoints: 1) the primary safety endpoint was the absence of any serious device related adverse event; and 2) the absence of any serious irritation of the anal canal or lower rectal mucosa due to near-continuous use of device during the study period. This was assessed via pre and post anal canal and lower rectal mucosa evaluations.

In addition, data was gathered and analyzed on usability, insert tolerability, likeability and preference over pad use.

Upon conclusion of the formal trial, the subjects were allowed to continue using the Renew Inserts under a compassionate use program. Please see Appendix 20 for a summary of this program.

5. Study Design

Once subjects were enrolled in the study, they were trained by a study nurse under the supervision of the principal investigator (PI) on how to use the Renew Insert device using the Instructions for Use (IFU). Following subject training, subjects began a 3-week treatment period using the Renew Insert device. The devices were self-administered and subjects were instructed to replace the inserts each time the inserts were removed or expelled, such that the inserts were worn continuously throughout the 3-week user study period.

Daily subject diary recordings were maintained throughout the study period. The daily subject diaries captured all bowel movement activity, and recorded when and how each Renew Insert was self-inserted and expelled.

Throughout the study, subjects visited the study site weekly for follow-up visits. At these weekly visits, the study nurse reviewed the subject's diary recordings from the previous week and interviewed the subject concerning their Insert use and tolerability, and distributed whatever study materials (diaries, Renew Inserts, etc.) were needed for the next week.

The study nurse maintained a weekly visit schedule with each subject throughout the duration of the study. In addition, the nurse telephoned the subjects twice a week between visits to ensure the daily subject diaries were being properly recorded. The nurse placed additional telephone calls to subjects at her discretion when she felt additional telephone follow-up improved diary compliance between weekly subject visits.

The Principal Investigator examined the subjects upon enrollment and again at the end of the 3-week Renew Insert device use period (end of week 3). In addition, the Principal Investigator was available during all weekly nurse visits in case his assistance was required.

6. Inclusion and Exclusion Criteria

Inclusion criteria:

- Females aged 40 years and older
- Minimum Wexner Bowel Incontinence score of 12, AND reported at least weekly leakage (score of 3 or 4) of at least 2 of the 3 Wexner scale stool types (solid, liquid and gas) for the last month prior to inclusion in the study
- Subjects had to comprehend the meaning of their participation in the study, and sign on the study's standard informed consent form
- Subjects had to understand and be capable to technically carry out their duties in the study, including self-administration of inserts and daily diary recordings.
- Subjects had to be fluent in English

Exclusion criteria:

- American Society of Anesthesiologists (ASA) score of 4 or higher (subjects with severe systemic disease that is a constant threat to life)
- Spinal cord injury or other major neurological diagnosis (Parkinson, multiple sclerosis, etc.)
- Known immune deficiency state
- Pregnancy
- Breastfeeding woman
- Inflammatory bowel disease
- Any subject requiring medication delivered by suppository
- Active perineal abscess or fistula
- Anismus which had not been completely resolved with treatment
- Active anal fissure
- Present rectal prolapse
- Third degree hemorrhoids or higher
- Anal stricture
- Rectal surgery in the past 6 months
- Subjects with known allergy to silicone or one of its components
- Subjects who are physically and/or mentally incapable of fully complying with the study's protocol
- Rectal bleeding
- Any medical condition which the PI deems not suitable for the subject to participate in the study

7. Study Analysis

On a daily basis during the three-week treatment period, subjects documented their use of Renew Inserts in the subject diaries. Renew collected and analyzed insert use data on all treated subjects, regardless of how long they used the Inserts or when they withdrew or discontinued their study participation. For example, if one subject used only one Insert during their study participation and another subject withdrew after 1 week of treatment, all available data from both of these subjects were included in the analysis.

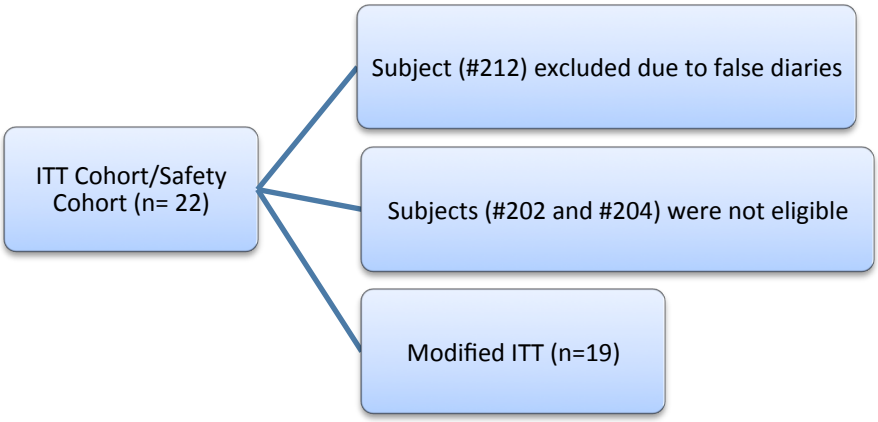
8. Statistical Methods and Analysis Cohorts

The study was designed to provide information regarding the frequency of Renew Insert loss with urination. Due to the small study size, the study was not designed nor expected to show statistical significance.

All subjects enrolled in the 3-Week Treatment Period had at least one exposure to the Insert. Therefore, the Intent-to-Treat ("ITT") cohort and the Safety Cohort included the same group of subjects (n=22): all subjects who used the Renew Insert at least once during the Treatment Period of the study. Protocol deviations and adverse event data were based on the Safety Cohort of 22 subjects.

The primary cohort for the analyses on insert usage, tolerability and subject preferences was the Modified ITT ("Modified ITT"). This cohort included 19 of the 22 enrolled subjects. Three subjects were not included because it was discovered that Subject #212 falsified their diaries and Subjects #206 and #202 did not meet inclusion criteria. Chart 1 further illustrates cohort characteristics.

Chart 1: Cohort Classification



a. Missing Data

If a subject was missing data for a given analysis, that subject was not included in the analysis where their data was missing. All data in this report specifies which cohort is being analyzed and which subject information is not included (if applicable).

Two subjects did not complete the study through week one (Subject IDs: #202 and #204) and usage data from three subjects (#212, #206 and #202) could not be analyzed. The two subjects who did not complete the study (#202 and #204) were included in safety data analysis and all subsequent analyses where data was available.

No special data handling conventions were used for dealing with missing values. Not all diaries were complete. However on average 93% of each subject's daily diary was complete, each day that was missing any piece of data was counted as incomplete for this analysis which is described in Table 1. This analysis does not include Subjects #202 or #204 who withdrew in the first week of the trial.

Table 1: Completion of Daily Diaries (Modified ITT* n=18)

Subject	Number of Incomplete Diary Days	Percentage of Daily Diary Completed
201	8	62%
203	1	95%
205	1	95%
207	3	86%
208	1	95%
209	2	90%
210	0	100%
211	1	95%
213	1	95%
214	0	100%
215	0	100%
216	0	100%
217	6	71%
218	1	95%
219	0	100%
220	0	100%
221	1	95%
222	0	100%
Average Percentage of Daily Diary Completion		93%

* Analysis excludes Subject #204

9. Results

Renew collected descriptive statistics for several parameters as recorded in subject daily diaries with emphasis on the frequency of insert loss with urination. The presented usage and tolerability data is derived from the Modified ITT population, as described above, which includes 19 out of the 22 subjects.

a. Demographics

The 19 females in the Modified ITT Cohort had a mean age of 71 years (max 87, min 56, median 72, STD 9.91), the full table with demographic data is in Appendix 1.

b. Baseline/Entry Parameters

As part of the entrance criteria, subjects had to have a minimum Wexner Bowel Incontinence score of 12 and reported at least weekly leakage (score of 3 or 4) of at least 2 of the 3 Wexner scale stool types (solid, liquid and gas) for the last month prior to inclusion in the study.

Upon enrollment to the study, subjects had an average total Wexner score of 16, an average Wexner Solid score of 3, average Wexner Liquid score of 3 and an average Wexner Gas score of 3. Complete analysis of Wexner scores for the cohort of 19 subjects is presented in Table 2 and complete data set is presented in Appendix 1.

Table 2: Wexner Scores of Subjects (Modified ITT n= 19)

WEXNER TOTAL		WEXNER SOLID		WEXNER LIQUID		WEXNER GAS	
Max	20	Max	4	Max	4	Max	4
Median	16	Median	3	Median	3	Median	4
Average	16	Average	3	Average	3	Average	3
STD	2.06	STD	1.33	STD	1.18	STD	1.33

In addition, the type of bowel incontinence (BI) that the subjects had was categorized into one of four types: passive, urge, mixed with passive type dominant, or mixed with urge type dominant. The number and percentage of each type in the study cohort is presented in Table 3. Approximately 37% of the subjects exhibited BI type 'urge' or 'mixed with dominant urge' whereas 58% of the subjects had 'passive' or 'mixed with dominant passive' BI type.

Table 3: Description of BI Type of Subjects (Modified ITT n=19)

BI Type	Number of Subjects	Percentage with Type Of BI
Passive	3	15.79%
Mixed w/dominant passive	8	42.11%
Urge	1	5.26%
Mixed w/dominant urge	6	31.58%
Unknown*	1	5.26%
	19	100.00

* BI type was not recorded for Subject #204

c. Expulsion Conditions

The primary method of collecting information on the use and expulsion of the inserts was through the daily diaries completed by the subjects. How many Inserts were used, expulsion circumstances, use of other incontinence products and a tolerability question were asked daily of the subjects. Weekly, the Nurse Study Coordinator presented a more in-depth tolerability questionnaire to the subjects. At the end of Week 3, a final questionnaire was also presented to examine other measures such as likability and intent to use the device in the future.

Subjects were instructed to replace the inserts each time they were manually removed or evacuated, such that the inserts were worn continuously throughout the 3-week user study period. Each subject was requested to summarize in their daily diary the following information: number of inserts expelled in toilet with bowel movement (BM), number of inserts expelled in toilet with gas, number of inserts expelled in toilet with urination, number of inserts expelled any other time, number of inserts discarded due to difficulties in inserting them, and the number of inserts discarded due to any other reason. Additionally, the subjects were asked to provide a daily rating, using a scale of 1 to 5, to describe the tolerability of insert use. At the end of each week the subjects were also asked specific tolerability questions focused on the insertion process.

A total of 1007 inserts were used in the study from which approximately 73% or 749 inserts were expelled in the toilet with bowel movement (BM), 67 inserts were expelled in toilet with gas, 96 inserts were

expelled in toilet with urination, 37 inserts were expelled any other time, 44 inserts were discarded due to difficulties in inserting them, 6 inserts were discarded due to any other reason, and 8 were used but the expulsion circumstance (with gas, with urination etc.) was not indicated in the patient diary. Table 4 illustrates the percentage of Inserts that were expelled for various reasons (i.e. expelled in toilet with BM, expelled in toilet with gas etc.) on average per subject.

Table 4: Analysis of Expulsion Conditions per Subject over Three-Week trial period (Modified-Intent to Treat Cohort n= 19)

	Percentage of Total Inserts Used					
	Expelled in Toilet with BM	Expelled in Toilet with Gas	Expelled in Toilet with Urination	Expelled Any Other Time	Discarded Due to Insertion Difficulty	Discarded Due to Any Other Reason
Average % per subject	72.78	4.85	10.09	4.25	5.17	0.64
STD	14.57	6.49	7.45	5.66	6.66	1.77

Of the Inserts used, 73% were expelled with a bowel movement, as designed. On average 10% of the Inserts were expelled or discarded for different reasons (i.e. either expelled any other time, due to Insertion difficulty or discarded due to any other reason), other than during a bowel movement or with urination, see Appendix 2 for complete data table.

As mentioned earlier, two of the subjects (#202 and #204) completed less than 1 week of the trial. Subject #202 was only included in the safety analysis since she did not have a qualifying Wexner Score. Subject #204 was included in safety analysis and subsequent usage analyses. Table 5 compares Modified ITT data and data excluding Subject #204.

Table 5: A Comparison of Expulsion Conditions [Modified ITT Cohort n=19 and Modified ITT Cohort Excluding Subject 204 n=18]

	Expelled in Toilet with BM			Expelled in Toilet with Gas			Expelled in Toilet with Urination		
	Modified ITT Cohort	Excluding 204	Percent Difference	Modified ITT Cohort	Excluding 204	Percent Difference	Modified ITT Cohort	Excluding 204	Percent Difference
Average % per subject	72.78	74.51	2.37%	4.85	5.09	4.98%	10.09	9.73	3.75%
STD	14.57	12.83	13.54%	6.59	6.69	1.58%	7.45	7.48	0.52%

As shown in Table 5, the statistical difference between the averages of these two groups is minimal (<5%) which supports inclusion of Subject #204 in analyses where data was available.

d. Frequency of Insert Loss with Urination

The primary objective of this study was to determine the frequency of involuntary insert loss during urination. Frequency of loss was calculated per subject as a percentage compared to the total inserts used throughout the 3-week study duration. As it can be seen below in Table 6, a total of 96 inserts were lost with urination, which represents 9.53% of the total number of 1007 inserts used in the study.

Table 6: Analysis of Inserts Lost with Urination (Modified ITT n=19)

	Total Inserts Lost with Urination	Percentage of Total Inserts Lost with Urination	Average Per Subject over 21 Day Trial	Average Loss Per Day with Urination
Number of Inserts* Lost with Urination	96	9.53%	5.05	0.24

Subjects averaged a loss of 5 Inserts to urination over the entire trial, resulting in less than 2 Inserts lost per week with urination. Although this is a minimal amount, this issue was further analyzed to better understand the reasons that may attribute to this loss.

Expulsion with urination was examined for any potential relation to the size of the insert used (medium, or large). It was also postulated that as the trial progressed, fewer Inserts might be lost with urination as subjects became more competent in insertion techniques and more attune to their bodily functions. To verify this assumption, a per subject review was performed. Tables 7 and 8 demonstrate if fewer Inserts were lost with urination over the trial period and if more of one size was lost with urination.

Table 7: Percentage of Inserts Lost Over 3 Weeks of Trial (Modified ITT* n=17)

	Lost in 1st Week	Lost in 2nd Week	Lost in 3rd Week
Average Percentage of Inserts Lost with Urination	57.02%	30.3%	12.68%

Table 8: Percentage of Inserts Lost Based on Size (Modified ITT* n=17)

	Size Medium	Size Large
Average Percentage of Inserts Per Subject Lost with Urination	54.07%**	45.93%**

* Subjects 221 and 222 did not lose any Inserts with urination and were not included in this analysis

** +/- 2% due to 2 instances of unclear size designation in subject diaries

Table 7 indicates that progressively fewer Inserts were lost to urination over the three-week study period. As seen in Table 8, the majority (54%) were lost were medium and 46% lost were Large (so neither size predominated). There were two scenarios in which diaries were unclear if 2 Inserts were either Large or Medium. To accommodate for this variation, analysis were done based on all 4 scenarios that could have resulted and averaged appropriately. Appendix 3 illustrates the complete data set.

It was important to understand if a change in Insert size resulted in fewer Inserts lost with urination. An analysis was done to determine if a subject's change in Insert size impacted the number of Inserts lost with urination. Table 9 illustrates that the number of subjects that changed sizes and experienced a decrease in number of Inserts lost to urination were comparable to subjects who changed Insert sizes and didn't experience a significant decrease in Inserts lost to urination (37% compared to 26%). The difference in the percentage of each size that was lost to urination had to be ≥ 50% for a subject's loss to urination be considered influenced by Insert size, Appendix 4 illustrates the complete data set.

Table 9: Analyses of Size Change and Impact on Loss to Urination (Modified ITT n=19)

Quantity lost with urination possibly associated with size of Insert?	Yes	No	Used Same Size Throughout Trial	Not Applicable
Total Subjects	7	5	5	2
Percentage of Total Subjects	37%	26%	26%	11%

Subjects who "Used the Same Size Throughout the Trial" only used Medium or Large Inserts thus a comparison could not be made. Two Subjects (#221 and #222) did not lose any Inserts to urination and were categorized as "Not Applicable" for this analysis. The data presented suggests that size did not impact loss with urination however, due to the small sample size there is not enough data collected to determine definitively if change of size was or was not the sole reason for Insert loss with urination.

e. Analysis of Pad Use

Pad use data was not initially designated for endpoint analysis. However, pad use data was deemed important to analyze as many of the subjects used pads to manage their ABL while also using the device.

Over the course of the trial, 85% of the subjects used pads at some point during the trial period, while approximately a third of subjects used pads every day of the trial. When asked about preference of BI treatment options at the Week 3 interview, 100% of subjects stated that they would use the inserts in the management of ABL, with 50% of subjects preferring Inserts over pads and the remainder choosing to wear both pads and Inserts. It is important to note that no subjects reported a preference of pads to Inserts at the final 3-week interview.

Table 10 further summarizes frequency of pad use and Table 11 details the preference data captured at the Week 3 interview; see Appendix 5 and 6 for the complete analysis.

Table 10: Summarizes Frequency of Pad Use (Modified ITT n=19)

	Number of Subjects	Percentage of Total Subjects
Never Used Pads	2	9.09%
Used Pads Less than 50% of the time	8	36.36%
Used Pads More than 50% of the time	11	50.00%
Used Pads 100% of the time	6	27.27%

Table 11: Preference of Pad or Insert Use at Week 3 Interview (Modified ITT* n=18).

	# of Subjects	Percentage of Total # of Subjects
Preferred Inserts either with or without pads	**18**	**100%**
• Preferred Inserts over Pads	9	50%
• Prefer to use both pads and Inserts	9	50%
Preferred Pads over Inserts	**0**	**0.00%**
No preference of pads vs. Inserts	**0**	**0.00%**

* Excludes Subject #204 due to termination before Week 3.

f. Insert Tolerability and Ease of Use

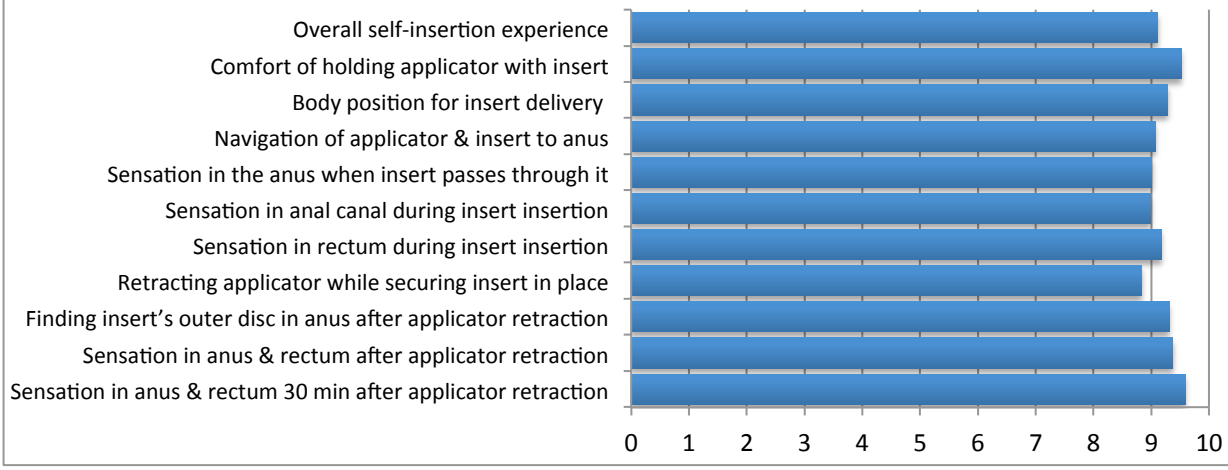
At the end of each day the subjects were asked to rate the general tolerability of using the Insert that day in their diary. On a scale of 1 to 5, where 1 was extremely intolerable/uncomfortable and 5 was extremely tolerable/comfortable, subjects reported an average daily tolerability rating of 4.14 over the 21 day trial period as shown below in Table 12 with complete data in Appendix 7.

Table 12: Analysis of Daily Tolerability Rating

	Average	Standard Deviation
Daily Tolerability Rating	4.14	0.83

In the 3 weekly interviews with the study nurse, each subject was requested to grade the following aspects related to the usability and self-insertion process of the Insert. The grading was done using a scale of 1 to 10, where 1 is '*very difficult, demanding and unfriendly*', and 10 is '*very easy, simple and comfortable*'. Graph 1 represents the mean of these statements of usability at the 3-week interview. The statements to the left of the bars represent the specific questions asked.

Graph 1: Insertion Tolerability Questions at Each Week



As illustrated in Graph 1, subjects reported an average score over 9.1 for the overall experience with the Renew Insert and an average score of 9.2 for all ease of insertion and comfort questions; see Appendix 8 for further data breakdown. These results demonstrate that the self-insertion process is simple and rated as a positive experience by all subjects.

g. Final Questionnaires

At the end of the 3-week study period, the Nurse Study Coordinator conducted a short interview with each subject to assess their overall satisfaction with the Renew Insert device. Table 13 depicts the questions asked at the final interview. This analysis is based on data from the Modified ITT Cohort.

Tables 13: Representation of Average Scores of Subject Responses at Week 3 Interview (Modified ITT n=18*).

QUESTIONS	SCALE	AVERAGE	STANDARD DEVIATION
Overall satisfaction	1-5 scale, 1 being "Not At All Satisfied" to 5 being "Extremely Satisfied".	4.4	0.70
Use of device in the future	1-5 scale, 1 being "Definitely Not Interested" to 5 being "Definitely Interested".	4.8	0.55
How much liked device	1-6 scale, 1 being "Not Like At All" to 6 being "Like Extremely Well".	5.2	1.02
Meeting expectations	1-3 scale, 1 being "Fall Short of Your Expectations" to 3 being "Exceeded Expectations".	2.4	0.70
Estimate of days per week device was used	1-7 scale, 1 being once a week to 7 being every day.	6.3	1.40
Where Subject used the device	1-3 scale, 1 being "Mostly Away from Home", 2 being "Mostly at Home", to 3 being "Both Away from Home and at Home".	2.2	1.00

*Excludes Subject #204 who withdrew/terminated prior to Week 3

The majority of subjects, 89% were "*extremely or very satisfied*" and 94% were "*definitely or probably interested*" in using the product if they were given the opportunity. The Insert scored a high likability rating of a 5.2 average on a 6-point scale with 6 being "*liked extremely well*". Subjects also reported they would use Inserts on a regular basis, approximately 6 days a week, and would use them at home and away from home.

The Renew Insert achieved high scores on all measures, indicating subjects would use the Insert if available to them. The complete table depicting the complete data set is in Appendix 9 and complete explanation of the scales used is in the attached sample CRF.

h. Safety Evaluation

No serious or unanticipated adverse events (AEs) occurred throughout the study. All subjects' anoscope exams conducted by the PI at the end of the trial period were normal. Subjects #202 and #204 did not have an anoscope exam since they withdrew in the first week of the study.

During the course of the three-week study, one adverse event was documented. After enrollment it was determined that Subject #210's pre-existing Proctalgia Fugax (functional anorectal pain) worsened while participating in the trial. The PI deemed this event as "probably" being related to the Insert usage. However, the subject completed the trial because the PI did not deem this exacerbation as a medical risk and the subject tolerated Insert use.

Under retrospective data review, other adverse events were identified through mention in the patient diaries. Since these adverse events were identified retrospectively their severity was not officially assessed. The majority of the AE's were related to the gastrointestinal system and were not attributed to the use of the Renew Insert. Accidental bowel leakage (ABL) was most prevalent in addition to diarrhea and complaints of bloating and gas. A summary of the AEs is presented in Table 14.

Table 14: Summary of Adverse Events of Safety Cohort (n=22)

Category	Description of Adverse Event	% of Subject that Have Experienced AEs
GI		
	ABL	36.36%
	Diarrhea	27.27%
	Bloating/Gas	22.73%
	Irritation/burning/pain w/Insertion	13.64%
	Constipation	13.64%
	Urgency (Fecal)	13.64%
	Upset Stomach	9.09%
	Hemorrhoids	9.09%
	Irritated Anus	9.09%
	Anal Bleeding	4.55%
	Burning w/use	4.55%
	Cramping	4.55%
	Nausea	4.55%
	IBS (severe)	4.55%
	Proctalgia Fugax – increase in severity	4.55%
GU		
	Decreased urine flow	4.55%
	Perianal irritation from yeast infection	4.55%
GENERAL		
	General sickness	4.55%
OTHER		
	Depression	4.55%

One AE which increased in severity was a pre-existing diagnosis (Subject #210 with Proctalgia Fugax) and was deemed related to the device use but was not deemed serious by the PI (and therefore was not reported). A more comprehensive overview of individual subjects that experienced AEs is referenced in Appendix 10.

i. Protocol Deviations

The protocol stipulated that subjects were to use one device at a time. The device was to be discarded after use or if they failed to insert it properly. The subjects were to document when they inserted a device, when it came out and under what circumstances it came out (i.e. with a bowel movement, during urination or gas etc.). All inventory was to be reconciled at the end of each week at the meeting with the study nurse.

The majority of the protocol deviations found were related to improper completion of diaries that resulted in inventory inconsistencies. Other deviations included using more than one device at a time and one involved a subject (#209) who attempted to re-insert the applicator to adjust the device. The Instructions for Use state that if a subject wishes to adjust a device, the entire device should be removed and a new device should be inserted. Re-insertion of the applicator was not recommended.

Three subjects (#206, #213, #217) unknowingly inserted more than 1 device. These protocol violations did not harm the subjects and all devices came out with a subsequent bowel movement. One subject confessed that she had falsified her diaries to stockpile the Inserts for future use, which resulted in falsified diaries. There was no way to verify if any her diaries were accurate and as stated earlier only safety data from this subject analyzed.

To be included in the study, subjects had to have a Wexner score of 12 or above. Retrospectively, it was determined that two subjects (#206 and #202) had an insufficient Wexner score, but were still treated. Subject #202 withdrew in Week 1 of the study and the limited data were omitted due to their ineligibility. At the Week 3 visit, Subject #206 was rescreened and had a qualifying Wexner of 14. All protocol deviations that were observed are summarized in Table 15 below.

Table 15: Summary of Protocol Deviations

Deviation Description	Subjects	Explanation and Resolution
Incomplete/Incorrect Diaries	201, 208, 218	Subjects initially had difficulty completing the diaries correctly, nurse study coordinator provided guidance and compliance improved.
Re-Use of Device	207	Subject removed device and reused it.
Incorrect Inventory Reconciliation	210, 211	Subjects did not accurately keep track of devices used and returned.
Subject continued treatment past study timeframe	211	Subject did not return devices at end of treatment period.
Subject stockpiling devices and falsifying diaries	212	Subject "confessed" to study nurse about falsifying the information in her diary. Subject completed study but usage data was not analyzed.

Deviation Description	Subjects	Explanation and Resolution
Use of multiple devices	206, 213, 217	Subjects were unaware of insertion of multiple devices until seeing 2 or 3 devices in the toilet after a BM, i.e., the devices were expelled with next BM. Neither pain nor discomfort was reported in relation to this event.
Re-insertion of applicator to adjust device	209	Subject used applicator to attempt to readjust device when not properly inserted.
Inclusion criteria not met and Subject enrolled	206, 202	Wexner Score provided during enrolment was verified and found to be inadequate, however, Subject completed trial.

10. Study Terminations and Withdrawals

A total of 22 subjects were enrolled and a total of 2 subjects (9%) withdrew consent or were terminated. During the first week of the three-week treatment Period, these 2 subjects were discontinued:

- Subject #202 withdrew from the study due to pain and irritation of the anal area and difficulty with inserting the device. The PI agreed with withdrawal and no anatomical issues were identified on exam.
- Subject #204 was terminated because she was unable to schedule a colonoscopy to complete the trial.

11. Discussion & Conclusions

This study was designed to provide information regarding the usability of the Renew Insert and, in particular, to assess the frequency of insert loss with urination.

The analysis of 22 subjects demonstrates that the Renew Insert is a safe, simple, and user-friendly device that can be easily applied by the user. The frequency of device loss with urination is low and does not present a major concern. The use of the proper device size (medium or large) may impact loss with urination and loss to urination did decrease over the 3-week period.

The study also showed that subjects were highly satisfied with the Inserts, with 100% of subjects choosing them to manage their accidental bowel leakage either alone or in conjunction with pads. At study exit, all subjects wished to continue using the product. In response, the PI recommended the company pursue a compassionate use exemption for the entire study population so that continued access to the Renew Inserts beyond the study period could be provided. Please refer to the Appendix 20 further more information regarding compassionate use.

