Final Clinical Study Report

Another Way Products, LLC

VIPON Tampon

Amended Version

January 04, 2013

This report is amended to add 95% confidence intervals to the treatment effects presented in Tables 7 and 8, and the corresponding write-up in Sections 2.5.3 and 2.5.4. This update also includes additional detail to the description of the statistical analyses in Appendix F. Note that no changes were made to the analyses or study conclusion, and these updates do not affect any other data in this report.

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1.0 General Information

1.1 Device Name & Description

The VIPON consists of a tampon with a battery powered vibration unit imbedded within, and an applicator for insertion of the tampon into the vagina. The VIPON tampon has received FDA clearance (k992493) with an indication for the absorption of menstrual fluid. The VIPON is an over-the-counter (OTC) device. The purpose of this study was to collect data to support an indication for relief of pain associated with menstruation.

The VIPON tampon produces vibratory stimulation that relieves minor muscle pain associated with menstruation. The vibration unit is located within the tampon and is completely covered by the pledget, preventing direct contact of the vibrating motor housing with vaginal mucosa. The battery is external to the body and is sealed inside the housing of the battery unit. The battery is a 1.5 volt alkaline button cell commonly used in watches and other consumer products. The battery unit is connected to the vibrating motor inside the tampon by insulated wiring which serves to transmit current to the motor and provides a means for removal of the tampon at the end of use. It has a push-button style power switch that allows the user to turn the vibration unit on or off.

The VIPON tampon has been tested for toxic shock syndrome in microbiological tests with acceptable results. The VIPON tampon has been demonstrated to be as safe as any other commercially available tampon.

1.2 Title of Study

A Randomized Four-Way Crossover Comparison Study of Pain Relief from Dysmenorrhea Between the VIPON Tampon and Ibuprofen.

1.3 Proposed Indication for Use

The VIPON is intended for pain relief associated with dysmenorrhea.

1.4 Sponsor Information

Another Way Products, LLC
Gerry Eftink
1-816-322-8000

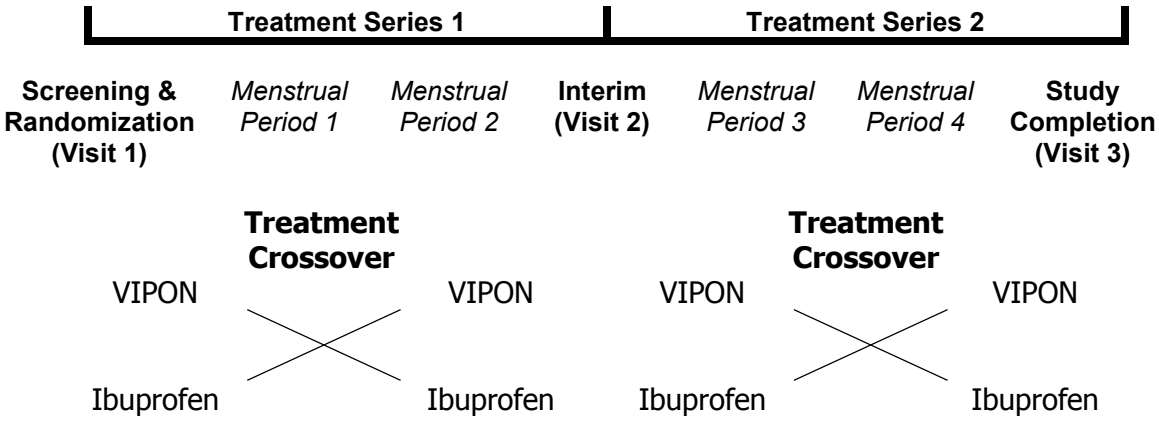
Medical Monitor
Michael L. Corrado, MD
267-744-6212

Drug Safety Officer:
Jose Zapatero, MD
267-744-6138

1.5 Clinical Study Design

This was a randomized, open-label, four-way crossover study, designed to compare the efficacy of the VIPON with Ibuprofen in relief of pain associated with dysmenorrhea. The study was conducted at two study sites. The study included a screening Visit 1 after which, upon meeting the inclusion criteria, subjects were randomized to use either VIPON or Ibuprofen during the first menstrual period. Subjects were instructed to use the crossover treatment for the next menstrual period. Subjects participated in the study for a total of four menstrual periods. An interim Visit 2 was scheduled after completion of 2 menstrual periods to review subject diaries for accuracy, safety assessment, and compliance. Additional investigational product was dispensed at Visit 2 for continuing subjects. Subjects were contacted 5 to 20 days prior to the expected date of each menstrual period to discuss compliance with study procedures. A study completion Visit 3 was scheduled at the end of the study to collect subject diaries, and assess safety and compliance. No follow-up assessments were performed upon study completion. At the onset of dysmenorrhea for each menstrual period, subjects were instructed to fill out the pain questionnaire in the subject diary prior to treatment (VIPON or Ibuprofen) (0 min), and at 15 min, 30 min, 1 hr, 2 hr, and 8 hr after treatment. Subjects were also instructed to complete the Quality of Life questionnaire (MOS-SF36, modified), included in the subject diary, immediately prior to treatment (VIPON or Ibuprofen) at the onset of menstrual pain, and at 8 hours after treatment for each menstrual period. An overview of the study design is shown in Figure 1.

Figure 1: Study Design



The primary objective of this study was to compare the efficacy of the VIPON with Ibuprofen in relieving pain in women with dysmenorrhea.

The secondary objectives were:

- To compare pain relief in symptom clusters (abdominal pain, back pain, cramps) between VIPON and Ibuprofen
- To compare Quality of Life between treatment with the VIPON and Ibuprofen
- To compare the time of pain relief between the VIPON and Ibuprofen
- To assess the safety of the VIPON

1.6 Dosage and Administration

Subjects were randomized to use either VIPON or up to 2 Ibuprofen tablets (200-400 mg Ibuprofen) during the first menstrual period. All subjects were required to use tampons for absorption of menstrual fluid during treatment and at least 2 hours post treatment. Subjects used the crossover treatment during the second menstrual period, which completed Treatment Series 1. A similar treatment sequence was randomly assigned during Treatment Series 2 for menstrual periods 3 and 4. Rescue medication was allowed once 2 hours had elapsed since administration of study treatment (test-of-cure).

2.0 Study Progression

2.1 Investigational Sites

Two investigational sites were trained and activated by the sponsor. Prior to study commencement at each center, Institutional Review Board (IRB) approval was obtained. Annual IRB renewal was obtained at each center and no IRB withdrew approval during the course of the study.

Each site had a Principal Investigator (PI) who signed an Investigator Agreement. All Agreements are on file with the sponsor. The two investigative centers were:

Site 01 University of Kansas Medical Center
John Calkins, MD
KU Medical Center
Department of OB/GYN
3901 Rainbow Blvd.
Kansas City, KS 66160

Site 02 Truman Medical Center
Julie Strickland, MD
Truman Medical Center
Department of OB/GYN, Ste. 739
2301 Holmes Street
Kansas City, MO 64108

2.2 Subject Disposition and Follow-up Compliance

The first subject was enrolled (screened and randomized) into the study November 13, 2006 and the final subject was enrolled on August 11, 2008.

Of the 115 subjects screened, 102 subjects returned for visit 2 and returned their pain assessments for the first 2 menstrual periods. Thirteen (13) subjects withdrew from the study after enrollment and did not return for the second visit. Eight (8) of the subjects were lost-to-follow-up, 3 decided not to continue participation, 1 subject stopped having menstrual periods after enrollment began and 1 was determined to be unable to tolerate Ibuprofen.

Four (4) subjects did not return for visit 3 and therefore no additional treatment information was collected.

Table 1 details the subject disposition and follow-up compliance per site.

Table 1: Subject Disposition/Follow-up Compliance

Site	Enrollment Period	Number Enrolled	Completed Visits			# Withdrew Early
			Visit 1	Visit 2	Visit 3	
01 Univ of Kansas Medical Center	12/04/06 to 04/26/07	51	51	48	48	3
02 Truman Medical Center	11/13/06 to 08/11/08	64	64	54	50	14
TOTAL	11/13/06 to 08/11/08	115	115	102	98	17

A complete listing of subjects enrolled at each investigational site can be found in Appendix A.

2.3 Investigational Device

No changes were made to the device or manufacturing processes during the course of the study. All unused product was returned to Sponsor at the end of the study.

2.4 Demographics

Table 2 summarizes the demographic data for the 115 subjects that were enrolled in the study.

Table 2: Demographics of Enrolled Subjects

Variable		01 Univ of Kansas Medical Center (n=51)	02 Truman Medical Center (n=64)	Total (n=115)
Age (years)	Mean ± Std Dev Range	31.2 ± 7.3 18.9 – 45.9	32.8 ± 8.7 18.1 – 48.1	32.1 ± 8.1 18.1 – 48.1
Weight (lbs)	Mean ± Std Dev Range	172.0 ± 57.1 74.0 – 312.0	169.8 ± 49.1 106.0 – 347.0	170.8 ± 52.6 74.0 – 347.0
Height (in)	Mean ± Std Dev Range	64.7 ± 2.2 59.0 – 71.0	64.5 ± 2.9 53.0 – 70.0	64.6 ± 2.6 53.0 – 71.0
Race	White Black Asian East Indian West Indian Indian Mulatto	34 (66.7%) 16 (31.4%) 0 (0.0%) 1 (2.0%) 0 (0.0%) 0 (0.0%) 0 (0.0%)	33 (51.6%) 26 (40.6%) 2 (3.1%) 0 (0.0%) 1 (1.6%) 1 (1.6%) 1 (1.6%)	67 (59.2%) 42 (36.5%) 2 (1.7%) 1 (0.9%) 1 (0.9%) 1 (0.9%) 1 (0.9%)

2.5 Summary of Efficacy Results

Data analysis for all endpoints was performed as detailed in Appendix F.

2.5.1. Efficacy Determination

The primary objective of the study was to compare the efficacy of the VIPON to Ibuprofen in relieving pain in women with dysmenorrhea. Efficacy was measured by assessing the modified Melzack-McGill pain response and the use of rescue medication at 2 hours after treatment. Success was defined as a 1-point or greater reduction on the 11-point scale as well as the lack of rescue medication usage at 2 hours post treatment. Using the criteria defined in the primary objective, all data were reviewed to determine each individual period's validity for inclusion in the analyses. As detailed in the next two paragraphs, there were 17 periods not included in the analyses in this report.

In order to ascertain efficacy of the treatment, the subjects needed to provide both pre treatment and post treatment scores in their diaries along with using the treatment. There were 2 cases in which a subject did not have any pain during her menstrual period and chose not to perform the randomized treatment (1 during period 1 and 1 during period 4). There was one case where the subject did not record the pain assessment at 2 hours post treatment (during period 1). There were also 4 times where the subject randomized to VIPON did not understand directions and took Ibuprofen at the same time as she started the VIPON treatment. Data for these 7 individual periods were therefore not included.

It was also noted that there were 10 cases in which a subject had a general pain assessment pre treatment and at 2 hours of "0" (i.e. no pain) indicating the subject did not experience dysmenorrhea during those periods. Data from those periods were therefore not used in the analysis.

Another 5 cases reported pre treatment pain of "0", however 4 experienced worsening pain post-treatment and 1 resorted to rescue medication within the 2 hour post treatment. These cases were considered treatment failures and are included in the analysis of this report because they experienced dysmenorrhea.

There were 102 subjects who returned a diary at Visit 2 which covered the first 2 menstrual periods and 98 subjects who returned a diary at Visit 3 (second 2 periods) such that the diary data could be used in the efficacy assessments. Table 3 details the available assessment data for each period for each treatment.

Table 3: Data Not Used for Efficacy Analyses

Menstrual Period	Returned Assessments	No Treatment	Both Treatments	No Pain Assessment 2 hours	No Pain Pre/2 hours	Used In analysis
VIPON						
1	46	0	0	1	0	45
2	57	0	2	0	2	53
3	51	0	1	0	3	47
4	47	0	1	0	0	46
IBUPROFEN						
1	56	1	0	0	2	53
2	45	0	0	0	2	43
3	47	0	0	0	0	47
4	51	1	0	0	1	49
OVERALL						
1	102	1	0	1	2	98
2	102	0	2	0	4	96
3	98	0	1	0	3	94
4	98	1	1	0	1	95

2.5.2. Primary Endpoint – General Pain Assessment

The change of general pain assessment from baseline to 2 hours post treatment was calculated and those with a reduction in pain of at least 1 point are summarized in Table 4. Over all menstrual periods the pain relief was comparable (79.6% for VIPON and 81.8% for Ibuprofen treatment groups).

Table 4: General Pain Relief at 2 Hours

Menstrual Period	VIPON Response Rate	Ibuprofen Response Rate
1	36/45 (80.0%)	44/53 (83.0%)
2	43/53 (81.1%)	33/43 (76.7%)
3	33/47 (70.2%)	40/47 (85.1%)
4	40/46 (87.0%)	40/49 (81.6%)
Over all periods	152/191 (79.6%)	157/192 (81.8%)

Subjects recorded the use of rescue pain medications within the first 2 hours. The percentage of subjects not taking rescue medication is shown in Table 5. The two groups had identical results for the number of subjects not resorting to rescue medication (92.7%).

Table 5: Non-use of Rescue Medications within 2 Hours

Menstrual Period	VIPON Subjects with no rescue meds	Ibuprofen Subjects with no rescue meds
1	44/45 (97.8%)	52/53 (98.1%)
2	48/53 (90.6%)	39/43 (90.7%)
3	41/47 (87.2%)	46/47 (97.9%)
4	44/46 (95.7%)	41/49 (83.7%)
Over all periods	177/191 (92.7%)	178/192 (92.7%)

Subjects showing a reduction of at least 1 point and who did not take rescue medication within the first 2 hours of treatment were considered treatment successes. Subjects with no reduction or a worsening in the pain assessment scale, or those who took rescue medication within the first 2 hours of treatment were considered treatment failures.

Table 6 details the percentage of successful subjects for each menstrual period assessment, as well as overall.

Table 6: Primary Endpoint: Treatment Success at 2 hours

Menstrual Period	VIPON Success Rate	Ibuprofen Success Rate
1	35/45 (77.8%)	43/53 (81.1%)
2	40/53 (75.5%)	30/43 (69.8%)
3	29/47 (61.7%)	39/47 (83.0%)
4	37/46 (80.4%)	33/49 (67.4%)
Over all periods	141/191 (73.8%)	145/192 (75.5%)

The number of subjects experiencing pain relief of at least 1 point and requiring no rescue medication was 73.8% and 75.5% for VIPON and Ibuprofen treatment groups, respectively.

The statistical analysis was carried out per plan and the resultant estimated difference in success between the treatment groups was -1.6% with a 95% confidence interval -9.8% to 6.6%. The non-inferiority margin of -10% is the lower bound of the confidence interval. Given that the non-inferiority margin of

-10% does not fall into the confidence interval the conclusion can be made that VIPON is non-inferior to Ibuprofen.

2.5.3. Secondary Endpoint – General Pain Assessment

The first secondary objective of the trial was to assess the decrease in the modified Melzack-McGill pain scale over time for each treatment group.

The mean changes in scores are displayed in Table 7 along with the treatment effect, and corresponding 95% confidence intervals (CI), from the modeling. The results of the modeling showed that there was a significant treatment effect for the VIPON treatment group of 0.56 points, with a 95% CI of (0.37, 0.76) and p-value <0.0001. The statistically significant overall treatment effect indicates that VIPON treatment is associated with an improvement in pain over time. This finding is likely driven by the statistically significant effects of VIPON over Ibuprofen up through 1 hour post treatment. At 2 and 8 hours, the treatment effect is still better, but not statistically significantly better.

Table 7: Decrease in General Pain Assessment Over Time

Time Point	VIPON Mean Score Change (Baseline-Time point)	Ibuprofen Mean Score Change (Baseline-Time point)	Treatment Effect Mean Score Change (95% CI)	p-value
Overall	N/A	N/A	**0.56 (0.37, 0.76)**	**<0.0001**
15 minutes	**0.91**	**0.19**	**0.74 (0.44, 1.04)**	**<0.0001**
30 minutes	**1.90**	**1.09**	**0.84 (0.46, 1.21)**	**<0.0001**
1 hour	**2.56**	**2.06**	**0.53 (0.08, 0.97)**	**0.0205**
2 hours	2.88	2.55	0.36 (-0.12, 0.84)	0.1427
8 hours	2.52	2.19	0.36 (-0.14, 0.86)	0.1619

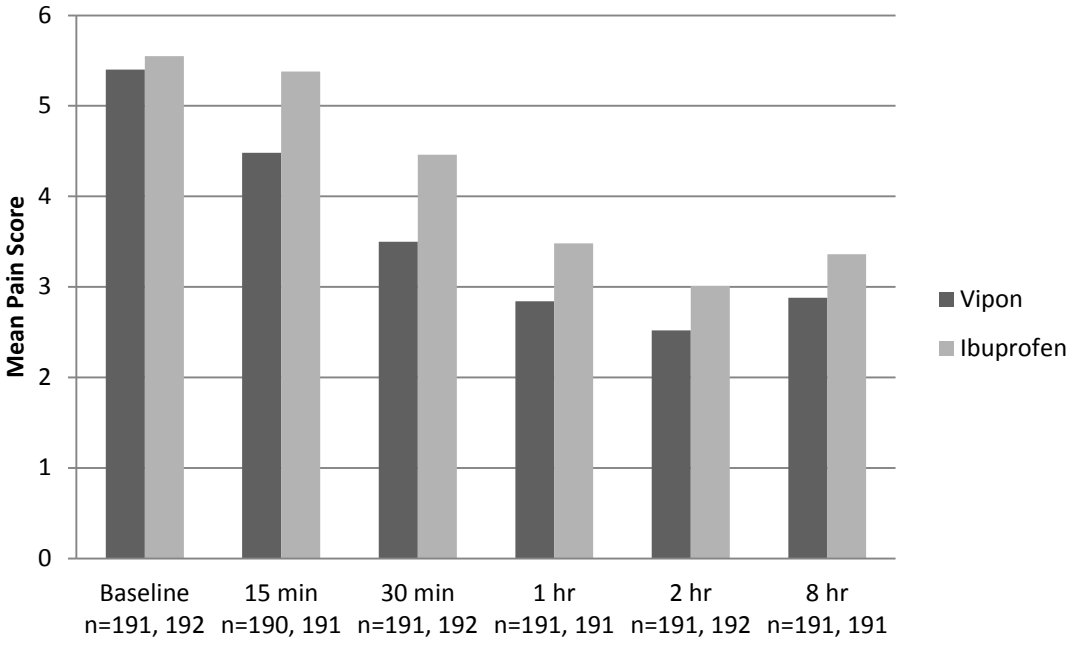
Abbreviation: CI = confidence interval.

Figure 2 shows the mean results of the general pain assessment from baseline through 8 hours for the treatment groups. The two groups report almost identical pain at baseline: average score of 5.3 versus 5.4 for the VIPON and Ibuprofen treated subjects, respectively.

While subjects treated with VIPON reported an average improvement of 17% at 15 minutes, subjects treated with Ibuprofen reported decreased pain of only 3% at the same interval, indicating VIPON's effectiveness at early relief of pain.

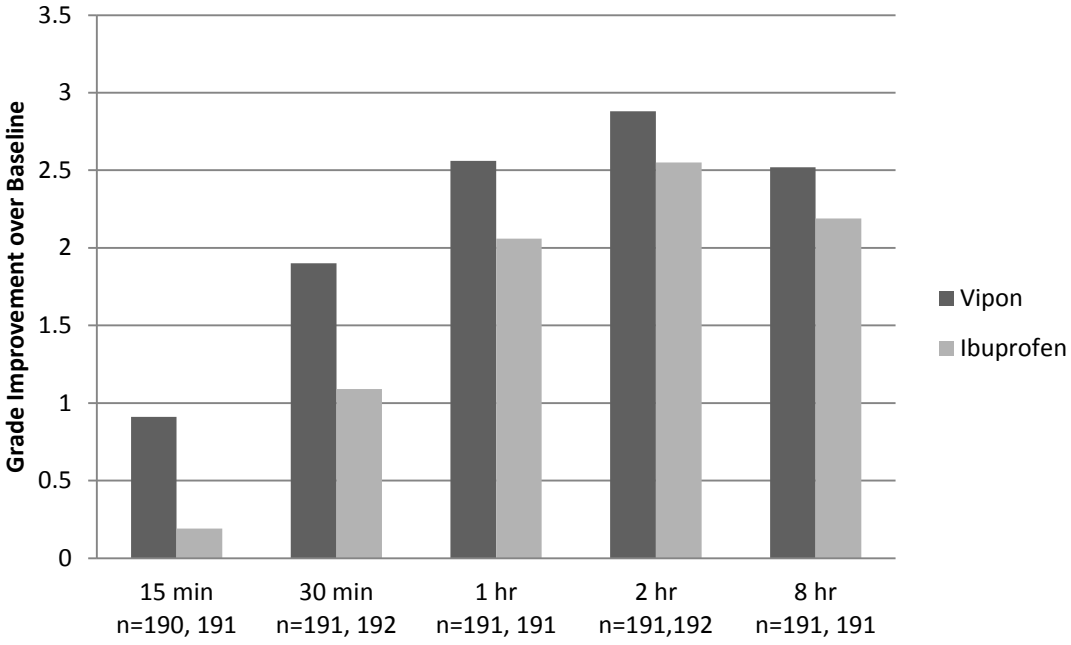
Subjects using the VIPON therapy continued to show more marked pain relief through 8 hours where both groups showed a slight decline.

Figure 2: Mean Pain Over Time – General Pain



Pain relief is significantly better in the subjects treated with VIPON compared to the subjects treated with Ibuprofen at 15 minutes, 30 minutes, and 1 hour (see Figure 3).

Figure 3: Pain Relief Over Time – General Pain



2.5.4. Secondary Endpoint – Symptom Clusters

Three symptom clusters with pain ratings from 0 (none) to 4 (intolerable) were obtained for abdominal pain, cramps and back pain.

Figure 4 through Figure 6 show average pain scores over time for each symptom cluster. The graphs show earlier and more marked reduction in pain scores over time for the VIPON treated subject group compared to the Ibuprofen treated subject group.

Figure 4: Mean Pain Over Time – Abdominal Pain

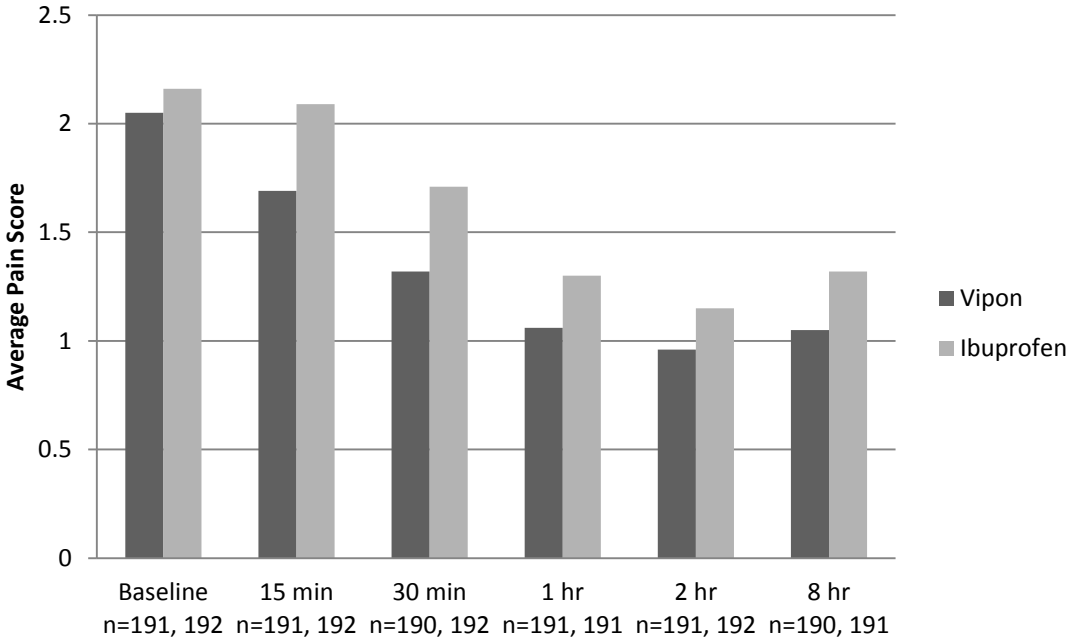


Figure 5: Mean Pain Over Time – Cramps

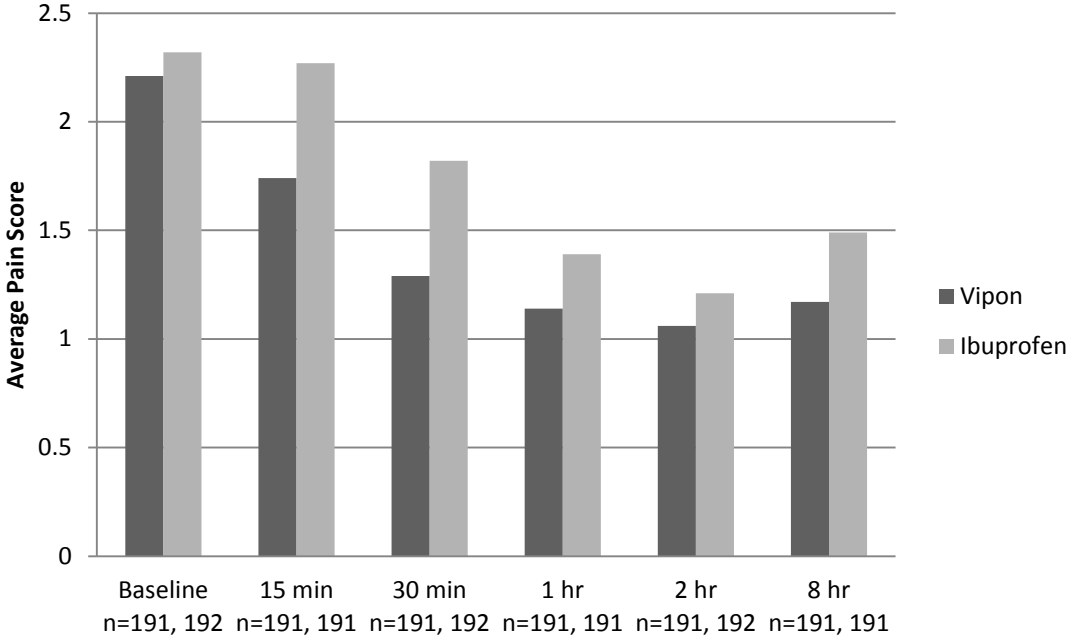
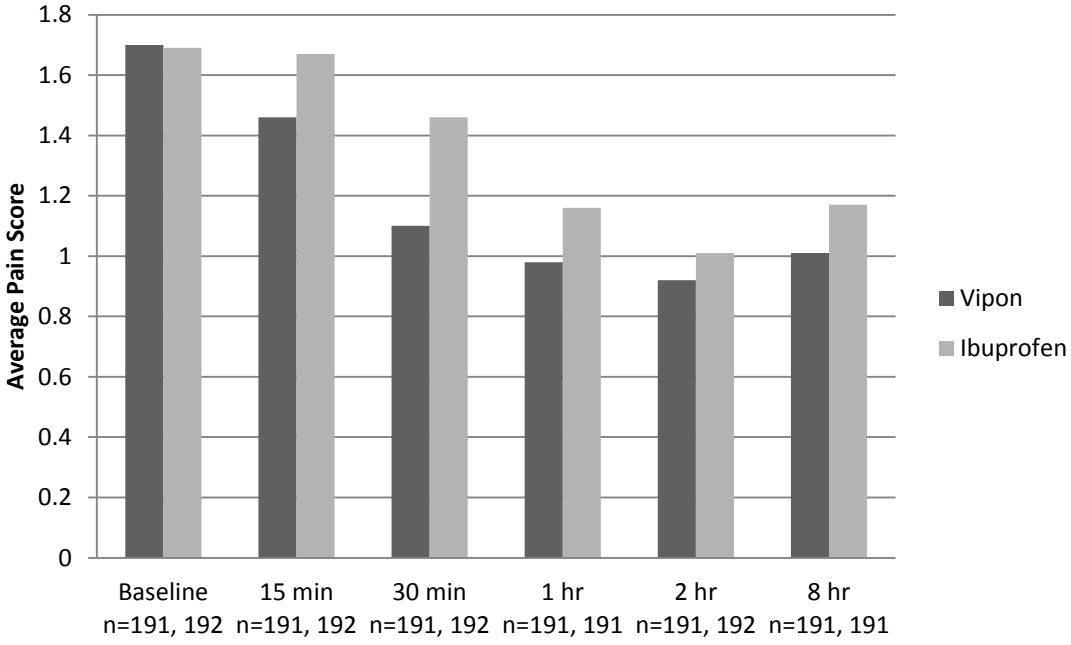


Figure 6: Mean Pain Over Time – Back Pain



The statistical analysis for symptoms clusters was performed in the same manner as the general pain assessment. The results were similar; across all three symptom clusters, the overall treatment effect demonstrated a statistically significant benefit from treatment with VIPON, with all p-values < 0.0001. Looking by timepoint, the statistical significance did not hold out to the 1 hour time point for these pain assessment measurements.

VIPON treated subjects obtained significantly more pain relief overall in each symptom cluster, and in each symptom cluster through 30 minutes post treatment. Table 8 details the symptom cluster results with the bolded lines representing the statistically significant time points. Figure 7 through Figure 9 display these results pictorially.

Table 8: Decrease in Symptom Cluster Pain Assessment over Time

Pain Measurement	**Time Point**	**VIPON Mean Score Change** (Baseline-Time point)	**Ibuprofen Mean Score Change** (Baseline-Time point)	**Treatment Effect Mean score Change** (95% CI)	**p-value**
Abdominal	**Overall**	N/A	N/A	**0.20 (0.12, 0.28)**	**<0.0001**
	15 minutes	**0.36**	**0.06**	**0.30 (0.17, 0.43)**	**<0.0001**
	30 minutes	**0.73**	**0.45**	**0.29 (0.11, 0.46)**	**0.0011**
	1 hour	0.99	0.84	0.15 (-0.04, 0.34)	0.1287
	2 hours	1.09	1.01	0.09 (-0.11, 0.29)	0.3898
	8 hours	0.99	0.83	0.16 (-0.04, 0.36)	0.1218
Cramps	**Overall**	N/A	N/A	**0.25 (0.17, 0.34)**	**<0.0001**
	15 minutes	**0.47**	**0.07**	**0.40 (0.26, 0.54)**	**<0.0001**
	30 minutes	**0.92**	**0.50**	**0.43 (0.25, 0.61)**	**<0.0001**
	1 hour	1.07	0.92	0.16 (-0.04, 0.36)	0.1207
	2 hours	1.15	1.11	0.05 (-0.16, 0.25)	0.6360
	8 hours	1.04	0.83	0.22 (-0.002, 0.435)	0.0520

Table 8: Decrease in Symptom Cluster Pain Assessment over Time, Continued

Back	**Overall**	N/A	N/A	**0.21 (0.13, 0.29)**	**<0.0001**
	15 minutes	**0.24**	**0.02**	**0.23 (0.10, 0.35)**	**0.0005**
	30 minutes	**0.60**	**0.23**	**0.37 (0.19, 0.54)**	**<0.0001**
	1 hour	0.71	0.54	0.18 (-0.01, 0.37)	0.0677
	2 hours	0.78	0.69	0.10 (-0.11, 0.30)	0.3451
	8 hours	0.69	0.52	0.17 (-0.03, 0.37)	0.0876

Abbreviation: CI = confidence interval.