12. APPENDICES

Appendix 1: Summary of Demographics and Wexner Scores

Subject	Age	Wexner Score	Wexner solid	Wexner liquid	Wexner gas	BI Type*
201	87	16	1	2	3	U
203	76	15	4	4	0	P
204	86	17	3	1	4	UNK
205	58	14	3	3	4	MP
207	63	12	1	3	4	MP
208	61	13	0	3	2	P
209	76	15	0	3	4	P
210	56	16	4	0	4	MU
211	72	20	4	4	4	MU
213	67	19	3	4	4	MU
214	63	17	4	2	4	MU
215	76	18	3	4	3	MP
216	65	16	4	2	2	MP
217	72	17	2	3	4	MP
218	78	16	4	4	0	MP
219	85	19	3	4	4	MP
220	82	16	3	1	4	MU
221	58	18	3	3	4	MP
222	71	18	3	3	4	MU
AVERAGE	71	16	3	3	3	
MAX	87	20	4	4	4	
MIN	56	12	0	0	0	
MEDIAN	72	16	3	3	4	
SD	9.91	2.06	1.33	1.18	1.33	

*BI Type, U= Urge, MU= Mixed Urge, P=Passive, MP= Mixed Passive, UNK=Unknown

Appendix 2: Expulsion Conditions From Daily Diaries
(Modified ITT n=19)

Percentage Per Subject						
Subject	**Expelled in Toilet with BM**	**Expelled in Toilet with gas**	**Expelled in Toilet with urination**	**Expelled any other time**	**Discarded Due to Insertion Difficulty**	**Discarded Due to Any Other Reason**
201	51.28	12.82	10.26	2.56	15.38	0.00
203	89.29	3.57	3.57	0.00	0.00	0.00
204*	41.67	50.00	16.67	16.67	16.67	0.00
205	71.15	3.85	15.38	0.00	7.69	0.00
207	55.00	18.33	20.00	0.00	5.00	0.00
208	78.57	4.76	11.90	0.00	4.76	0.00
209	57.14	2.38	28.57	0.00	4.76	2.38
210	82.72	4.94	11.11	1.23	0.00	0.00
211	66.04	23.58	3.77	6.60	1.89	0.00
213	73.33	0.00	5.00	0.00	20.00	0.00
214	82.61	0.00	10.14	1.45	5.80	0.00
215	89.09	0.00	7.27	1.82	0.00	0.00
216	60.00	0.00	20.00	5.00	15.00	0.00
217	68.00	0.00	8.00	16.00	0.00	0.00
218	72.97	1.35	9.46	12.16	1.35	2.70
219	89.33	4.00	4.00	2.67	0.00	0.00
220	82.67	5.33	8.00	2.67	0.00	0.00
221	93.33	6.67	0.00	0.00	0.00	0.00
222	78.57	0.00	0.00	11.90	0.00	7.14

*Subject #204 completed 3 days of trial

Appendix 3: Inserts Lost to Urination from Daily Diaries (Modified ITT n=19)

Subject	# Of Inserts expelled w/urination	Week 1	Week 2	Week 3	Notes regarding size or timing of Insert loss
201	4	Size: Medium Inserts Lost: 1	Size: Large Inserts Lost: 3	Size: Medium Inserts Lost: 0	Majority of Inserts lost were size Large, and lost in Week 2.
203	1	Size: Large Inserts Lost: 1	Size: Large Inserts Lost: 0	Size: Large Inserts Lost: 0	Subject only lost 1 Insert in Week 1.
204	2	Size: Large Inserts Lost: 2	Size: N/A Inserts Lost: N/A	Size: N/A Inserts Lost: N/A	Subject enrolled for 3 days, lost 2 Inserts.
205	8	Size: Medium Inserts Lost: 6	Size: Large Inserts Lost: 1	Size: Large Inserts Lost: 1	Subject lost more Inserts to urination initially and lost more Medium sized Inserts overall.
207	12	Size: Medium Inserts Lost: 4	Size: Large Inserts Lost: 6	Size: Large Inserts Lost: 2	Subject wore both sizes and lost Inserts of both sizes.
208	5	Size: Medium Inserts Lost: 4	Size: Large Inserts Lost: 0	Size: Medium Inserts Lost: 1	Subject used both sizes and lost only Medium sized Inserts.
209	12	Size: Medium Inserts Lost: 8	Size: Medium/Large Inserts Lost: 2 Large, 1+/- M/L*	Size: Large Inserts Lost: 1	Subject used both sizes and majority of lost Inserts were size Medium in Week 1.
210	9	Size: Medium Inserts Lost: 0	Size: Medium Inserts Lost: 8	Size: Large Inserts Lost: 1	Subject used both sizes and primarily lost Medium sized Inserts in the 2nd week.
211	4	Size: Medium/Large Inserts Lost: 1 Medium, 1 Large, 1 +/- Medium/Large*	Size: Large Inserts Lost: 1	Size: Large Inserts Lost: 0	Subject used size Medium/Large in the first week and lost some of each size.
213	3	Size: Medium Inserts Lost: 1	Size: Medium/Large Inserts Lost: 1 Medium and 1 Large	Size: Medium Inserts Lost:0	Subject lost 3 Inserts during trial of both sizes.
214	7	Size: Medium Inserts Lost: 5	Size: Medium Inserts Lost: 1	Size: Medium Inserts Lost: 1	Subject lost majority of Inserts in the first week and only used Size Medium.
215	4	Size: Large Inserts Lost: 4	Size: Large Inserts Lost: 0	Size: Large Inserts Lost: 0	Subject lost all Inserts in the first week and only used Size Large.
216	8	Size: Medium Inserts Lost: 0	Size: Large Inserts Lost: 5	Size: Medium Inserts Lost: 3	Subject lost both size Large and Medium Inserts throughout trial.
217	2	Size: Medium	Size: Large	Size: Large	Subject used both sizes

Subject	# Of Inserts expelled w/urination	Week 1	Week 2	Week 3	Notes regarding size or timing of Insert loss
		Inserts Lost: 2	Inserts Lost: 0	Inserts Lost: 0	and lost only Medium sized Inserts.
218	7	Size: Medium	Size: Large	Size: Large	Subject lost both sized Inserts over 3 weeks.
		Inserts Lost: 3	Inserts Lost: 2	Inserts Lost: 2	
219	2	Size: Medium	Size: Medium	Size: Medium	Subject used Medium sized Inserts and lost 2 during trial.
		Inserts Lost: 0	Inserts Lost: 1	Inserts Lost: 1	
220	6	Size: Medium	Size: Medium	Size: Large	Subject used both sizes and primarily lost Medium sized Inserts in the first week.
		Inserts Lost: 4	Inserts Lost: 1	Inserts Lost: 1	
221	0	Size: Medium	Size: Medium	Size: Medium	Subject did not lose any Inserts.
		Inserts Lost: 0	Inserts Lost: 0	Inserts Lost: 0	
222	0	Size: Medium	Size: Medium/Large	Size: Large	Subject did not lose any Inserts.
		Inserts Lost: 0	Inserts Lost: 0	Inserts Lost: 0	
TOTAL	94				

*Unable to identify size of Insert that was expelled with urination based on inconsistencies in diaries.

Appendix 4: Quantity of Inserts Lost Due to Size and Timing from Daily Diaries (Modified ITT n=19)

Subject	# of Inserts expelled w/urination	Percentage Lost in 1st Week	Percentage Lost in 2nd Week	Percentage Lost in 3rd Week	TOTAL	Percentage Lost M	Percentage Lost L	TOTAL	Difference Between Sizes	Size impact loss?
201	4	25.00%	75.00%	0.00%	100.00%	25.00%	75.00%	100.00%	50.00%	YES
203	1	100.00%	0.00%	0.00%	100.00%	0.00%	100.00%	100.00%	100.00%	NO: One Size
204	2	100.00%	0.00%	0.00%	100.00%	0.00%	100.00%	100.00%	100.00%	NO: One Size
205	8	75.00%	12.50%	12.50%	100.00%	75.00%	25.00%	100.00%	50.00%	YES
207	12	33.33%	50.00%	16.67%	100.00%	33.33%	66.67%	100.00%	33.33%	NO
208	5	80.00%	0.00%	20.00%	100.00%	100.00%	0.00%	100.00%	100.00%	YES
209	12	66.67%	25.00%	8.33%	100.00%	**Scenario A***		100.00%		
						66.67%	33.33%		33.33%	NO**
						Scenario B*				
						75.00%	25.00%		50.00%	YES**
210	9	0.00%	88.89%	11.11%	100.00%	88.89%	11.11%	100.00%	77.78%	YES
211	4	75.00%	25.00%	0.00%	100.00%	**Scenario C***		100.00%		
						50.00%	50.00%		0.00%	NO**
						Scenario D*				
						25.00%	75.00%		50.00%	YES**
213	3	33.33%	66.67%	0.00%	100.00%	100.00%	0.00%	100.00%	33.33%	NO
214	7	71.43%	14.29%	14.29%	100.00%	100.00%	0.00%	100.00%	100.00%	NO: One Size
215	4	100.00%	0.00%	0.00%	100.00%	0.00%	100.00%	100.00%	100.00%	NO: One Size
216	8	0.00%	62.50%	37.50%	100.00%	37.50%	62.50%	100.00%	25.00%	NO
217	2	100.00%	0.00%	0.00%	100.00%	100.00%	0.00%	100.00%	100.00%	YES
218	7	42.86%	28.57%	28.57%	100.00%	42.86%	57.14%	100.00%	14.29%	NO
219	2	0.00%	50.00%	50.00%	100.00%	50.00%	50.00%	100.00%	0.00%	NO: One Size
220	6	66.67%	16.67%	16.67%	100.00%	83.33%	16.67%	100.00%	66.67%	YES
TOTAL	94									
	AVERAGE	53.46%	25.75%	10.78%						
					Average (BC Scenario) **	54.07%	45.93%			

* Scenario A/B/C/D: Two potential scenarios had to be computed because for both Subject 209 and 211 it was unclear if 1 documented Insert was size M or L.
** Scenario B and C were included in analysis, A &D were excluded. This resulted in both a Medium and Large Insert to be counted as lost to urination in the analysis as to not skew the designation of Inserts lost to either size group.

Appendix 5: Frequency of Pad Use from Daily Diary Entries (Modified ITT Cohort n=19).

Subject Code	% of Study Days that subject Used Pads
201	52.38%
203	85.71%
205	0.00%
207	4.76%
208	19.05%
209	47.62%
210	100.00%
211	61.90%
213	9.52%
214	100.00%
215	9.52%
216	28.57%
217	95.24%
218	95.24%
219	100.00%
220	100.00%
221	0.00%
222	100.00%
204	100.00%
AVERAGE	58.40%

Appendix 6: Pads Analysis
Response to question at Week 3 (Modified ITT n=19)
"If the Renew (Enshur) insert were available to you alongside pads, which would you prefer?"
"1"- Prefer Renew (Enshur) Inserts, "2"-Prefer Pads, "3"-No Preference, "4"-Would use both"

Subject Code	Response to Preference of device vs. pad at Week 3
201	4
203	4
204*	
205	1
207	1
208	1
209	1
210	4
211	4
213	1
214	4
215	1
216	1
217	1
218	4
219	4
220	4
221	1
222	4
% of subjects that Prefer Inserts Over Pads (1)	50%
% of subjects that Prefer Pads Over Inserts (2)	0%
% of subjects that have no preference (3)	0%
% of subjects who would use both (4)	50%

* Excludes Subject 204 due to withdrawal in Week 1.

Appendix 7: Analysis of Daily Tolerability Rating
(Modified ITT n=19)

Response to question:
"Please tell us how tolerable/comfortable the Anal Inserts that you used today were…"
1-Extremely Intolerable/Uncomfortable
2-Somewhat Intolerable/Uncomfortable
3-Neither Tolerable Nor Intolerable
4-Somewhat Tolerable/Comfortable
5-Extremely Tolerable/Comfortable

Subject	Average Daily Tolerability Rating
201	3.54
203	5.00
204*	4.00
205	4.43
207	4.67
208	3.48
209	5.00
210	2.95
211	5.00
213	4.60
214	4.95
215	5.00
216	4.38
217	4.45
218	4.35
219	2.05
220	4.00
221	3.00
222	3.90
Average	4.14
SD	0.83

* 204 completed 3 days of the study

Appendix 8: Insertion tolerability assessed by Nurse Study Coordinator's interview of Subject's comfort with insertion steps and associated sensations with very difficult =1 and 10 =very easy/comfortable (Modified ITT n=19)

	Average per Subject										
	Insertion Steps and Associated Sensations										
Subject	Comfort of holding applicator with insert	Body position for insert delivery	Navigation of applicator & insert to anus	Sensation in the anus when insert passes through it	Sensation in anal canal during insert insertion	Sensation in rectum during insert insertion	Retracting applicator while securing insert in place	Finding insert's outer disc in anus after applicator retraction	Sensation in anus & rectum after applicator retraction	Sensation in anus & rectum 30 min after applicator retraction	Overall self-insertion experience
201	9.33	8.33	7.00	6.00	2.00	8.67	8.00	10.00	10.00	**	7.00
203	10.00	10.00	10.00	10.00	10.00	10.00	10.00	9.67	10.00	**	10.00
205	7.67	8.00	8.67	7.33	8.33	7.33	7.00	9.00	8.33	9.00	8.67
207	10.00	9.67	10.00	9.33	9.33	9.33	9.00	10.00	8.00	**	9.00
208	10.00	9.67	8.67	9.67	9.67	8.33	10.00	10.00	9.00	**	9.67
209	10.00	10.00	10.00	9.33	10.00	10.00	8.00	9.33	10.00	10.00	10.00
210	10.00	10.00	9.33	10.00	10.00	10.00	7.67	10.00	10.00	10.00	7.33
211	10.00	9.67	9.67	10.00	10.00	10.00	10.00	10.00	10.00	10.00	9.83
213	10.00	9.33	9.00	9.00	9.33	9.33	8.67	9.67	9.67	10.00	9.67
214	10.00	9.67	8.50	9.67	10.00	9.67	8.33	9.00	9.67	10.00	8.50
215	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
216	9.33	7.67	9.33	9.00	9.33	9.33	8.67	10.00	8.67	9.67	9.00
217	9.33	8.33	8.33	7.67	8.33	9.00	9.00	8.17	9.67	9.67	9.33
218	9.33	9.83	9.33	9.50	10.00	8.50	8.50	9.67	9.67	10.00	9.67
219	7.00	7.67	7.00	9.00	9.00	9.33	8.67	8.33	8.67	7.33	8.33
220	9.67	9.50	9.00	9.33	8.67	9.33	8.00	8.33	8.33	9.17	9.17
221	10.00	10.00	9.33	8.33	7.67	7.33	10.00	6.67	9.33	10.00	9.33
222	9.67	9.67	10.00	9.00	10.00	9.67	9.33	9.67	9.67	9.33	9.33
204*											
Max	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00	10.00
Min	7.00	7.67	7.00	2.00	2.00	2.00	1.00	6.00	3.00	7.33	2.00
Median	10.00	9.67	9.33	9.33	9.50	9.33	8.67	9.67	9.67	10.00	9.33
Average	9.52	9.28	9.06	9.01	8.98	9.18	8.82	9.31	9.37	9.58	9.10
STD	1.42	0.85	0.93	1.07	1.89	0.85	0.92	0.92	0.68	0.74	0.87
Mean of Average Scores	9.2										

*Subject 204 was not enrolled long enough to provide this data. ** Subjects were not asked this question.

Appendix 9: Overall Experience Assessed Through Nurse Interview at Week 3 (Modified to Intent Cohort n=19).

Subject	1. Overall satisfaction	2. Use of device in the future	3. Meeting expectation	4. How much liked the device	7. Preference device vs. pad	8. Estimated times per week to use device	9. Where use device
201	4	5	2	4	4	7	3
203	5	5	3	6	4	7	3
204*							
205	4	5	2	5	1	5	1
206	4	5	2	5	1	5	3
207	5	5	2	6	1	7	3
208	4	5	3	6	1	5	3
209	5	5	3	6	1	7	1
210	4	5	1	3	4	7	1
211	4	3	2	5	4	7	3
213	5	5	3	6	1	7	3
214	5	5	3	6	4	7	3
215	5	5	3	6	1	7	1
216	5	5	3	6	1	7	3
217	5	4	3	5	1	5	1
218	3	5	2	5	4	7	3
219	3	4	2	3	4	7	1
220	5	5	2	5	4	7	3
221	4	5	1	5	1	5	1
222	5	5	3	6	4	2	3
Max	5	5	3	6	4	7	3
Min	3	3	1	3	1	2	1
Median	5	5	2	5	1	7	3
Average	4.4	4.8	2.4	5.2	2.4	6.2	2.3
STD	0.69	0.54	0.68	0.99	1.54	1.39	0.99

* 204 completed 3 days of the study

1. **Overall, how satisfied were you with the Renew (Enshur) anal insert device you used during the past 3 weeks?**
    - 1-Not at all satisfied, 2-Not very satisfied, 3-Somewhat satisfied, 4-Very satisfied, 5-Extremely Satisfied
2. **Overall, how likely would you be to use the Renew (Enshur) anal insert device if it were available for you to continue using?**
    - 1-Definitely not interested, 2-Probably not interested, 3- Might or might not be interested, 4-Probably interested, 5-Definitely interested
3. **Based on your initial first impressions, did the Renew (Enshur) anal insert device...**
    - 1-Falls short of your expectations, 2-Meet your expectations, 3-Exceed your expectations
4. **Which statement best describes how much you LIKED the Renew (Enshur) anal insert device?**
    - 1-Not like at all, 2-Like slightly, 3-Like somewhat, 4-Like quite well, 5-Like very well, 6-Like extremely well
7. **If the Renew (Enshur) insert were available to you alongside pads, which would you prefer?**
    - 1-Prefer Renew (Enshur) Inserts, 2-Prefer pads, 3-No preference, 4-Would use both
8. **And how many times per week do you think you would use the Renew (Enshur) inserts?**
9. **And do you think you would use the Inserts...**
    - 1-Mostly away from home, 2-Mostly at home, 3-Both away from

Appendix 10: Adverse Events per Subject Collected from AE reports and Retrospectively from Review of Diaries (ITT cohort n=22).

Code Subject	201	202	205	206	207	208	209	210	211	212	213	214	215	216	217	218	219	220	221	222	TOTAL
Description																					
General Sickness	1																				1
GI																					
Diarrhea			1		1	1				1		1	1								6
Bloating/Gas	1			1	1			1									1				5
Irritation/Burning/pain w/Insertion		**1**			1		1														3
Constipation			1	1													1				3
Upset Stomach				1													1				2
Urgency (Fecal)						1			1											1	3
Hemorrhoids	1				1																2
Irritated Anus					1															1	2
Anal Bleeding				1																	1
Burning w/use					1																1
Cramping	1																				1
Nausea																		1			1
IBS (severe)						1															1
Proctalgia fugax - increase in severity							**1**														1
GU																					
Decreased urine flow																1					1
Perianal Irritation from yeast infection															1						1
OTHER																					
ABL					1	1		1					1	1		1		1	1		8
Displacement			1	1		1															3
Involuntary Expulsion														1	1		1				3
Depression														1							1
																			TOTAL		49

Subjects #203 and #204 did not experience any AE's.

Appendix 11: Protocol

Enshur, Inc.

Study Protocol:

Enshur Plug Loss User Study (PLUS) to Observe Anal Insert Loss With Urination

Study protocol number: 200CLD

Reviewed & Approved by	Title	Signature	Date
Kelly Lewis Brezoczky	Chief Operating Officer		2/23/2009

Revision History

Rev.	Written by	Date	ECO	Description of Change

This protocol and related documents are the confidential property of Enshur, Inc.

No unpublished information contained herein may be disclosed without the prior written approval of Enshur, Inc.

INVESTIGATOR PROTOCOL AGREEMENT

Study Protocol number: 200CLD

I have read and understand this protocol and agree to:

Perform and conduct the study as outlined in the protocol herein;

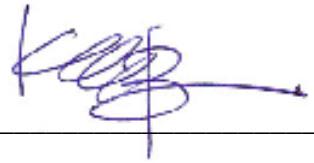
Maintain the confidentiality of all information received or developed in connection with this protocol;

I accept my obligations related to the Institutional Review Board (WIRB), Informed Consent and Protocol.

_____ _____ ___February 27, 2009_____

Investigator's Signature Date

Mark M. Segall, M.D.
Medical License Number: CA GO24951
15195 National Ave
Suite 202
Los Gatos, CA 95032



_____ _____February 27, 2009_____

Enshur, Inc. Date

Kelly Lewis Brezoczky
Chief Operating Officer
532 Emerson Street
Palo Alto, CA 954301

ENSHUR INCORPORATED

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ENSHUR INCORPORATED

1. STUDY PROTOCOL SYNOPSISIS

Sponsor:	Enshur, Inc., 532 Emerson Street, Palo Alto, CA 94301 USA
Title:	Enshur Plug Loss User Study (PLUS) to Observe Anal Insert Loss With Urination
Study design:	Prospective, open label, single-arm, non-randomized study designed to observe the frequency of Enshur Anal Insert loss with urination in patients with accidental bowel leakage due to fecal incontinence
Number of patients:	15-20
Patients:	Patients suffering from accidental bowel leakage due to moderate-to-severe fecal incontinence
Clinical sites:	The medical office of Dr. Mark M. Segall, M.D. and the Samaritan Endoscopy Center, Los Gatos, CA
Timing:	Spring 2008. Patients will be enrolled to participate in a 3 week observational user study
Study objective:	To better understand the frequency of Enshur Anal Insert loss with urination as anecdotally reported in the Netherlands pilot study
Primary endpoint:	The study has 2 primary endpoints as follows: 1. Frequency of Enshur Anal Insert loss with urination—to measure how frequently patients experience Anal Insert loss with urination 2. Safety—as measured by no serious device related adverse events
Secondary endpoint	The study has 1 secondary endpoints as follows: 1. Safety—no serious irritation of the anal canal or lower rectal mucosa with a near-continuous use of device during the study period
Methods:	Patient screening: Wexner Fecal Incontinence Scale (to assess whether fecal incontinence severity meets Inclusion criteria) Upon patient enrollment: Patient history, digital rectal exam, Anoscopy, Sigmoidoscopy; and for those patients who have not had a Colonoscopy in the past 36 months, Colonoscopy (to rule out other conditions) During study period: Daily diary recordings; visual analog scales Upon study completion: Anoscopy to check condition of anal canal mucosa

2. INTRODUCTION

This document describes a short 3 week Enshur PLUS clinical research protocol to observe the frequency of Enshur Anal Insert loss with urination. This study protocol follows upon Enshur's experience from two small European feasibility studies: a first-in-human, 3-patient proof-of-concept study conducted in Turkey in 2007; and a 6 patient pilot study, which is presently underway at the Academic Medical Center (AMC) in the Netherlands. All of the Enshur European clinical pilot work to date shows the Enshur Insert to be both effective and tolerable in moderate-to-severe fecal incontinence patients, with no adverse events reported.

Importantly, with 4 patients completed in the Netherlands pilot study, the FDA has agreed the Enshur Anal Insert device may proceed to a US pivotal study. The US pivotal study will be conducted at the Cleveland Clinic under the supervision of Dr Steven D. Wexner (author of the Wexner Scale for Fecal Incontinence).

The proposed short 3 week Enshur PLUS clinical study is being conducted to better understand the frequency of Enshur Anal Insert loss with urination. Anal Insert loss with urination was observed in the Netherlands pilot study among all patients. However, this reporting was anecdotal and not formally recorded in the patient diaries. Because the frequency of Anal Insert loss with urination is presently not well enough understood, the company would like to conduct a short 3 week user study to better understand the frequency of Anal Insert loss due to urination prior to beginning the US pivotal study. An interim summary of the Netherlands patient data is attached in **Appendix 1**.

The proposed Enshur PLUS clinical study has also been discussed with FDA and the Agency expressed no concerns about proceeding with this study prior to the start of the US pivotal study.

The proposed clinical study will be conducted in compliance with the protocol, Good Clinical Practices standards and associated regulations, and all applicable research requirements. Western Institutional Review Board ("WIRB") is expected to serve as the study's IRB monitor.

3. BACKGROUND

Fecal incontinence ("FI") can dramatically disrupt the lives of people who suffer from it. Very few benign medical situations cause as much embarrassment and impaired quality of life as the lack of control of bowel movements. Poor control of bowel movements can be a result of many conditions such as: congenital defects (such as imperforated anus), anorectal trauma, weakness of the pelvic floor muscles and nerve damage, or part of a systematic illness such as diabetes and scleroderma. However, the most common cause of fecal incontinence is probably pelvic floor weakness or anatomical damage due to obstetric trauma. During vaginal delivery, tears of the birth canal can damage the anterior portion of the circular anal sphincter muscles which are located in the narrow septum between the anus and rectum and the vagina. In addition, pressure applied by the fetus before and during birth and the stretching of the pudendal nerves in the

pelvic floor can damage the pudendal nerves. Obstetric damage can remain asymptomatic for many years, due to the compensation made by the other pelvic muscles.

It is estimated that up to 22% of woman above the age of 60 suffer from some degree of fecal incontinence (Bharucha A, 2005). However, many believe that this estimation does not fully reflect reality, due to the fact that large portions of those suffering from fecal incontinence do not seek medical treatment, due to embarrassment or absence of knowledge of treatment options. In addition, some primary care physicians do not initiate discussions about fecal incontinence or are not fully aware of treatment modalities and, therefore, many patients suffer this condition in silence and at great psychological expense (Norton N, 2008; Kuehn B, 2006).

A wide array of treatment options allow some degree of improvement in quality of life in those suffering from fecal incontinence. In mild cases, the ability to match a suitable diet with the combination of anti-diarrhea medications and fiber supplements may improve quality of life. Retraining of the pelvic floor muscles, with or without biofeedback, is a non-invasive treatment, which to date constitutes the first line of treatment in patients with mild to moderate incontinence, and partially may improve control and quality of life in 65–89% of patients (according to various series of studies). However, this treatment only rarely can restore full controllability without any on-going incidents of incontinence (Ozturk R, 2004).

Several more invasive treatment methods have been developed as well. These methods include a variety of interventional treatments, some that are minimally invasive, such as the delivery of bulking agents into the sphincters which thicken the tissue around the anal canal. However, the results of injectable bulking agents suggest that although they may improve control, they rarely achieve full control and long term follow up shows gradual deterioration of any initial beneficial effect. Other approaches require surgical intervention, such as the implant of active prosthetics around the anus or pacemakers implanted on the sacral nerves roots (not yet approved in the United States). More invasive procedures for the treatment of incontinence, such as the implantation of prosthetic sphincters, involve major surgery, are associated with a significant risk of complications, and may not be suitable for high risk patients.

It should also be noted that globally (outside the United States) there are anal plugs available for patients who suffer fecal incontinence. While these plugs have been proven safe and effective, they are generally not tolerable, and therefore not in widespread use. This is because the plugs are made of porous, semi-absorbent material (like tampons) and their diameter is significantly larger than the diameter of an empty rectum or of the anal canal even at full relaxation. As a result, the pressure applied on the rectum and anal canal walls causes a severe urge for immediate defecation. Over a third of patients in the clinical trials of these plugs drop out of the study (Deutekom M 2005). Figures 1A and 1B show two types of anal plugs commercially available in Europe; specifically, Figure 1A shows a Coloplast polyurethane anal plug and Figure 1B shows a MedSSE polyvinyl-alcohol anal tampon (both are superimposed on the rectal anatomy).

Figure 1A. Coloplast polyurethane anal tampon.

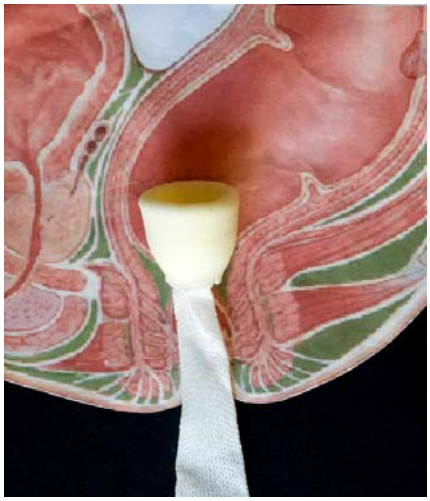
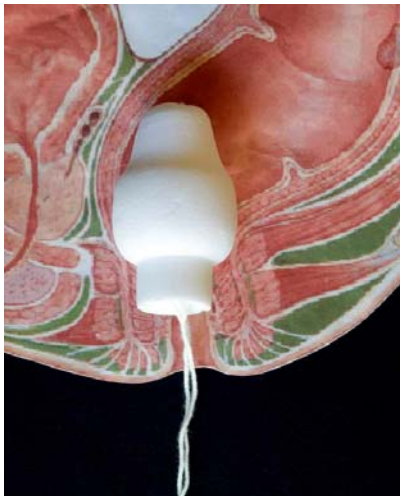


Figure 1B. MedSSE polyvinyl-alcohol anal tampon.