Symptom Cluster results showing pain relief (difference in score from baseline) are displayed pictorially in Figure 7 through Figure 9.

Figure 7: Pain Relief Over Time – Abdominal Pain

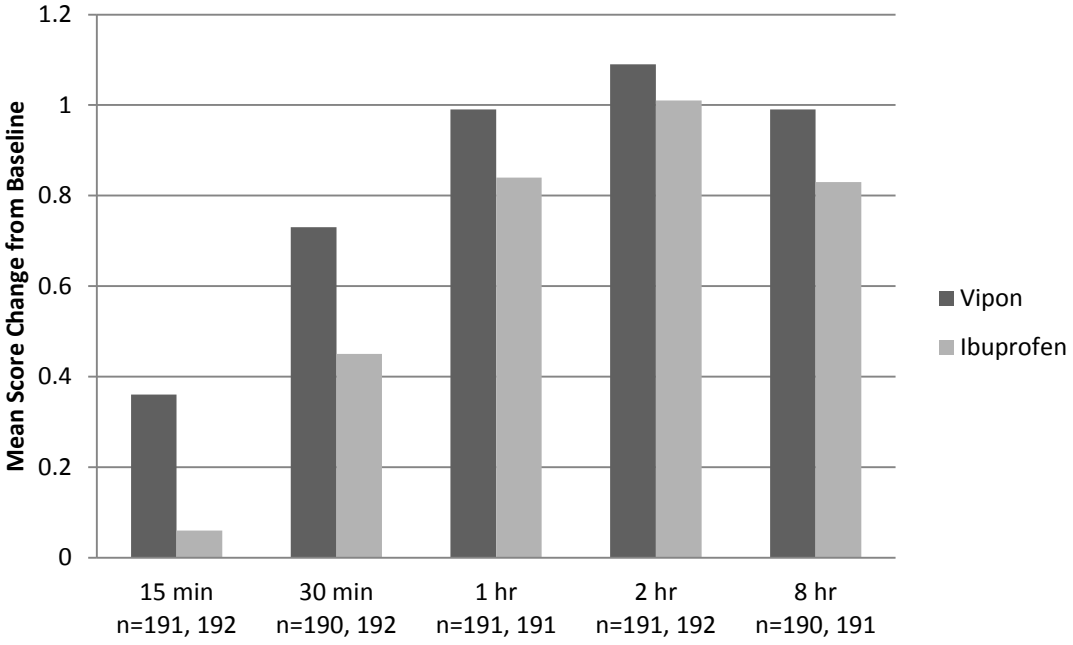


Figure 8: Pain Relief Over Time – Cramps

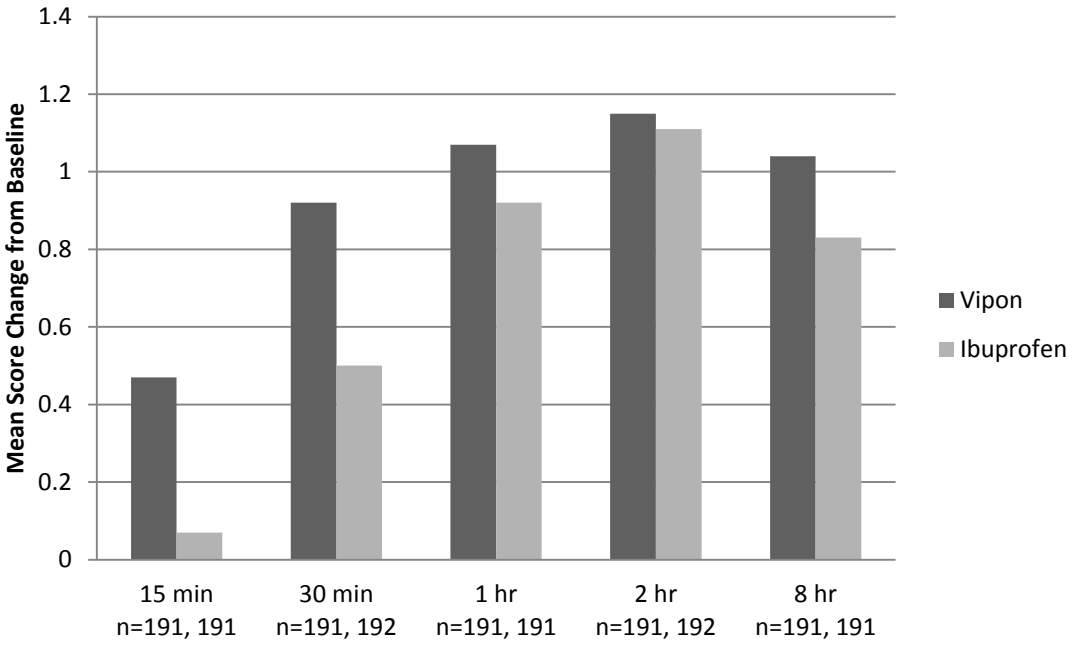


Figure 9: Pain Relief Over Time – Back Pain

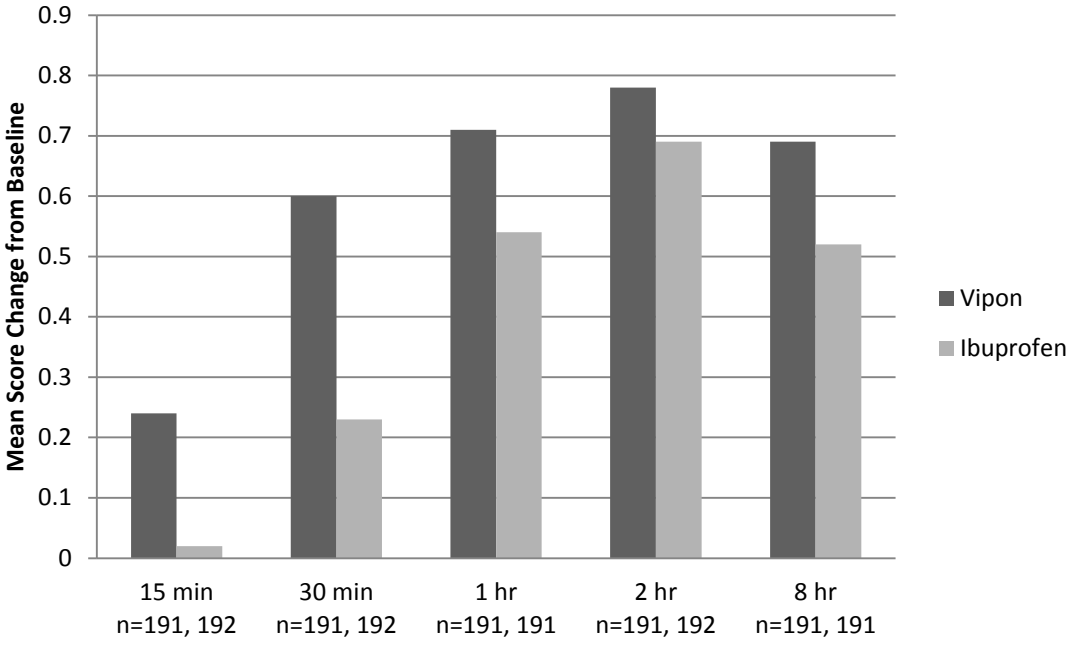


Figure 10 through Figure 14 show pain relief (as defined by difference in score from baseline) for all three pain clusters, one time interval per graph.

As previously shown, VIPON treated subjects experienced significantly more pain relief than Ibuprofen treated subjects at 15 and 30 minutes post-treatment. At 1 hour, VIPON treated subjects continued to report increased pain relief over the 30 minute time point results. These data demonstrate that the VIPON treatment was comparable to Ibuprofen treatment.

Figure 10: Pain Relief in Symptom Clusters
15 Minutes Post-Treatment

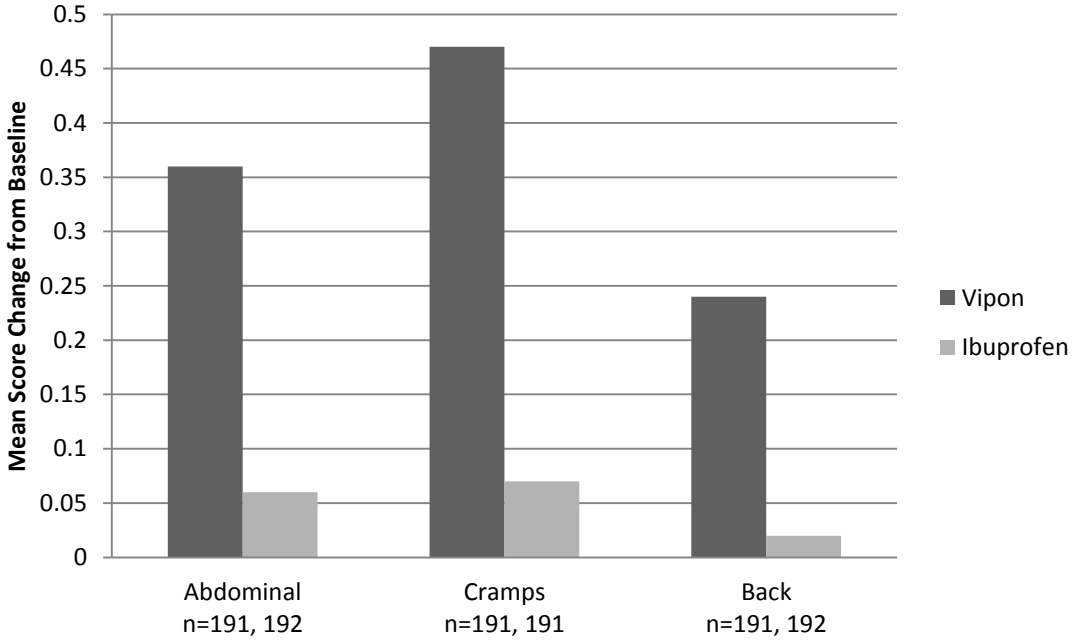


Figure 11: Pain Relief in Symptom Clusters
30 Minutes Post-Treatment

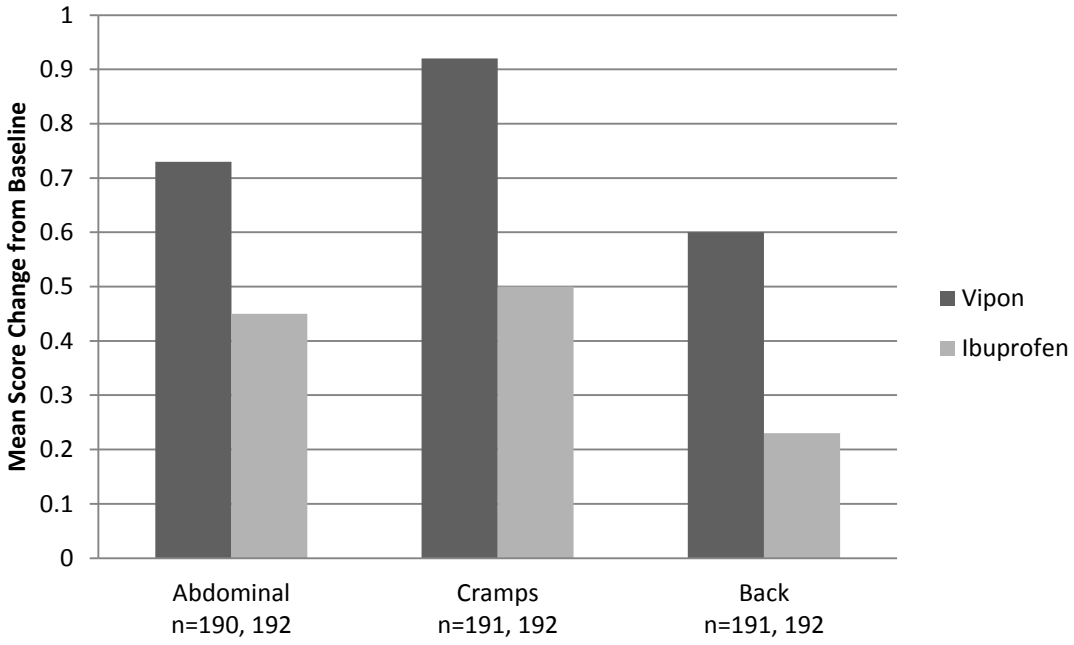
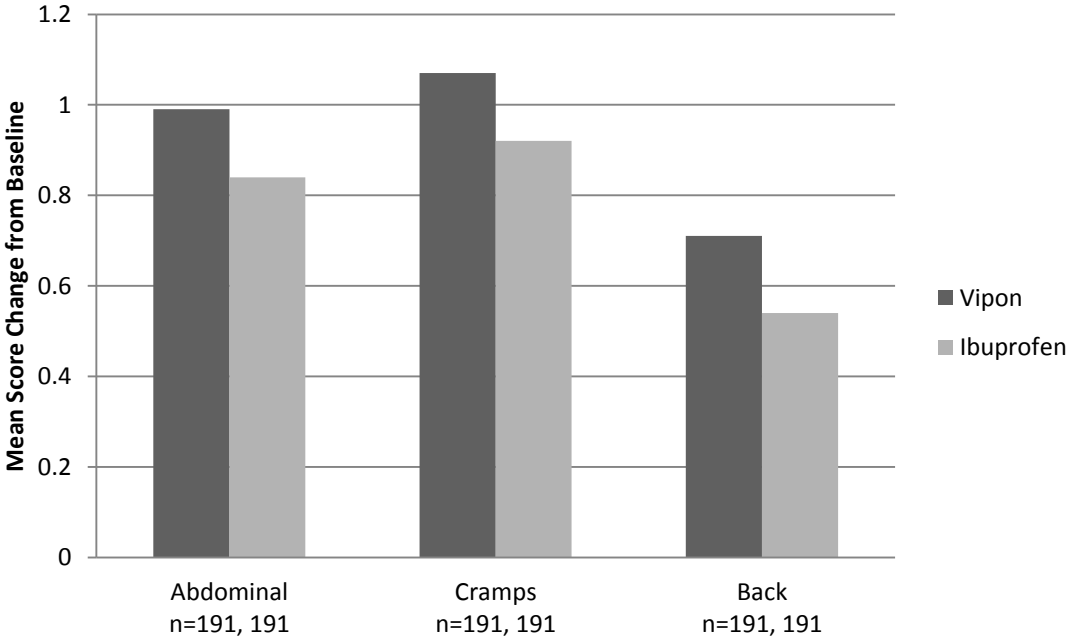
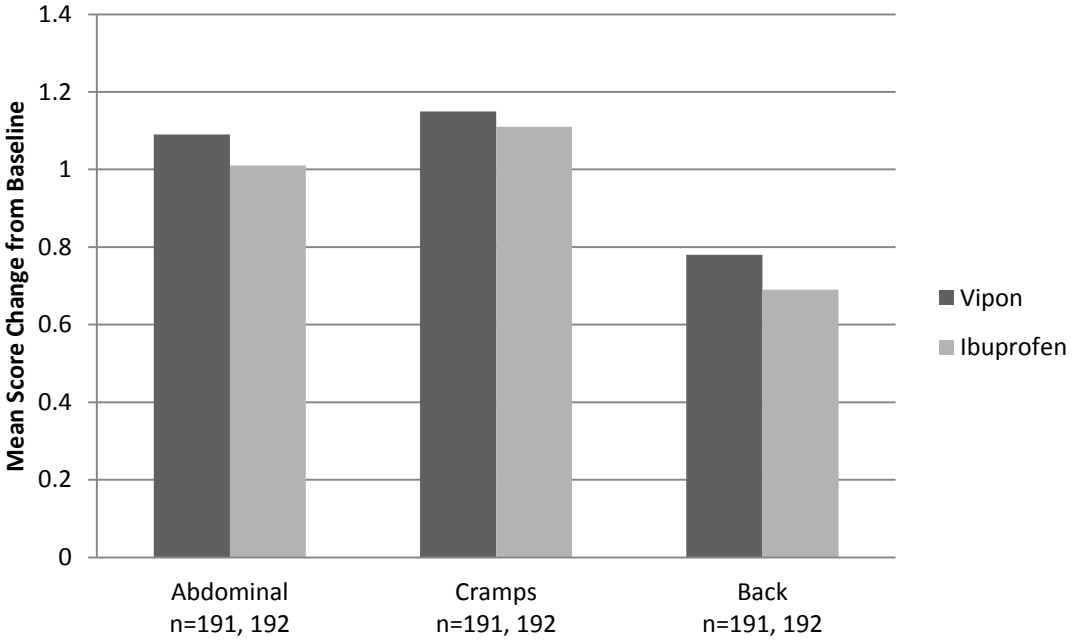


Figure 12: Pain Relief in Symptom Clusters
1 Hour Post-Treatment



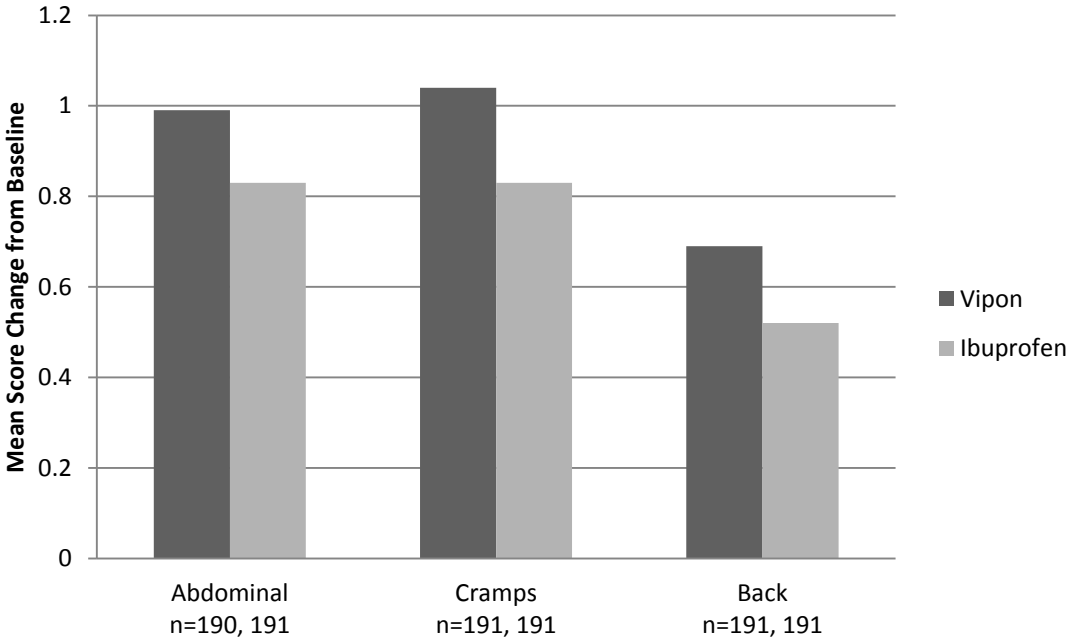
As shown in Figure 13, pain relief improves slightly for all subjects at 2 hours. While the VIPON group still reported greater pain relief, the Ibuprofen subjects reported greater improvement between 1 and 2 hours compared to VIPON subjects as pain relief approaches equalization between the two groups. Improvement has leveled off across all subjects as Ibuprofen appears to be reaching optimal relief at this time.

Figure 13: Pain Relief in Symptom Clusters
2 Hours Post-Treatment



As shown in Figure 14, results at 8 hours post treatment show a slight decline in pain relief compared to the 2 hour interval for both groups in all categories.

Figure 14: Pain Relief in Symptom Clusters
8 Hours Post-Treatment



2.5.5. Secondary Endpoint – Quality of Life

Each subject completed an SF-36 survey at baseline and at the 8-hour post treatment assessment. The SF-36 instrument is validated for 1-week and 6-week recall periods and therefore no scoring or analyses could be validly performed.

2.5.6. Secondary Endpoint – Time to Pain Relief

Time to pain relief was measured as a reduction of at least 1 point in the Melzack-McGill scale. The times to first improvement were analyzed separately for each menstrual period using Kaplan-Meier survival analysis. A log-rank test was used to compare the two treatments and the results are detailed in Table 9.

There is no evidence of differences between the two treatments.

Table 9: Time to Pain Relief Log-Rank Test

Menstrual Period	Log-rank p-value
1	0.4328
2	0.8059
3	0.3822
4	0.2207

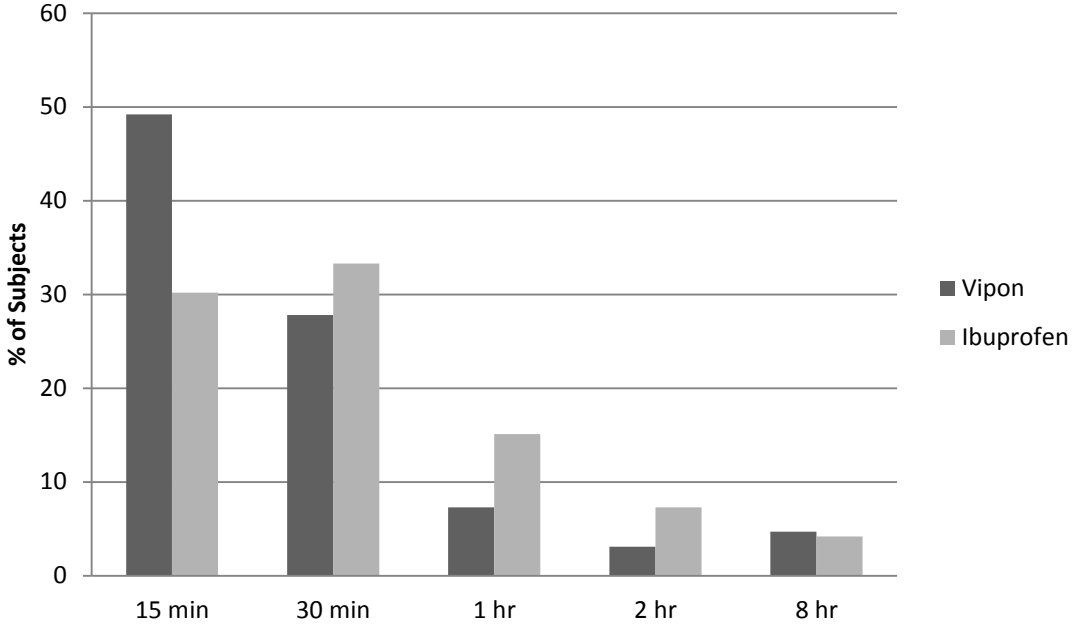
VIPON has demonstrated a capacity for early pain relief in previous sections of this report. Table 10 displays the frequency of subjects who experienced the first 1-point reduction in pain on the modified Melzack-McGill scale at each time point. Figure 15 displays the results graphically.

A greater number of VIPON subjects achieved the 1-point reduction at 15 minutes post-treatment (49.2%) as compared to the Ibuprofen group (30.2%), and 77% of VIPON subjects achieved that reduction by 30 minutes post treatment. Approximately 35% of Ibuprofen subjects did not achieve the 1-point reduction within 1 hour.

Table 10: Time Point of Earliest 1-Point Reduction in General Pain

Assessment Interval	VIPON Response n/191 (%)	Ibuprofen Response n/192 (%)
15 minutes	94 (49.2%)	58 (30.2%)
30 minutes	53 (27.8%)	64 (33.3%)
1 hour	14 (7.3%)	29 (15.1%)
2 hours	6 (3.1%)	14 (7.3%)
8 hours	9 (4.7%)	8 (4.2%)
No reduction	15 (7.9%)	19 (9.9%)

Figure 15: Earliest 1-Point Pain Reduction



2.5.7. Secondary Endpoint – Use of Rescue Medications

The use of rescue medication was the final efficacy endpoint studied. A statistical model was performed to test for treatment equality. The result was a non-significant p-value of 0.9874 meaning that there was no statistically significant difference in the use of rescue medication between the two treatment groups.

2.6 Subset Analysis – Treatment Success Subjects Only

Subjects were considered treatment successes if they reported a 1-point or greater reduction on the 11-point modified Melzack-McGill scale as well as the lack of rescue medication usage at 2 hours post treatment. Only subjects defined as successful are included in this section.

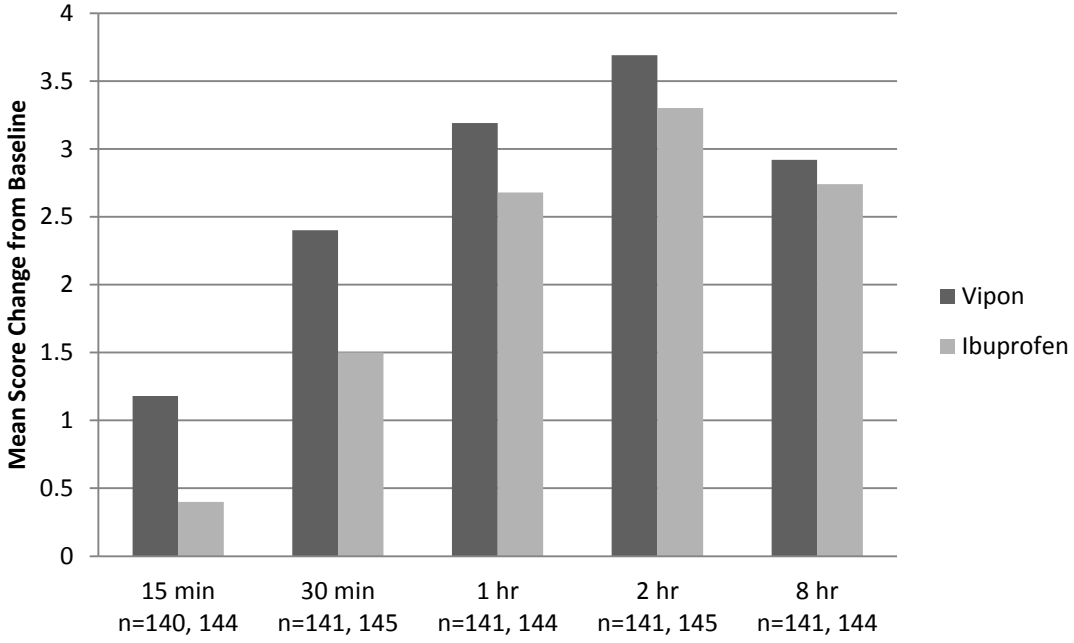
Baseline pain was identical in the 2 groups with average scores of 5.8. At 2 hours post-treatment, the VIPON subjects reported a 64% drop in general pain compared to the Ibuprofen group at 57%.

Table 11: Mean General Pain – Treatment Success Subjects

Time Point	VIPON Pain Response N=141	Ibuprofen Pain Response N=145
Baseline	5.8	5.8
2 hours	2.1	2.5

Figure 16 displays the difference in general pain relief between the VIPON and Ibuprofen treatment success subjects at each time point collected. At 15 minutes post-treatment, VIPON subjects show a decrease in pain three times greater than the Ibuprofen group: average scores of 1.2 compared to 0.4. VIPON subjects continue reporting pain relief substantially higher than the Ibuprofen subjects, although the gap narrows over time as Ibuprofen pain relief is realized.

Figure 16: General Pain Relief Over Time – Treatment Success Subjects



Successful subjects were also analyzed for the first time interval at which they reported at least a 1-point reduction in pain on the modified Melzack-McGill scale. These results reiterate the faster effect experienced with the VIPON treatment as evidenced by 58.2% of VIPON subjects achieving a 1-point reduction in general pain at 15 minutes versus only 35.2% of Ibuprofen subjects. By the 30 minute timepoint, 86.5% of VIPON users achieved a 1-point reduction compared to 75.9% of Ibuprofen users.

Table 12: Time Point of Earliest 1-Point Reduction in General Pain - Treatment Success Subjects

Assessment Interval	VIPON Response n/141 (%)	Ibuprofen Response n/145 (%)
15 minutes	82 (58.2%)	51 (35.2%)
30 minutes	40 (28.4%)	59 (40.7%)
1 hour	13 (9.2%)	24 (16.6%)
2 hours	6 (4.3%)	11 (7.6%)
8 hours	0 (0.0%)	0 (0.0%)

2.7 Subset Analysis – Subject With Strong Baseline Pain

Subjects who reported general pain score of at least 7 at baseline were considered to have 'strong pain'. Of those 124 periods in which the subject started with 'strong pain', 84% of those treated with VIPON and 81% of those treated with Ibuprofen were successful per the primary efficacy endpoint (a 1-point pain score reduction and no use of rescue medication). This difference was not statistically significant. The data show that the VIPON was as effective as Ibuprofen.

Subjects with strong baseline pain were reviewed for the first 1-point reduction in general pain. In this subgroup, VIPON subjects again showed earlier relief of pain versus the Ibuprofen subjects at 15 minutes: 56.1% and 32.8%, respectively. By the 30 minute time-point, 86.0% of VIPON subjects were reporting at least a 1-point relief of pain compared to 70.1% of Ibuprofen subjects. Table 13 details the results.

Table 13: Time Point of Earliest 1-Point Reduction in General Pain – Subjects with Strong Baseline Pain (7+)

Assessment Interval	VIPON Response n/57 (%)	Ibuprofen Response n/67 (%)
15 minutes	32 (56.1%)	22 (32.8%)
30 minutes	17 (29.8%)	25 (37.3%)
1 hour	5 (8.8%)	13 (19.4%)
2 hours	0 (0.0%)	2 (3.0%)
8 hours	2 (3.5%)	3 (4.5%)
No reduction	1 (1.8%)	2 (3.0%)

2.8 Summary of Safety Results

Physical examination and vital signs were measured at each subject visit to assist in determining if any safety or tolerability issues were seen such that an adverse event would be reported.

Adverse events were recorded and relatedness to the study product was assessed by the investigator. Adverse event data for all 115 enrolled subjects were summarized for the safety analysis.

2.8.1. Adverse Event Definitions

The protocol defines adverse events as follows:

Adverse Event: Any untoward medical occurrence in a subject or clinical investigation subject administered an investigational product and which does not necessarily have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including an abnormal finding), symptom, or disease temporally associated with the use of an investigational product, whether or not related to the investigational product.

Any new occurrence, or a pre-existing condition that worsens in severity or frequency from baseline, will be considered AEs if they:

- Result in discontinuation from the study,
- Require treatment or any other therapeutic intervention,
- Are associated with clinical signs or symptoms judged by the investigator to have a significant clinical impact.

Serious Adverse Event (SAE): Any untoward medical occurrence that at any dose:

- Results in death;
- Is life-threatening (The subject was at risk of death at the time of the event. It does not refer to an event, which hypothetically might have caused death if it were more severe);
- Requires in-patient hospitalization or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Is a congenital anomaly/birth defect.

2.8.2. Device-Related Adverse Event Summary

For each adverse event collected, investigators were required to assess the relatedness of the event to the investigational product. Table 14 summarizes the single device-related adverse event that occurred during the study. Relation to the investigational device was deemed "possible" for the event in Table 14. No events were deemed "probable" or "very likely" related to the investigational device. Other events whose relation to the investigational product was deemed "doubtful" or "not related" were not included in Table 14.