In the United States, there is also an FDA-cleared silicone bowel catheter device with a balloon cuff (ProCon2), which obstructs the lower rectum and prevents the loss of fecal material. This device is more complicated to use than an anal plug and must be manually inflated upon insertion, then deflated and removed prior to defecation. The catheter balloon is filled with 30 cc of water and may cause restricted blood flow to the surrounding capillaries, so its use beyond 8 hours is not recommended.

Figure 2. The ProCon2 device superimposed on the rectal anatomy.

Despite all of the options available to patients suffering from fecal incontinence, there is general consensus that many patients fail conservative treatments and/or do not receive complete control from more invasive treatments over time. Further, ongoing seepage of even small amounts of feces—solids and/or liquids—can cause a great deal of patient suffering. Even when this soiling is absorbed using a pad, it is frequently accompanied by a substantial bad odor which causes great embarrassment and patient anguish. Likewise, the continuous contact of the fecal substance with the skin around the anus can cause substantial skin breakdown, irritation, itching, and pain. Therefore, despite improvement in control, many treated patients continue to suffer the effects of fecal incontinence. Hence, there remains a large unmet clinical need for improved treatments for accidental bowel leakage due to fecal incontinence.

4. DEVICE DESCRIPTION

A. Intended Use/Indications for Use

The Enshur Insert is a single use anal insert device intended to act as a barrier to the passage of fecal matter through the rectum. The device is intended for self-insertion after a demonstration of use.

The Enshur Insert is indicated for the management of accidental bowel leakage due to fecal incontinence.

B. Technological Characteristics

The Enshur Insert is comprised of two main components: a soft silicone anal insert and a finger tip applicator. The device comes pre-assembled in individual, single use blister packs. **Figure 3** shows the Enshur Insert on the fingertip of a patient. **Figure 4** and **Table 1** show and describe the functions of all of the Enshur Insert components and packaging materials.

Figure 3. The Enshur Insert on the Fingertip of a Patient

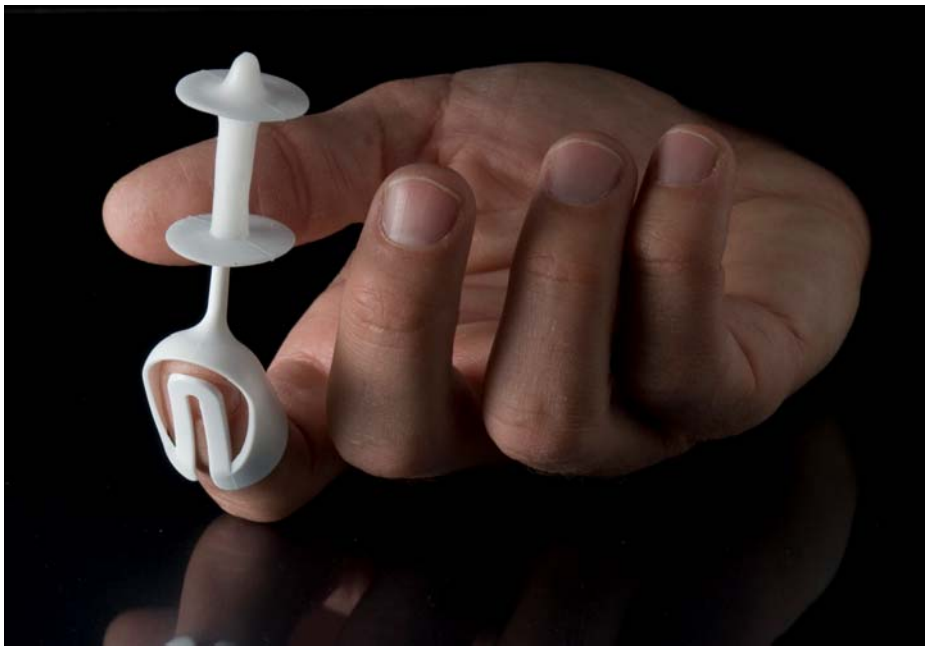


Figure 4. Enshur Insert Device Components and Packaging

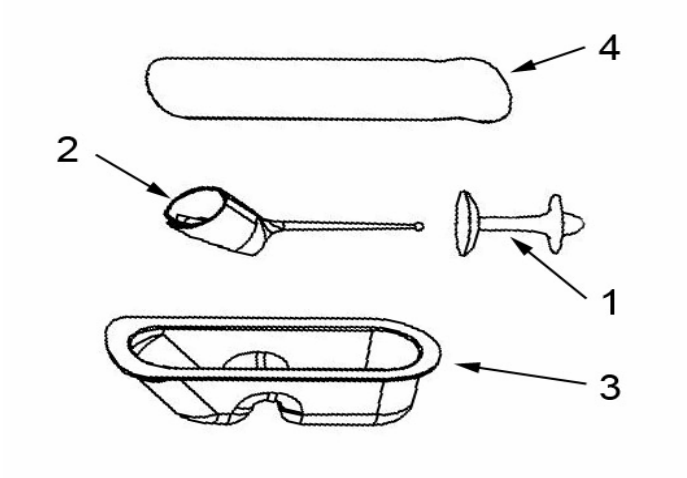


Table 1. Components of the Enshur Insert

Device Components	Part name	Material	Function
1	Enshur Anal Insert	Silicone (shore A3)	Seals lower rectum and reduces accidental bowel leakage due to fecal incontinence
2	Applicator	Polypropylene	Used to insert the Silicone anal plug in the anal canal
Packaging			
3	Blister package	Polystyrene	Contains the Silicone anal plug in a non-sterile package
4	Blister cover	Nylon or Tyvek	Peel-off cover, heat welded to the blister pack

1. The Enshur Insert

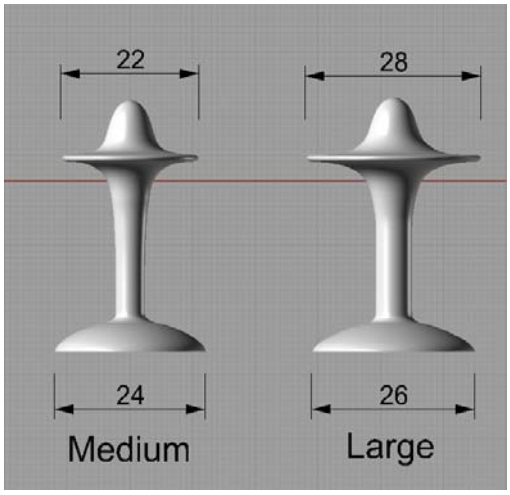
The Enshur Insert is manufactured from very soft, fully-polymerized, shore hardness A3 medical grade silicone. **Figure 5** shows the ease with which the Enshur Insert is deformed. This softness is a key factor in making the Enshur Insert safe, as well as imperceptible to the user.

Figure 5. Demonstration of the softness and deformability of the Enshur Insert

a. Size

As depicted in **Figure 6**, below, the Enshur Insert is available in two sizes: medium and large. The differences in size are primarily the diameter of the upper portion of the Enshur Insert and the lower disk. The various sizes are designed to accommodate a variety of lower rectum anatomies. The length of the Enshur Insert, regardless of size, is 40 mm. The upper disc diameter of the Enshur Insert ranges from 22–28 mm and the external lower disc diameter ranges from 24–26 mm.

Figure 6. Dimensions of Medium, and Large Enshur Inserts (mm).



Figures 7 and **8** below show an Enshur Insert positioned over the rectal anatomy and in a cast of the lower rectum and anal canal of an FI patient.

Figure 7. The Enshur Insert superimposed on the anatomy of the anal canal with a blue cast of the lower rectum and anal canal of an actual FI patient on the right.

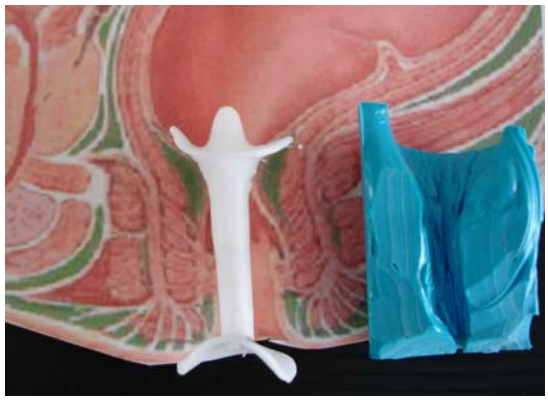
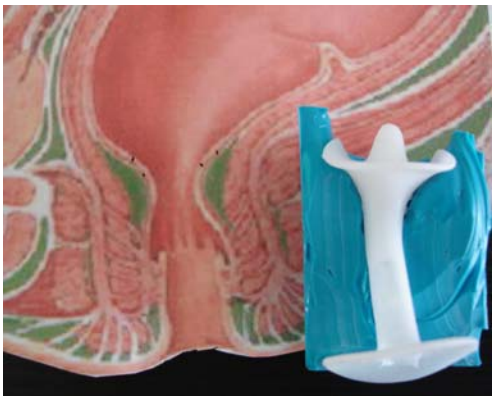


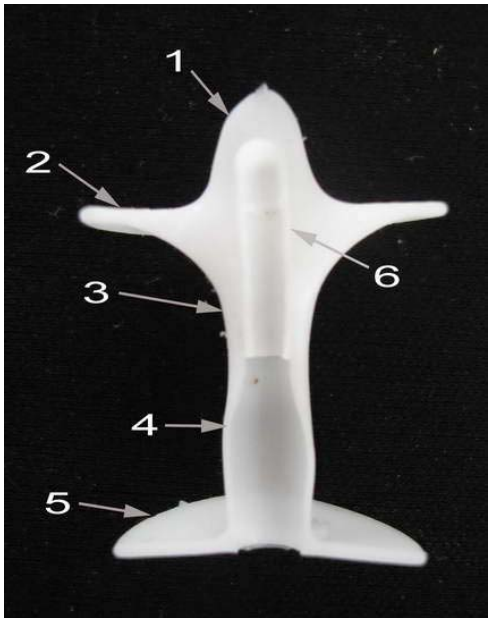
Figure 8. The Enshur Insert fitted into the cast of the rectum and anal canal of an actual FI patient.



Six key features of the Enshur Insert, which are depicted in **Figure 9**, below, include:

1. Nose cone for easy insertion,
2. Soft upper disk for sealing at bottom of rectum,
3. Cylindrical seal against the anal canal high pressure zone,
4. Thin highly-elastic stem to accommodate variable length anal canals,
5. Bottom disk which rests outside the anus to retain Insert in position,
6. Internal sleeve to prevent applicator perforation.

Figure 9. Key features of the Enshur Insert



2. Internal Sleeve

The internal sleeve of the Enshur Insert is made of shore hardness A20 medical-grade silicone. The internal sleeve is permanently press fit inside the Enshur Insert and serves to prevent perforation of the device by the applicator rod. (See **Figure 9**, feature 6, above).

3. Applicator

The fingertip applicator of the Enshur Insert is made of medical grade polycarbonate. The rod of the applicator is positioned inside the Enshur Insert and enters 5 cm into the anal canal in order to insert the device. This applicator is highly flexible, as is shown in **Figure 10**, below, in order to prevent damage to the anal canal in the unlikely event that the applicator comes into direct contact with the anal canal. The fingertip applicator and Enshur Insert come preassembled, as depicted in **Figure 3**. Both the applicator and Enshur Insert are single use devices.

Figure 10. The applicator is highly flexible to prevent damage to the anal canal.

4. Packaging

The Enshur Insert comes packaged individually in non-sterile, single use polyethylene teraphthalate (PET) blister packs with a heat-welded, peel-off, nylon cover.

C. Principles of Operation

The Enshur Insert is a simple-to-use, patient inserted device. **Figure 3**, above, shows the Enshur Insert positioned on the fingertip of a patient and ready for self-insertion.

Conceptually, the Enshur Insert is self-inserted into the anus and anal canal with a motion similar to inserting a tampon. Once the patient removes the Enshur Insert from the blister pack, they simply position the applicator on their finger (See **Figure 3**) and then push the Enshur Insert gently into the anus until the fingertip applicator touches the entrance of the anus. The top disk of the Enshur Insert is soft and flexible (1 mm thick shore hardness A3 silicone) and folds backwards during insertion into the anal canal, thereby minimizing resistance to insertion. Once the patient feels the fingertip applicator at the entrance to the anus, the patient gently withdraws his finger with the applicator, thus properly positioning the Enshur Insert in the lower rectum and anal canal. (See **Figure 7**, above). During applicator withdrawal, the Enshur Insert easily slides off of the applicator because the resistance of the rectum against the upper portion of the Enshur Insert is higher than the friction holding the Enshur Insert on the applicator. The bottom disk of the Enshur Insert remains outside the anus to keep the device positioned in the anal canal and to prevent migration of the Enshur Insert into the rectum. The fingertip applicator is discarded and the Enshur Insert remains in position until it is evacuated naturally and effortlessly during the patient's next bowel movement, without further intervention by the patient.

The Enshur Insert is designed to remain in place until the patient's next natural bowel movement, after which the patient should insert a new Enshur Insert. The Enshur Insert is intended for continuous wear for patients who suffer accidental bowel leakage due to fecal incontinence.

Should a patient desire to remove an Enshur Insert at any time, the patient can simply pull on the Enshur Insert's external bottom disc, positioned just outside the anus (see **Figure 7**, feature 5). Using this technique, the Enshur Insert can be removed with very little effort.

Note that in the Netherlands pilot study, it was anecdotally reported that occasionally an Enshur Insert came out when the patient sat down to urinate. While this did not affect patient overall satisfaction with the device, nor did it raise questions related to safety or efficacy, the company is interested in better understanding the frequency with which insert loss with urination occurs prior to beginning the US pivotal study. This is the sole purpose of the proposed Enshur PLUS short 3 week clinical study.

5. INSTRUCTIONS FOR USE

The following provides an overview of the step-by-step instructions for use. The Instructions for Use (IFU) and Frequently Asked Questions (FAQ) are attached as **Appendix 4**.

1. Wash your hands. Do not use an Enshur Insert package unless it is fully sealed. Carefully peel the top of the package label back to fully expose the Enshur Insert.
2. Insert index finger into fingertip applicator.
3. With one foot resting up on toilet, reach under lifted leg to position top of Enshur Insert at anus.
4. Relax your muscles, and gently push the Enshur Insert into anus until the fingertip applicator touches the anus. Stop applying pressure once you feel the fingertip applicator pressing up against the outer anus as the Insert is now in place.
5. Once the fingertip applicator is touching the anus, gently withdraw fingertip applicator. The bottom disc of the Enshur Insert should be resting just outside the anus.

   Important: If the Enshur Insert comes out of the anus or is not seated well against the anus, do not try and push it in further with the applicator or your finger. Instead, remove the Enshur Insert by pulling on the bottom disc resting outside the anus and discard. Open a new Enshur Insert package and repeat steps 1–5, using slightly greater pressure to push the fingertip applicator against the anus to insert the Enshur Insert slightly deeper.

6. Discard fingertip applicator and wash hands.
7. Replace your Enshur Insert after your next natural bowel movement.

6. RISK BENEFITS

The potential adverse events that may be associated with the Enshur Insert are anticipated to be primarily gastrointestinal system related events associated with the presence of the Enshur Insert in the rectum and anal canal.

It is very important to emphasize, that while there are always potential risks associated with the use of anal plugs in general, as well as risks specific to the Enshur Insert, these risks are considered minimal. In a variety of conventional commercial anal plug studies in Europe, the main adverse event associated with the plug has been a significant urge to evacuate (due to the plug's porous, semi-absorbent nature and large size). As the Enshur Insert is a smaller, non-porous, soft silicone insert, the risks associated with the Enshur Insert are considered to be lower than those of commercially available anal plug products.

The specific potential adverse events associated with the Enshur Insert are described below:

The potential risks associated with the Enshur Insert upon insertion are:

- Unintentional wounding of the external anus, anal canal, or rectal wall during the insertion process.
- Unintentional perforation of the anal canal or rectum during the insertion process.
- Unintentional insertion of the device too deeply in the rectum and anal canal such that the entire Enshur Insert, including the lower disk, rests above the anal canal in the lower rectum until it will be evacuated in the next bowel movement.

Potential risks associated with the Enshur Insert being present in the rectum and anal canal are:

- Feeling of discomfort
- Pain
- Erosion
- Feeling of burning
- Feeling of itching
- Edema
- Swelling
- Feeling of numbness
- Urge to evacuate
- Device migration

Potential risks associated with the Enshur Insert if the patient were to pull the Enshur Insert out once inserted:

- Partial or full tearing of the insert's 'anchoring' bottom disc (see Figure 9 feature 5) from the body of the insert, resulting in the remainder of the insert remaining in the lower rectum and anal canal until it will be evacuated in the next bowel movement.
- In spite of the force applied to manually evacuate the insert, the insert is enveloped with hard feces and, thus, may not evacuate easily with subsequent bowel movements.

Potential risks associated with Enshur Insert evacuation:

- The insert becomes enveloped with hardened feces, and does not naturally evacuate as a part of the natural bowel movement.
- The insert gets stuck in the anal canal, thus blocking natural bowel movement.
- While the company has not observed any prior incident of blockage or obstruction, the insertion of a temporary insert into the rectum and anal canal may lead to a risk of obstruction.

To minimize these potential risks, a number of safety measures have been taken into consideration in designing the Enshur Insert. These measures include:

- The size and shape of the insert's delivery tip are smaller than the applicator tips broadly used in commercial anal plug applicators. The rod of the applicator is highly flexible to accommodate the curvature of the anal canal. The applicator rod is also designed to collapse in case of a misdirected insertion.
- The Enshur Insert size and design have been minimized to easily enter the anus, anal canal, and lower rectum.
- The Enshur Insert material is a soft, medical-grade, silicone that has a superb long-term safety record in long term contact with a broad variety of human tissues. The Enshur Insert is highly deformable and can be evacuated in any orientation in its entirety through the anal canal without damaging the anal canal tissue or causing discomfort. The Enshur Insert is smaller and of similar hardness of fecal matter, which naturally flows through the anus.
- A patient may choose to lubricate the insert's distal (nose cone) end, reducing friction and thus minimizing the probability of tissue penetration by the insert during insertion.
- The Enshur Insert's bottom disk remains outside the anus, enabling the patient to manually remove the insert at any time, if so desired.

Possible Benefits

The Enshur Insert has been designed to reduce the incidence of involuntary soiling in patients who suffer accidental bowel leakage due to fecal incontinence. The Enshur Insert is self-delivered by the patient; the design and size of the plug allow for sealing the involuntary passage of fecal material from the rectum into the anal canal. Note that to date in the small based European pilot study, the Enshur Insert is proving to be effective at reducing bowel leakage and patients report that the device is highly tolerable.

7. HUMAN CLINICAL INVESTIGATIONS

To date, the company has conducted two small European clinical studies in the development and initial feasibility testing of the Enshur Insert. Each of these studies is described below.

1. Proof-of-Concept Study

The company conducted a small proof-of-concept study in Turkey in 2007. This study was conducted by Professor Bulent Mentes at Gazi University Hospital in Ankara, Turkey. The three patient study was conducted with Ethical Committee approval and was the first in-man anatomical study, which served as the basic proof-of-concept for the Enshur Insert design. Specifically, the study examined the feasibility of the Enshur Insert's significantly smaller design compared to other commercially available plugs for management of fecal incontinence.

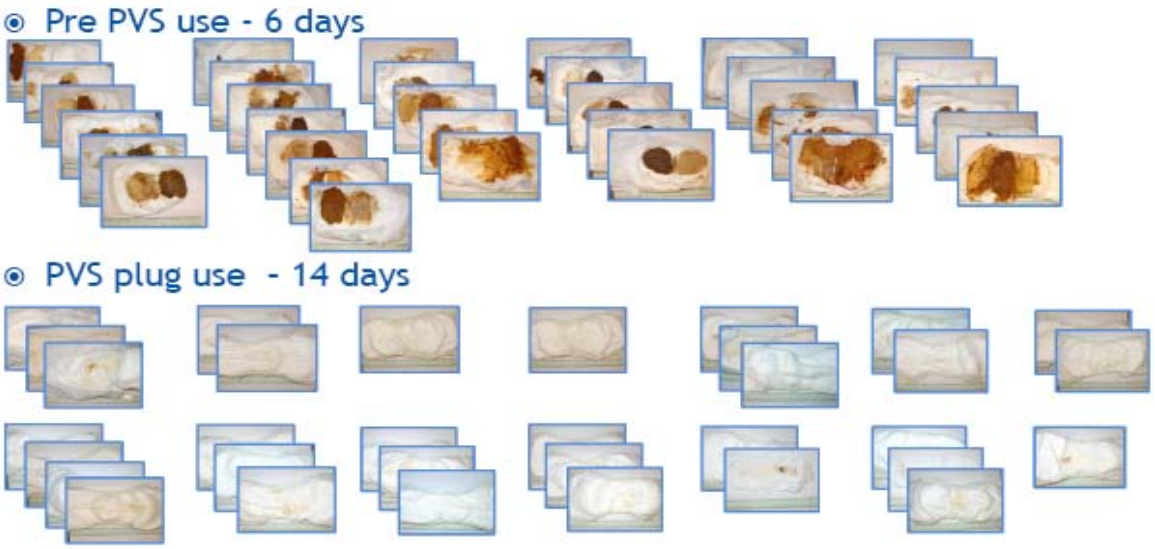
In this study, dental casting material in the form of liquid Poly Vinyl Siloxane (PVS) was injected into the subject's anal canal where it hardened in-situ into an anal plug that conformed to the anatomy of the subject. When the PVS material hardened, it formed a plug that conformed exactly to the subject's anatomy. The company hypothesized that this type of plug could be both

efficacious and tolerable. An example of the in-situ PVS anal plug that was formed by a patient who participated in this study is shown in **Figure 12**, below.

Figure 12. PVS plug formed in the anal canal of a patient in the Turkey feasibility trial.

During the study, subjects evacuated the PVS plugs during their normal bowel movements, with no further intervention required. **Figure 13**, below, shows an example of a subject's FI condition at baseline (pre-PVS use) and during the treatment period.

Figure 13. Turkish feasibility study. Patient data before and during PVS in-situ forming plug.



No formal report of the study was completed; however, based on informal communications with the primary study investigator, Enshur understands that patients reported the PVS plugs were tolerable and resulted in reduced soiling. Significantly, Enshur is unaware of any adverse events that occurred during the study.

The PVS plugs created during this study provided the first-in-human impressions of the rectal anatomy of FI patients. The negative casts of the PVS rectal anatomy impressions served as the basis for the present pre-formed silicone Enshur Insert design.

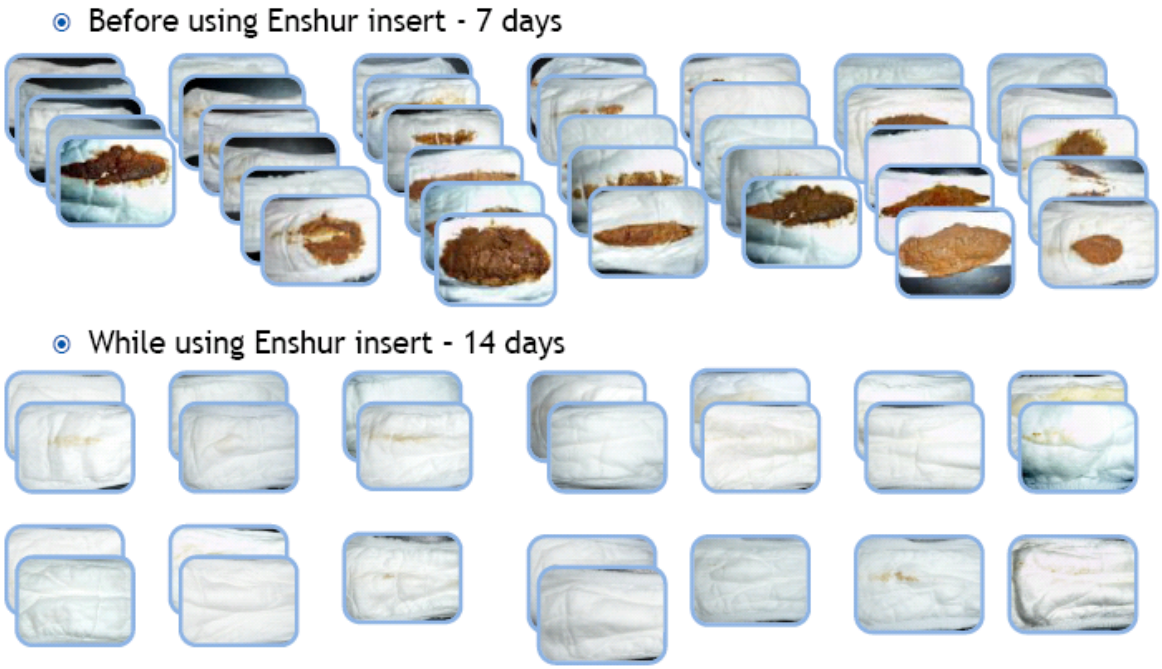
2. European Pilot Study

The company is currently conducting a small-based European pilot study in the Netherlands at the Academic Medical Center, Amsterdam. This six patient pilot study is being conducted by Dr J. Frederik M. Slors, M.D., PhD, Department of Surgery/Colorectal Surgery. This study is a prospective, open-label, single-arm, non-randomized study where subjects serve as their own controls. Each subject's baseline fecal incontinence condition is established by using the Wexner (U.S.) and St Mark's (U.K.) scales and daily diary entries of their bowel behavior, as well as photographic recording of the pads subjects are required to wear as part of the study. The baseline phase is followed by a treatment phase in which subjects use the Enshur Inserts continuously for a four-week period, while maintaining daily diary entries and photographic recordings. The final phase of the study is a one week return to baseline, during which subjects no longer use the Enshur Inserts, but continue to maintain daily diary and photographic recordings of their bowel behavior.

Note that the six-week Netherlands study protocol was submitted to the AMC Ethical Committee. However, the present small-based pilot study received an Ethical Committee exemption due to the low perceived safety risk associated with the Enshur Insert.

Although this study is not complete, preliminary reports indicate that subjects have been highly satisfied with the Enshur Inserts. There have been no adverse events reported and subjects have conveyed anecdotally the Enshur Inserts are virtually imperceptible and highly tolerable. Further, subjects are experiencing a noticeable reduction in bowel leakage as shown in **Figure 14**, below. This figure shows one subject's photographic records of the pads used during the baseline (control) period and those used during the treatment phase, while using the Enshur Inserts. During the treatment phase, this subject also reported more normal bowel movements than previously experienced. An interim summary of the Netherlands patient data is attached in **Appendix 1**.

Figure 14. European Pilot Study. Patient data before and during Enshur Insert use.



8. STUDY CONDUCT

Title	Enshur Plug Loss User Study (PLUS) to Observe Anal Insert Loss With Urination
Protocol	200CLD
Device	Enshur Anal Insert
Study Center	The medical office of Dr. Mark M. Segall, M.D. and the Samaritan Endoscopy Center, Los Gatos, CA
Sponsor	Enshur, Inc., 532 Emerson Street, Palo Alto, CA 94301 USA
IRB	Western Institutional Review Board (WIRB)
Indication	The Enshur Insert is indicated for the management of accidental bowel leakage due to fecal incontinence.

9. STUDY OBJECTIVES

The primary objective of this study is to better understand the frequency of Enshur Anal Insert loss (or expulsion) with urination. The study will also monitor the safety of the Enshur Insert for near continuous use throughout the 3-week study period. The primary safety endpoint will be the absence of any serious device related adverse events.

The study also has a secondary safety endpoint of not having any serious irritation of the anal canal or lower rectal mucosa due to near-continuous use of device during the study period. This will be assessed via pre and post anal canal and lower rectal mucosa evaluations.

10. STUDY DESIGN

Study Design	Prospective, open label, single-arm, non-randomized study designed to observe the frequency of Enshur Anal Insert loss with urination in patients with accidental bowel leakage due to fecal incontinence.
Timing	Spring 2008 3-week clinical study.
Number of patients:	15-20
Patients:	Patients suffering from moderate to severe accidental bowel leakage due to fecal incontinence
Protocol Overview:	Once patients have been enrolled in the study, they will be trained by a nurse under the supervision of the PI on how to use the Enshur Anal Insert device. Following this patient training, patients will begin a 3-week treatment period using the Enshur Anal Insert device. The devices will be self-administered and patients will be instructed to replace the inserts each time they are naturally evacuated with a bowel movement, such that the inserts are worn continuously throughout the 3-week user study period. Daily patient diary recordings will be maintained throughout the study period. The daily patient diaries will capture all bowel movement activity, as well as record when and how each Enshur Anal Insert is self-inserted and expelled. Throughout the study, patients will visit the study site weekly for Principal Investigator supervised Nurse follow up. At these weekly visits, the Nurses will review the patient's diary recordings from the previous week, complete a weekly questionnaire, and distribute whatever study materials (diaries, Enshur Inserts, etc) are needed for the next week. The Nurses will maintain a weekly visit schedule with each patient throughout the duration of the study. In addition, the Nurses will telephone the patients twice a week between visits to ensure the daily patient diaries are being properly recorded. The Nurses may also place additional telephone calls to patients at their discretion if they believe additional telephone follow-up would improve diary compliance between weekly patient visits. The Principal Investigator will examine the patients upon enrollment and again at the end of the 3 week Enshur Insert device use period (end of week 3). In addition, the Principal Investigator will be available during all weekly Nurse visits should Investigator assistance be required.

	For more detail see Study Procedures table in **Appendix 3**.
Inclusion Criteria	❑ Females aged 40 years and older ❑ Minimum Wexner Fecal Incontinence score or 12, AND reported at least weekly (score of 3 or 4) leakage of at least 2 of the 3 Wexner scale stool types (solid, liquid and gas) for the last month prior to inclusion in the study. The Wexner Scale is attached in **Appendix 2**. ❑ Patient must be able to comprehend the meaning of his/her participation in the study, and sign on the study's standard informed consent form. ❑ The patient understands and is capable to technically carry out his/her duties in the study, including self-administration of inserts and daily diary recordings. ❑ Patient must be fluent in English
Exclusion Criteria	❑ American Society of Anesthesiologists (ASA) score of 4 or higher (patients with severe systemic disease that is a constant threat to life) ❑ Spinal cord injury or other major neurological diagnosis (Parkinson, MS, etc) ❑ Known immune deficiency state ❑ Pregnancy ❑ Breastfeeding woman ❑ Inflammatory bowel disease ❑ Any patient requiring medication delivered by suppository ❑ Active perianal abscess or fistula ❑ Anismus which had not been completely resolved with treatment ❑ Active anal fissure ❑ Present rectal prolapse ❑ Third degree hemorrhoids or higher ❑ Anal stricture ❑ Rectal surgery in the past 6 months ❑ Patients with known allergy to silicone or one of its components ❑ Patients who are physically and/or mentally incapable of fully complying with the study's protocol

Patient Enrollment	Patients will be recruited from 3 sources: ❑ Newspaper advertising (to be followed by call center screening, then follow up Investigator staff telephone screening) ❑ Sponsor database of 10-12 consumers who have participated in previous consumer research regarding fecal incontinence who have expressed interest in being contacted for future research (letters will be sent to these consumers with instructions to telephone Investigator if interested; Investigator staff will conduct telephone screening) ❑ The Principal Investigator (will advise patients study is underway and screen patients if interested) Once patients have been screened by the Investigator staff to meet Inclusion/Exclusion criteria, and they express interest in being considered for participation in the study, they will be scheduled for a Screening appointment with the Principal Investigator. At the Screening appointment, the Principal Investigator will confirm the patient meets the study requirements and review the study protocol and informed consent. After this appointment, if the patient is qualified and still interested in participating in the study, they will be scheduled for a follow up Enrollment appointment. At the Enrollment appointment, the Principal Investigator will obtain the patient's informed consent and conduct the enrollment examinations—medical history recording, digital rectal exam, anoscope exam and sigmoidoscope exam. Any enrolled patient that has not had a Colonoscopy in the past 36 months, will also be scheduled for a colonoscopy to confirm that there are no other major GI disorders other than FI. Only patients who continue to meet the study requirements after the Enrollment appointment examinations will be continued in the study.
Patient Education and Training	All patients will be trained by the Nurse on how to use the Enshur Anal Insert. The Principal Investigator will be available during this training. The Enshur Anal Insert device use patient training will be conducted using the IFU and Frequently Asked Questions (see **Appendix 4**). Patients will also be instructed in how to properly complete the daily diary (see **Appendix 5**)

11. INFORMED CONSENT

Informed consent for the study is being separately submitted to WIRB.

12. PATIENT CONFIDENTIALITY

The company complies with the principle of patient's right to protection against invasion of privacy. Throughout this trial, all data will be identified only by an identification number and patient initials. The data will be blinded in all data analyses. The patient's informed consent is required to permit authorized company personnel (Study Monitor, Auditor, Investors, and Consultants) and relevant regulatory agencies to have direct access to personal medical data to ensure high quality standards of the study. The study subject should also be informed if privacy rights under this study are exempt from the confidentiality provisions of the Health Insurance Portability and Access Act of 1996 pursuant to 45 CFR § 512(b)(iii) and, if so, what components of study subject confidentiality will be maintained and by whom.

13. PATIENT DISCONTINUATION

If a patient is withdrawn from the study or fails to return either at his or her request or at the Principal Investigator's sole discretion, every effort should be made to determine the reason. This information will be recorded on the patient's case report form ("CRF").

Upon withdrawal, the patient will return to the Principal Investigator or nurse, as applicable, any remaining Enshur Inserts not used until the day of withdrawal.

14. INVESTIGATIVE CENTER SELECTION CRITERIA

This study is a company sponsored clinical trial. The Principal Investigator of the study is Dr. Mark M. Segall, M.D., a very well respected colorectal surgeon in the San Francisco Bay Area. The study will be conducted at his medical offices and, for those patients requiring Colonoscopy, at the Samaritan Endoscopy Center in Los Gatos, California.

15. INSTITUTIONAL REVIEW BOARD

Western Institutional Review Board ("WIRB") will be the approving IRB for the Enshur Plug Loss User Study (PLUS) to Observe Anal Insert Loss With Urination.

16. STUDY PROCEDURES

See Study Procedures table in **Appendix 3**.

17. STATISTICAL PLAN

The study is designed to provide information regarding the frequency of Enshur Anal Insert loss with urination. However, due to the small planned sample size of 15-20 patients—which is

considered adequate by the sponsor and Principal Investigator for this type of study—the study is not designed nor expected to show statistical significance. The company will collect descriptive statistics for the following parameters:

- Frequency of Enshur Anal Insert loss with urination as recorded in patient daily diaries

Adverse events will be coded and presented according to coding dictionary MedDRA system organ class and preferred term. All adverse events will be presented by frequency, severity, and relation to the study device.

Note that in the Netherlands pilot study there have been no adverse events of any kind reported.

18. SUBJECT POPULATION(S) FOR ANALYSIS

The entire study population will be analyzed.

19. SAFETY AND ADVERSE EVENTS

Adverse events either reported by patients participating in the study or observed by the Principal Investigator will be assessed by the Investigator and will be individually listed on the adverse event form after the patient has signed the informed consent, and throughout the study. The following information will be recorded: the specific event or condition, whether the event was present pre-study, the dates and times of occurrence, duration, severity, relationship to the Enshur Insert, specific countermeasures, and outcome.

Note that all observed serious or unexpected adverse events, whether deemed device related or not, will be fully recorded and reported in writing by the Principal Investigator to Enshur, Inc. within 24 hours of becoming aware of the event and to WIRB within 48 hours of becoming aware of the event. The Principal Investigator will also need to complete the CRF Serious Adverse Event Form and fax it to the Enshur Medical Monitor, Alfred L. Hurwitz, M.D.

Pursuant to 21 C.F.R. § 812.146(b), the sponsor will immediately evaluate any unanticipated adverse device effect. The results of such an evaluation will be reported to FDA, the reviewing IRB, and study investigators within 10 working days after the sponsor first receives notice of the effect, as required under 21 C.F.R. § 812.150(b).

Any additional information (follow-up) about any serious or unexpected adverse event unavailable at the initial reporting should be forwarded by the site to the Enshur Medical Monitor as soon as they become available.

Enshur will also submit serious or unexpected adverse event reports to the local authorities, if required, according to all WIRB guidelines and local regulations.

20. SAFETY MONITORING BOARD

Alfred L. Hurwitz, M.D. will serve as the Medical Monitor for the proposed Enshur PLUS clinical study. .

21. STUDY MONITORING, AUDITING, AND INSPECTING

Study monitoring, auditing and inspecting will occur weekly.

22. REGULATORY OR HEALTH AUTHORITY AUDITS

Regulatory authorities may request access to all study records.

23. CASE REPORT FORMS

Patients will complete a daily diary for each day of participation in the study. These diaries will become part of the patients CRF.

The Enshur Inserts will be kept in a secure, limited-access, room temperature storage area at the investigational site. Only authorized personnel will have access to the study devices.

Once dispensed to patients enrolled in the study, the Enshur Inserts do not require any special handling. Patients will be instructed to store the devices at room temperature where they typically maintain personal hygiene products.

24. DEVICE ACCOUNTABILITY

Complete traceability records will be kept of all devices during the study. Specifically, a study accountability log will be completed to maintain accurate records of all Enshur Insert study inventory.

25. DISPENSING OF STUDY DEVICE

Enshur Inc. will supply the Enshur Inserts to the investigational site. The Enshur Inserts will come in non-sterile, single use blister packages and will be appropriately labeled.

The Enshur Inserts will be manufactured and packaged in Israel by Enshur Inc. and/or its designated sub-contractors in compliance with the GMP principles and guidelines applicable to investigational medical devices of a similar gastrointestinal nature.

26. RETURN OR DESTRUCTION OF STUDY DEVICE

All unused study devices will be returned to the Principal Investigator at the end of each week of the study period. These unused study devices will first be properly accounted for in the Enshur

Insert PLUS study device accountability log and then will be returned to the company sponsor and destroyed.

27. RECORDS RETENTION

The Principal Investigator will retain copies of the approved protocol, completed CRFs, informed consent documents, relevant source documents, and all other supporting documentation related to the project in a secured and safe facility for one of the following periods based on notification from the Sponsor:

- A period of at least 6 months after completion of the clinical study of the investigational product as confirmed by the Sponsor;
- Or longer if required by local regulations.

These files must be made available for inspection upon reasonable request by authorized representatives of Enshur Inc. or the corresponding regulatory agencies.

Enshur Inc. will provide the Principal Investigator with information concerning the current status of the investigational medical device as it relates to the investigator's obligation for the retention of study records. The Principal Investigator should contact Enshur Inc. prior to disposing of any such records and to provide written notification to the Sponsor of any change in the location, disposition, or custody of the study files. Enshur Inc. will arrange for continued storage of all records, if necessary.

28. PROTOCOL MODIFICATIONS

All protocol modifications will be recorded according to good quality document control best practices. All modifications and revisions will be noted and summarized on the front cover of this protocol document, and reported to WIRB as required.

29. REFERENCES

- Bharucha A., Gastroenterology 2005; 129: 42–49: Prevalence and Burden of Fecal Incontinence: A Population Based Study in Women.
- Kuehn B., JAMA 2006; 295(12): 1362-1363: Silence Masks Prevalence of Fecal Incontinence.
- Norton, N., Digestive Disease Week 2008: Fecal Incontinence Quality of Life Impact.
- Ozturk, R., Aliment Pharacol Ther. 2004 Sept 15; 20(6): 667–74: Long-term outcome and objective changes of anorectal function after biofeedback therapy for faecal incontinence.
- Deutekom, M., Cochrane Database of Systemic Reviews 2005; Issue 3: Art. No. CD005086: Plugs for containing faecal incontinence (review).

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APPENDIX 1

Netherlands Pilot Study to Determine the Safety and Preliminary Effectiveness of the Enshur Anal Insert Interim Report (as submitted to FDA)

Background

The company is currently conducting a 6 patient European pilot study of the Enshur device in the Netherlands at the Academic Medical Center, Amsterdam. The study is a prospective, open-label, single arm, non-randomized study where subjects serve as their own controls. Subjects were enrolled based upon having a screening fecal incontinence condition equivalent to a Wexner score of 10 or greater, as well as a demonstrated one week baseline condition also equivalent to a minimum Wexner score of 10. The baseline condition was established by using daily diary entries of their bowel behavior, as well as photographic recording of the pads subjects are required to wear as part of the study.

The baseline phase was followed by a treatment phase in which subjects use the Enshur Inserts continuously for a 3-4 week period, while maintaining daily diary entries and photographic recordings. The final phase of the study is a one week return to baseline, during which subjects no longer use the Enshur Inserts, but continue to maintain daily diary and photographic recordings of their bowel behavior.

This interim report summarizes the data collected for the first 4 patients enrolled in the study.

Safety

Although this study is not complete, no adverse events were reported among the 4 subjects who have completed the study. Further, all of the subjects chose to continue using the device post the study period, and no adverse events have been reported. Of note, as of December 2008, one patient has been using the device regularly and safely with no adverse events for 9 months.

Device Satisfaction

Usability data suggests that the Enshur device was well received in terms of overall patient experience. Note that the study protocol called for patients to complete a 3 week treatment phase, but that Patients 1 and 2 completed a 4 week treatment phase at the request of the company. This fourth week was added to gain experience with an alternative Large size of the device.

Enshur Usability Experience				
	Insert Use			
Overall Experience	Week 1	Week 2	Week 3	Week 4
1=Very Negative; 10=Very Positive				
Patient 1	9	10	4	8
Patient 2	9	9	9	10
Patient 3	8	7	8	NA
Patient 4	1	10	10	NA

Perceived Insert Importance to Quality of Life				
1=Not Important; 10=Highly Important				
Patient 1	10	10	10	10
Patient 2	9	9	9	10
Patient 3	5	8	10	NA
Patient 4	10	10	10	NA
Future Desire to Use Inserts				
1=Would not use; 10=Would use continuously				
Patient 1	10	10	10	10
Patient 2	10	10	10	10
Patient 3	10	10	10	NA
Patient 4	9	8	10	NA

Notes:
Overall Experience ratings: Patient 1 rated Week 3 as a 4 due to the device sticking to the applicator rod. This was a device related internal applicator rod lubrication issue and not patient related. The lubrication issue has been resolved; Patient 4 rated Week 1 as a 1 due to having her husband assist with insertion this week.

Device East of Use

Ease of Use and Insertion data suggests that the Enshur device was both easy to use and tolerable. Note that the lower Week 4 scores of Patient 1 related to sizing. Patients 1 and 2 used an alternate Large sized insert during this week that Patient 1 found uncomfortable.

Enshur Insertion Experience				
1-10 scale: 1=Very difficult; 10= Very easy/comfortable				
	Week 1	**Week 2**	**Week 3**	**Week 4**
The comfort of holding the applicator with the insert in hand				
Patient 1	10	10	10	6
Patient 2	8	10	10	10
Patient 3	10	10	10	NA
Patient 4	10	10	10	NA
The lubrication of the insert prior to delivery				
Patient 1	10	10	10	10
Patient 2	8	10	10	10
Patient 3	9	10	9	NA
Patient 4	5	10	10	NA
Navigation of the insert into the anus				
Patient 1	9	9	9	10
Patient 2	8	10	10	10
Patient 3	10	9	9	NA
Patient 4	9	10	10	NA
Sensation in the anus when the insert passes through the anus				
Patient 1	10	10	10	5
Patient 2	8	10	10	10
Patient 3	8	9	9	NA
Patient 4	10	10	9	NA
Sensation in the anal canal during insert insertion				

Patient 1	9	10	9	5
Patient 2	8	9	10	10
Patient 3	9	9	9	NA
Patient 4	9	10	10	NA
Sensation in the rectum during insert insertion				
Patient 1	9	9	10	5
Patient 2	8	9	10	10
Patient 3	9	8	8	NA
Patient 4	10	10	10	NA
Retracting applicator while securing insert in the rectum and anal canal				
Patient 1	10	10	1	6
Patient 2	6	5	10	10
Patient 3	6	4	8	NA
Patient 4	10	8	10	NA
Sensation in the anus and rectum area immediately after application retraction				
Patient 1	9	10	9	6
Patient 2	7	9	10	10
Patient 3	8	9	8	NA
Patient 4	7	9	9	NA

Efficacy

Patients were enrolled in the study based upon having a demonstrated fecal incontinence condition equivalent to a Wexner Fecal Incontinence score of 10 or greater. In general, this level of fecal incontinence condition is equivalent to a patient experiencing 3 or more leakage episodes per week. All subjects enrolled met this criteria both at the screening and baseline phases.

The pilot study had also intended to calculate Wexner scores on all patients at the end of the treatment phase as this is the anticipated primary efficacy endpoint in future pivotal studies. Unfortunately, two things happened in the pilot study: First, end treatment phase Wexner scores were not calculated on all patients in the study and this data is unavailable. Second, while all patients noticed a reduction in soiling when using the Enshur device as noted in their patient diary and photographic recordings, due to how the Wexner scale works, the 3-4 week treatment phase was too short to have an impact on the patient's end treatment phase Wexner scores.

In sum, the Netherlands pilot study interim data has not provided a validated read on efficacy. While the company believes the Enshur device was efficacious based on patient satisfaction and evidence provided in the patient diary recordings, a longer treatment phase is required when using the Wexner scale to assess efficacy. Based on the FDA's guidance, the US pivotal study will include a 90 day treatment phase which the company believes will overcome this limitation of the pilot study.

Other Findings

Plug Loss

It was noted that each of the 4 patients experienced some plug loss during urination. The plug loss was recorded anecdotally in the patient diary recordings, and did not impact patient

acceptance of the device or device safety. Patients also anecdotally conveyed that the plug loss was not a major concern during the study, as the expelled device was simply replaced with a new device when this happened. Patients also conveyed the plug loss was not inconvenient since it happened when they were on the toilet urinating and they were in the bathroom anyway.

Although the company judges this plug loss as a non-significant finding that did not affect device safety and efficacy, the company believes it prudent to better understand this finding. The pilot study did not include any formal recording of plug loss, and the company believes it would be helpful to better understand the frequency with which this is occurring and whether device size plays a role in the occurrence.

Conclusion

Overall, the company believes the Netherlands Pilot Study Interim data supports the FDA guidance to proceed into a US pivotal study. The interim results of this study demonstrate that the device is safe and that patients are highly satisfied with the Enshur Anal Insert. Further, patients enrolled in the study all expressed interest in continuing to use the device beyond the study period. The only finding the company would like to follow up on prior to starting the US pivotal study relates to plug loss. The company believes a 3-4 week investigation of this finding would be prudent prior to proceeding into the pivotal study.

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APPENDIX 2

PATIENT ENROLLMENT

WEXNER FECAL INCONTINENCE SCALE

The Enshur PLUS clinical study will enroll subjects who experience regular ongoing accidental bowel leakage who are of moderate to severe fecal incontinence as assessed using the Wexner Fecal Incontinence Scale.

To qualify for the study, subjects must:

- experience at least weekly (minimum score 3) on two of the three stool types (solid, liquid, gas);
- AND have a total Wexner score of 12 or higher

					Wexner Scale:
Soiling Type and Frequency	Never	Less Than Once A Month	Monthy	Weekly	Daily
No Control—Solids	0	1	2	3	4
No Control—Liquids	0	1	2	3	4
No Control—Gas	0	1	2	3	4
Use of Pads	0	1	2	3	4
Quality of Life Impact	0	1	2	3	4
Total Score:					Full Continence = 0; Fully Incontinent = 20

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APPENDIX 3

STUDY PROCEDURES

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PROCEDURES	SCREENING PHASE	ENROLLMENT PHASE	21 DAY DEVICE USE PHASE																					STUDY COMPLETION
Day In Study	-45-0	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Principal Investigator Visit		**1**								**2**							**3**							**4**
Nurse Visit		1								2							3							4
Nurse Telephone Call				1			2					3			4				5		6			
CALL CENTER SCREENING PHASE																								
Call center fields calls generated by clinical study advertising	x																							
Call center forwards potential research subjects who pass telephone screen	x																							
INVESTIGATOR SUPERVISED SCREENING PHASE																								
Investigator sends letter to sponsor database of consumers who have given permission to be contacted for future research; and to referring physicians to advise of clinical study	x																							
Investigator staff fields screening calls generated by invitation letters sent by study staff; or places follow up telephone call to potential research subjects who are forwarded by call center	x																							
For sujbects who pass follow up Investigator screen, they are scheduled for Screening Appointment with Investigator	x																							
INVESTIGATOR SCREENING APPOINTMENT																								
Confirm subjects meets Inclusion/Exclusion criteria	x																							
Review study protocol, procedures, and participation requirements	x																							
Review informed consent	x																							
INVESTIGATOR ENROLLMENT APPOINTMENT																								
Obtain signed written informed consent		x																						
Complete medical history		x																						
Conduct physical exam		x																						
Conduct digital rectal exam		x																						
Conduct analscope exam		x																						
Conduct sigmoidoscope exam		x																						
Schedule colonoscopy (if necessary per protocol)		x																						
Conduct colonoscopy (if necessary per protocol)		x																						
Confirm patient still meets Inclusion/Exclusion criteria		x																						
ENROLL PATIENT		x																						

ENSHUR INCORPORATED

PROCEDURES	SCREENING PHASE	ENROLLMENT PHASE	21 DAY DEVICE USE PHASE																					STUDY COMPLETION
Day In Study	-45-0	0	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	20	21	22
Principal Investigator Visit		**1**								**2**							**3**							**4**
Nurse Visit		1								2							3							4
Nurse Telephone Call				1			2					3			4				5		6			
INVESTIGATOR SUPERVISED PATIENT EDUCATION & TRAINING																								
Review subject participation requirements		x								x							x							
Review IFU/FAQ		x								x							x							
Train subject how to use device		x								x							x							
Train subject how to complete daily diary		x								x							x							
Review how to contact study staff at any time		x								x							x							
INVESTIGATOR SUPERVISED WEEKLY SUBJECT VISITS																								
External anal examination by nurse										x							x							x
Investigator examination (if necessary)										x							x							x
Review completeness of Daily Patient Diaries										x							x							x
Interview patient based on Weekly Nurse Questionnaire										x							x							x
Collect Daily Patient Diaries from previous week										x							x							x
Provide subject with devices for next week of study		x								x							x							
Record all devices distributed and received in study inventory log		x								x							x							x
PATIENT DAILY DIARY RECORDINGS																								
Complete daily diary			x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	x	
INVESTIGATOR STUDY COMPLETION APPOINTMENT																								
Conduct physical exam																								x
Conduct digital rectal exam																								x
Conduct analscope exam																								x
Conduct sigmoidoscope exam																								x

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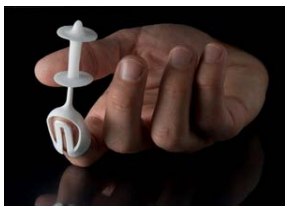
APPENDIX 4

INSTRUCTIONS FOR USE (IFU) & FREQUENTLY ASKED QUESTIONS (FAQ)

Note that the company is presently having illustrations made for the IFU as described below. These illustrations will be forwarded to WIRB as soon as they are available.

STEP BY STEP: HOW TO USE THE ENSHUR ANAL INSERT DEVICE

Step	Illustration	Text Instruction
1	Show two side by side images: first cut away image will show corner of top label being peeled back (1A); second larger image will show what package looks like fully opened with Insert resting inside package (1B).	**Wash your hands.** Do not use an Insert package unless it is fully sealed. Carefully peel the top of the package label back to fully expose the Anal Insert as shown in Figures 1A and 1B.
2	Show index finger placed inside finger tip applicator just prior to lifting Insert out of package (2A) Show fingertip applicator Insert resting correctly on finger and ready for insertion.  (2B)	**Insert index finger into fingertip applicator and lift Insert out of package** as shown in Figures 2A and 2B**. The Insert is now ready to use.**
3	Show illustration of person standing in insertion position, with arm extended around and behind bottom, and Insert tip at anus.	**With one foot resting up on toilet, reach under lifted leg to position top of Insert at anus.**

4	Show insertion process in 2 images: first as close up of insert at anus just prior to insertion (5A); and second, during middle of insertion with fingertip applicator touching anus (5B) Examples below:  (5A)  (5B)	**Relax your muscles, and gently push the Insert into anus until the fingertip applicator touches the anus as shown in Figures 5A and then 5B. Stop applying pressure once you feel the fingertip applicator pressing up against the outer anus as the insert is now in place.**
5	Show image of applicator rod out of anus and Insert resting inside anus and bottom disc just outside anus.	**Once the fingertip applicator is touching the anus, gently withdraw fingertip applicator. The bottom disc of the insert should be resting just outside the anus.** *Important: If the Insert comes out of the anus or is not seated well against the anus, do not try and push it in further with the applicator or your finger. Instead, remove it by pulling on the bottom disc resting outside the anus and discard Insert. Then open a new Insert package and repeat steps 1–5, this time pushing the finger tip applicator a little bit harder up against the*

		anus to insert the Insert slightly deeper into the anus.
6	Show image of applicator rod going into trash can	**Discard fingertip applicator and wash hands.**
7		**Replace your Insert after your next natural bowel movement.**

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FREQUENTLY ASKED QUESTIONS

1. **Does inserting an Enshur Insert hurt?**

   The Enshur Inserts are easy to insert and use. Just follow the step-by-step directions. Inserting an Enshur Insert should not hurt.

   If you are having trouble inserting the Enshur Inserts, please contact the Nurse Study Coordinator at Dr Segall's office at telephone: 408-358-3500.

2. **How do I know when my Enshur Insert is in place?**

   When the Enshur Insert is in the right place, you won't feel any discomfort. If you do feel discomfort, remove and discard the Insert. Then open a new Insert and repeat step by step directions again. You may want to try pushing the finger tip applicator a little bit harder against the anus to insert the Insert slightly deeper into the anal canal. Always leave the bottom disc outside your body. Wash your hands. That's all there is to it.

3. **Can an Enshur Insert get lost inside my body?**

   No, Enshur Inserts are designed so the lower rectum and walls of the anal canal hold the Enshur Insert in place. In the unlikely event an Enshur Insert would travel up into the rectum, it would be harmlessly and naturally expelled with your next bowel movement. Enshur Inserts are also made out of very soft, medical grade silicone, which is pliable and should not cause any rectal obstruction.

   If at any time you believe an entire Insert is up inside your body, please contact the Nurse Study Coordinator at Dr Segall's office at telephone: 408-358-3500.

4. **Can I shower, bathe and be physically active when I'm wearing my Enshur Insert?**

   Yes, you can maintain all of your regular activities while using an Enshur Insert.

5. **What if the recommended insertion position of standing with one foot up on the toilet is uncomfortable or makes me feel unstable?**

   You may want to try sitting or squatting over the toilet and reaching either between or behind your legs. You should use the insertion position that is most comfortable for you.

6. **How often should I wear my Enshur Insert?**

   You should wear your Insert until your next natural bowel movement. The Insert will be naturally expelled with your next bowel movement. After you complete your bowel movement, you should insert a new Insert.

7. **How do I remove my Enshur Insert?**

   You should not remove your Insert as it is designed to be naturally expelled with your next bowel movement. If for some reason you feel a need to remove it, simply pull on the external disc resting just outside your anus and the Insert is easily removed.

8. **What if my Enshur Insert is difficult to remove?**

   Again, the Insert is not intended to be removed. But if for some reason you cannot remove it, please contact Dr Segall's office immediately at telephone: 408-358-3500.

   Note: If at any time during the study period you experience any issues with the Anal Insert devices provided to you, please contact your Nurse study coordinator at Dr Segall's office as soon as possible

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APPENDIX 5

PATIENT DAILY DIARY

PLEASE BE SURE TO RECORD ALL OF THE INSERT DEVICES YOU USE EACH DAY

IT IS ALSO IMPORTANT TO RECORD ALL OF THE BOWEL MOVEMENTS YOU HAVE EVERY DAY

Please record both your CONTROLLED and UNCONTROLLED bowel movements:

- **CONTROLLED bowel movements are when you made it to the toilet and opened your bowel in the toilet**
- **UNCONTROLLED bowel movements are when you experienced accidental soiling while either trying to make it to the toilet or because you were unaware you were having a bowel movement**

THANK YOU FOR COMPLETING THIS DAILY DIARY

PLEASE REMEMBER TO BRING YOUR DAILY DIARIES TO YOUR NEXT SCHEDULED APPOINTMENT

THE STUDY NURSE WILL BE REVIEWING YOUR DIARIES WITH YOU

SHOULD YOU NEED TO CONTACT THE STUDY STAFF REGARDING THIS DIARY OR FOR ANY REASON,

PLEASE DO NOT HESITATE TO CONTACT THE STUDY NURSE AT DR SEGALL'S OFFICE AT TEL: 358-3500

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DAILY BOWEL MOVEMENT AND INSERT USE DIARY

In the table that follows, please place a tick mark to record the times of all of your bowel movements. Please also place a tick mark at the times that you put in a new Insert device, and the times they came out.