Table 14: Summary of Investigator Reported Events Related to the Investigational Device

Event	Treatment	Number of Events	Number of Subjects (% of subjects)
Headache	VIPON	1	1 (1.0%)

Details of this reported device-related adverse event related to the treatment and/or the treatment procedure is located in Appendix C.

2.8.3. Non Device-Related Adverse Event Summary

A total of 106 other events were reported during the study whose relation to the investigational product was deemed "doubtful" or "not related" by the investigator. A complete list of all investigator reported adverse events not related to the treatment and/or the treatment procedure is located in Appendix D.

2.8.4. Serious Adverse Events

Two (2) of the enrolled subjects each experienced serious adverse events. Neither event was related to the investigational product.

A summary of the serious adverse events are listed in Table 15.

Table 15: Serious Adverse Events

Subject ID	Treatment Dates	Event	AE Onset Date	Severity	Relation to study Treatment	Severity	Outcome	Duration of event
2010	1) 12/20/06 2) 01/18/07 3) 02/21/07 4) 03/18/07	Pregnancy	05/22/07	Mild	Not related	Mild	Resolved 01/25/08	248
2054	1) 06/09/08 2) 07/25/08	Appendicitis	08/07/08	Severe	Not related	Severe	Resolved 08/12/08	5

Subject 2010 began her last menstrual period of the study on March 18, 2007. Visit 3 was conducted on May 29, 2007, at which time a positive pregnancy test, conducted on May 22, 2007, was reported by the subject. A Completion/Early Withdrawal CRF was signed by the investigator on June 15, 2007. It was later confirmed by source documentation that a full-term live birth occurred on January 25, 2008.

2.8.5. Unlisted (Unexpected) Adverse Event

An unlisted/unexpected AE is one that the nature or severity of which is not consistent with the applicable product information for an unapproved investigational product or package insert/summary of product characteristics for an approved product.

No Unlisted or Unexpected Adverse Events occurred in the study.

2.8.6. Pregnancies

Pregnancies occurring after the first intake of the investigational products were considered immediately reportable events. Reporting of pregnancies was required within one day of the investigator learning of the event by use of the Serious Adverse Event Form for Clinical Trials. Follow-up information regarding the outcome of the pregnancy and any postnatal sequelae in the infant was required.

There was 1 pregnancy reported during the course of this study; see Section 2.8.4 for details.

2.8.7. Deaths

No deaths occurred during the course of the study.

2.9 Description of Deviations from the Investigational Plan

There were 50 deviations to the VIPON Investigational Plan reported by investigators or identified during study monitoring visits for the 115 subjects enrolled into the study.

The deviations from the investigational plan are summarized in Table 16 below. Protocol deviations affecting the data were either addressed in the analysis programming, such as subjects not adhering to the randomization schedule, or were not thought to affect the outcomes of the study.

A complete listing of protocol deviations can be found in Appendix E.

Table 16: Summary of Protocol Deviations All Enrolled Subjects

Protocol Deviation Category	Protocol Deviation Specified	Number of deviations
Subject enrolled outside of inclusion/exclusion criteria		1
Rescue medication taken within 2 hours of treatment		28
Other	Study product not used in sequential periods	8
Other	Randomization not followed	9
Other	Subject used own Ibuprofen	3
Other	Treatment done 1 hour prior to pre-dose pain assessment	1
TOTAL		**50**

3.0 Published Articles

The data collected in this study have not been included in any presentations or publications.

4.0 Changes In Investigational Plan

The study began under investigational plan version 04-May-05. One amendment dated 21-Feb-06, was implemented during the course of the study. The main difference in the amendment was the addition of a telephone follow-up.

5.0 Summary

The primary objective of this study was to compare the efficacy of the VIPON with Ibuprofen in relieving pain in women with dysmenorrhea. In comparing treatment effectiveness of these two groups, the following conclusions were supported:

- VIPON was non-inferior to Ibuprofen in relieving pain at 2 hours post-treatment as demonstrated by a reduction in pain score of at least 1 point and non-use of rescue medications within the first 2 hours of treatment. Subjects treated with the VIPON were successful per these criteria at a rate of 73.8% compared to 75.5% subjects treated with Ibuprofen.
- There was no difference in the use of rescue medication within 2 hours between the two groups.
- VIPON was statistically significantly better than Ibuprofen at general-pain-relief at 15 minutes, 30 minutes and 1 hour post-treatment, and overall.
- When evaluating symptom clusters (abdominal pain, cramps, and back pain), VIPON was statistically significantly better than Ibuprofen in each individual measure at 15 minutes and 30 minutes post treatment, and overall.
- Time to achieve a 1-point reduction in pain score was faster in subjects treated with VIPON compared to Ibuprofen. Overall, 77.0% of VIPON subjects achieved a 1-point reduction in pain score within 30 minutes compared to 63.5% using Ibuprofen.
- When evaluating time to a 1-point reduction in pain score for just those subjects who actually achieved a 1-point reduction, 58.2% of VIPON subjects achieved a 1-point reduction in pain score within 15 minutes compared to 35.2% using Ibuprofen. At 30 minutes, the rates were 86.5% and 75.9% for VIPON and Ibuprofen, respectively.
- For subjects experiencing 'strong pain' (defined as pain score of 7 or greater), the effectiveness of the VIPON was again comparable to Ibuprofen. Specifically, 84% of subjects treated with VIPON were able to achieve a 1-point reduction in general pain with no rescue medication compared to 81% with Ibuprofen.

These results demonstrate that the VIPON is as effective as Ibuprofen in relieving pain associated with dysmenorrhea, although with a faster time to pain relief.

The safety profile of the VIPON was also shown to be acceptable as demonstrated by a very low rate of adverse effects deemed related to the treatment. Only one adverse event collected during the study was reported in a subject during their treatment with the VIPON. Given the extremely low rate of events, these data confirm that the VIPON device is a safe alternative to Ibuprofen.

At least 50% of all menstruating women experience appreciable pain at some time during their menstruation. An estimated 600 million work hours are lost annually to this affliction with an average loss of time of two or more workdays per year per female employee.[1] indicating the need for effective pain relief options. This study has demonstrated that the VIPON can be safely used in a clinical setting and that it is as effective (i.e., non-inferior) as Ibuprofen for relief of pain associated with dysmenorrhea. Furthermore, the VIPON was able to offer pain relief significantly faster than Ibuprofen, offering a viable treatment alternative for women with menstrual pain.

[1] Jones AB. Managing the pain of primary and secondary dysmenorrhea. Nursing Times. 2004; 100(10): 40-3

Appendix A: Investigational Site Subject Listing (n=115 enrolled subjects)										
ID	**Treatment Period 1**		**Treatment Period 2**		**Treatment Period 3**		**Treatment Period 4**		**Age**	**Subject Completed Study**
	Date	**Treatment**	**Date**	**Treatment**	**Date**	**Treatment**	**Date**	**Treatment**		
1001	12/19/06	Ibuprofen	01/09/06*	VIPON	02/07/07	Ibuprofen	03/06/07	VIPON	27.1	Yes
1002	12/11/06	Ibuprofen	01/04/07	VIPON	01/28/07	Ibuprofen	02/21/07	VIPON	30.8	Yes
1003	.	.	.	.	.	.	.	.	32.9	No
1004	12/14/06	Ibuprofen	01/09/07	VIPON	01/31/07	VIPON	03/01/07	Ibuprofen	34.1	Yes
1005	12/22/07**	Ibuprofen	01/12/07	VIPON	02/03/07	Ibuprofen	02/24/07	VIPON	38.2	Yes
1006	01/02/07	Ibuprofen	01/26/07	VIPON	03/16/07	Ibuprofen	04/18/07	VIPON	43.2	Yes
1007	01/04/07	Ibuprofen	02/07/07	VIPON	03/08/07	Ibuprofen	04/07/07	VIPON	28.1	Yes
1008	01/15/07	VIPON	02/14/07	Ibuprofen	03/14/07	Ibuprofen	04/16/07	VIPON	37.4	Yes
1009	01/05/07	Ibuprofen	02/24/07	VIPON	03/19/07	VIPON	04/19/07	Ibuprofen	43.8	Yes
1010	01/02/07	VIPON	01/28/07	Ibuprofen	02/25/07	VIPON	04/22/07	Ibuprofen	34.1	Yes
1011	12/26/06	Ibuprofen	01/19/07	VIPON	02/13/07	VIPON	03/08/07	Ibuprofen	18.9	Yes
1012	01/09/07	Ibuprofen	02/06/07	VIPON	04/04/07	Ibuprofen	05/01/07	VIPON	26.1	Yes
1013	01/23/07	VIPON	03/20/07	Ibuprofen	04/20/07	Ibuprofen	05/16/07	VIPON	25.4	Yes
1014	01/13/07	VIPON	02/10/07	Ibuprofen	03/10/07	VIPON	04/06/07	Ibuprofen	44.1	Yes
1015	01/17/07	Ibuprofen	02/15/07	VIPON	03/16/07	VIPON	04/16/07	Ibuprofen	34.2	Yes
1016	01/13/07	VIPON	02/07/07	Ibuprofen	03/07/07	Ibuprofen	04/02/07	VIPON	34.0	Yes
1017	01/17/07	Ibuprofen	02/12/07	VIPON	03/08/07	VIPON	04/03/07	Ibuprofen	33.6	Yes
1018	01/20/07	Ibuprofen	02/23/07	VIPON	03/23/07	VIPON	04/21/07	Ibuprofen	25.2	Yes

*We believe this date to be in error and that the correct date is 01/09/07. This error does not affect any results presented in this report.
**We believe this date to be in error and that the correct date is 12/22/06. This error does not affect any results presented in this report.

Appendix B: Investigational Site Subject Listing (n=115 enrolled subjects)										
ID	Treatment Period 1		Treatment Period 2		Treatment Period 3		Treatment Period 4		Age	Subject Completed Study
	Date	Treatment	Date	Treatment	Date	Treatment	Date	Treatment		
1019	01/27/07	Ibuprofen	02/22/07	VIPON	03/14/07	Ibuprofen	04/08/07	VIPON	34.9	Yes
1020	.	.	.	.	.	.	.	.	22.1	No
1021	01/31/07	Ibuprofen	03/01/07	VIPON	03/30/07	VIPON	05/02/07	Ibuprofen	29.9	Yes
1022	01/30/07	Ibuprofen	02/26/07	VIPON	03/27/07	Ibuprofen	04/23/07	VIPON	23.6	Yes
1023	01/29/07	VIPON	02/24/07	Ibuprofen	03/24/07	VIPON	04/26/07	Ibuprofen	36.0	Yes
1024	01/31/07	Ibuprofen	02/28/07	VIPON	03/28/07	VIPON	04/25/07	Ibuprofen	21.9	Yes
1025	02/23/07	VIPON	03/15/07	Ibuprofen	04/26/07	Ibuprofen	05/28/07	VIPON	23.7	Yes
1026	02/15/07	Ibuprofen	03/15/07	VIPON	04/13/07	Ibuprofen	05/10/07	VIPON	30.6	Yes
1027	02/22/07	VIPON	03/21/07	Ibuprofen	04/18/07	VIPON	05/16/07	Ibuprofen	23.6	Yes
1028	.	.	.	.	.	.	.	.	25.4	No
1029	02/27/07	VIPON	03/27/07	Ibuprofen	04/26/07	VIPON	05/25/07	Ibuprofen	45.3	Yes
1030	03/01/07	VIPON	03/24/07	Ibuprofen	04/20/07	Ibuprofen	05/17/07	VIPON	23.4	Yes
1031	03/18/07	Ibuprofen	04/12/07	VIPON	05/13/07	Ibuprofen	06/05/07	VIPON	33.5	Yes
1032	03/24/07	VIPON	04/20/07	Ibuprofen	05/20/07	Ibuprofen	06/16/07	VIPON	35.8	Yes
1033	03/27/07	Ibuprofen	04/25/07	VIPON	05/24/07	VIPON	06/22/07	Ibuprofen	21.9	Yes
1034	03/23/07	VIPON	04/26/07	Ibuprofen	05/17/07	VIPON	06/17/07	Ibuprofen	45.9	Yes
1035	03/29/07	Ibuprofen	04/30/07	VIPON	05/25/07	Ibuprofen	06/20/07	VIPON	36.6	Yes
1036	04/04/07	VIPON	05/02/07	Ibuprofen	05/30/07	VIPON	06/28/07	Ibuprofen	25.5	Yes
1037	05/01/07	Ibuprofen	06/02/07	VIPON	07/06/07	VIPON	08/03/07	Ibuprofen	28.0	Yes
1038	04/08/07	Ibuprofen	04/30/07	VIPON	05/24/07	VIPON	06/17/07	Ibuprofen	43.2	Yes

Appendix B: Investigational Site Subject Listing (n=115 enrolled subjects)										
ID	Treatment Period 1		Treatment Period 2		Treatment Period 3		Treatment Period 4		Age	Subject Completed Study
	Date	Treatment	Date	Treatment	Date	Treatment	Date	Treatment		
1039	04/30/07	Ibuprofen	05/24/07	VIPON	07/15/07	VIPON	08/09/07	Ibuprofen	36.1	Yes
1040	04/13/07	Ibuprofen	05/10/07	VIPON	06/07/07	Ibuprofen	07/05/07	VIPON	30.0	Yes
1041	04/19/07	Ibuprofen	05/17/07	VIPON	06/17/07	VIPON	07/12/07	Ibuprofen	27.5	Yes
1042	04/20/07	VIPON	05/18/07	Ibuprofen	06/18/07	VIPON	07/12/07	Ibuprofen	38.9	Yes
1043	04/19/07	Ibuprofen	05/14/07	VIPON	06/09/07	Ibuprofen	07/03/07	VIPON	33.9	Yes
1044	04/20/07	Ibuprofen	05/21/07	VIPON	06/19/07	VIPON	07/13/07	Ibuprofen	21.2	Yes
1045	05/10/07	Ibuprofen	06/08/07	VIPON	07/10/07	VIPON	08/08/07	Ibuprofen	21.3	Yes
1046	04/26/07	VIPON	05/24/07	Ibuprofen	06/21/07	Ibuprofen	07/19/07	VIPON	28.8	Yes
1047	05/15/07	VIPON	06/12/07	Ibuprofen	07/10/07	VIPON	08/08/07	Ibuprofen	26.0	Yes
1048	05/02/07	VIPON	06/08/07	Ibuprofen	07/06/07	Ibuprofen	08/01/07	VIPON	42.9	Yes
1049	05/22/07	Ibuprofen	06/19/07	VIPON	07/17/07	Ibuprofen	08/13/07	VIPON	24.8	Yes
1050	05/03/07	Ibuprofen	05/31/07	VIPON	06/26/07	VIPON	07/26/07	Ibuprofen	33.3	Yes
1051	05/20/07	VIPON	06/17/07	Ibuprofen	07/15/07	VIPON	08/12/07	Ibuprofen	24.0	Yes
2001	11/14/06	VIPON	12/14/06	Ibuprofen	01/10/07	VIPON	02/11/07	Ibuprofen	35.2	Yes
2002	11/25/06	Ibuprofen	12/26/06	VIPON	01/27/07	Ibuprofen	02/28/07	VIPON	19.0	Yes
2003	12/08/06	Ibuprofen	01/06/07	VIPON	02/01/07	VIPON	02/26/07	Ibuprofen	32.9	Yes
2004	.	.	.	.	.	.	.	.	42.2	No
2005	.	.	.	.	.	.	.	.	44.0	No
2006	11/25/06	Ibuprofen	12/23/06	VIPON	02/14/07	Ibuprofen	03/14/07	VIPON	41.3	Yes
2007	.	.	.	.	.	.	.	.	43.0	No

Appendix B: Investigational Site Subject Listing (n=115 enrolled subjects)										
ID	Treatment Period 1		Treatment Period 2		Treatment Period 3		Treatment Period 4		Age	Subject Completed Study
	Date	Treatment	Date	Treatment	Date	Treatment	Date	Treatment		
2008	11/21/06	Ibuprofen	12/19/06	VIPON	01/16/07	VIPON	02/11/07	Ibuprofen	38.1	Yes
2009	11/22/06	VIPON	12/21/06	Ibuprofen	01/19/07	Ibuprofen	02/18/07	VIPON	27.8	Yes
2010	12/20/06	Ibuprofen	01/18/07	VIPON	02/21/07	Ibuprofen	03/18/07	VIPON	28.0	Yes
2011	12/17/06	VIPON	01/11/07	Ibuprofen	.	.	.	.	31.0	No
2012	12/13/06	VIPON	01/09/07	VIPON	02/06/07	Ibuprofen	03/02/07	VIPON	28.2	Yes
2013	12/27/07	.	01/24/07	VIPON	02/21/07	Ibuprofen	03/22/07	VIPON	32.4	Yes
2014	.	.	.	.	.	.	.	.	20.0	No
2015	01/26/07	VIPON	02/23/07	Ibuprofen	03/23/07	VIPON	04/19/07	Ibuprofen	38.9	Yes
2016	02/10/07	VIPON	03/10/07	Ibuprofen	04/06/07	VIPON	05/27/07	Ibuprofen	32.6	Yes
2017	01/25/07	VIPON	02/22/07	Ibuprofen	03/15/07	VIPON	04/13/07	Ibuprofen	43.7	Yes
2018	02/17/07	Ibuprofen	03/16/07	VIPON	04/07/07	Ibuprofen	05/20/07	VIPON	43.9	Yes
2019	02/23/07	VIPON	03/25/07	Ibuprofen	04/23/07	VIPON	05/20/07	Ibuprofen	40.5	Yes
2020	.	.	.	.	.	.	.	.	28.5	No
2021	.	.	.	.	.	.	.	.	23.1	No
2022	.	.	.	.	.	.	.	.	33.0	No
2023	02/22/07	Ibuprofen	03/28/07	VIPON	.	.	.	.	23.0	No
2024	03/09/07	VIPON	04/07/07	Ibuprofen	06/27/07	Ibuprofen	07/22/07	VIPON	48.1	Yes
2025	03/28/07	VIPON	04/24/07	Ibuprofen	05/23/07	VIPON	06/22/07	Ibuprofen	22.9	Yes
2026	02/28/07	Ibuprofen	03/28/07	VIPON	04/25/07	Ibuprofen	05/23/07	VIPON	23.3	Yes
2027	03/21/07	VIPON	04/19/07	Ibuprofen	05/23/07	Ibuprofen	06/27/07	VIPON	23.0	Yes

Appendix B: Investigational Site Subject Listing (n=115 enrolled subjects)										
ID	Treatment Period 1		Treatment Period 2		Treatment Period 3		Treatment Period 4		Age	Subject Completed Study
	Date	Treatment	Date	Treatment	Date	Treatment	Date	Treatment		
2028	03/24/07	VIPON	04/28/07	Ibuprofen	.	.	.	.	23.8	No
2029	.	.	.	.	.	.	.	.	24.8	No
2030	03/12/07	VIPON	04/07/07	Ibuprofen	05/16/07	VIPON	06/15/07	Ibuprofen	41.3	Yes
2031	04/12/07	VIPON	05/11/07	Ibuprofen	06/20/07	VIPON	07/18/07	.	19.9	Yes
2032	03/24/07	Ibuprofen	04/20/07	VIPON	05/18/07	Ibuprofen	06/11/07	VIPON	44.4	Yes
2033	03/14/07	VIPON	05/07/07	Ibuprofen	06/29/07	Ibuprofen	08/01/07	VIPON	26.2	Yes
2034	03/28/07	Ibuprofen	04/29/07	VIPON	05/31/07	Ibuprofen	06/28/07	VIPON	23.5	Yes
2035	05/24/07	VIPON	06/21/07	Ibuprofen	07/21/07	VIPON	08/23/07	Ibuprofen	45.4	Yes
2036	.	.	.	.	.	.	.	.	32.1	No
2037	06/26/07	Ibuprofen	07/24/07	VIPON	09/05/07	Ibuprofen	10/03/07	VIPON	25.5	Yes
2038	07/11/07	VIPON	08/15/07	Ibuprofen	09/11/07	Ibuprofen	10/08/07	VIPON	28.9	Yes
2039	06/10/07	Ibuprofen	07/04/07	VIPON	10/20/07	VIPON	11/19/07	Ibuprofen	38.7	Yes
2040	06/02/07	Ibuprofen	06/30/07	VIPON	08/23/07	VIPON	09/20/07	Ibuprofen	29.7	Yes
2041	06/12/07	VIPON	07/10/07	Ibuprofen	08/12/07	VIPON	09/15/07	Ibuprofen	18.1	Yes
2042	07/04/07	Ibuprofen	08/01/07	VIPON	09/04/07	Ibuprofen	10/29/07	VIPON	19.4	Yes
2043	07/25/07	VIPON	08/25/07	Ibuprofen	09/27/07	Ibuprofen	10/28/07	VIPON	41.4	Yes
2044	08/12/07	Ibuprofen	09/13/07	VIPON	10/13/07	Ibuprofen	11/15/07	VIPON	36.0	Yes
2045	09/28/07	Ibuprofen	10/21/07	VIPON	11/25/07	VIPON	12/23/07	Ibuprofen	34.4	Yes
2046	09/22/07	VIPON	10/21/07	Ibuprofen	11/23/07	Ibuprofen	12/22/07	VIPON	25.9	Yes
2047	12/04/07	Ibuprofen	01/21/08	VIPON	02/13/08	VIPON	03/10/08	Ibuprofen	25.1	Yes

Appendix B: Investigational Site Subject Listing (n=115 enrolled subjects)										
ID	Treatment Period 1		Treatment Period 2		Treatment Period 3		Treatment Period 4		Age	Subject Completed Study
	Date	Treatment	Date	Treatment	Date	Treatment	Date	Treatment		
2048	.	.	.	.	.	.	.	.	27.4	No
2049	03/21/08	Ibuprofen	04/19/08	VIPON	05/22/08	Ibuprofen	06/11/08	VIPON	36.1	Yes
2050	05/26/08	VIPON	06/28/08	Ibuprofen	07/23/08	Ibuprofen	08/23/08	VIPON	23.8	Yes
2051	05/20/08	Ibuprofen	07/25/08	VIPON	08/14/08	VIPON	09/12/08	Ibuprofen	27.4	Yes
2052	05/12/08	VIPON	06/08/08	Ibuprofen	07/04/08	VIPON	07/29/08	Ibuprofen	42.5	Yes
2053	06/03/08	Ibuprofen	07/10/08	VIPON	08/14/08	VIPON	09/16/08	Ibuprofen	40.6	Yes
2054	06/09/08	VIPON	07/25/08	Ibuprofen	.	.	.	.	40.4	No
2055	06/17/08	VIPON	07/14/08	Ibuprofen	08/10/08	VIPON	09/05/08	Ibuprofen	44.5	Yes
2056	07/09/08	VIPON	07/26/08	Ibuprofen	08/24/08	VIPON	09/20/08	Ibuprofen	44.6	Yes
2057	07/26/08	Ibuprofen	08/25/08	VIPON	09/17/08	VIPON	10/09/08	Ibuprofen	39.5	Yes
2058	07/12/08	Ibuprofen	08/09/08	VIPON	09/05/08	Ibuprofen	10/02/08	VIPON	42.5	Yes
2059	08/01/08	Ibuprofen	08/27/08	VIPON	09/22/08	Ibuprofen	10/19/08	VIPON	41.4	Yes
2060	07/28/08	VIPON	08/26/08	Ibuprofen	09/17/08	VIPON	10/13/08	Ibuprofen	44.7	Yes
2061	08/17/08	Ibuprofen	09/17/08	VIPON	10/15/08	VIPON	11/13/08	Ibuprofen	31.6	Yes
2062	07/29/08	Ibuprofen	08/30/08	VIPON	10/03/08	Ibuprofen	11/09/08	VIPON	19.6	Yes
2063	08/10/08	VIPON	09/07/08	Ibuprofen	10/04/08	Ibuprofen	10/31/08	VIPON	37.3	Yes
2064	08/13/08	VIPON	09/09/08	Ibuprofen	10/05/08	VIPON	11/01/08	Ibuprofen	20.9	Yes

Appendix C: Investigator Reported Adverse Events – Related to Investigational Device										
ID	**Treatment Period 1**	**Treatment Period 2**	**Treatment Period 3**	**Treatment Period 4**	**Event**	**Onset Date of Event**	**Severity**	**Relation to Study Tmt**	**Outcome**	**Duration of Event (Days)**
1013	01/23/07 VIPON	03/20/07 Ibuprofen	04/20/07 Ibuprofen	05/16/07 VIPON	Headache	01/23/07	Mild	Possible	Resolved	0

Appendix D: Investigator Reported Adverse Events – Not Related to Investigational Device												
ID	**Treatment 1 Date**	**Treatment 2 Date**	**Treatment 3 Date**	**Treatment 4 Date**	**Event**	**Onset Date**	**Severity**	**Related**	**Outcome**	**Resolution Date**	**Duration**	**Completed Study**
1001	12/19/06	01/09/06	02/07/07	03/06/07	Upper respiratory infection	01/06/07	Moderate	Not Related	Resolved	01/17/07	11	Yes
1003	.	.	.	.	Chest pain	12/13/06	Moderate	Doubtful	Persisted	.	.	No
1003	.	.	.	.	Pericarditis	12/13/06	Moderate	Doubtful	Persisted	.	.	No
1003	.	.	.	.	Rectal bleeding	01/01/07	Moderate	Not Related	Persisted	.	.	No
1005	12/22/07	01/12/07	02/03/07	02/24/07	Neck pain	12/21/06	Moderate	Not Related	Resolved	12/21/06	0	Yes
1005	12/22/07	01/12/07	02/03/07	02/24/07	Headache	01/15/07	Severe	Not Related	Resolved	01/15/07	0	Yes
1005	12/22/07	01/12/07	02/03/07	02/24/07	Stomach pain	01/12/07	Severe	Not Related	Resolved	01/13/07	1	Yes
1005	12/22/07	01/12/07	02/03/07	02/24/07	Diarrhea	01/14/07	Moderate	Not Related	Resolved	01/14/07	0	Yes
1005	12/22/07	01/12/07	02/03/07	02/24/07	Neck pain	01/11/07	Severe	Not Related	Resolved	01/11/07	0	Yes
1005	12/22/07	01/12/07	02/03/07	02/24/07	Headache	01/11/07	Severe	Not Related	Resolved	01/11/07	0	Yes
1005	12/22/07	01/12/07	02/03/07	02/24/07	Depression	02/02/07	Moderate	Not Related	Persisted	.	.	Yes
1006	01/02/07	01/26/07	03/16/07	04/18/07	Peridontal surgery	12/15/06	Moderate	Not Related	Resolved	12/15/06	0	Yes
1006	01/02/07	01/26/07	03/16/07	04/18/07	Dental pain	12/15/06	Moderate	Not Related	Resolved	12/23/06	8	Yes
1006	01/02/07	01/26/07	03/16/07	04/18/07	Upper respiratory infection	04/03/07	Moderate	Not Related	Resolved	04/17/07	14	Yes
1010	01/02/07	01/28/07	02/25/07	04/22/07	Right labial biopsy	01/11/07	Mild	Not Related	Resolved	01/11/07	0	Yes
1011	12/26/06	01/19/07	02/13/07	03/08/07	Headache	01/15/07	Moderate	Not Related	Resolved	01/15/07	0	Yes

Appendix D: Investigator Reported Adverse Events – Not Related to Investigational Device												
ID	**Treatment 1 Date**	**Treatment 2 Date**	**Treatment 3 Date**	**Treatment 4 Date**	**Event**	**Onset Date**	**Severity**	**Related**	**Outcome**	**Resolution Date**	**Duration**	**Completed Study**
1012	01/09/07	02/06/07	04/04/07	05/01/07	Daytime hypersomina	03/09/07	Moderate	Not Related	Persisted	.	.	Yes
1012	01/09/07	02/06/07	04/04/07	05/01/07	Intense headache	02/06/07	Severe	Not Related	Resolved	02/06/07	0	Yes
1013	01/23/07	03/20/07	04/20/07	05/16/07	Stomach flu	05/14/07	Moderate	Not Related	Resolved	05/15/07	1	Yes
1013	01/23/07	03/20/07	04/20/07	05/16/07	Back ache	05/14/07	Moderate	Not Related	Resolved	05/15/07	1	Yes
1016	01/13/07	02/07/07	03/07/07	04/02/07	Upper respiratory infection	03/15/07	Moderate	Not Related	Resolved	03/25/07	10	Yes
1017	01/17/07	02/12/07	03/08/07	04/03/07	Strep throat	03/28/07	Severe	Not Related	Resolved	04/09/07	12	Yes
1019	01/27/07	02/22/07	03/14/07	04/08/07	Acne	02/07/07	Moderate	Not Related	Persisted	.	.	Yes
1019	01/27/07	02/22/07	03/14/07	04/08/07	Fatique	02/27/07	Moderate	Not Related	Persisted	.	.	Yes
1019	01/27/07	02/22/07	03/14/07	04/08/07	Sinusitis	02/26/07	Moderate	Not Related	Resolved	03/08/07	10	Yes
1021	01/31/07	03/01/07	03/30/07	05/02/07	Chest congestion	05/06/07	Moderate	Not Related	Resolved	05/09/07	3	Yes
1022	01/30/07	02/26/07	03/27/07	04/23/07	Upper respiratory infection	02/12/07	Moderate	Not Related	Resolved	02/21/07	9	Yes
1023	01/29/07	02/24/07	03/24/07	04/26/07	Generalized body aches	02/13/07	Moderate	Not Related	Resolved	02/14/07	1	Yes
1023	01/29/07	02/24/07	03/24/07	04/26/07	Cough	02/14/07	Severe	Not Related	Resolved	02/21/07	7	Yes
1024	01/31/07	02/28/07	03/28/07	04/25/07	Yest infection	02/05/07	Mild	Not Related	Resolved	02/07/07	2	Yes
1024	01/31/07	02/28/07	03/28/07	04/25/07	Sinus infection	04/11/07	Moderate	Not Related	Resolved	04/19/07	8	Yes
1024	01/31/07	02/28/07	03/28/07	04/25/07	Yeast infection	04/16/07	Mild	Not Related	Resolved	04/20/07	4	Yes