Time	Controlled BM: Opened Bowel in Toilet	Uncontrolled BM: Experienced Accident/ Soiling	Put New Insert In	Time Insert Came Out	Did Insert come out with a BM in the toilet? Yes/ No	If No, please describe how and when the Insert came out. Please be sure to record ANY instance when an Insert came out when it did not come out with a bowel movement (BM)
12:00am						
12:30am						
1:00am						
1:30am						
2:00am						
2:30am						
3:00am						
3:30am						
4:00am						
4:30am						
5:00am						
5:30am						
6:00am						
6:30am						
7:00am						
7:30am						
8:00am						
8:30am						
9:00am						
9:30am						
10:00am						
10:30am						

11:00am						
Time	Controlled BM: Opened Bowel in Toilet	Uncontrolled BM: Experienced Accident/ Soiling	Put New Insert In	When Insert Came Out	Did Insert come out with a BM in the toilet? Yes/ No	If No, please describe how and when the Insert came out. Please be sure to record ANY instance when an Insert came out when it did not come out with a bowel movement (BM)
11:30am						
12:00pm						
12:30pm						
1:00pm						
1:30pm						
2:00pm						
2:30pm						
3:00pm						
3:30pm						
4:00pm						
4:30pm						
5:00pm						
5:30pm						
6:00pm						
6:30pm						
7:00pm						
7:30pm						
8:00pm						
8:30pm						
9:00pm						
9:30pm						
10:00pm						
10:30pm						
11:00pm						
11:30pm						

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DAILY ANAL INSERT USE EXPERIENCE SUMMARY

In TOTAL, beginning with the first Anal Insert you used today, **how many Anal Inserts did you use today?** Please record all the Anal Inserts you used today, including any that you might have had to discard for any reason	**Record Number Here:**	
Did you wear an Anal Insert while you were **sleeping last night**? **If NO, please describe:**	Yes	No
Did you use the Anal Inserts at all times when you were **at home** today? **If NO, please describe:**	Yes	No
Did you use the Anal Inserts at all times when you were **away from home** today? **If NO, please describe:**	Yes	No
Did you **have any trouble inserting** the Anal Inserts today? **If YES, please describe completely:**	Yes	No
Did you **have to discard any Anal Inserts today** either because you had difficulty inserting it properly or for any other reason? **If YES, please describe:**	Yes	No

Please tell us how tolerable/ comfortable the Anal Inserts were that you used today.
Would you say the silicone anal plugs were (**please check only one response**)

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Extremely Intolerable/ Uncomfortable	Somewhat Intolerable/ Uncomfortable	Neither Tolerable Nor Intolerable	Somewhat Tolerable/ Comfortable	Extremely Tolerable/ Comfortable

Please answer the following questions:	Yes	No	If YES, please describe:
Did you wear pads today?			
Did you take any anti-diarrhea medications today?			
Did you administer an enema or suppository today?			

Please record any other comments you have for the study researchers here:

THANK YOU FOR COMPLETING THIS DAILY DIARY
SHOULD YOU NEED TO CONTACT THE STUDY STAFF FOR FOR ANY REASON,
PLEASE DO NOT HESITATE TO CONTACT THE STUDY NURSE AT DR SEGALL'S OFFICE AT TEL: 358-3500

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: Enshur Plug Loss User Study (PLUS) to Observe Anal Insert Loss With Urination

PROTOCOL NO.: 200CLD
WIRB® Protocol #20090416

SPONSOR: Enshur, Inc.
Palo Alto, California
United States

INVESTIGATOR: Mark M. Segall, M.D.
Suite 202
15195 National Avenue
Los Gatos, California 95032-2631
United States

SITE(S): Mark M. Segall, M.D., A Medical Corporation
Suite 202
15195 National Avenue
Los Gatos, California 95032
United States

Samaritan Endoscopy Center
Suite 204
15195 National Avenue
Los Gatos, California 95032
United States

STUDY-RELATED PHONE NUMBER(S): Mark M. Segall, M.D.
408-358-3500 (24 hours)

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

SUMMARY

You are being asked to be in a research study. The purpose of this consent form is to help you decide if you want to be in the research study. Please read this form carefully. To be in a research study you must give your informed consent. "Informed consent" includes:

- Reading this consent form,
- Having the study doctor or staff explain the research study to you,
- Asking questions about anything that is not clear, and
- Taking home an unsigned copy of this consent form. This gives you time to think about it and to talk to family or friends before you make your decision.

You should not join this research study until all of your questions are answered.

Things to know before deciding to take part in a research study:

- The main goal of a research study is to learn things to help patients in the future.
- The main goal of regular medical care is to help each patient.
- No one can promise that a research study will help you.
- Taking part in a research study is entirely voluntary. No one can make you take part.
- If you decide to take part, you can change your mind later on and withdraw from the research study.
- The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.
- Parts of this study may involve standard medical care. Standard care is the treatment normally given for a certain condition or illness.
- This study will also involve the use of an investigational Anal Insert medical device. An investigational device is one that has not been approved by the U.S. Food & Drug Administration (FDA).
- After reading the consent form and having a discussion with the research staff, you should know which parts of the study are experimental and which are standard medical care.
- Your medical records may become part of the research record. If that happens, your medical records may be looked at and/or copied by the sponsor of this study and government agencies or other groups associated with the study.
- Your medical insurance may be billed for any standard medical care you receive during the research study. If your insurance company is billed then it may have access to the research records. Insurance companies may not pay for treatment that is part of a research study. Taking part in a research study could affect your current or future insurance coverage.

After reading and discussing the information in this consent form you should know:

- Why this research study is being done;
- What will happen during the research;
- What drug or device or procedures will be used;
- Any possible benefits to you;

- The possible risks to you;
- The other medical procedures, drugs or devices that could be used instead of being in this research study; and
- How problems will be treated during the study and after the study is over.

If you take part in this research study, you will be given a copy of this signed and dated consent form.

PURPOSE OF THE STUDY
The purpose of this study is to observe how well the Anal Insert investigational medical device stays in place. The investigational device, once inserted, is designed to stay in place until it is expelled with a natural bowel movement. The purpose of this study is to observe whether the investigational medical device is expelled at any other times, especially during urination.

Previously, the investigational Anal Insert medical device in this study was studied in the Netherlands at the Academic Medical Center (AMC) under the supervision of Dr. Frederick Slors. Four subjects completed a 7-8 week study of the investigational medical device. These four subjects found the device to be both effective and tolerable at helping to control their accidental bowel leakage due to bowel incontinence. There were also no adverse events reported. However, the subjects noted that sometimes the investigational medical device came out at unintended times.

This study is being conducted to better understand how frequently the investigational medical device is expelled with a natural bowel movement, and if and how frequently, it comes out at any other times.

PROCEDURES
If you provide informed consent and enroll in the study, you will receive the following exams at their Enrollment appointment:

- Digital rectal exam
- Anoscope exam
- Sigmoidoscope exam

All of the above procedures are standard of care for a patient presenting with accidental bowel leakage due to bowel incontinence.

In addition, if you have not had a colonoscopy in the past 36 months, you will be scheduled for a colonoscopy to rule out other medical conditions before participating in the research study. Typically, standard of care is colonoscopy every 5-10 years. Thus, if you are scheduled for colonoscopy and have had the procedure more than 3, but less than 5-10 years ago, the procedure would be an additional procedure and not standard of care. After the Enrollment appointment, if you still qualify for the study, you will be trained how to use the investigational Anal Insert medical device and will be provided product and daily diaries to begin participation in the study.

At the completion of the study, you will again receive the following exams:

- □ Digital rectal exam
- □ Anoscope exam
- □ These exams are being conducted to observe the anal mucosa at the completion of the study and are additional exams that you might not otherwise receive as standard of care, but are required as part of the study plan.

There will be no placebo in this study.

RISKS AND DISCOMFORTS
RELATED TO THE INVESTIGATIONAL MEDICAL DEVICE

The potential risks associated with the investigational Enshur Anal Insert medical device are anticipated to be largely associated with the presence of the investigational device in the rectum and anal canal.

The risks specific to the investigational Anal Insert medical device are considered minimal. In a variety of conventional commercial anal plug studies in Europe, the main adverse event associated with anal plugs has been a significant urge to evacuate (due to the plug's porous, semi-absorbent nature and large size). Because the investigational Anal Insert in this study is a smaller, non-porous, soft silicone insert, the risks associated with the investigational Enshur Anal Insert are considered to be lower than those of commercially available U.S. Food and Drug Administration (FDA) cleared anal plug products.

There have been no adverse events reported with the investigational Enshur Anal Insert device among the four subjects who have used the device in a 7-8 week clinical study in the Netherlands.

The specific potential adverse events associated with the investigational Enshur Anal Insert device are described below:

The potential risks associated with the investigational device upon insertion are:

- □ Unintentional wounding of the external anus, anal canal, or rectal wall during the insertion process.
- □ Unintentional perforation (causing a hole) of the anal canal or rectum during the insertion process.
- □ Unintentional insertion of the device too deeply, such that the entire investigational device rests above the anal canal in the lower rectum until it will be evacuated in the next bowel movement.

Potential risks associated with the investigational device being present in the rectum and anal canal are:

- □ Discomfort
- □ Pain
- □ Erosion (breakdown of tissues)
- □ Burning
- □ Itching
- □ Swelling
- □ Numbness
- □ Urge to have a bowel movement
- □ Device migration (moving out of place)

Potential risks associated with investigational device upon evacuation:

- □ The device becomes enveloped with hardened feces, and does not naturally evacuate as a part of the natural bowel movement.
- □ The insert gets stuck in the anal canal, thus blocking natural bowel movement.

Measures to minimize potential risks include:

- □ The size and shape of the insert's delivery tip are smaller than the applicator tips broadly used in commercial anal plug applicators. The rod of the applicator is highly flexible to accommodate the curvature of the anal canal. The applicator rod is also designed to collapse in case of a misdirected insertion.
- □ The investigational Anal Insert device size and design have been minimized to easily enter the anus, anal canal, and lower rectum.
- □ The investigational Anal Insert device material is a soft, medical-grade, silicone that has a superb long-term safety record in long term contact with a broad variety of human tissues. The investigational device is highly deformable and can be evacuated in any orientation in its entirety through the anal canal without damaging the anal canal tissue or causing discomfort. The device is also smaller and of similar hardness of fecal matter, which naturally flows through the anus.
- □ You may choose to lubricate the insert's distal (nose cone) end, reducing friction and thus minimizing the probability of tissue penetration by the insert during insertion.
- □ The device bottom disk remains outside the anus, enabling the patient to manually remove the insert at any time, if so desired.

There may be side effects that are not known at this time.

Your condition may not get better or may get worse during this study.

Only you should use the study anal insert device. It must be kept out of the reach of children or anyone else who may not be able to read or understand the label.

If you suspect that you have become pregnant, you must notify the study doctor immediately.

RISKS AND DISCOMFORTS
RELATED TO THE ANOSCOPE AND SIGMOIDOSCOPE EXAMS
The risks associated with the standard of care anoscope and sigmoidoscope exams are attached below. You must sign a separate consent form to have the anoscope and sigmoidoscope exams.

RISKS AND DISCOMFORTS
RELATED TO COLONOSCOPY (FOR THOSE RESEARCH SUBJECTS WHO HAVE NOT HAD ONE IN THE PAST 36 MONTHS)
The risks associated with the standard of care colonoscopy exam is attached below. You must sign a separate consent form to have the colonoscopy exam.

NEW INFORMATION
You will be told about anything new that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

BENEFITS
Your accidental bowel leakage may improve while you are in this study; however, this cannot be promised. The results of this study may help people with accidental bowel leakage due to bowel incontinence in the future.

COSTS
If you qualify for the study after the Enrollment appointment, you will have no costs for study procedures and appointments as described in the consent form. The sponsor will pay all costs related to the Enrollment, Weekly, and Study Completion appointments and insurance will not be billed for the procedures in these appointments.

If you have not had a colonoscopy in the past 36 months and are scheduled for a colonoscopy, insurance will be billed. The sponsor will pay all costs of the colonoscopy procedure not covered by insurance.

Enshur will provide the investigational Anal Insert device free of charge during this study.

If you are disqualified for the study after the Enrollment appointment due to having a condition which would exclude you from participating in the research study, your insurance will be billed for treatment of this condition. You will then be billed for the costs of the treatment of this condition not covered by insurance.

If you develop a condition that requires medical care during the course of the study period, insurance will be billed for this condition. You will be billed for the costs of the treatment of this condition not covered by insurance.

Ask your study doctor to discuss the costs that will or will not be covered by the sponsor. This discussion should include the costs of treating side effects. Otherwise, you might have unexpected expenses from being in this study.

PAYMENT FOR PARTICIPATION
If you still qualify for the study after the Enrollment appointment, you will be scheduled for three additional weekly study appointments. At each of these three appointments, you will receive a $50 gift card for each completed weekly diary and study visit. If you do not finish the study, you will be paid only for the visits you have completed.

If you complete all of the study daily diaries and weekly study visits, you will receive an additional $ 100 gift card at the completion of the study.

ALTERNATIVE TREATMENT
This is not a treatment study. Your alternative is not to participate in this study.

CONFIDENTIALITY
Information from this study will be given to the sponsor. "Sponsor" includes any persons or companies which are contracted by the sponsor to have access to the research information during and after the study.

The information will also be given to the U.S. Food and Drug Administration (FDA). It may be given to governmental agencies in other countries where the study drug may be considered for approval. Medical records which identify you and the consent form signed by you will be looked at and/or copied for research or regulatory purposes by:

- the sponsor;

and may be looked at and/or copied for research or regulatory purposes by:

- the FDA;
- Department of Health and Human Services (DHHS) agencies;
- governmental agencies in other countries; and
- the Western Institutional Review Board® (WIRB®).

Absolute confidentiality cannot be guaranteed because of the need to give information to these parties. The results of this research study may be presented at meetings or in publications. Your identity will not be disclosed in those presentations.

COMPENSATION FOR INJURY
If you are injured or get sick as a result of being in this study, call the study doctor immediately. The study doctor will provide emergency medical treatment. Your insurance will be billed for this treatment. The sponsor will pay any charges that your insurance does not cover. No other payment is routinely available from the study doctor or sponsor.

By signing this consent form, you will not give up any legal rights.

VOLUNTARY PARTICIPATION AND WITHDRAWAL
Taking part in this study is voluntary. You may decide not to take part or you may leave the study at any time. Your decision will not cause any penalty or loss of benefits to which you are entitled.

The study doctor or the sponsor may stop your participation in this study at any time without your consent for any of the following reasons:

- it is in your best interest;
- you do not later consent to any future changes that may be made in the study plan;
- if you are not compliant with the study daily diary requirements;
- or for any other reason.

If you leave the study before the planned final visit, you may be asked by the study doctor to have some of the end of study procedures done.

SOURCE OF FUNDING FOR THE STUDY
The sponsor, Enshur, Inc., will pay for this research study.

QUESTIONS
Contact Dr. Mark M. Segall at 408-358-3500 (24 hours) for any of the following reasons:

- if you have any questions about this study or your part in it
- if you feel you have had a research-related injury or a bad reaction to the study device, or
- if you have questions, concerns, or complaints about the research

If you have questions about your rights as a research subject or if you have questions, concerns, or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)
3535 Seventh Avenue, SW
Olympia, Washington 98502
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com.

WIRB is a group of people who independently review research.

WIRB will not be able to answer some types of questions, such as questions about appointment times. You may contact WIRB if you cannot reach the research team or if you want to talk to someone else.

Do not sign this consent form unless you have had a chance to ask questions and have gotten satisfactory answers.

If you agree to be in this study, you will receive a signed and dated copy of this consent form and the Experimental Subject's Bill of Rights for your records.

CONSENT
I have read this consent form. All my questions about the study and my part in it have been answered. I freely consent to be in this research study.

By signing this consent form, I have not given up any of my legal rights.

_____
Subject Name (printed)

CONSENT SIGNATURE:

_____ _____
Signature of Subject Date

_____ _____
Signature of Person Conducting Informed Consent Discussion Date

CONSENT FOR EXAMINATION FOR ANOSCOPE AND SIGMOIDOSCOPE EXAMS

In order to accurately assess you for participation in the research study, the following exams will be performed at the Enrollment appointment:

- Digital rectal exam
- Anoscope exam
- Sigmoidoscope exam

These exams are standard of care for patients who experience accidental bowel leakage due to bowel incontinence.

ANOSCOPE - a short instrument to examine the anus and hemorrhoid area.

PROCTOSCOPE – (rigid sigmoidoscope, proctosigmoidoscope) – a rigid 25 centimeter lighted instrument to examine the inner lining of the rectum.

If an abnormality (such as polyps or cancer) is found, a biopsy or polypectomy is usually performed at the time.

RISKS
The above procedures, as with any procedures, have some risk. The main risks with these procedures are bleeding or perforation (a hole caused) of the bowel. With any procedure, there is a risk of death.

CONSENT:
I have read the above information. I agree to participate in this study. I have discussed the risks, benefits, alternatives, and have been given an opportunity to ask questions.

By signing this consent form, I have not given up any of my legal rights.

_____
Subject Name (printed)

CONSENT SIGNATURE:

_____ _____
Signature of Subject Date

_____ _____
Signature of Person Conducting Informed Consent Discussion Date

CONSENT FOR COLONOSCOPY EXAMINATION

Colonoscopy is a procedure in which the clinician can look into your colon with a flexible lighted tube. This tube is about the thickness of your index finger and is inserted into the rectum and advanced slowly into the colon (large intestine). A small amount of tissue (biopsy) may be removed for examination in the laboratory under a microscope. Polyps (abnormal growths from the colon lining), if present, will also be removed and sent for tissue analysis.

If you have not had a colonoscopy in the past 36 months, you will be scheduled for a colonoscopy to rule out other medical conditions before participating in the research study. Typically, standard of care is colonoscopy every 5-10 years. Thus, if you are scheduled for colonoscopy and have had the procedure more than 3, but less than 5- 10 years ago, the procedure will be an additional procedure

The benefits of the procedure include the early diagnosis and assistance with the treatment of disease. Those diseases might include colorectal cancer.

There are risks to this procedure, although we believe that the potential benefits outweigh the risks.

- Bleeding is rare, but possible. With severe bleeding, you might even need blood transfusions or require surgery.
- Perforation (a small hole through the bowel wall) is rare, but if it happens, you would probably need to be hospitalized and have surgery.
- The medication that we give to prevent pain and discomfort can cause adverse reactions. If these medications are injected, they can cause redness and swelling of the arm. Any medication can cause an allergic or adverse reaction.
- With any procedure, there is a risk of death.

There are alternatives to colonoscopy, including x-ray studies, but they do not allow us to directly see the areas or take a biopsy. If you have questions about this procedure, please ask us. There is a small possibility that a significant lesion can be missed with a colonoscopy exam.

CONSENT:
I have discussed the risks, benefits, alternatives, and have been given an opportunity to ask questions.

I ACKNOWLEDGE THAT I HAVE BEEN INSTRUCTED BY DR. SEGALL, OR HIS STAFF, TO TAKE MY REGULAR HEART AND BLOOD PRESSURE MEDICATION WITH SIPS OF WATER THE -MORNING OF THE PROCEDURE AND THAT I NEED A FRIEND OR FAMILY MEMBER TO DRIVE ME HOME AFTER THE PROCEDURE. NO EXCEPTIONS.

I have read the above and agree to allow Dr. Segall to perform the colonoscopy with biopsies and polyp removal, if needed.

By signing this consent form, I have not given up any of my legal rights.

_____
Subject Name (printed)

CONSENT SIGNATURE:

_____ _____
Signature of Subject Date

_____ _____
Signature of Person Conducting Informed Consent Discussion Date

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information may be used and given to others?
The study doctor will get your personal and medical information. For example:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits.
- Information gathered for this research about:
  - Physical exams
  - Test results
  - Diaries and questionnaires
- Records about the study device.

Who may use and give out information about you?
The study doctor and the study staff.

Who might get this information?

- The sponsor of this research. "Sponsor" means any persons or companies that are:
  - working for or with the sponsor, or
  - owned by the sponsor.

Your information <u>may</u> be given to:

- The U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- Governmental agencies in other countries and
- Western Institutional Review Board® (WIRB®)

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to see if the research was done right.

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

May I withdraw or revoke (cancel) my permission?
This permission will be good until December 31, 2011.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
There is a risk that your information will be given to others without your permission.

Authorization:
I have been given the information about the use and disclosure of my health information for this research study. My questions have been answered.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

_____
Subject Name (printed)

AUTHORIZATION SIGNATURE:

_____	_____
Signature of Subject	Date
_____	_____
Signature of Person Conducting Informed Consent Discussion	Date

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

California law, under Health & Safety Code Section 24172, requires that anyone who is asked to be in a research study (medical experiment), or who is asked to agree for someone else to be in a research study, has the right to know the following:

1. Both the nature and reason for the research study or experiment.

2. What will happen during the research study, and what drug or device will be used.

3. Any expected discomforts and risks from taking part in the research.

4. Any possible benefits to being in the research.

5. The risks and benefits of any non-experimental medical procedures, drugs, or devices that could be used instead of being in the research.

6. How research related complications will be treated during and after the research study is over.

7. Questions can be asked about the research and about anything that will be done during the research study.

8. The research subject can stop taking part in the research study at any time for any reason without penalty or loss of benefits.

9. A copy of their signed and dated consent form will be given to subjects.

10. The research subject can take the time needed to decide if they want to take part in the research study. No one can pressure, force or unduly influence any person to take part in research.

_____ _____

Signature of Subject Date

_____ _____

Signature of Witness Date

APPROVED
Mar 16, 2009
WIRB®

RESEARCH SUBJECT INFORMATION AND CONSENT FORM

TITLE: Enshur Plug Loss User Study (PLUS) to Observe Anal Insert Loss With Urination

PROTOCOL NO.: 200CLD
WIRB® Protocol #20090416

SPONSOR: Enshur, Inc.
Palo Alto, California
United States

INVESTIGATOR: Mark M. Segall, M.D.
Suite 202
15195 National Avenue
Los Gatos, California 95032-2631
United States

SITE(S): Mark M. Segall, M.D., A Medical Corporation
Suite 202
15195 National Avenue
Los Gatos, California 95032
United States

Samaritan Endoscopy Center
Suite 204
15195 National Avenue
Los Gatos, California 95032
United States

STUDY-RELATED PHONE NUMBER(S): Mark M. Segall, M.D.
408-358-3500 (24 hours)

This consent form may contain words that you do not understand. Please ask the study doctor or the study staff to explain any words or information that you do not clearly understand. You may take home an unsigned copy of this consent form to think about or discuss with family or friends before making your decision.

SUMMARY

You are being asked to be in a research study. The purpose of this consent form is to help you decide if you want to be in the research study. Please read this form carefully. To be in a research study you must give your informed consent. "Informed consent" includes:

- Reading this consent form,
- Having the study doctor or staff explain the research study to you,

- Asking questions about anything that is not clear, and
- Taking home an unsigned copy of this consent form. This gives you time to think about it and to talk to family or friends before you make your decision.

You should not join this research study until all of your questions are answered.

Things to know before deciding to take part in a research study:

- The main goal of a research study is to learn things to help patients in the future.
- The main goal of regular medical care is to help each patient.
- No one can promise that a research study will help you.
- Taking part in a research study is entirely voluntary. No one can make you take part.
- If you decide to take part, you can change your mind later on and withdraw from the research study.
- The decision to join or not join the research study will not cause you to lose any medical benefits. If you decide not to take part in this study, your doctor will continue to treat you.
- Parts of this study may involve standard medical care. Standard care is the treatment normally given for a certain condition or illness.
- This study will also involve the use of an investigational Anal Insert medical device. An investigational device is one that has not been approved by the U.S. Food & Drug Administration (FDA).
- After reading the consent form and having a discussion with the research staff, you should know which parts of the study are experimental and which are standard medical care.
- Your medical records may become part of the research record. If that happens, your medical records may be looked at and/or copied by the sponsor of this study and government agencies or other groups associated with the study.
- Your medical insurance may be billed for any standard medical care you receive during the research study. If your insurance company is billed then it may have access to the research records. Insurance companies may not pay for treatment that is part of a research study. Taking part in a research study could affect your current or future insurance coverage.

After reading and discussing the information in this consent form you should know:

- Why this research study is being done;
- What will happen during the research;
- What drug or device or procedures will be used;
- Any possible benefits to you;
- The possible risks to you;
- The other medical procedures, drugs or devices that could be used instead of being in this research study; and
- How problems will be treated during the study and after the study is over.

If you take part in this research study, you will be given a copy of this signed and dated consent form.

PURPOSE OF THE STUDY

The purpose of this study is to observe how well the Anal Insert investigational medical device stays in place. The investigational device, once inserted, is designed to stay in place until it is

expelled with a natural bowel movement. The purpose of this study is to observe whether the investigational medical device is expelled at any other times, especially during urination.

Previously, the investigational Anal Insert medical device in this study was studied in the Netherlands at the Academic Medical Center (AMC) under the supervision of Dr. Frederick Slors. Four subjects completed a 7-8 week study of the investigational medical device. These four subjects found the device to be both effective and tolerable at helping to control their accidental bowel leakage due to fecal incontinence. There were also no adverse events reported. However, the subjects noted that sometimes the investigational medical device came out at unintended times.

This study is being conducted to better understand how frequently the investigational medical device is expelled with a natural bowel movement, and if and how frequently, it comes out at any other times.

PROCEDURES
If you provide informed consent and enroll in the study, you will receive the following exams at their Enrollment appointment:

- Digital rectal exam
- Anoscope exam
- Sigmoidoscope exam

All of the above procedures are standard of care for a patient presenting with accidental bowel leakage due to fecal incontinence.

In addition, if you have not had a colonoscopy in the past 36 months, you will be scheduled for a colonoscopy to rule out other medical conditions before participating in the research study. Typically, standard of care is colonoscopy every 5-10 years. Thus, if you are scheduled for colonoscopy and have had the procedure more than 3, but less than 5-10 years ago, the procedure would be an additional procedure and not standard of care. After the Enrollment appointment, if you still qualify for the study, you will be trained how to use the investigational Anal Insert medical device and will be provided product and daily diaries to begin participation in the study.

At the completion of the study, you will again receive the following exams:

- □ Digital rectal exam
- □ Anoscope exam
- □ Sigmoidoscope exam These exams are being conducted to observe the anal mucosa at the completion of the study and are additional exams that you might not otherwise receive as standard of care, but are required as part of the study plan.

There will be no placebo in this study.

RISKS AND DISCOMFORTS
RELATED TO THE INVESTIGATIONAL MEDICAL DEVICE

The potential risks associated with the investigational Enshur Anal Insert medical device are anticipated to be largely associated with the presence of the investigational device in the rectum and anal canal.

The risks specific to the investigational Anal Insert medical device are considered minimal. In a variety of conventional commercial anal plug studies in Europe, the main adverse event associated with anal plugs has been a significant urge to evacuate (due to the plug's porous, semi-absorbent nature and large size). Because the investigational Anal Insert in this study is a smaller, non-porous, soft silicone insert, the risks associated with the investigational Enshur Anal Insert are considered to be lower than those of commercially available U.S. Food and Drug Administration (FDA) cleared anal plug products.

There have been no adverse events reported with the investigational Enshur Anal Insert device among the four subjects who have used the device in a 7-8 week clinical study in the Netherlands.

The specific potential adverse events associated with the investigational Enshur Anal Insert device are described below:

The potential risks associated with the investigational device upon insertion are:

- □ Unintentional wounding of the external anus, anal canal, or rectal wall during the insertion process.
- □ Unintentional perforation (causing a hole) of the anal canal or rectum during the insertion process.
- □ Unintentional insertion of the device too deeply, such that the entire investigational device rests above the anal canal in the lower rectum until it will be evacuated in the next bowel movement.

Potential risks associated with the investigational device being present in the rectum and anal canal are:

- □ Discomfort
- □ Pain
- □ Erosion (breakdown of tissues)
- □ Burning
- □ Itching
- □ Swelling
- □ Numbness
- □ Urge to have a bowel movement
- □ Device migration (moving out of place)

Potential risks associated with investigational device upon evacuation:

- □ The device becomes enveloped with hardened feces, and does not naturally evacuate as a part of the natural bowel movement.
- □ The insert gets stuck in the anal canal, thus blocking natural bowel movement.

Measures to minimize potential risks include:

- □ The size and shape of the insert's delivery tip are smaller than the applicator tips broadly used in commercial anal plug applicators. The rod of the applicator is highly flexible to accommodate the curvature of the anal canal. The applicator rod is also designed to collapse in case of a misdirected insertion.
- □ The investigational Anal Insert device size and design have been minimized to easily enter the anus, anal canal, and lower rectum.
- □ The investigational Anal Insert device material is a soft, medical-grade, silicone that has a superb long-term safety record in long term contact with a broad variety of human tissues. The investigational device is highly deformable and can be evacuated in any orientation in its entirety through the anal canal without damaging the anal canal tissue or causing discomfort. The device is also smaller and of similar hardness of fecal matter, which naturally flows through the anus.
- □ You may choose to lubricate the insert's distal (nose cone) end, reducing friction and thus minimizing the probability of tissue penetration by the insert during insertion.
- □ The device bottom disk remains outside the anus, enabling the patient to manually remove the insert at any time, if so desired.

There may be side effects that are not known at this time.

Your condition may not get better or may get worse during this study.

Only you should use the study anal insert device. It must be kept out of the reach of children or anyone else who may not be able to read or understand the label.

If you suspect that you have become pregnant, you must notify the study doctor immediately.

RISKS AND DISCOMFORTS
RELATED TO THE ANOSCOPE AND SIGMOIDOSCOPE EXAMS
The risks associated with the standard of care anoscope and sigmoidoscope exams are attached below. You must sign a separate consent form to have the anoscope and sigmoidoscope exams.

RISKS AND DISCOMFORTS
RELATED TO COLONOSCOPY (FOR THOSE RESEARCH SUBJECTS WHO HAVE NOT HAD ONE IN THE PAST 36 MONTHS)
The risks associated with the standard of care colonoscopy exam is attached below. You must sign a separate consent form to have the colonoscopy exam.

NEW INFORMATION
You will be told about anything new that might change your decision to be in this study. You may be asked to sign a new consent form if this occurs.

BENEFITS
Your accidental bowel leakage may improve while you are in this study; however, this cannot be promised. The results of this study may help people with accidental bowel leakage due to fecal incontinence in the future.

COSTS
If you qualify for the study after the Enrollment appointment, you will have no costs for study procedures and appointments as described in the consent form. The sponsor will pay all costs related to the Enrollment, Weekly, and Study Completion appointments and insurance will not be billed for the procedures in these appointments.

If you have not had a colonoscopy in the past 36 months and are scheduled for a colonoscopy, insurance will be billed. The sponsor will pay all costs of the colonoscopy procedure not covered by insurance.

Enshur will provide the investigational Anal Insert device free of charge during this study.

If you are disqualified for the study after the Enrollment appointment due to having a condition which would exclude you from participating in the research study, your insurance will be billed for treatment of this condition. You will then be billed for the costs of the treatment of this condition not covered by insurance.

If you develop a condition that requires medical care during the course of the study period, insurance will be billed for this condition. You will be billed for the costs of the treatment of this condition not covered by insurance.

Ask your study doctor to discuss the costs that will or will not be covered by the sponsor. This discussion should include the costs of treating side effects. Otherwise, you might have unexpected expenses from being in this study.

PAYMENT FOR PARTICIPATION
If you still qualify for the study after the Enrollment appointment, you will be scheduled for three additional weekly study appointments. At each of these three appointments, you will receive a $50 gift card for each completed weekly diary and study visit. If you do not finish the study, you will be paid only for the visits you have completed.

If you complete all of the study daily diaries and weekly study visits, you will receive an additional $ 100 gift card at the completion of the study.

ALTERNATIVE TREATMENT
This is not a treatment study. Your alternative is not to participate in this study.

CONFIDENTIALITY
Information from this study will be given to the sponsor. "Sponsor" includes any persons or companies which are contracted by the sponsor to have access to the research information during and after the study.

The information will also be given to the U.S. Food and Drug Administration (FDA). It may be given to governmental agencies in other countries where the study drug may be considered for approval. Medical records which identify you and the consent form signed by you will be looked at and/or copied for research or regulatory purposes by:

- the sponsor;

and may be looked at and/or copied for research or regulatory purposes by:

- the FDA;
- Department of Health and Human Services (DHHS) agencies;
- governmental agencies in other countries; and
- the Western Institutional Review Board® (WIRB®).

Absolute confidentiality cannot be guaranteed because of the need to give information to these parties. The results of this research study may be presented at meetings or in publications. Your identity will not be disclosed in those presentations.

COMPENSATION FOR INJURY
If you are injured or get sick as a result of being in this study, call the study doctor immediately. The study doctor will provide emergency medical treatment. Your insurance will be billed for this treatment. The sponsor will pay any charges that your insurance does not cover. No other payment is routinely available from the study doctor or sponsor.

By signing this consent form, you will not give up any legal rights.

VOLUNTARY PARTICIPATION AND WITHDRAWAL
Taking part in this study is voluntary. You may decide not to take part or you may leave the study at any time. Your decision will not cause any penalty or loss of benefits to which you are entitled.

The study doctor or the sponsor may stop your participation in this study at any time without your consent for any of the following reasons:

- it is in your best interest;
- you do not later consent to any future changes that may be made in the study plan;
- if you are not compliant with the study daily diary requirements;
- or for any other reason.

If you leave the study before the planned final visit, you may be asked by the study doctor to have some of the end of study procedures done.

SOURCE OF FUNDING FOR THE STUDY
The sponsor, Enshur, Inc., will pay for this research study.

QUESTIONS
Contact Dr. Mark M. Segall at 408-358-3500 (24 hours) for any of the following reasons:

- if you have any questions about this study or your part in it
- if you feel you have had a research-related injury or a bad reaction to the study device, or
- if you have questions, concerns, or complaints about the research

If you have questions about your rights as a research subject or if you have questions, concerns, or complaints about the research, you may contact:

Western Institutional Review Board® (WIRB®)
3535 Seventh Avenue, SW
Olympia, Washington 98502
Telephone: 1-800-562-4789 or 360-252-2500
E-mail: Help@wirb.com.

WIRB is a group of people who independently review research.

WIRB will not be able to answer some types of questions, such as questions about appointment times. You may contact WIRB if you cannot reach the research team or if you want to talk to someone else.

Do not sign this consent form unless you have had a chance to ask questions and have gotten satisfactory answers.

If you agree to be in this study, you will receive a signed and dated copy of this consent form and the Experimental Subject's Bill of Rights for your records.

CONSENT
I have read this consent form. All my questions about the study and my part in it have been answered. I freely consent to be in this research study.

By signing this consent form, I have not given up any of my legal rights.

_____
Subject Name (printed)

CONSENT SIGNATURE:

_____ _____
Signature of Subject Date

_____ _____
Signature of Person Conducting Informed Consent Discussion Date

CONSENT FOR EXAMINATION FOR ANOSCOPE AND SIGMOIDOSCOPE EXAMS

In order to accurately assess you for participation in the research study, the following exams will be performed at the Enrollment appointment:

- Digital rectal exam
- Anoscope exam
- Sigmoidoscope exam

These exams are standard of care for patients who experience accidental bowel leakage due to fecal incontinence.

ANOSCOPE - a short instrument to examine the anus and hemorrhoid area.

FLEXIBLE SIGMOIDOSCOPE - a longer, flexible instrument to examine the inner lining of the rectum and lower colon.

If an abnormality (such as polyps or cancer) is found, a biopsy or polypectomy is usually performed at the time.

RISKS
The above procedures, as with any procedures, have some risk. The main risks with these procedures are bleeding or perforation (a hole caused) of the bowel. With any procedure, there is a risk of death.

CONSENT:
I have read the above information. I agree to participate in this study. I have discussed the risks, benefits, alternatives, and have been given an opportunity to ask questions.

By signing this consent form, I have not given up any of my legal rights.

_____
Subject Name (printed)

CONSENT SIGNATURE:

_____ _____
Signature of Subject Date

_____ _____
Signature of Person Conducting Informed Consent Discussion Date

CONSENT FOR COLONOSCOPY EXAMINATION

Colonoscopy is a procedure in which the clinician can look into your colon with a flexible lighted tube. This tube is about the thickness of your index finger and is inserted into the rectum and advanced slowly into the colon (large intestine). A small amount of tissue (biopsy) may be removed for examination in the laboratory under a microscope. Polyps (abnormal growths from the colon lining), if present, will also be removed and sent for tissue analysis.

If you have not had a colonoscopy in the past 36 months, you will be scheduled for a colonoscopy to rule out other medical conditions before participating in the research study. Typically, standard of care is colonoscopy every 5-10 years. Thus, if you are scheduled for colonoscopy and have had the procedure more than 3, but less than 5- 10 years ago, the procedure will be an additional procedure

The benefits of the procedure include the early diagnosis and assistance with the treatment of disease. Those diseases might include colorectal cancer.

There are risks to this procedure, although we believe that the potential benefits outweigh the risks.

- Bleeding is rare, but possible. With severe bleeding, you might even need blood transfusions or require surgery.
- Perforation (a small hole through the bowel wall) is rare, but if it happens, you would probably need to be hospitalized and have surgery.
- The medication that we give to prevent pain and discomfort can cause adverse reactions. If these medications are injected, they can cause redness and swelling of the arm. Any medication can cause an allergic or adverse reaction.
- With any procedure, there is a risk of death.

There are alternatives to colonoscopy, including x-ray studies, but they do not allow us to directly see the areas or take a biopsy. If you have questions about this procedure, please ask us. There is a small possibility that a significant lesion can be missed with a colonoscopy exam.

CONSENT:
I have discussed the risks, benefits, alternatives, and have been given an opportunity to ask questions.

I ACKNOWLEDGE THAT I HAVE BEEN INSTRUCTED BY DR. SEGALL, OR HIS STAFF, TO TAKE MY REGULAR HEART AND BLOOD PRESSURE MEDICATION WITH SIPS OF WATER THE -MORNING OF THE PROCEDURE AND THAT I NEED A FRIEND OR FAMILY MEMBER TO DRIVE ME HOME AFTER THE PROCEDURE. NO EXCEPTIONS.

I have read the above and agree to allow Dr. Segall to perform the colonoscopy with biopsies and polyp removal, if needed.

By signing this consent form, I have not given up any of my legal rights.

Subject Name (printed)

CONSENT SIGNATURE:

Signature of Subject	Date
Signature of Person Conducting Informed Consent Discussion	Date

AUTHORIZATION TO USE AND DISCLOSE INFORMATION FOR RESEARCH PURPOSES

What information may be used and given to others?
The study doctor will get your personal and medical information. For example:

- Past and present medical records
- Research records
- Records about phone calls made as part of this research
- Records about your study visits.
- Information gathered for this research about:
  - Physical exams
  - Test results
  - Diaries and questionnaires
- Records about the study device.

Who may use and give out information about you?
The study doctor and the study staff.

Who might get this information?

- The sponsor of this research. "Sponsor" means any persons or companies that are:
  - working for or with the sponsor, or
  - owned by the sponsor.

Your information <u>may</u> be given to:

- The U.S. Food and Drug Administration (FDA)
- Department of Health and Human Services (DHHS) agencies
- Governmental agencies in other countries and
- Western Institutional Review Board® (WIRB®)

Why will this information be used and/or given to others?

- to do the research,
- to study the results, and
- to see if the research was done right.

If the results of this study are made public, information that identifies you will not be used.

What if I decide not to give permission to use and give out my health information?
Then you will not be able to be in this research study.

May I review or copy my information?
Yes, but only after the research is over.

May I withdraw or revoke (cancel) my permission?
This permission will be good until December 31, 2011.

You may withdraw or take away your permission to use and disclose your health information at any time. You do this by sending written notice to the study doctor. If you withdraw your permission, you will not be able to stay in this study.

When you withdraw your permission, no new health information identifying you will be gathered after that date. Information that has already been gathered may still be used and given to others.

Is my health information protected after it has been given to others?
There is a risk that your information will be given to others without your permission.

Authorization:
I have been given the information about the use and disclosure of my health information for this research study. My questions have been answered.

I authorize the use and disclosure of my health information to the parties listed in the authorization section of this consent for the purposes described above.

_____
Subject Name (printed)

AUTHORIZATION SIGNATURE:

_____ _____
Signature of Subject Date

_____ _____
Signature of Person Conducting Informed Consent Discussion Date

EXPERIMENTAL SUBJECT'S BILL OF RIGHTS

California law, under Health & Safety Code Section 24172, requires that anyone who is asked to be in a research study (medical experiment), or who is asked to agree for someone else to be in a research study, has the right to know the following:

1. Both the nature and reason for the research study or experiment.

2. What will happen during the research study, and what drug or device will be used.

3. Any expected discomforts and risks from taking part in the research.

4. Any possible benefits to being in the research.

5. The risks and benefits of any non-experimental medical procedures, drugs, or devices that could be used instead of being in the research.

6. How research related complications will be treated during and after the research study is over.

7. Questions can be asked about the research and about anything that will be done during the research study.

8. The research subject can stop taking part in the research study at any time for any reason without penalty or loss of benefits.

9. A copy of their signed and dated consent form will be given to subjects.

10. The research subject can take the time needed to decide if they want to take part in the research study. No one can pressure, force or unduly influence any person to take part in research.

_____ _____

Signature of Subject Date

_____ _____

Signature of Witness Date

Appendix 12: Sample Case Report Forms

PATIENT ENROLLMENT

	Date	Reference / Comments
Obtain Informed Consent		See Enrollment Appointment source document
Subject Profile		Age: Wexner: BI Type:
Colonoscopy Required		No / Yes, Date:
PI Consent to Enroll Patient		See Enrollment Appointment source document
Patient Training Completed		See Enrollment Appointment source document

INSERT USE: SELF-INSERTION TOLERABILITY

Nurse recording of the subject's scoring on 1-10 scale:
1=Very Difficult; 10=Very Easy/Comfortable
See Page 2 of Weekly Nurse Visit Source Documents

	WEEK 1	WEEK 2	WEEK 3	AVG
Date of Weekly Visit				
The comfort of holding the applicator with the insert in the hand				
The body position you enter for insert delivery Position used:				
Navigation of the applicator & insert to the anus				
Sensation in the anus when the insert passes through the anus				
Sensation in the anal canal during insert insertion				
Sensation in the rectum during insert insertion				
Retracting the applicator while securing the insert in the lower rectum and anal canal				
Finding the insert's outer disc the anus after full applicator retraction				
Sensation in the anus and rectum area immediately after application retraction				
Overall self-insertion experience 1= Very Negative; 10=Very Positive				

INSERT USE: SUMMARY OF INSERTS USED

DEVICE INVENTORY & DAILY DIARY

See Page 3 of Weekly Nurse Visit Source Documents

	Total Inserts Out	Total Inserts Returned	Inserts Used This Week INVENTORY	Inserts Used This Week DAILY DIARY	Difference between Inventory vs Diary
WEEK 1 Size:					
WEEK 2 Size:					
WEEK 3 Size:					
TOTAL					

	Explanation for any difference between Inventory vs Daily Diary
WEEK 1	
WEEK 2	
WEEK 3	

INSERT USE: SUMMARY OF INSERTS USED

DAILY DIARY

See Page 4 of Subject Daily Diaries

Day	Size	Total Number Inserts Used	Total Expelled in Toilet with BM	Total Expelled In Toilet with GAS	Total Expelled In Toilet with URINATION	Total Expelled Any Other Time	Total Discarded Due to Insertion Difficulty	Total Discarded Due to Any Other Reason
1-__/__/09								
2-__/__/09								
3-__/__/09								
4-__/__/09								
5-__/__/09								
6-__/__/09								
7-__/__/09								
__/__/09								
9-__/__/09								
10-__/__/09								
11-__/__/09								
12-__/__/09								
13-__/__/09								
14-__/__/09								
15-__/__/09								
16-__/__/09								
17-__/__/09								
18-__/__/09								
19-__/__/09								
20-__/__/09								
21-__/__/09								
TOTAL								

INSERT USE: SUMMARY OF INSERTS USED

DAILY DIARY

See Pages 4-5 of Subject Daily Diaries

Day	Size	Wear At Night	Wear At Home	Wear Away From Home	Trouble Inserting	Daily Tolerability Rating (scale 1-5)	Wear Pads Today	Take AD Meds, Enema or Supp Today
1-__/__/09								
2-__/__/09								
3-__/__/09								
4-__/__/09								
5-__/__/09								
6-__/__/09								
7-__/__/09								
8-__/__/09								
9-__/__/09								
10-__/__/09								
11-__/__/09								
12-__/__/09								
13-__/__/09								
14-__/__/09								
15-__/__/09								
16-__/__/09								
17-__/__/09								
18-__/__/09								
19-__/__/09								
20-__/__/09								
21-__/__/09								
TOTAL								

Are there any comments for this CRF? ☐ Yes ☐ No

Date [DD/MM/YY]	Page	Comment (Please Print)	Initials of person recording the comment
___/___/___			
___/___/___			
___/___/___			
___/___/___			
___/___/___			
___/___/___			

ADVERSE EVENTS

Were any Adverse Events reported? See Weekly Nurse Visit Source Documents

WEEK 1	Yes / No	If Yes, please specify in Attachment A
WEEK 2	Yes / No	If Yes, please specify in Attachment A
WEEK 3	Yes / No	If Yes, please specify in Attachment A

END OF STUDY

1. Date of subject's final study visit: ☐☐ ☐☐ ☐☐☐☐ (Day Month Year)

2. Was the subject's analscope exam at final study visit normal? Yes / No

If No, please specify:

2. Has the subject successfully completed the study? Yes / No If No, please specify below

Reason for not completing the study:

A ☐ Technical Problems, specify:

B ☐ Consent Withdrawn, specify:

C ☐ Protocol Violation, specify:

D ☐ Investigator's discretion, specify:

E ☐ Adverse Event (complete and attach AE Form)

F ☐ Other, specify:

Week 1 of 3	Nurse Week One Insert Use Appointment	Subj Code: _____
Enshur 200CLD	Insert Size: _____ Box: _____	Page 1 of 5

❑ Date:	❑ Seen by (initials):
❑ Next Weekly Visit Appt Scheduled ❑ Date & Time:	❑ Terminated: Yes / No ❑ Reason:

Nurse Weekly Appointment Procedure	Initial Completed	Comments
1. Nurse Study Coordinator to conduct Weekly Visit Interview		
2. Nurse Study Coordinator to review subject's daily diary		
3. Nurse Study Coordinator to review subject responsibilities and provide inserts for next week		
▪ Review Patient Responsibilities		
▪ Review Daily Diary		
▪ Send subject home with daily diary and inserts for next week (and record in disbursement log)		
4. Did Dr Segall need to see subject this week. If so, describe:		Yes / No
5. Were any Adverse Events reported this week?		Yes / No If Yes, please complete CRF Attachment A
6. Did subject earn retail gift card this week		Yes / No

Nurse Study Coordinator Weekly Visit Interview

1. Please interview and ask subject to grade the following aspects relating to the **usability and self insertion process** of the Enshur insert during the last 7 days. Ask subject to respond using scale of 1 to 10, where **1** is: very difficult, demanding and unfriendly, and **10** is: very easy, simple and comfortable:

	Nurse reporting of the patient's scoring Very difficult = 1 Very easy / comfortable = 10									
The comfort of holding the applicator with the insert in the hand:	1	2	3	4	5	6	7	8	9	10
The body position you enter for insert delivery:	1	2	3	4	5	6	7	8	9	10
Navigation of the applicator & insert to the anus:	1	2	3	4	5	6	7	8	9	10
Sensation in the anus when the insert passes through the anus:	1	2	3	4	5	6	7	8	9	10
Sensation in the anal canal during insert insertion:	1	2	3	4	5	6	7	8	9	10
Sensation in the rectum during insert insertion:	1	2	3	4	5	6	7	8	9	10
Retracting the applicator while securing the insert in the lower rectum and anal canal	1	2	3	4	5	6	7	8	9	10
Finding the insert's outer disc the anus after full applicator retraction:	1	2	3	4	5	6	7	8	9	10
Sensation in the anus and rectum area immediately after application retraction:	1	2	3	4	5	6	7	8	9	10

2. Please ask the subject to rate the **overall experience associated with the Enshur insert self insertion process during the last 7 days**, where **1** is: insertion was complex, difficult and uncomfortable, resulting in an overall very negative experience, and **10** is: insertion was straight forward, simple, comfortable, resulting in an overall very positive experience:

   Very negative experience = 1 Very positive Experience = 10

1	2	3	4	5	6	7	8	9	10

3. Completeness of daily patient questionnaire documentation (mark √ if OK):

Day	Date	BM diary	Page 4	Page 5
1	___/___/2009			
2	___/___/2009			
3	___/___/2009			
4	___/___/2009			
5	___/___/2009			
6	___/___/2009			
7	___/___/2009			

4. Insert Use Summary

Total Inserts Out	Total Inserts Returned	Inserts Used This Week

Day	Date	Total Number Inserts Used	Total Expelled in Toilet with BM	Total Expelled Other Times*	Total Not Accounted For	*When Expelled Other Times
1	___/___/2009					
2	___/___/2009					
3	___/___/2009					
4	___/___/2009					
5	___/___/2009					
6	___/___/2009					
7	___/___/2009					
	TOTAL					

Week 1 of 3	Nurse Week One Insert Use Appointment	Subj Code: _____
Enshur 200CLD	Insert Size: _____ Box: _____	Page 4 of 5

Nurse study coordinator to record any additional comments here:

Enshur 200CLD	Nurse Week Two Insert Use Appointment	Subj Code: _____
Week 2 of 3	Insert Size: _____ Box: _____	Page 1 of 4

❑ Date:	❑ Seen by (initials):
❑ Next Weekly Visit Appt Scheduled ❑ Date & Time:	❑ Terminated: Yes / No ❑ Reason:

Nurse Weekly Appointment Procedure	Initial Completed	Comments
1. Nurse Study Coordinator to conduct Weekly Visit Interview		
2. Nurse Study Coordinator to review subject's daily diary		
3. Nurse Study Coordinator to review subject responsibilities and provide inserts for next week		
▪ Review Patient Responsibilities		
▪ Review Daily Diary		
▪ Send subject home with daily diary and inserts for next week (and record in disbursement log)		
4. Did Dr Segall need to see subject this week. If so, describe:		Yes / No
5. Were any Adverse Events reported this week?		Yes / No If Yes, please complete CRF Attachment A
6. Did subject earn retail gift card this week		Yes / No

Nurse Study Coordinator Weekly Visit Interview

1. Please interview and ask subject to grade the following aspects relating to the **usability and self insertion process** of the Enshur insert during the last 7 days. Ask subject to respond using scale of 1 to 10, where **1** is: very difficult, demanding and unfriendly, and **10** is: very easy, simple and comfortable:

	Nurse reporting of the patient's scoring Very difficult = 1 Very easy / comfortable = 10									
The comfort of holding the applicator with the insert in the hand:	1	2	3	4	5	6	7	8	9	10
The body position you enter for insert delivery:	1	2	3	4	5	6	7	8	9	10
Navigation of the applicator & insert to the anus:	1	2	3	4	5	6	7	8	9	10
Sensation in the anus when the insert passes through the anus:	1	2	3	4	5	6	7	8	9	10
Sensation in the anal canal during insert insertion:	1	2	3	4	5	6	7	8	9	10
Sensation in the rectum during insert insertion:	1	2	3	4	5	6	7	8	9	10
Retracting the applicator while securing the insert in the lower rectum and anal canal	1	2	3	4	5	6	7	8	9	10
Finding the insert's outer disc the anus after full applicator retraction:	1	2	3	4	5	6	7	8	9	10
Sensation in the anus and rectum area immediately after application retraction:	1	2	3	4	5	6	7	8	9	10

2. Please ask the subject to rate the **overall experience associated with the Enshur insert self insertion process during the last 7 days**, where **1** is: insertion was complex, difficult and uncomfortable, resulting in an overall very negative experience, and **10** is: insertion was straight forward, simple, comfortable, resulting in an overall very positive experience:

   Very negative experience = 1 Very positive Experience = 10

1	2	3	4	5	6	7	8	9	10

3. Completeness of daily patient questionnaire documentation (mark √ if OK):

Day	Date	BM diary	Page 4	Page 5
1	___/___/2009			
2	___/___/2009			
3	___/___/2009			
4	___/___/2009			
5	___/___/2009			
6	___/___/2009			
7	___/___/2009			

4. Insert Use Summary

Total Inserts Out	Total Inserts Returned	Inserts Used This Week

Day	Date	Total Number Inserts Used	Total Expelled in Toilet with BM	Total Expelled Other Times*	Total Not Accounted For	*When Expelled Other Times
1	___/___/2009					
2	___/___/2009					
3	___/___/2009					
4	___/___/2009					
5	___/___/2009					
6	___/___/2009					
7	___/___/2009					
	TOTAL					

Enshur 200CLD	Nurse Week Two Insert Use Appointment	Subj Code: _____
Week 2 of 3	Insert Size: _____ Box: _____	Page 4 of 4

Nurse study coordinator to record any additional comments here:

Enshur 200CLD	Nurse Week Three Insert Use Appointment	Subj Code: _____
Week 3 of 3	Insert Size: _____ Box: _____	Page 1 of 7

❑ Date:	❑ Seen by (initials):

Nurse Weekly Appointment Procedure	Initial Completed	Comments
1. Nurse Study Coordinator to conduct Weekly Visit Interview		
2. Nurse Study Coordinator to review subject's daily diary		
4. Dr Segall to conduct exit exams		Normal anatomy: Yes / No
5. Were any Adverse Events reported this week?		Yes / No If Yes, please complete CRF Attachment A
6. Did subject earn retail gift card this week Did subject earn bonus retail gift card this week		Yes / No Yes / No
7. Subject End of Study portion of CRF completed		Yes / No
8. Subject willing to stay in company database		Yes / No

Nurse Study Coordinator Weekly Visit Interview

1. Please interview and ask subject to grade the following aspects relating to the **usability and self insertion process** of the Enshur insert during the last 7 days. Ask subject to respond using scale of 1 to 10, where **1** is: very difficult, demanding and unfriendly, and **10** is: very easy, simple and comfortable:

	Nurse reporting of the patient's scoring Very difficult = 1 Very easy / comfortable = 10									
The comfort of holding the applicator with the insert in the hand:	1	2	3	4	5	6	7	8	9	10
The body position you enter for insert delivery:	1	2	3	4	5	6	7	8	9	10
Navigation of the applicator & insert to the anus:	1	2	3	4	5	6	7	8	9	10
Sensation in the anus when the insert passes through the anus:	1	2	3	4	5	6	7	8	9	10
Sensation in the anal canal during insert insertion:	1	2	3	4	5	6	7	8	9	10
Sensation in the rectum during insert insertion:	1	2	3	4	5	6	7	8	9	10
Retracting the applicator while securing the insert in the lower rectum and anal canal	1	2	3	4	5	6	7	8	9	10
Finding the insert's outer disc the anus after full applicator retraction:	1	2	3	4	5	6	7	8	9	10
Sensation in the anus and rectum area immediately after application retraction:	1	2	3	4	5	6	7	8	9	10

2. Please ask the subject to rate the **overall experience associated with the Enshur insert self insertion process during the last 7 days**, where **1** is: insertion was complex, difficult and uncomfortable, resulting in an overall very negative experience, and **10** is: insertion was straight forward, simple, comfortable, resulting in an overall very positive experience:

   Very negative experience = 1 Very positive Experience = 10

1	2	3	4	5	6	7	8	9	10

3. Completeness of daily patient questionnaire documentation (mark √ if OK):

Day	Date	BM diary	Page 4	Page 5
1	___/___/2009			
2	___/___/2009			
3	___/___/2009			
4	___/___/2009			
5	___/___/2009			
6	___/___/2009			
7	___/___/2009			

4. Insert Use Summary

Total Inserts Out	Total Inserts Returned	Inserts Used This Week

Day	Date	Total Number Inserts Used	Total Expelled in Toilet with BM	Total Expelled Other Times*	Total Not Accounted For	*When Expelled Other Times
1	___/___/2009					
2	___/___/2009					
3	___/___/2009					
4	___/___/2009					
5	___/___/2009					
6	___/___/2009					
7	___/___/2009					
	TOTAL					

Please ask subjects to consider their overall experience using the Enshur anal insert over the past 3 weeks when answering the following questions:

1. **Overall, how satisfied were you with the Enshur anal insert device you used during the past 3 weeks?**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Not At All Satisfied	Not Very Satisfied	Somewhat Satisfied	Very Satisfied	Extremely Satisfied

Probe: **And why did you just say you were** [insert response] **with the insert?**

2. Overall, how likely would you be to use the Enshur anal insert device if it were available for you to continue using?

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Definitely Not Interested	Probably Not Interested	Might or Might Not Be Interested	Probably Interested	Definitely Interested

Probe: **And why did you just say you** [insert response] **in using the insert in the future?**

3. **Based upon your intial first impressions, did the Enshur anal insert device...**

☐ 1	☐ 2	☐ 3
Fall short of your expectations	Meet your expectations	Exceed your expectations

Probe: **And why did you just say the Enshur inserts** [insert reponse]**?**

4. **Which statement best describes how much you LIKED the Enshur anal insert device?**

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5	☐ 6
Not Like At All	Like Slightly	Like Somewhat	Like Quite Well	Like Very Well	Like Extremely Well

5. **Based on your experience, what would you say are the things you LIKED about the Enshur insert?** [Probe fully]

6. **Based on your experience, what would you say are the things you DISLIKED about the Enshur insert?** [Probe fully]

7. **If the Enshur insert were available to you alongside pads, which would you prefer?**

☐ 1	☐ 2	☐ 3	☐ 4
Prefer Enshur Inserts	Prefer Pads	No Preference	Would use both

Probe: **Why?**

8. **And how many times per week do you think you would use the Enshur inserts?**

9. **And do you think you would you use the inserts…**

☐ 1	☐ 2	☐ 3
Mostly Away From Home	Mostly At Home	Both Away From Home and At Home

10. And if the cost of these inserts were $2 per insert, and most people expect to use 1-2 inserts per day, which statement below best describes how you feel about the value of this product?