Appendix D: Investigator Reported Adverse Events – Not Related to Investigational Device												
ID	**Treatment 1 Date**	**Treatment 2 Date**	**Treatment 3 Date**	**Treatment 4 Date**	**Event**	**Onset Date**	**Severity**	**Related**	**Outcome**	**Resolution Date**	**Duration**	**Completed Study**
1025	02/23/07	03/15/07	04/26/07	05/28/07	Right knee meniscus tear	03/16/07	Moderate	Not Related	Resolved	05/20/07	65	Yes
1025	02/23/07	03/15/07	04/26/07	05/28/07	Headache	03/01/07	Moderate	Not Related	Resolved	03/01/07	0	Yes
1025	02/23/07	03/15/07	04/26/07	05/28/07	Respiratory infection with chest congestion	04/28/07	Moderate	Not Related	Resolved	05/03/07	5	Yes
1025	02/23/07	03/15/07	04/26/07	05/28/07	Right knee pain meniscus tear	05/20/07	Severe	Not Related	Resolved	05/31/07	11	Yes
1025	02/23/07	03/15/07	04/26/07	05/28/07	Right knee pain meniscus tear	05/31/07	Moderate	Not Related	Persisted	.	.	Yes
1025	02/23/07	03/15/07	04/26/07	05/28/07	Headache	05/30/07	Moderate	Not Related	Resolved	05/30/07	0	Yes
1029	02/27/07	03/27/07	04/26/07	05/25/07	~"Twisted~" back	03/19/07	Mild	Not Related	Resolved	03/19/07	0	Yes
1029	02/27/07	03/27/07	04/26/07	05/25/07	Intestinal cramps	03/27/07	Severe	Not Related	Resolved	03/28/07	1	Yes
1029	02/27/07	03/27/07	04/26/07	05/25/07	Tick bite	04/30/07	Mild	Not Related	Resolved	04/30/07	0	Yes
1029	02/27/07	03/27/07	04/26/07	05/25/07	Tick bite inflammation	05/09/07	Mild	Not Related	Resolved	05/18/07	9	Yes
1033	03/27/07	04/25/07	05/24/07	06/22/07	Headache	04/12/07	Moderate	Not Related	Resolved	04/26/07	14	Yes
1033	03/27/07	04/25/07	05/24/07	06/22/07	Headache	06/23/07	Moderate	Not Related	Resolved	06/23/07	0	Yes
1033	03/27/07	04/25/07	05/24/07	06/22/07	Headache	06/17/07	Moderate	Not Related	Resolved	06/17/07	0	Yes
1033	03/27/07	04/25/07	05/24/07	06/22/07	Colposcopy	05/11/07	Moderate	Not Related	Resolved	05/11/07	0	Yes
1035	03/29/07	04/30/07	05/25/07	06/20/07	Sunburn upper back/arms	04/29/07	Moderate	Not Related	Resolved	05/10/07	11	Yes
1037	05/01/07	06/02/07	07/06/07	08/03/07	Headache	04/20/07	Severe	Not Related	Resolved	04/30/07	10	Yes

Appendix D: Investigator Reported Adverse Events – Not Related to Investigational Device												
ID	**Treatment 1 Date**	**Treatment 2 Date**	**Treatment 3 Date**	**Treatment 4 Date**	**Event**	**Onset Date**	**Severity**	**Related**	**Outcome**	**Resolution Date**	**Duration**	**Completed Study**
1038	04/08/07	04/30/07	05/24/07	06/17/07	Anxiety	04/19/07	Mild	Not Related	Resolved	04/22/07	3	Yes
1038	04/08/07	04/30/07	05/24/07	06/17/07	Anxiety	04/22/07	Moderate	Not Related	Resolved	04/24/07	2	Yes
1038	04/08/07	04/30/07	05/24/07	06/17/07	Anemia	04/23/07	Moderate	Not Related	Persisted	.	.	Yes
1039	04/30/07	05/24/07	07/15/07	08/09/07	Right knee pain	07/10/07	Moderate	Not Related	Resolved	07/13/07	3	Yes
1039	04/30/07	05/24/07	07/15/07	08/09/07	Right achilles tendon pain	07/30/07	Moderate	Not Related	Persisted	.	.	Yes
1040	04/13/07	05/10/07	06/07/07	07/05/07	Bronchitis	04/29/07	Moderate	Not Related	Resolved	05/05/07	6	Yes
1040	04/13/07	05/10/07	06/07/07	07/05/07	Root canal procedure and packing	06/04/07	Moderate	Not Related	Persisted	.	.	Yes
1040	04/13/07	05/10/07	06/07/07	07/05/07	Dental infection	06/04/07	Moderate	Not Related	Persisted	.	.	Yes
1040	04/13/07	05/10/07	06/07/07	07/05/07	Dental pain	06/04/07	Moderate	Not Related	Persisted	.	.	Yes
1045	05/10/07	06/08/07	07/10/07	08/08/07	Upper Respiratory Infection	08/03/07	Mild	Not Related	Resolved	08/05/07	2	Yes
1046	04/26/07	05/24/07	06/21/07	07/19/07	Swollen bruised right eye	05/07/07	Severe	Not Related	Resolved	05/19/07	12	Yes
1047	05/15/07	06/12/07	07/10/07	08/08/07	Headache	05/18/07	Mild	Not Related	Resolved	05/18/07	0	Yes
1049	05/22/07	06/19/07	07/17/07	08/13/07	Poison ivy reaction	06/11/07	Mild	Not Related	Resolved	06/23/07	12	Yes
1050	05/03/07	05/31/07	06/26/07	07/26/07	Urinary tract infection	05/04/07	Severe	Not Related	Resolved	05/07/07	3	Yes
1050	05/03/07	05/31/07	06/26/07	07/26/07	Headache	05/03/07	Severe	Not Related	Resolved	05/03/07	0	Yes
1050	05/03/07	05/31/07	06/26/07	07/26/07	Insect bite	06/05/07	Severe	Not Related	Resolved	06/08/07	3	Yes

Appendix D: Investigator Reported Adverse Events – Not Related to Investigational Device												
ID	**Treatment 1 Date**	**Treatment 2 Date**	**Treatment 3 Date**	**Treatment 4 Date**	**Event**	**Onset Date**	**Severity**	**Related**	**Outcome**	**Resolution Date**	**Duration**	**Completed Study**
1050	05/03/07	05/31/07	06/26/07	07/26/07	Insect bite	06/11/07	Severe	Not Related	Resolved	06/15/07	4	Yes
1051	05/20/07	06/17/07	07/15/07	08/12/07	Right ankle pain	07/04/07	Severe	Not Related	Resolved	07/06/07	2	Yes
2001	11/14/06	12/14/06	01/10/07	02/11/07	Strep throat	12/18/07	Mild	Not Related	Resolved	12/22/07	4	Yes
2002	11/25/06	12/26/06	01/27/07	02/28/07	Sebaceous cyst on chin	12/26/06	Moderate	Not Related	Resolved	01/07/07	12	Yes
2010	12/20/06	01/18/07	02/21/07	03/18/07	Pregnancy	05/22/07	Mild	Not Related	Resolved	01/25/08	248	Yes
2015	01/26/07	02/23/07	03/23/07	04/19/07	Dental abscess	04/23/07	Moderate	Not Related	Resolved	05/01/07	8	Yes
2015	01/26/07	02/23/07	03/23/07	04/19/07	Shoulder pain	03/02/07	Mild	Not Related	Resolved	03/03/07	1	Yes
2016	02/10/07	03/10/07	04/06/07	05/27/07	Cellulitis	03/01/07	Moderate	Not Related	Resolved	03/18/07	17	Yes
2016	02/10/07	03/10/07	04/06/07	05/27/07	Cellulitis	05/18/07	Moderate	Not Related	Resolved	06/15/07	28	Yes
2016	02/10/07	03/10/07	04/06/07	05/27/07	Lymphedema	02/28/07	Severe	Not Related	Resolved	03/19/07	19	Yes
2017	01/25/07	02/22/07	03/15/07	04/13/07	Upper respiratory infection	02/26/07	Mild	Not Related	Resolved	03/03/07	5	Yes
2017	01/25/07	02/22/07	03/15/07	04/13/07	Elevated blood pressure	01/23/07	Mild	Not Related	Unknown	.	.	Yes
2017	01/25/07	02/22/07	03/15/07	04/13/07	Elevated blood pressure	05/25/07	Mild	Not Related	Unknown	.	.	Yes
2018	02/17/07	03/16/07	04/07/07	05/20/07	Low back pain	04/15/07	Moderate	Not Related	Unknown	.	.	Yes
2019	02/23/07	03/25/07	04/23/07	05/20/07	Headache	03/08/07	Mild	Not Related	Resolved	03/08/07	0	Yes
2019	02/23/07	03/25/07	04/23/07	05/20/07	Headache	03/15/07	Mild	Not Related	Resolved	03/15/07	0	Yes

Appendix D: Investigator Reported Adverse Events – Not Related to Investigational Device												
ID	**Treatment 1 Date**	**Treatment 2 Date**	**Treatment 3 Date**	**Treatment 4 Date**	**Event**	**Onset Date**	**Severity**	**Related**	**Outcome**	**Resolution Date**	**Duration**	**Completed Study**
2019	02/23/07	03/25/07	04/23/07	05/20/07	Cramps	03/25/07	Moderate	Not Related	Resolved	03/27/07	2	Yes
2019	02/23/07	03/25/07	04/23/07	05/20/07	Chills	03/25/07	Moderate	Not Related	Resolved	03/27/07	2	Yes
2027	03/21/07	04/19/07	05/23/07	06/27/07	Headache	05/19/07	Mild	Not Related	Resolved	05/19/07	0	Yes
2030	03/12/07	04/07/07	05/16/07	06/15/07	Rash right antecubital area	07/18/07	Moderate	Not Related	Unknown	.	.	Yes
2039	06/10/07	07/04/07	10/20/07	11/19/07	Giardia	09/07/07	Severe	Not Related	Resolved	09/29/07	22	Yes
2039	06/10/07	07/04/07	10/20/07	11/19/07	Cryptosporidiosis	09/07/07	Severe	Not Related	Resolved	09/29/07	22	Yes
2039	06/10/07	07/04/07	10/20/07	11/19/07	Sinus infection	10/08/07	Moderate	Not Related	Resolved	10/12/07	4	Yes
2039	06/10/07	07/04/07	10/20/07	11/19/07	Strep throat	09/18/07	Moderate	Not Related	Resolved	09/27/07	9	Yes
2039	06/10/07	07/04/07	10/20/07	11/19/07	Yeast vaginitis	10/13/07	Mild	Not Related	Resolved	10/15/07	2	Yes
2039	06/10/07	07/04/07	10/20/07	11/19/07	Sinus infection	06/15/07	Severe	Not Related	Resolved	06/20/07	5	Yes
2039	06/10/07	07/04/07	10/20/07	11/19/07	Sinus infection	07/15/07	Severe	Not Related	Resolved	07/26/07	11	Yes
2039	06/10/07	07/04/07	10/20/07	11/19/07	Mountain sickness	07/01/07	Moderate	Not Related	Resolved	07/10/07	9	Yes
2043	07/25/07	08/25/07	09/27/07	10/28/07	Sinusitis	10/20/07	Moderate	Not Related	Resolved	10/28/07	8	Yes
2043	07/25/07	08/25/07	09/27/07	10/28/07	Bronchitis	10/20/07	Moderate	Not Related	Resolved	10/28/07	8	Yes
2046	09/22/07	10/21/07	11/23/07	12/22/07	Decreased appetite	10/21/07	Mild	Not Related	Resolved	10/21/07	0	Yes
2049	03/21/08	04/19/08	05/22/08	06/11/08	Sinus infection	04/25/08	Moderate	Not Related	Resolved	05/08/08	13	Yes

Appendix D: Investigator Reported Adverse Events – Not Related to Investigational Device												
ID	**Treatment 1 Date**	**Treatment 2 Date**	**Treatment 3 Date**	**Treatment 4 Date**	**Event**	**Onset Date**	**Severity**	**Related**	**Outcome**	**Resolution Date**	**Duration**	**Completed Study**
2051	05/20/08	07/25/08	08/14/08	09/12/08	Vaginal yeast infection	08/14/08	Mild	Not Related	Resolved	08/16/08	2	Yes
2053	06/03/08	07/10/08	08/14/08	09/16/08	Cold	09/09/08	Mild	Not Related	Resolved	09/17/08	8	Yes
2054	06/09/08	07/25/08	.	.	Bronchitis	06/08/08	Moderate	Not Related	Resolved	07/15/08	37	Unknown
2054	06/09/08	07/25/08	.	.	Appendicitis	08/07/08	Severe	Not Related	Resolved	08/12/08	5	Unknown
2056	07/09/08	07/26/08	08/24/08	09/20/08	Menorrhagia	07/14/08	Moderate	Not Related	Resolved	07/19/08	5	Yes
2056	07/09/08	07/26/08	08/24/08	09/20/08	Hypercholesterolemia	09/15/08	Moderate	Not Related	Persisted	.	.	Yes
2056	07/09/08	07/26/08	08/24/08	09/20/08	Hypertension	09/15/08	Moderate	Not Related	Persisted	.	.	Yes
2060	07/28/08	08/26/08	09/17/08	10/13/08	Sinusitis	10/16/08	Moderate	Not Related	Resolved	10/20/08	4	Yes
2063	08/10/08	09/07/08	10/04/08	10/31/08	Upper respiratory infection	11/01/08	Severe	Not Related	Resolved	11/10/08	9	Yes
2063	08/10/08	09/07/08	10/04/08	10/31/08	Joint swelling	11/02/08	Moderate	Not Related	Resolved	11/10/08	8	Yes

Appendix E: Listing of Protocol Deviations									
ID	**Treatment 1 Date**	**Treatment 2 Date**	**Treatment 3 Date**	**Treatment 4 Date**	**Deviation Date**	**Type of Deviation**	**Type of Deviation, Other specify**	**Timing**	**Description**
1002	12/11/06	01/04/07	01/28/07	02/21/07	01/04/07	Rescue medication taken outside of window		Period 2	
1006	01/02/07	01/26/07	03/16/07	04/18/07	01/26/07	Rescue medication taken outside of window		Period 2	
1006	01/02/07	01/26/07	03/16/07	04/18/07	03/02/07	Other	No study product used for 3rd period	Period 3	Subject forgot to use study ibuprofen for 3rd period, notified coord., coord. notified sponsor sponsor instructed coord to have subject use ibuprofen for period 4 and vipon for period 5.
1008	01/15/07	02/14/07	03/14/07	04/16/07	03/14/07	Other	Randomization not followed	Period 3	Subject randomized to use Vipon on 3rd treatment period and was counseled to do so on Visit 2. However, subject used ibuprofen. Sponsor was notified and subject will use the Vipon for her fourth treatment period.
1009	01/05/07	02/24/07	03/19/07	04/19/07	02/06/07	Other	No study product used for 2nd period	Period 2	Subject stated her life was ~"busy~" and she did not use the Vipon for her 2nd period but will use it for the next period. INC Research notified.

Appendix E: Listing of Protocol Deviations

ID	Treatment 1 Date	Treatment 2 Date	Treatment 3 Date	Treatment 4 Date	Deviation Date	Type of Deviation	Type of Deviation, Other specify	Timing	Description
1010	01/02/07	01/28/07	02/25/07	04/22/07	03/28/07	Other	Study product not used for 4th period	Period 4	Subject did not have pain with 3rd period therefore she did not use study drug ibuprofen. She was advised to use the study ibuprofen with her next period.
1012	01/09/07	02/06/07	04/04/07	05/01/07	02/07/07	Other	Study product not used for period 2	Period 2	Subject reported an intense headache and took two ibuprofen, menstrual pain eased and she fell asleep. She did not use the Vipon. Will use for next period.
1013	01/23/07	03/20/07	04/20/07	05/16/07	02/26/07	Other	Study ibuprofen not taken for period 2	Period 2	Subject did not have menstrual pain during 2nd period, therefore did not take study ibuprofen, she will do so next period. INC research notified
1015	01/17/07	02/15/07	03/16/07	04/16/07	02/27/07	Other	Subject uses personal ibuprofen instead of study ibuprofen	Period 1	Subject took 2 ibuprofen for a total of 400 mg that were her personal stock instead of the study ibuprofen provided. Sponsor notified.
1021	01/31/07	03/01/07	03/30/07	05/02/07	05/02/07	Rescue medication taken outside of window		Period 4	
1023	01/29/07	02/24/07	03/24/07	04/26/07	03/24/07	Rescue medication taken outside of window		Period 3	Rescue med taken 1 hour and 30 minutes after treatment. Protocol window is 2 hours after treatment.