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Very Poor Value	Somewhat Poor Value	Average Value	Fairly Good Value	Very Good Value

11. At what price do you think the inserts would be a good value?

12. Based on your experience using the Enshur inserts, is there anything you feel you could do more of or do that you were perhaps limiting yourself before?

CONTINUED ON NEXT PAGE

Nurse study coordinator to record any additional comments here:

Subject Code _____	Daily Diary Day #____	Date_____

THANK YOU FOR COMPLETING THIS DAILY DIARY

PLEASE BEGIN USING THE INVESTIGATIONAL INSERT DEVICES AFTER YOUR FIRST BOWEL MOVEMENT ON:

_____

Please be sure to record ALL of the insert devices you use each day

It is also important to record ALL of the bowel movements you have each day

Please record both your CONTROLLED and UNCONTROLLED bowel movements:

- **CONTROLLED bowel movements are when you made it to the toilet and opened your bowel in the toilet**
- **UNCONTROLLED bowel movements are when you experienced accidental soiling while either trying to make it to the toilet or because you were unaware you were having a bowel movement**

PLEASE ALSO REMEMBER TO BRING YOUR DAILY DIARIES TO YOUR NEXT SCHEDULED APPOINTMENT
The Study Nurse will be reviewing your diaries with you

YOUR NEXT SCHEDULED APPOINTMENT IS ON: _____

SHOULD YOU NEED TO CONTACT THE STUDY STAFF REGARDING THIS DIARY OR FOR ANY REASON, PLEASE DO NOT HESITATE TO CONTACT THE STUDY NURSE AT DR SEGALL'S OFFICE AT TEL: 506-6559

Subject Code _____ Insert Size _____	Daily Diary Day #____	Date_____

DAILY BOWEL MOVEMENT AND INSERT USE DIARY

In the table that follows, please place a tick mark to record the times of all of your bowel movements. Please also place a tick mark at the times that you put in a new Insert device, and the times they came out.

Time	Controlled BM: Opened Bowel in Toilet	Uncontrolled BM: Experienced Accident/ Soiling	Time Insert Came Out	Time Put New Insert In	Did Insert come out WITH a BM in the toilet? Yes/ No	If No, please describe how and when the Insert came out. Please be sure to record ANY instance when an Insert came out when it did not come out with a bowel movement (BM)
12:00am						
12:30am						
1:00am						
1:30am						
2:00am						
2:30am						
3:00am						
3:30am						
4:00am						
4:30am						
5:00am						
5:30am						
6:00am						
6:30am						
7:00am						
7:30am						

Subject Code _____ Insert Size _____	Daily Diary Day #____	Date_____

Time	Controlled BM: Opened Bowel in Toilet	Uncontrolled BM: Experienced Accident/ Soiling	Time Insert Came Out	Time Put New Insert In	Did Insert come out WITH a BM in the toilet? Yes/ No	If No, please describe how and when the Insert came out. Please be sure to record ANY instance when an Insert came out when it did not come out with a bowel movement (BM)
8:00am						
8:30am						
9:00am						
9:30am						
10:00am						
10:30am						
11:00am						
11:30am						
12:00pm						
12:30pm						
1:00pm						
1:30pm						
2:00pm						
2:30pm						
3:00pm						
3:30pm						
4:00pm						
4:30pm						
5:00pm						
5:30pm						
6:00pm						
6:30pm						

Subject Code _____ Insert Size _____	Daily Diary Day #____	Date_____

7:00pm						
7:30pm						
8:00pm						
8:30pm						
9:00pm						
9:30pm						
10:00pm						
10:30pm						
11:00pm						
11:30pm						

PLEASE CONTINUE TO NEXT PAGE

Subject Code _____ Insert Size _____	Daily Diary Day #____	Date_____

DAILY INSERT USE EXPERIENCE SUMMARY

In TOTAL, beginning with the first Anal Insert you used today, **how many anal inserts did you use today? Please record all the anal inserts you used today, including any that you might have had to discard for any reason**	**Record Number Here:**	
In TOTAL, how many of the anal inserts you used today were expelled into the toilet with a BM?	**Record Number Here:**	
Did any anal inserts come out with urination today? **Circle: YES / NO** **If YES, please describe:**	**Record Number Here:**	
Did any anal inserts come out with gas today? **Circle: YES / NO** **If YES, please describe:**	**Record Number Here:**	
Did any anal inserts come out at any other times OTHER than with a BM today? **If YES, please describe:** **Circle: YES / NO**	**Record Number Here:**	
Did you **have to discard any anal inserts today** either because you had difficulty inserting it properly or for any other reason? **Circle: YES / NO**	**Record Number Here:**	
Did you wear an anal insert while you were **sleeping last night**? **If NO, please describe:**	Yes	No
Did you use the anal inserts at all times when you were **at home** today? **If NO, please describe:**	Yes	No
Did you use the anal inserts at all times when you were **away from home** today? **If NO, please describe:**	Yes	No

Subject Code _____ Insert Size _____	Daily Diary Day #____	Date_____

Did you **have any trouble inserting** the Anal Inserts today? **If YES, please describe completely:**	Yes	No

Please tell us how tolerable/ comfortable the Anal Inserts that you used today were....

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Extremely Intolerable/ Uncomfortable	Somewhat Intolerable/ Uncomfortable	Neither Tolerable Nor Intolerable	Somewhat Tolerable/ Comfortable	Extremely Tolerable/ Comfortable

Please answer the following questions:	**Yes**	**No**	**If YES, please describe:**
Did you wear pads today?			
Did you take any anti-diarrhea medications today?			
Did you administer an enema or suppository today?			

Subject Code _____ Insert Size _____	Daily Diary Day #____	Date_____

Please record any other comments you have for the study researchers here:

THANK YOU FOR COMPLETING THIS DAILY DIARY
SHOULD YOU NEED TO CONTACT THE STUDY STAFF FOR FOR ANY REASON,
PLEASE DO NOT HESITATE TO CONTACT THE STUDY NURSE AT DR SEGALL'S OFFICE AT TEL: 506-6559

Appendix 13: Institutional Review Board

WESTERN INSTITUTIONAL REVIEW BOARD® (WIRB®)
3535 Seventh Avenue, SW-Olympia, Washington 98502-5010
P.O. Box 12029-Olympia, Washington 98508-2029
Phone: (800) 562-4789, (360) 252-2500 Fax: (360) 252-2498

PANEL SEVEN
[Effective March 11, 2010]

CHAIRMAN
Theodore D. Schultz

PANEL CHAIR
Barbara A. Cook

MEMBERS						
LAST NAME	**FIRST NAME**	**DEGREES & LICENSES**	**PRIMARY SPECIALTY OR OCCUPATION**	**PHYSICIAN SCIENTIST/ OTHER SCIENTIST/ NON-SCIENTIST**	**GENDER**	**WIRB AFFILIATED**
Casson ≺	Henry I.	MD	Anesthesiologist, Cardiologist	PS	M	None
Cook ☼□≺≺	Barbara A.	BS	Social Scientist, State Human Rights Commission	NS	F	None
Fitzgerald ≺≺	Mary	BA	Public Relations and Photography	NS	F	None
Jacob ≺≺	Jean P.	MA	Counselor, Child/Family	NS	F	None
McCleary ≺≺≺	Leila O.	PhD	Clinical Biochemist	OS	F	None
Moore Lewis ≺≺	Barbara	MPA	Administrator	NS	F	None
Rivera-Lee ≺≺≺	Susan	BSN	Nursing	OS	F	None
Vasek ☼≺	Constance D.	MD	Emergency Physician, Family Practice	PS	F	WIRB Affiliated
Weyrauch ☼≺	Karl F.	MD, MPH	Family Physician	PS	M	None
ALTERNATE MEMBERS						
Abreha ≺≺≺	Yemane Teklai	PhD	Physiologist	OS	M	None
Alemu ≺	Shitaye	MD	Internal Medicine	PS	F	None
Anannamcharoen ≺	Sahaphol	MD	Surgeon	PS	M	None
Arend ☼□≺≺≺	Brenda M.	BA, MA	Speech Language Pathologist	OS	F	None
Awah ≺≺≺	Paschal	PhD	Medical Anthropology	OS	M	None
Bennett ≺	Michael	MD, PhD	Anesthesiologist	PS	M	None
Benson ≺≺	Barbara A.	MA	Psychology – Counselor	NS	F	WIRB Affiliated
Bouillon-Jensen ≺≺≺	Cindy	BS, MA	Medical Technology, Medical Ethics	OS	F	None
Broberg ☼❖≺	Lucille R.	MD	Pediatrician	PS	F	WIRB Affiliated
Cabrera ≺	Rene	MD	Internist	PS	M	None
Caceres ≺≺≺	Sonia	MA	Psychologist	OS	F	None
Capra ≺≺	Paul	MDiv, MEd	Business Executive	NS	M	None
Cavazos ☼≺	Nora M.	MD	Biostatistician	PS	F	None
Chamnanvanakij ≺	Sangkae	MD	Pediatrician	PS	F	None
Chang ≺	Fung-Wei	MD	Administrator/ OB/GYN	PS	M	None
Chen ≺≺≺	Shu-Yu	MS, BS	Oncology Nurse	OS	F	None
Choi	Hyun Il	MD	OB/GYN	PS	M	None
Cifuentes-Hiss ☼≺≺	Yolanda S.	BS	Spanish Instructor	NS	F	None
Coates ☼≺≺≺	Cathy	AA, ATA	Medical Assistant/Phlebotomist	OS	F	WIRB Affiliated
Collingwood ≺≺≺	Cynthia	PhD	Psychologist	OS	F	None
Copple ≺≺	Dwayne E.	Esq.	Attorney	NS	M	None
Crabs ☼□≺	Jack M.	MD	Internist	PS	M	None
Cummings ☼≺≺≺□	Mariella H.	RN, MS	Nursing Administration	OS	F	None
Dierdorff ≺	John T.	DO	Obstetrics/Gynecology	PS	M	None
Djokam Tamo ≺	Rosine	PhD	Lecturer/Researcher	OS	F	None
Dunkerson ≺≺	Duane	BA, MA	Freelance Editor	NS	M	None
Dunlop ☼≺≺≺	Cheryl	BSN, MA, MiT	Educator/Writer	OS	F	WIRB Affiliated
Emerson ☼≺	Ruth T.	MD	Family Practice	PS	F	None
Ennever ≺≺≺	Fanny K.	Ph.D.	Environmental Scientist	OS	F	WIRB Affiliated

≺ May substitute for any Physician Scientist
≺≺ May substitute for any Non-Scientist
≺≺≺ May substitute for any Other Scientist
* Chair Designee
☼ Expedited Reviewer
□ Executive Policy Committee Member
※ Knowledgeable in Complementary or Alternative Healthcare
Ⓟ Prisoner Representative
❖ Canadian Citizen or Permanent Resident
⟠ Knowledgeable in Canadian Ethics
⌗ Knowledgeable in Canadian Law

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Phone: (800) 562-4789, (360) 252-2500 Fax: (360) 252-2498

ALTERNATE MEMBERS (Continued)						
Ennever ≺	John F.	MD, PhD	Pediatrician	PS	M	WIRB Affiliated
Fairbrook ≺	David L.	MD	Internist	PS	M	None
Flannery ≺≺	Ann R.	BA	Insurance Underwriter	NS	F	None
Fornoff ≺≺≺	Carolyn	RN	Nursing, Critical Care	OS	F	None
Gadde ☼□≺≺	Ronald A.	DMin	Minister	NS	M	None
Gallo ☼≺≺≺	Natalie	BHSc	Administrator	OS	F	WIRB Affiliated
Gamache ≺≺	Maryann	BS	Educator	NS	F	None
Geissler ≺	Francis T.	PhD, MD	Ophthalmologist	PS	M	None
Guan ≺≺≺	Xin	MA, Acupuncture	Masters in Traditional Chinese Medicine; Acupuncture Doctor Degree	OS	M	None
Han ≺	Airi	MD	Surgery	PS	F	None
Hanlon ≺≺	Sharlene	BS	Administrator	NS	F	None
Hojem ☼≺≺≺	Barbara	BSN, RN	Nursing	OS	F	WIRB Affiliated
Holm ☼□≺≺≺	Margaret	JD, RN	Attorney, Family Law	OS	F	None
Holman ≺≺	Robert E.	BS, MBA	Chemical Engineer	NS	M	None
Honeyman-Huff ≺≺	Carole	BA, HDip.	Photographer (Medical/Forensic/General)	NS	F	WIRB Affiliated
Hu ≺≺≺	Teh-Min	PhD, MS, BS	Pharmacologist	OS	M	None
Jacobs ☼□≺≺	William C.	BA	Consultant, Political Science	NS	M	None
Jeong ≺≺≺	Ihn Sook	RN, MPH, PhD	Nursing, Public Health, Epidemiologist	OS	F	None
Johns	Nutjaree P.	PharmD, Ph.D	Pharmaceutical Sciences Professor	OS	F	None
Jotwani ≺≺≺	Geeta	PhD	Genomics, Molecular Medicine, Stem Cell Research	OS	F	None
Kaltwasser ≺	Gustavo A.	MD	Infectious Disease	PS	M	None
Kaufman ☼≺	Thomas I.	MD	Emergency Physician	PS	M	WIRB Affiliated
Kim ≺	Bong-Seog	MD, PhD	Administrator/Internist	PS	M	None
Kim ≺	Ock-Joo	MD, PhD	Medical Historian	PS	F	None
King ☼□≺≺	Kay L.	JD	Attorney	NS	F	None
Kirchheim ≺	Dieter	MD	Urologist	PS	M	None
Komwilaisak ≺	Ratana	MD	Associate Professor/ Maternal-Fetal Medicine	PS	F	None
Koo ≺≺	Young-Mo	PhD	Philosophy	NS	M	None
Krug ≺	James A.	MD	OB/GYN	PS	M	WIRB Affiliated
Kumar ≺	Rachakulla Hari	MBBS, DPH	Communicable Diseases, Nutrition	PS	M	None
Kumar ≺≺≺	Vijay	PhD	Physiologist	OS	M	None
Kumaran ≺	Paul	MBBS, MPH, BA	Public Health, Psychology	PS	M	None
Lakewold ☼≺≺≺	Dorothy S.	BS, MT	Medical Technologist	OS	F	None
Lane ≺≺	Jeffrey	JD	Attorney	NS	M	None
Laosee ≺≺≺	Orapin	MPH,MSc,BNs	Public Health, Nursing	OS	F	None
Lee ≺≺≺	Hwei-Ling	PhD	Biostatistician	OS	F	None
Lee ≺≺	Kwai-Fong (Doris)	MA	Administrator	NS	F	None
Lertsithichai ≺	Panuwat	MD	Surgeon	PS	M	None
Liu ≺	Hai Tao (Heidi)	MD	General Practitioner	PS	F	None
Lu ≺≺≺	Qi	BA	Public Health	OS	M	None
Luk ≺	Hsiang-Ning	MD	Anesthesiologist	PS	M	None
Lundborg ≺≺	Rose Ann	MSW	Family Counselor	NS	F	None
Magalhaes	Pollyana A.	RN	Nursing	OS	F	None
Mahaisavariya ≺	Punkae	MD	Dermatologist/Pathologist	PS	F	None
Manaloto ≺≺	Renato	LLB, MA, BA	Attorney, Bioethicist	NS	M	None
Manochiopinig	Sriwimon	PhD	Communications Disorders/Physical Therapy	OS	F	None
Mathur ≺≺≺	Roli	PhD	Genetics	OS	F	None
McNeill ※❖☼□≺≺≺	John H.	MSc, PhD	Pharmaceutical Science	OS	M	None

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ALTERNATE MEMBERS (Continued)							
Moats		Bernadette		Realtor®	NS	F	WIRB Affiliated
Moore	≺≺	Jacqueline P.	BA	Community Volunteer	NS	F	None
Mossman	☼≺≺≺	Shannon	RN	Nursing	OS	F	WIRB Affiliated
Mulate	≺	Yimtubezinash	MD, PhD	Microbiologist	PS	F	None
Munoz	≺	Agueda	MD	Family Practice	PS	F	None
Nimnuan	≺	Chaichana	MD, PhD	Psychiatrist	PS	M	None
Oberg	☼□*≺≺	James C.	BS, MS, MBA	Administrator	NS	M	None
Ognall	☼□*≺	Michael J.	MD	Family Physician	PS	M	None
Oh	≺	Myungho	MD, PhD	Neonatologist	PS	M	None
Olson	≺≺≺	Linda J.	MSN, RN	Nursing Administration	OS	F	None
Orive	≺≺≺	Otto	CLS	Medical Technologist	OS	M	WIRB Affiliated
Pacheco Garrido	≺	Hernan	MD	OB/GYN	PS	M	None
Padget	≺≺≺	Laurie	RN	Nursing	OS	F	None
Panichkul	≺	Suthee	MD	OB/GYN	PS	M	None
Parke	≺≺≺	Jeffrey	DVM, MS	Veterinarian	OS	M	None
Perrin	≺	Laurence	MD	OB/GYN	PS	M	None
Pogonea	≺	Ina	MD	Rheumatologist, Pharmacologist	PS	F	None
Powell	☼≺≺≺	Maura	BA	Clinical Research Coordinator	OS	F	WIRB Affiliated
Quan	≺	Arlen	MD	Psychiatrist	PS	M	None
Reese	☼□*Ⓟ≺	Adele B.N.	MD	Psychiatrist, Adult and Child	PS	F	None
Reese	≺	Owen G.	MD	Nephrologist	PS	M	None
Richert	≺	Charles A.	MD	Pathologist	PS	M	None
Rogov	≺	Eugene	MD, PhD, JD	General Practitioner	PS	M	None
Roice		Wayne	BS	Administrator	NS	M	None
Rumble	≺≺	Jeanine	BA	Program Coordinator	NS	F	None
Sarymsakova	≺	Bakhyt	MD, PhD, DSc	Immunology, Infectious Diseases	PS	F	None
Savardekar	≺	Lalita	MBBS	General Practitioner	PS	F	None
Schultz	☼□≺≺	Theodore D.	JD	Attorney	NS	M	None
Sharma	≺≺≺	Meenakshi	PhD	Cardiovascular Disease	OS	F	None
Shin	≺	Hee-Young	MD, PhD	Preventative Medicine	PS	M	None
Sirichotiyakul	≺	Supatra	MD	OB/GYN	PS	F	None
Son	≺≺	Ge-Yong	JD	Attorney	NS	M	None
Songpatanasilp	≺	Thawee	MD, MSc	Orthopedist	PS	M	None
Steen	☼□≺≺	David S.	MTh	Minister	NS	M	None
Su	≺≺≺	Ya-Hui	BSN, MSN	Oncology Nurse	OS	F	None
Swier	☼□≺≺	Dick W.	BS	Aviation	NS	M	None
Tanudsintum	≺	Surasek	MD	Anesthesiologist	PS	M	None
Taylor	☼≺	Robert A.	DO, JD	Emergency Physician, Attorney	PS	M	WIRB Affiliated
Torres	≺≺≺	Cristina	PhD	Professor	OS	F	None
Tudor	≺≺	Katherine White	JD	Attorney	NS	F	None
Vasishth	≺≺≺	Veena	BS, MT	Medical Technologist	OS	F	None
Vazeux	☼≺	Rosemay	MD	Hematologist	PS	F	WIRB Affiliated
Vleck	☼≺	Jan P.	MD	Family Practice	PS	M	WIRB Affiliated
Waite	☼≺	Bradley E.	DO	Emergency Physician	PS	M	WIRB Affiliated
Wells	☼≺	Christine R.	MD	Neurologist	PS	F	WIRB Affiliated
West	≺≺	Susan	BA	Educator	NS	F	WIRB Affiliated
Wilkerson	≺≺	E. Duane	MDiv, MPH	Consultant, Behavioral/Social Science	NS	M	None
Williams	☼≺≺≺	Susan	RN, MHA	Health Administration	OS	F	None
Wongwai	≺	Phanthipha	MD	Ophthalmology	PS	F	None
Wu	≺≺≺	Rong	MMSc	Hospital Management	OS	F	None
Xue	≺	Di	MD, MPH, PhD	Public Health	PS	F	None

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ALTERNATE MEMBERS (Continued)							
Yee	≺≺≺	Winnie L.	PhD	Pharmaceutical Sciences	OS	F	None
Yimtae	≺	Kwanchanok	MD	Otolaryngologist	PS	F	None
Young	≺≺	Artee F.	PhD, JD	Educator, Attorney	NS	F	None
Yu	≺	Zhi Qing	MD	Pediatric Cardiologist	PS	M	None

SIGNATURE AUTHORITY			
Chairman	Theodore D. Schultz, JD	Panel Chair	David S. Steen, MTh
Panel Chair	Brenda M. Arend, BA, MA	Panel Chair	Dick W. Swier, BS
Panel Chair	Barbara Cook, BS	Panel Member	Lucille Broberg, MD
Panel Chair	Mariella Cummings, RN, MS	Panel Member	Jan Vleck, MD
Panel Chair	Jack M. Crabs, MD	Panel Member	Bradley Waite, DO
Panel Chair	Ronald A. Gadde, D.Min	Panel Member	Robert A. Taylor, DO, JD
Panel Chair	Margaret Holm, JD, RN	Vice President, Medical Affairs	John F. Ennever, PhD, MD
Panel Chair	William C. Jacobs, BA	Regulatory Analyst	James R. Baldwin, PhD
Panel Chair	Kay King, JD	Subject Complaint Representative	Barbara Benson, MA
Panel Chair	*John H. McNeill, MSc, PhD		

* Documents Specific to Panel 10

CONSULTING REVIEW						
LAST NAME	**FIRST NAME**	**DEGREES & LICENSES**	**PRIMARY SPECIALTY OR OCCUPATION**	**PHYSICIAN SCIENTIST/ OTHER SCIENTIST/ NON-SCIENTIST**	**GENDER**	**WIRB AFFILIATED**
Alderman	Beth W.	MD, MPH	Epidemiologist	PS	F	None
Basch	Christa	MD	Rheumatologist	PS	F	WIRB-Affiliated
Besio	Mauricio	MD	OB/GYN	PS	M	None
Bonifield	James G.	MD	Radiologist	PS	M	None
Brown	John A.	DMD	Dentist	PS	M	None
Brunton	Robert I.	MD	Ophthalmologist	PS	M	None
Cataletto	Mary	MD	Pediatric Pulmonologist and Critical Care Specialist	PS	F	None
Cherlow	Joel M.	MD	Radiation Oncologist	PS	M	None
Davis	Glenn G.	PhD	Agronomist	OS	M	None
Deitz	David M.	MD	Vascular Surgeon	PS	M	None
Forster	Mary S.	MD	Invitro Fertilization	PS	F	None
Gombert	Wendy M.	PhD	Developmental Biology/Gene Transfer	OS	F	None
Hall	Deborah K.	MD	Pediatrician	PS	F	None
Harper	Lonnie	MD	Oncologist	PS	M	None
Havlak	Dixie R.	BS, RD, CD	Registered Dietician	OS	F	None
Hoffmeister	Richard	MD	Orthopedist	PS	M	None
Holcenberg	John S.	MD	Pediatric Oncologist	PS	M	None
Huang	Jin	BA	Pharmacist	OS	M	None
Kilduff	James	MD	Urologist	PS	M	None
Kooiker	John E.	MD	Psychiatrist	PS	M	None
Kretschmer	Louis F.	MD	Orthopedist	PS	M	None
McCabe, III	Marshall E.	MD	Gastroenterologist & Hepatologist	PS	M	None
McCowen	Karl D.	MD	Endocrinologist	PS	M	None
McCune	David E.	MD	Oncologist/Hematologist	PS	M	None
Murphy	Ann E.	MD	Oncologist	PS	F	None
Nykanen	David	MD	Pediatric Cardiologist	PS	M	None
Osborn	Dustan C.	MD	Oncologist	PS	M	None
Ott	Carl R.	MD	Internist	PS	M	None

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CONSULTING REVIEW (continued)						
Palma Wenzel	Maria Ines	MD	Psychiatrist	PS	F	None
Plotkin	Michael D.	MD	Ophthalmologist	PS	M	None
Robertson	Paul	MD	Oncologist	PS	M	None
Sahm	Roger A.	MD	Medical Devices	PS	M	None
Smith	Ronald P.	MD	Radiologist	PS	M	None
Sorokin Mackinson	Patricia	MPH	Professor	NS	F	None
Vossler	David G.	MD	Neurology/Neurophysiology	PS	M	None
Wark	Robert S.	MD	Cardiologist	PS	M	None
Wolfe	Christopher L.	MD	Cardiologist	PS	M	None
Wu	Thomas	MD	Gynecologist & Obstetrician	PS	M	None
Yee	Lorrin K.	MD	Oncologist	PS	M	None

Summary of Changes:

- Wayne Roice, B.S. has been added as a member of Panel Two and an alternate of Panels One, Three, Four, Five, Six, Seven, Eight, Eleven, Twelve, Thirteen and Fourteen.

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Appendix 14: List of Investigator and Medical Monitor

Principal Investigator

Dr. Mark Segall
15195 National Ave
Ste 202
Los Gatos, CA 95032

Medical Monitor

Dr. Alfred Hurwitz
455 O'Connor Drive
San Jose, CA 95128

MARK M. SEGALL, M.D., F.A.C.S., F.A.S.C.R.S.

PERSONAL DATA:

- Born: January 20, 1948 - New York, New York
- Status: Married, four children.
- Licenses to practice medicine in California and Michigan.

EDUCATION:

- University of Michigan Medical School, 1968 - 1972, received Medical Degree June 1972.
- Undergraduate education at the University of Michigan, 1966 - 1968 and Wayne State University, 1965 - 1966.

PROFESSIONAL TRAINING:

- Colon and Rectal Surgery Fellowship, University of Minnesota Hospitals- Minneapolis, Minnesota, July 1979 - June 1980.
- Surgical Residency - William Beaumont Hospital - Royal Oak, Michigan, July 1975- June, 1979.
- Surgical Internship - UCLA Center for the Health Sciences - Los Angeles, CA, June 1972 - June 1973.

BOARD CERTIFICATION:

- American Board of Surgery - No. 25836, April 14, 1980, valid until July 1, 1990
- American Board of Surgery - No. 25933, October 13, 1989 (recertification, valid until July 1, 2000)
- American Board of Surgery - No. 25933, October 16, 1998 (recertification, valid until July 1, 2010)
- American Board of Colon and Rectal Surgery - No.734, September 27, 1980

EXPERIENCE:

- Practice of Colon and Rectal Surgery - 15195 National Avenue #202, Los Gatos, CA 95032. February 1983 - present.
- Clinical Assistant Professor, Department of Surgery - Stanford University Medical School, 1990 - 2001.
- Clinical Instructor, Department of Surgery - Stanford University Medical School, 1985 - 1990.
- Clinical instructor, Department of Surgery - Wayne State University School of Medicine,1981 - 1984.
- Practice of Colon and Rectal Surgery, Michigan Colon & Rectal Surgeons, P.C. – 18161 West 13 Mile Road, Southfield, Michigan 48076. July 1980 - February 1983.
- Family Practice of Medicine - Southern California Permanente Medical Group - West Los Angeles, CA, 1973 - 1975.

PROFESSIONAL ACTIVITIES:

- Chairman of Surgical Services, Good Samaritan Hospital of Santa Clara Valley, 1998-1999
- Chairman of the Division of General Surgery, Good Samaritan Hospital of Santa Clara Valley, 1995-7
- Chairman of the Awards Committee, American Society of Colon and Rectal Surgeons, 1994-95
- Fellow, Southwestern Surgical Congress. 1989-1994
- Society of American Gastrointestinal Endoscopic Surgeons. 1988-1999.
- President of the Northern California Society of Colon and Rectal Surgeons. 1987-88 and 1988-89.
- San Jose Surgical Society. 1987 - Present.
- Little Learners. 1986 - Present.
- Santa Clara Surgical Society. 1986 - Present.
- Fellow, American College of Surgeons. 1985 - Present.
- Fellow, American Society of Colon and Rectal Surgeons. 1984 - Present.
- Northwest Society of Colon and Rectal Surgeons. 1983 - Present.
- Northern California Society of Colon and Rectal Surgeons. 1983 - Present.
- Santa Clara County Medical Society. 1983 - Present.
- California Medical Association. 1983 - Present.
- American Medical Association. 1983 - 1998.
- Detroit Surgical Association. 1980 - 1983.
- Michigan Society of Colon and Rectal Surgeons. 1980 - 1983.
- Midwest Society of Colon and Rectal Surgeons. 1980 - 1983.

AWARDS:

- Ohio Valley Society of Colon and Rectal Surgeons Award, May 1980, for paper presented at the 79th Annual Meeting of the American Society of Colon and Rectal Surgeons.
- American Cancer Society, Santa Clara County chapter, Professional Volunteer of the Year Award, 1988.
- Listed in "Best Doctors in the Bay Area," San Francisco Focus Magazine: March, 1997; January/February 2003.
- Listed in "Top Doctors: The Valley's Best," San Jose Magazine: March/April, 1999; March/April, 2000; March 2001; March 2002. (Beginning March 2003, changed method for "Top Doctors" to listing all the physicians in the Santa Clara County Medical Society, of which I am a member)

PUBLICATIONS:

- Advanced Carcinoma of the Rectum. Perspectives in Colon Rectal Surg. 1994: 7:235-244.
- The resectional re-operation rate for Crohn's disease in a general community hospital. Dis Colon Rectum. 1983; 26: 305-9.
- Colonoscopic extraction of dentures. Gastrointestinal Endosc. 1983; 29: 142-3.
- Recurrence rate for Crohn's disease in a community hospital. In University of Minnesota Principles of Colon and Rectal Surgery Course Outline. Pp. 87-8, October 20-23, 1983.
- Testicular abscess from a rectal tumor. Dis Colon Rectum 1982; 25:731-2.
- Therapeutic choices for recurrent carcinoma of the rectum. In University of Minnesota Principles of Colon and Rectal Surgery Course Outline. Pp. 293-5, October 21-24, 1981.
- Abdominoperineal resection for recurrent cancer after anterior resection. Dis Colon Rectum. 1981; 24: 80-4.

- Recurrent Crohn's disease; surgical management. In University of Minnesota Principles of Colon and Rectal Surgery Course Outline. Pp. 143-6, May 9-10, 1980; and in University of Minnesota Principles of Colon and Rectal Surgery Course Outline. Pp. 113-5, October 20-23, 1982.
- Value of multiple rectal and colonic biopsies as a predictor of malignant change in the colitic patient. In University of Minnesota Principles of Colon and Rectal Surgery Course Outline. Pp. 113-5, October 20-23, 1982.
- Infraclavicular subclavian venous catheterization. Surg Gynecol Obstet 1979; 148: 925-6.

PERSONAL:

- Board of Directors, California Amateur Hockey Association, 1997 – 1999.
- Vice President, Santa Clara Valley Hockey Association 1995
- Secretary and Executive Board, Los Gatos Little League 1991 – 1993.

Revised 08/2007

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INVESTIGATOR PROTOCOL AGREEMENT

Study Protocol number: 200CLD

I have read and understand this protocol and agree to:

Perform and conduct the study as outlined in the protocol herein;

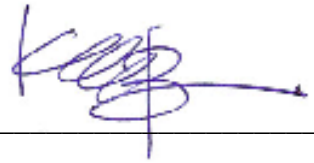
Maintain the confidentiality of all information received or developed in connection with this protocol;

I accept my obligations related to the Institutional Review Board (WIRB), Informed Consent and Protocol.

_____ _____ ___February 27, 2009_____

Investigator's Signature Date

Mark M. Segall, M.D.
Medical License Number: CA GO24951
15195 National Ave
Suite 202
Los Gatos, CA 95032



_____ _____February 27, 2009_____

Enshur, Inc. Date

Kelly Lewis Brezoczky
Chief Operating Officer
532 Emerson Street
Palo Alto, CA 954301

Appendix 15: Publications Referenced

Bharucha, A. (2005). Prevalence and burden of bowel incontinence: a population based study in women. *Gastroenterology, 129,* p 42-49.

Brunner, M. Droegemueller, C., Rivers, S. & Dueser, W.E. (2012) Prevention of incontinence-related skin breakdown for acute and critical care patients: comparison of two products. *Urologic Nursing, 32*(3).

Deutekom, M. (2005). Plugs for containing faecal incontinence. *Cochrane Database of Systematic Reviews, 3.*

Keuhn, B. (2006). Silence masks prevalence of bowel incontinence. *JAMA*, *295*(12), p. 1362-1363.

Norton, N. (2008). Bowel incontinence quality of life impact. *Digestive Disease Week.*

Ozturk, R. (2004). Long-term outcome and objective changes of anorectal function after biofeedback therapy for faecal incontinence. *Alimentary Pharmacology and Therapeutics,*

Appendix 16: Wexner Bowel Incontinence Scale

Wexner Scale:					
Soiling Type and Frequency	Never	Less Than Once A Month	Monthly	Weekly	Daily
No Control—Solids	0	1	2	3	4
No Control—Liquids	0	1	2	3	4
No Control—Gas	0	1	2	3	4
Use of Pads	0	1	2	3	4
Quality of Life Impact	0	1	2	3	4
Total Score:					Full Continence = 0; Fully Incontinent = 20

Reference: J. Marcio N. Jorge, M.D., Steven D. Wexner, M.D. Etiology and Management of Fecal Incontinence, Diseases of the Colon & Rectum, Volume 36, Number 1, January 1993

Appendix 17: Subject Daily Diary

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APPENDIX 5

PATIENT DAILY DIARY

PLEASE BE SURE TO RECORD ALL OF THE INSERT DEVICES YOU USE EACH DAY

IT IS ALSO IMPORTANT TO RECORD ALL OF THE BOWEL MOVEMENTS YOU HAVE EVERY DAY

Please record both your CONTROLLED and UNCONTROLLED bowel movements:

- **CONTROLLED bowel movements are when you made it to the toilet and opened your bowel in the toilet**
- **UNCONTROLLED bowel movements are when you experienced accidental soiling while either trying to make it to the toilet or because you were unaware you were having a bowel movement**

THANK YOU FOR COMPLETING THIS DAILY DIARY

PLEASE REMEMBER TO BRING YOUR DAILY DIARIES TO YOUR NEXT SCHEDULED APPOINTMENT

THE STUDY NURSE WILL BE REVIEWING YOUR DIARIES WITH YOU

SHOULD YOU NEED TO CONTACT THE STUDY STAFF REGARDING THIS DIARY OR FOR ANY REASON,

PLEASE DO NOT HESITATE TO CONTACT THE STUDY NURSE AT DR SEGALL'S OFFICE AT TEL: 358-3500

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DAILY BOWEL MOVEMENT AND INSERT USE DIARY

In the table that follows, please place a tick mark to record the times of all of your bowel movements. Please also place a tick mark at the times that you put in a new Insert device, and the times they came out.

Time	Controlled BM: Opened Bowel in Toilet	Uncontrolled BM: Experienced Accident/ Soiling	Put New Insert In	Time Insert Came Out	Did Insert come out with a BM in the toilet? Yes/ No	If No, please describe how and when the Insert came out. Please be sure to record ANY instance when an Insert came out when it did not come out with a bowel movement (BM)
12:00am						
12:30am						
1:00am						
1:30am						
2:00am						
2:30am						
3:00am						
3:30am						
4:00am						
4:30am						
5:00am						
5:30am						
6:00am						
6:30am						
7:00am						
7:30am						
8:00am						
8:30am						
9:00am						
9:30am						
10:00am						
10:30am						

11:00am						
Time	Controlled BM: Opened Bowel in Toilet	Uncontrolled BM: Experienced Accident/ Soiling	Put New Insert In	When Insert Came Out	Did Insert come out with a BM in the toilet? Yes/ No	If No, please describe how and when the Insert came out. Please be sure to record ANY instance when an Insert came out when it did not come out with a bowel movement (BM)
11:30am						
12:00pm						
12:30pm						
1:00pm						
1:30pm						
2:00pm						
2:30pm						
3:00pm						
3:30pm						
4:00pm						
4:30pm						
5:00pm						
5:30pm						
6:00pm						
6:30pm						
7:00pm						
7:30pm						
8:00pm						
8:30pm						
9:00pm						
9:30pm						
10:00pm						
10:30pm						
11:00pm						
11:30pm						

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DAILY ANAL INSERT USE EXPERIENCE SUMMARY

In TOTAL, beginning with the first Anal Insert you used today, **how many Anal Inserts did you use today?** Please record all the Anal Inserts you used today, including any that you might have had to discard for any reason	**Record Number Here:**	
Did you wear an Anal Insert while you were **sleeping last night**? **If NO, please describe:**	Yes	No
Did you use the Anal Inserts at all times when you were **at home** today? **If NO, please describe:**	Yes	No
Did you use the Anal Inserts at all times when you were **away from home** today? **If NO, please describe:**	Yes	No
Did you **have any trouble inserting** the Anal Inserts today? **If YES, please describe completely:**	Yes	No
Did you **have to discard any Anal Inserts today** either because you had difficulty inserting it properly or for any other reason? **If YES, please describe:**	Yes	No

Please tell us how tolerable/ comfortable the Anal Inserts were that you used today.
Would you say the silicone anal plugs were (**please check only one response**)

☐ 1	☐ 2	☐ 3	☐ 4	☐ 5
Extremely Intolerable/ Uncomfortable	Somewhat Intolerable/ Uncomfortable	Neither Tolerable Nor Intolerable	Somewhat Tolerable/ Comfortable	Extremely Tolerable/ Comfortable

Please answer the following questions:	Yes	No	If YES, please describe:
Did you wear pads today?			
Did you take any anti-diarrhea medications today?			
Did you administer an enema or suppository today?			

Please record any other comments you have for the study researchers here:

THANK YOU FOR COMPLETING THIS DAILY DIARY
SHOULD YOU NEED TO CONTACT THE STUDY STAFF FOR FOR ANY REASON,
PLEASE DO NOT HESITATE TO CONTACT THE STUDY NURSE AT DR SEGALL'S OFFICE AT TEL: 358-3500

Appendix 18: Instructions for Use and Frequently Asked Questions

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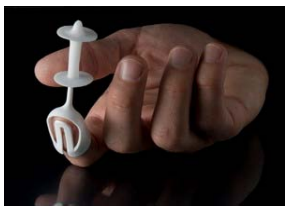
INSTRUCTIONS FOR USE (IFU) & FREQUENTLY ASKED QUESTIONS (FAQ)

Note that the company is presently having illustrations made for the IFU as described below. These illustrations will be forwarded to WIRB as soon as they are available.

STEP BY STEP: HOW TO USE THE ENSHUR ANAL INSERT DEVICE

Step	Illustration	Text Instruction
1	Show two side by side images: first cut away image will show corner of top label being peeled back (1A); second larger image will show what package looks like fully opened with Insert resting inside package (1B).	**Wash your hands.** Do not use an Insert package unless it is fully sealed. Carefully peel the top of the package label back to fully expose the Anal Insert as shown in Figures 1A and 1B.
2	Show index finger placed inside finger tip applicator just prior to lifting Insert out of package (2A) Show fingertip applicator Insert resting correctly on finger and ready for insertion.  (2B)	**Insert index finger into fingertip applicator and lift Insert out of package** as shown in Figures 2A and 2B**. The Insert is now ready to use.**
3	Show illustration of person standing in insertion position, with arm extended around and behind bottom, and Insert tip at anus.	**With one foot resting up on toilet, reach under lifted leg to position top of Insert at anus.**

4	Show insertion process in 2 images: first as close up of insert at anus just prior to insertion (5A); and second, during middle of insertion with fingertip applicator touching anus (5B) Examples below:  (5A)  (5B)	**Relax your muscles, and gently push the Insert into anus until the fingertip applicator touches the anus as shown in Figures 5A and then 5B. Stop applying pressure once you feel the fingertip applicator pressing up against the outer anus as the insert is now in place.**
5	Show image of applicator rod out of anus and Insert resting inside anus and bottom disc just outside anus.	**Once the fingertip applicator is touching the anus, gently withdraw fingertip applicator. The bottom disc of the insert should be resting just outside the anus.** *Important: If the Insert comes out of the anus or is not seated well against the anus, do not try and push it in further with the applicator or your finger. Instead, remove it by pulling on the bottom disc resting outside the anus and discard Insert. Then open a new Insert package and repeat steps 1–5, this time pushing the finger tip applicator a little bit harder up against the*

		anus to insert the Insert slightly deeper into the anus.
6	Show image of applicator rod going into trash can	**Discard fingertip applicator and wash hands.**
7		**Replace your Insert after your next natural bowel movement.**

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FREQUENTLY ASKED QUESTIONS

1. **Does inserting an Enshur Insert hurt?**

   The Enshur Inserts are easy to insert and use. Just follow the step-by-step directions. Inserting an Enshur Insert should not hurt.

   If you are having trouble inserting the Enshur Inserts, please contact the Nurse Study Coordinator at Dr Segall's office at telephone: 408-358-3500.

2. **How do I know when my Enshur Insert is in place?**

   When the Enshur Insert is in the right place, you won't feel any discomfort. If you do feel discomfort, remove and discard the Insert. Then open a new Insert and repeat step by step directions again. You may want to try pushing the finger tip applicator a little bit harder against the anus to insert the Insert slightly deeper into the anal canal. Always leave the bottom disc outside your body. Wash your hands. That's all there is to it.

3. **Can an Enshur Insert get lost inside my body?**

   No, Enshur Inserts are designed so the lower rectum and walls of the anal canal hold the Enshur Insert in place. In the unlikely event an Enshur Insert would travel up into the rectum, it would be harmlessly and naturally expelled with your next bowel movement. Enshur Inserts are also made out of very soft, medical grade silicone, which is pliable and should not cause any rectal obstruction.

   If at any time you believe an entire Insert is up inside your body, please contact the Nurse Study Coordinator at Dr Segall's office at telephone: 408-358-3500.

4. **Can I shower, bathe and be physically active when I'm wearing my Enshur Insert?**

   Yes, you can maintain all of your regular activities while using an Enshur Insert.

5. **What if the recommended insertion position of standing with one foot up on the toilet is uncomfortable or makes me feel unstable?**

   You may want to try sitting or squatting over the toilet and reaching either between or behind your legs. You should use the insertion position that is most comfortable for you.

6. **How often should I wear my Enshur Insert?**

   You should wear your Insert until your next natural bowel movement. The Insert will be naturally expelled with your next bowel movement. After you complete your bowel movement, you should insert a new Insert.

7. **How do I remove my Enshur Insert?**

   You should not remove your Insert as it is designed to be naturally expelled with your next bowel movement. If for some reason you feel a need to remove it, simply pull on the external disc resting just outside your anus and the Insert is easily removed.

8. **What if my Enshur Insert is difficult to remove?**

   Again, the Insert is not intended to be removed. But if for some reason you cannot remove it, please contact Dr Segall's office immediately at telephone: 408-358-3500.

   Note: If at any time during the study period you experience any issues with the Anal Insert devices provided to you, please contact your Nurse study coordinator at Dr Segall's office as soon as possible

Appendix 19: Study Coordinator Weekly Interview Guide

Week 1 of 3	Nurse Insert Use Week One Appointment	Subj Code: _____

❑ **Date:**	❑ **Seen by (initials):**
❑ **Next Weekly Visit Appt Scheduled** ❑ **Date & Time:**	❑ **Terminated: Yes / No** ❑ **Reason:**

Nurse Weekly Appointment Procedure	Initial Completed	Comments
1. Nurse Study Coordinator to conduct Weekly Visit Interview		
2. Nurse Study Coordinator to review subject's daily diary		
3. Nurse Study Coordinator to review subject responsibilities and provide inserts for next week		
▪ **Review Patient Responsibilities**		
▪ **Review Daily Diary**		
▪ **Send subject home with daily diary and inserts for next week (and record in disbursement log)**		
4. Did Dr Segall need to see subject this week. If so, describe:		**Yes / No**

Nurse Study Coordinator Weekly Visit Interview

1. Please interview and ask subject to grade the following aspects relating to the usability and self insertion process of the Enshur insert during the last 7 days. Ask subject to respond using scale of 1 to 10, where **1** is: very difficult, demanding and unfriendly, and **10** is: very easy, simple and comfortable:

	Nurse reporting of the patient's scoring **Very difficult = 1 Very easy / comfortable = 10**									
The comfort of holding the applicator with the insert in the hand:	1	2	3	4	5	6	7	8	9	10
The body position you enter for insert delivery:	1	2	3	4	5	6	7	8	9	10
Navigation of the applicator & insert to the anus:	1	2	3	4	5	6	7	8	9	10
Sensation in the anus when the insert passes through the anus:	1	2	3	4	5	6	7	8	9	10
Sensation in the anal canal during insert insertion:	1	2	3	4	5	6	7	8	9	10
Sensation in the rectum during insert insertion:	1	2	3	4	5	6	7	8	9	10
Retracting the applicator while securing the insert in the lower rectum and anal canal	1	2	3	4	5	6	7	8	9	10
Finding the insert's outer disc the anus after full applicator retraction:	1	2	3	4	5	6	7	8	9	10
Sensation in the anus and rectum area immediately after application retraction:	1	2	3	4	5	6	7	8	9	10

2. Please ask the subject to rate the overall experience associated with the Enshur insert self insertion process during the last 7 days, where **1** is: insertion was complex, difficult and uncomfortable, resulting in an overall very negative experience, and **10** is: insertion was straight forward, simple, comfortable, resulting in an overall very positive experience:

   Very negative experience = 1 Very positive Experience = 10

1	2	3	4	5	6	7	8	9	10

3. Completeness of daily patient questionnaire documentation (mark √ if OK):

Day	Date	BM diary	Page 4	Page 5
1	___/___/2009			
2	___/___/2009			
3	___/___/2009			
4	___/___/2009			
5	___/___/2009			
6	___/___/2009			
7	___/___/2009			

4. Insert Use Summary

Day	Date	Total Number Inserts Used	Total Expelled in Toilet with BM	Total Expelled Other Times*	Total Not Accounted For	*When Expelled Other Times
1	___/___/2009					
2	___/___/2009					
3	___/___/2009					
4	___/___/2009					
5	___/___/2009					
6	___/___/2009					
7	___/___/2009					

Week 1 of 3	Nurse Insert Use Week One Appointment	Subj Code: _____

Appendix 20: Compassionate Use (CU)

Introduction

The 200CLD study demonstrated that subjects were highly satisfied with the Inserts and wished to continue use. A CU exemption for the entire study population was adopted for continued access to the Renew Inserts. CU was offered to all 200CLD subjects and 16 subjects agreed to continue using the Insert; the program began in October/November of 2009 and ended in July of 2012.

Objective

The objectives of the CU program were to provide the device for subjects from the 200 CLD trial that were interested in using the Insert to control their ABL. In addition, data on Insert usage, ease of use and overall satisfaction was collected. Any adverse events related to the use of the Insert were also compiled.

Ethics

In a conference call on August 19, 2009, FDA supported the PI and company's compassionate use for these subjects. On August 26, 2009, the FDA responded to the company stating that the CU did not need FDA approval, but rather it should be managed through WIRB. The CU exemption was approved by WIRB on September 21, 2010.

An addendum to the protocol was requested and approved by WIRB in January of 2012 to reduce in-person interviews to every 3 months and conduct phone interviews with the participants in the months in between those in person meetings.

Study Design

This was a component of the non-randomized non-experimental study CLD 200 study. Quantitative and qualitative data from subjects enrolled in CU were collected from personal subject diaries and through in person and telephone interviews.

Study Procedures

Subjects came to the office of Dr. Segall each month where they returned unused product, received product for the next month and completed surveys. Before the beginning of the CU program each subject's Wexner score was recalculated. A protocol change was approved by WIRB to reduce in person visits with supplemental telephone interviews; Table A below further outlines these procedures.

Table A: Study Procedures

Time Frame	Frequency of In-Person Interviews	Frequency of Telephone Interviews
10/2009-1/2012	Monthly	N/A
1/2012-5/2012	Quarterly	Every Month Without In-Person Interview

Study Population

The population consisted of 16 subjects who were previously enrolled in the 200 CLD study. Some subjects' data could not be analyzed due to protocol violations or subject withdrawal or termination. The Compassionate Use program was stopped in July, 2012 because product was not available.

Study Analysis

The Intent-to-Treat cohort for the Compassionate Use program consisted of 16 subjects interested in further use of the Insert. Upon retrospective review, analysis of data from two of these subjects was disqualified from the demographic, tolerability and usage analysis (Subjects #206 who did not meet eligibility criteria and #212 who admitted to falsifying diary entries). This Modified-Intent-to-Treat cohort (n=14) was analyzed for tolerability and usage. The entire Intent-to-Treat Cohort (n=16) was analyzed for safety.

Despite an established data collection schedule there are some data missing from the monthly telephone interviews and quarterly in-person interviews. No special data handling conventions were used for dealing with missing values.

Results

The demographics of the Compassionate Use Modified ITT Cohort were similar to the Modified ITT population in the 200 CLD study. Table B below summarizes the demographics of the Modified ITT Cohort in the CU study.

Table B: Demographics (Modified ITT n=14)

Number of Subjects	14
Average Age	69
Standard Deviation Age	9.40
Average Wexner at Start of CU	15
Standard Deviation Wexner at Start of CU	2.63

Subjects participated for 14 months in the CU program, but the time enrolled was highly variable. Table C below presents the duration of time subjects were involved.

Table C: Analysis of Duration of Enrollment (Modified ITT n=14)

Average Number of Months in CU	14
Standard Deviation	8.79

Inventory Section

Unlike the 200CLD study, subjects in the CU cohort were not asked to use the Inserts continuously but at their discretion. On average, subjects used one Insert per day. Table D illustrates Insert usage by the participants over their varying length of CU involvement.

Table D: Average Insert Usage Per Day (Modified ITT n=14)

Average Insert Use Per Day	1
Standard Deviation	.64

Participants were asked monthly either via telephone or through in-person interviews about the ease of use of the Insert. Table E below shows that subjects found the Insert easy to use.

Table E: Ease of Use*
(Modified ITT n=14)

Average Ease of Use*	9
Standard Deviation	1.01

***Question Asked for Table E:**
"*We would like you to think about your experience inserting the Renew Insert over the past __ weeks, Overall, how would you rate the Renew Insert ease of use during the past __ weeks, where":*

- "1" is: "insertion was complex, difficult and uncomfortable, resulting in an overall very negative experience", and "10" is: insertion was straight forward, simple, comfortable, resulting in an overall very positive experience?"

Insert Satisfaction was rated on a 1-5 scale with 5 being 'extremely satisfied', utilizing the same scale implemented in the 200CLD. Table F below shows that Insert Satisfaction remained high for the CU Cohort.

Table F: Insert Satisfaction
(Modified ITT n=16)

Average Insert Satisfaction*	4
Standard Deviation	.58

***Question Asked for Table F**:
"*Overall, how satisfied were you with the Renew Inserts you used during the past __ weeks*?"

1- Not At All Satisfied
2- Not Very Satisfied
3- Somewhat satisfied
4- Very Satisfied
5- Extremely Satisfied

Adverse Events (AEs)

There were no AE's documented during the CU program but upon retrospective diary analysis, AEs were identified. There were no serious AE's captured in the telephone/in-person interviews and no subjects discontinued use of the Inserts because of its' comfort or tolerability. Table G below outlines all AEs experienced by the Compassionate Use cohort.

Table G: Analysis of AEs reported (ITT=16)

	Number of Participants that Reported AE	% of Total that Reported AE
ABL with or without Insert in place	8	50.00%
Increased Gas	1	6.25%
Diarrhea	1	6.25%
IBS	1	6.25%
Constipation	1	6.25%
Hemorrhoid	1	6.25%
General Sickness	2	12.50%
Bladder Infection	1	6.25%
Back Injury	1	6.25%
Hernia Surgery	1	6.25%
Surgery due to Motor Vehicle Accident	1	6.25%

	Number of Participants that Reported AE	% of Total that Reported AE
Insert Displacement	1	6.25%

Half of subjects experienced ABL while enrolled, however, it cannot be determined if this occurred while they were using the Insert, since continued use was not required. Subject #208 reported they had symptoms of Irritable Bowel Syndrome, which the Subject was diagnosed with before the 200 Trial and subsequent CU enrollment.

Protocol Deviations

Subject #202 did not have a qualifying Wexner score and Subject #212 falsified diaries. Both subjects were included in the CU program but were only included in safety analysis in this report. Subject #219, also disclosed that she gave her Inserts to a friend and after this disclosure, WIRB was notified and the Subject was terminated.

Follow-up with patients was inconsistent. There were 7 participants remaining after January of 2012. None of the subjects were seen at the scheduled quarterly meeting in April of 2012 due to staff changes at Renew Medical Inc., but these 7 subjects were all seen in July of 2012.

Study Terminations and Withdrawals

Eleven subjects withdrew from the CU program before it was ended in July of 2012 for various reasons. Table I below is a complete analysis of the subjects that withdrew or were terminated.

Table I: Analysis of Withdrawals and *Terminations (ITT n=16)

Subject Withdrawal	# Months in CU	Reason for Withdrawal/Termination
213	2	Lost to Follow-up
215	2	ABL improved
214	3	ABL improved
212	3	ABL with Insert
208	6	Lost to Follow-up
205	10	ABL with Insert
219*	11	Protocol Violation
221	13	ABL improved
210	16	ABL improved
217	19	Injured in Motor Vehicle Accident

*Subject #219 was terminated upon disclosure that subject gave Inserts to a friend (non-study participant)

Nine subjects withdrew from the Compassionate Use Program. Four of the subjects did not continue with Compassionate Use program because their ABL improved. Three of these four Subjects changed medication while the fourth subject credited a surgical procedure for improvement in their ABL. Two

subjects stopped using the Insert because they were still experiencing ABL while using the device. Table J below is an analysis of the top withdrawal explanations.

Table J: Reasons for Withdrawal from Compassionate Use (ITT n=16)

Reason for Withdrawal	# of Subjects	Percentage of Total Subjects Who Withdrew
ABL Improved	4	44%
ABL with Insert	2	22%
Lost to Follow-Up	2	22%

As indicated the majority of Subjects that withdrew from the Compassionate Use Program was due to improvement in their ABL and reduced need for the device.

Discussion and Conclusion

The Compassionate Use program allowed for continued use of the Insert among 73% of the original subjects, or 16 participants, from the 200 CLD study for an average period of on average 14 months. All subjects reported consistent high satisfaction and ease of use of the Insert. Subjects used on average one Insert a day and no significant adverse events were reported. Roughly 44% of the subjects withdrew from the study because their ABL had improved; the Insert was not was not found to be helpful in managing their ABL (22%); or the subjects were lost to follow-up (22%) or suffered an unrelated injury (11%).

Inventory reconciliation difficulties and other protocol deviations made data analysis cumbersome; however, this was not found to affect the overall conclusions derived from this evaluation.