Appendix E: Listing of Protocol Deviations

ID	Treatment 1 Date	Treatment 2 Date	Treatment 3 Date	Treatment 4 Date	Deviation Date	Type of Deviation	Type of Deviation, Other specify	Timing	Description
1023	01/29/07	02/24/07	03/24/07	04/26/07	04/20/07	Rescue medication taken outside of window		Period 4	Rescue med taken at same time as treatment. Protocol window is 2 hours after treatment.
1032	03/24/07	04/20/07	05/20/07	06/16/07	04/20/07	Rescue medication taken outside of window		Period 2	Rescue med, 2 tabs of Ibuprofen (400 mg) taken 1/2 hour after treatment
1032	03/24/07	04/20/07	05/20/07	06/16/07	05/20/07	Rescue medication taken outside of window		Period 3	Rescue med, 2 tabs of Ibuprofen (400 mg) taken 45 min after treatment. Protocol window is 2 hours or later.
1034	03/23/07	04/26/07	05/17/07	06/17/07	05/17/07	Rescue medication taken outside of window		Period 3	Subject took rescue med 1 hour after treatment. Protocol window for rescue med is >= 2 hours post treatment
1034	03/23/07	04/26/07	05/17/07	06/17/07	05/17/07	Rescue medication taken outside of window		Period 4	
1036	04/04/07	05/02/07	05/30/07	06/28/07	06/28/07	Rescue medication taken outside of window		Period 4	Rescue med taken 1 hour and 10 minutes after treatment. Protocol window is >= 2 hrs after treatment.

Appendix E: Listing of Protocol Deviations

ID	Treatment 1 Date	Treatment 2 Date	Treatment 3 Date	Treatment 4 Date	Deviation Date	Type of Deviation	Type of Deviation, Other specify	Timing	Description
1037	05/01/07	06/02/07	07/06/07	08/03/07	08/03/07	Rescue medication taken outside of window		Period 4	Rescue med taken 1 hour and 4 minutes after treatment. Protocol window for rescue meds is >= 2 hours after treatment
1039	04/30/07	05/24/07	07/15/07	08/09/07	07/03/07	Other	Study product Vipon not used for periods	Period 3	Subject did not have dysmenorrhea with her third treatment period therefore did not use the Vipon she was randomized to, will use Vipon for next period
1046	04/26/07	05/24/07	06/21/07	07/19/07	07/19/07	Other	Subject used own Ibuprofen, did not follow randomization	Period 4	Subject used own Ibuprofen for rescue med during treatment period 4 after using the Vipon she returned the unused study rescue Ibuprofen 2 tabs.
2002	11/25/06	12/26/06	01/27/07	02/28/07	11/13/06	Subject enrolled outside of incl/excl		Visit 1	Inclusion criteria #2 answered ~"No~", all inclusion criteria must be answered ~"Yes~" to enroll subject. Subject was enrolled and completed study.
2002	11/25/06	12/26/06	01/27/07	02/28/07	11/25/06	Other	Randomization schedule not followed by subject	Period 1	Randomized to use Vipon cycle 1, ibuprofen cycle 2, Vipon cycle 3, ibuprofen cycle 4. Subject used ibuprofen cycle 1, Vipon cycle 2, ibuprofen cycle 3, Vipon cycle 4.

Appendix E: Listing of Protocol Deviations

ID	Treatment 1 Date	Treatment 2 Date	Treatment 3 Date	Treatment 4 Date	Deviation Date	Type of Deviation	Type of Deviation, Other specify	Timing	Description
2003	12/08/06	01/06/07	02/01/07	02/26/07	01/06/07	Rescue medication taken outside of window		Period 2	Subject did not take study rescue med Ibuprofen, she took other rescue < 2 hours after treatment. Protocol rescue med window is >= 2 hours post treatment.
2006	11/25/06	12/23/06	02/14/07	03/14/07	11/25/06	Other	Treatment done 1 hour prior to assessment	Period 1	Treatment for period 1 done 1 hour prior to pre-dose pain assessment. Instructions to assess pain pre-dose.
2009	11/22/06	12/21/06	01/19/07	02/18/07	01/19/07	Other	Randomization schedule not followed by subject	Period 3	Subject randomized to use Vipon for cycle 3 but used ibuprofen instead
2010	12/20/06	01/18/07	02/21/07	03/18/07	02/21/07	Other	Randomization schedule not followed by subject	Period 3	Subject used ibuprofen treatment for cycle 3, and should have used Vipon
2011	12/17/06	01/11/07	Not done	Not done	01/11/07	Rescue medication taken outside of window		Period 2	
2012	12/13/06	01/09/07	02/06/07	03/02/07	01/09/07	Other	Randomization schedule not followed by subject	Period 2	Subject issued one Vipon tampon at visit #1, however marked in diary for treatments 1 and 2 that Vipon was used. Should have been used in treatment 1 only.
2013	12/27/07	01/24/07	02/21/07	03/22/07	12/27/07	Other	Subj. did not use any treatment for period 1	Period 1	Subject did not use Ibuprofen treatment she was randomized to for period 1, she did not use any treatment, no dysmenorrhea

Appendix E: Listing of Protocol Deviations

ID	Treatment 1 Date	Treatment 2 Date	Treatment 3 Date	Treatment 4 Date	Deviation Date	Type of Deviation	Type of Deviation, Other specify	Timing	Description
2016	02/10/07	03/10/07	04/06/07	05/27/07	04/06/07	Other	Randomization schedule not followed by subject	Period 3	Randomized to ibuprofen cycle 3 / Vipon cycle 4 - used Vipon cycle 3 and ibuprofen cycle 4
2016	02/10/07	03/10/07	04/06/07	05/27/07	05/27/07	Rescue medication taken outside of window		Period 4	Rescue med, 400 mg Ibuprofen, taken 1 hour after treatment. Protocol rescue med window states rescue med can be taken >= 2 hours post treatment.
2019	02/23/07	03/25/07	04/23/07	05/20/07	02/23/07	Rescue medication taken outside of window		Period 1	
2019	02/23/07	03/25/07	04/23/07	05/20/07	03/25/07	Rescue medication taken outside of window		Period 2	Rescue med, 2 tablets of Aleve, taken 1 hour post treatment. Protocol rescue med window is >= 2 hours post treatment.
2019	02/23/07	03/25/07	04/23/07	05/20/07	05/20/07	Rescue medication taken outside of window		Period 4	Rescue med taken 1 hour after treatment. Protocol rescue med window is >= 2 hours post treatment.
2030	03/12/07	04/07/07	05/16/07	06/15/07	05/16/07	Other	Randomization schedule not followed by subject	Period 3	Randomized to use ibuprofen cycle 3, but used Vipon instead
2031	04/12/07	05/11/07	06/20/07	07/18/07	07/18/07	Other	Subject did not use treatment for 4th period	Period 4	Subject did not have enough pain to use study treatment for period 4.

Appendix E: Listing of Protocol Deviations

ID	Treatment 1 Date	Treatment 2 Date	Treatment 3 Date	Treatment 4 Date	Deviation Date	Type of Deviation	Type of Deviation, Other specify	Timing	Description
2034	03/28/07	04/29/07	05/31/07	06/28/07	05/31/07	Other	Randomization schedule not followed by subject	Period 3	Randomized to use Vipon for cycle 3, but used ibuprofen instead
2039	06/10/07	07/04/07	10/20/07	11/19/07	10/20/07	Rescue medication taken outside of window		Period 3	Rescue med taken 1 hour after treatment. Protocol rescue med window is >= 2 hours post treatment.
2042	07/04/07	08/01/07	09/04/07	10/29/07	10/29/07	Other	Subject forgot to use study treatment 4	Period 4	Subject forgot to use cycle 4 treatment with menses 10/2/07, but used treatment 4 with menses beginning 10-29-07
2047	12/04/07	01/21/08	02/13/08	03/10/08	02/13/08	Rescue medication taken outside of window		Period 3	Rescue med taken 1 hour post treatment. Protocol rescue med window is >=2 hours post treatment
2051	05/20/08	07/25/08	08/14/08	09/12/08	07/25/08	Rescue medication taken outside of window		Period 2	Rescue med taken 1 hour and 9 minutes after treatment. Protocol rescue med window >= 2 hours post treatment.
2051	05/20/08	07/25/08	08/14/08	09/12/08	08/19/08	Rescue medication taken outside of window		Period 3	Rescue med taken 1 hour and 54 min after treatment. Protocol rescue med >= 2 hours post treatment
2052	05/12/08	06/08/08	07/04/08	07/29/08	07/29/08	Rescue medication taken outside of window		Period 4	Rescue med taken at same time as treatment. Protocol rescue med window is >= 2 hours post treatment.

Appendix E: Listing of Protocol Deviations

ID	Treatment 1 Date	Treatment 2 Date	Treatment 3 Date	Treatment 4 Date	Deviation Date	Type of Deviation	Type of Deviation, Other specify	Timing	Description
2057	07/26/08	08/25/08	09/17/08	10/09/08	08/25/08	Rescue medication taken outside of window		Period 2	Rescue med taken 1 hour and 37 minutes after treatment. Protocol rescue med window is >= 2 hours post treatment.
2057	07/26/08	08/25/08	09/17/08	10/09/08	09/17/08	Rescue medication taken outside of window		Period 3	Rescue med taken 25 minutes after treatment. Protocol rescue med window is >= 2 hours post treatment.
2058	07/12/08	08/09/08	09/05/08	10/02/08	09/05/08	Other	Randomization schedule not followed by subject	Period 3	Randomized to use Vipon cycle 3 and ibuprofen cycle 4 - instead, used ibuprofen cycle 3 / Vipon cycle 4.
2058	07/12/08	08/09/08	09/05/08	10/02/08	10/02/08	Rescue medication taken outside of window		Period 4	Rescue med taken 50 minutes after treatment. Protocol rescue med window is >= 2 hours post treatment.
2059	08/01/08	08/27/08	09/22/08	10/19/08	08/01/08	Rescue medication taken outside of window		Period 1	Rescue med taken 1 hour and 40 minutes after treatment. Protocol rescue med window is >= 2 hours post treatment.
2063	08/10/08	09/07/08	10/04/08	10/31/08	10/31/08	Rescue medication taken outside of window		Period 4	Rescue med taken 1 hour post treatment. Protocol rescue med window is >= 2 hours post treatment.
2064	08/13/08	09/09/08	10/05/08	11/01/08	09/09/08	Rescue medication taken outside of window		Period 2	Rescue med taken 1 hour and 45 minutes after treatment. Protocol rescue med window is >= 2 hours post treatment.

Appendix F: Statistical Analysis Details

Primary Endpoint - Pain Assessment

Efficacy of pain was made using the modified Melzack-McGill numerical pain scale questionnaire. Subjects rated pain intensity during each treatment event on a scale from 0 to 10 where 0 = no pain and 10 = worst pain. For the primary endpoint, the changes from baseline to hour 2 were studied. Subjects showing at least a 1-point reduction on the 11-point scale were deemed successful. Subjects showing no reduction were deemed failures. For the VIPON treatment period, the use of rescue medication within the first 2 hours was also considered a failure. Each subject contributed 4 binary outcome measurements (2 from each treatment) and statistical analysis was performed using a generalized linear mixed model. Calculations were carried out using SAS PROC GLIMMIX. Estimates of π_{VIPON}, of $\pi_{Ibuprofen}$ and of the difference $\pi_{VIPON} - \pi_{Ibuprofen}$ were computed, along with standard errors. An approximate 95% confidence interval for the difference $\pi_{VIPON} - \pi_{Ibuprofen}$ was computed as estimated difference $\pm$ 1.96 standard errors of the difference.

The SAS code used to execute the model is copied below, to provide the full detail of the model. Note that PROC GENMOD was used instead of GLIMMIX. However, this does not change the results of the model, as GENMOD is a subset of the GLIMMIX procedure:

```
**** PRIMARY ENDPOINT;
PROC GENMOD DATA=TOTPAIN DESCENDING;
     CLASS PATID TREATX;
     MODEL PSUCCESS = TREATX / DIST=BIN LINK=IDENTITY;
     REPEATED SUBJECT=PATID / CORR=CS;
     ESTIMATE "Difference between Treatment Groups" TREATX 1 -1;
     LABEL TREATX='TREATMENT';
     TITLE2 'PRIMARY ENDPOINT';
     TITLE3 'O=VIPON, 1=IBUPROFEN';
RUN;
```

Secondary Endpoint - Pain Assessment

Each subject assessed pain at baseline and at five follow-up times ranging from 15 minutes to 8 hours from the start of treatment. A five-component measure was obtained by subtracting the baseline score from each of the follow-up scores, and the time profile of the score reduction analyzed using a mixed model analysis of variance using SAS PROC MIXED. The parameters were estimated using the maximum likelihood method, and model was fit using an unstructured covariance matrix. The successive pain score decreases were the dependent variable. Treatment, center, period, sequence and the treatment*period interaction were treated as fixed effects and subject as a random effect. The least squares means of period by treatment was computed and analyzed to explicate the time profile of pain reduction with each treatment.

The SAS code used to execute the model is copied below, to provide the full detail of the model:

```
**** SECONDARY ENDPOINT - GENERAL PAIN DIFFERENCES;
OPTIONS PAGENO=1 LS=80 PS=55;
PROC MIXED DATA=PAINALL METHOD=ML;
     CLASS TREATX SITEID PERIOD SEQUENCE PATID;
     MODEL GENDIFF=TREATX SITEID PERIOD SEQUENCE TREATX*SEQUENCE / S CHISQ CL;
           REPEATED SEQUENCE / TYPE=UN R;
           ESTIMATE "Treatment Effect" TREATX 1 -1;
           ESTIMATE "Treatment Effect at 15 min"   TREATX*SEQUENCE 1 0 0 0 0   -1 0 0 0 0   TREATX 1 -1 / CL;
     ESTIMATE "Treatment Effect at 30 min"   TREATX*SEQUENCE 0 1 0 0 0   0 -1 0 0 0   TREATX 1 -1 / CL;
     ESTIMATE "Treatment Effect at 1 hour"   TREATX*SEQUENCE 0 0 1 0 0   0 0 -1 0 0   TREATX 1 -1 / CL;
     ESTIMATE "Treatment Effect at 2 hours"  TREATX*SEQUENCE 0 0 0 1 0   0 0 0 -1 0   TREATX 1 -1 / CL;
     ESTIMATE "Treatment Effect at 8 hours"  TREATX*SEQUENCE 0 0 0 0 1   0 0 0 0 -1   TREATX 1 -1 / CL;
     TITLE2 'SECONDARY ENDPOINT: GENERAL PAIN DIFFERENCES';
RUN;
```

Secondary Endpoint – Symptom Clusters

Three symptom clusters were obtained for abdominal pain, back pain and cramps. The statistical analysis was performed the same as the secondary pain assessment endpoint. Note that SAS PROC MIXED models were executed for each of the three symptom clusters, using the code presented above after replacing the outcome variable corresponding to each symptom cluster.

Secondary Endpoint – Quality of Life

Each subject completed an SF-36 survey at baseline and at the 8-hour post treatment assessment. The SF-36 instrument is validated for 1-week and 6-week recall periods so a full analysis could not be completed.

Secondary Endpoint – Time to pain relief

Pain relief is interpreted as meaning a reduction of at least 1 point in the Melzack-McGill scale. From the five-time-point profile provided for each treatment episode, a determination will be made of the first time showing this degree of improvement over baseline. These times to first improvement were analyzed separately for each menstrual period using Kaplan-Meier survival analysis. Center was a stratifying variable, and a log-rank test was used to compare the two treatments.

Secondary Endpoint – Use of Rescue medications

Each subject provided a binary indicator for each menstrual period of whether or not she used rescue medication. These indicators were analyzed using generalized linear mixed modeling, implemented using SAS PROC GENMOD. The statistical model specifications were the same as those used for the primary efficacy endpoint, but tested the two treatments for equality.