Medtronic

Enterra® Therapy

Gastric Electrical Stimulation System

Humanitarian Device: Authorized by Federal (U.S.A.) Law for use in treatment of chronic intractable (drug refractory) nausea and vomiting secondary to gastroparesis of diabetic or idiopathic etiology. The effectiveness of this device for this use has not been demonstrated.

Clinical summary

Rx only

Table of contents

Refer to the indications sheet for indications and related information.

Refer to the appropriate information for prescribers booklet for contraindications, warnings, precautions, adverse events summary, individualization of treatment, patient selection, use in specific populations, resterilization, and component disposal.

Refer to the device implant manual for device description, package contents, device specifications, battery information, and instructions for use.

Enterra Therapy clinical studies

Patients with drug-refractory gastroparesis of diabetic or idiopathic etiologies were evaluated in the following clinical studies: the World Wide Anti-Vomiting Electrical Stimulation study (WAVESS), the WAVESS Compassionate Use study (WCU), and the Compassionate Use Electrical Stimulation study (CUESS).

World Wide Anti-Vomiting Electrical Stimulation study (WAVESS)

The WAVESS study was a double-blind, randomized cross-over study that enrolled a total of 33 subjects. The study was designed to collect both safety and effectiveness information.

WAVESS study objective

The primary endpoint of the study was a reduction in vomiting frequency, as measured by patient diaries. The treatment was considered successful if a reduction in vomiting frequency by at least 80% was observed during the cross-over period of the study with the ON-mode stimulation, when compared to the OFF-mode stimulation.

The secondary endpoints in the study were quality of life (measured with the Medical Outcomes study Short-Form 36 Health Survey), body mass index, hypoglycemic attacks (diabetic group only), subjective symptoms documented by a clinical status interview, glycosylated hemoglobin, and gastric emptying documented with a gastric emptying test.

WAVESS entry criteria

The inclusion criteria for the study included:

- Symptomatic gastroparesis ≥ 1 year, as documented by an initial Gastric Emptying Test (GET)
- Refractory or intolerant to at least two antiemetic and two prokinetic drug classes
- On stable medical therapy, and, if applicable, stable nutritional support during the month prior to enrollment
- Frequency of vomiting > 7 vomiting episodes per week, as documented with a baseline patient diary
- Delayed gastric emptying, defined by greater than 60% retention at two hours and > 10% retention at four hours, as measured by standardized gastric emptying testing

The exclusion criteria included:

- Organ transplant
- Organic obstruction
- Pseudo-obstruction
- Prior gastric surgery

- Scleroderma
- Amyloidosis
- History of seizures
- Peritoneal or unstable dialysis
- Chemical dependency
- Pregnancy
- Primary eating or swallowing disorders
- Psychogenic vomiting
- Implanted electronic medical devices
- Age < 18 or > 70 years

WAVESS study enrollment

Enrollment and follow-up in the WAVESS study was as follows:

Table 1. Enrollment in WAVESS study

Number of subjects	at enrollment	implanted > 30 days	implanted > 60 days	implanted > 6 months	implanted > 12 months
(N)	33	33	33	27	24

WAVESS study demographics

A total of 33 subjects were enrolled in the WAVESS study. The demographic information on these subjects is presented in Table 2.

Table 2. Patient demographics

	Diabetic (N=17)	Idiopathic (N=16)	Total (N=33)
Gender (M/F)	9/8 F	0/16 F	9/24 F
Age, mean	38.1	41.1	39.6
BMI, mean	24.7	22.9	23.7
Gastric retention (mean/median)%			
@2 hours	79.7/80.0	73.1/76.5	76.5/78.0
@4 hours	53.2/51.0	34.3/28.0	44.0/34.0

WAVESS study design

Subjects satisfying entry criteria received gastric stimulation systems that included an implanted neurostimulator connected to two unipolar leads that were implanted in the

muscle wall of the stomach on the greater curvature at the limit of the corpus-antrum. All subjects received a Model 7425 implantable neurostimulator and a pair of Model 4300[1] leads. The stimulation parameters used in the study were: Intensity: 5 mA, Pulse Width: 330 µsec, Frequency: 14 Hz. The neurostimulator was set to deliver a pair of pulses at these parameters every five seconds continuously 24 hours per day.

The study was conducted in two phases:

1. Phase I was a double blind crossover study with evaluations prior to implant and at 30 days and 60 days post-implant. Subjects were randomly assigned to stimulation on and off for the first month after implant and were crossed to off and on for the second month. Subjects were blinded as to which stimulation sequence they received.
2. Phase II was an unblinded open label study with follow-up at six and twelve months. After the crossover period was complete, the subjects were asked which month of the crossover stimulation they preferred. After the selection was made, the study blind was broken. The subjects then received stimulation (on or off) consistent with their preference.

The primary and the secondary endpoints, except gastric emptying, were measured at baseline, 30 days, 60 days, six months, and twelve months postrandomization. Gastric emptying was measured at baseline, and six and twelve months postrandomization.

Primary endpoint evaluations included weekly vomiting frequency and patient preference within Phase I of the study. Secondary endpoint evaluations included gastric retention, hypoglycemic attacks, upper GI symptoms, and quality of life using the Medical Outcomes study Short-Form 36 Health Survey.

WAVESS Compassionate Use study (WCU)

In contrast to the WAVESS study design, the WCU study was an unblinded, open label study. Upon implantation of the device within each patient, the stimulation therapy was immediately initiated without a randomized on/off cross-over period.

The WAVESS Compassionate Use study (WCU) was an open label, non-randomized study that included a total of 18 subjects. The WCU study was designed to provide safety (adverse events) information on gastric stimulation.

WCU study objective

The purpose of the WCU study was to provide treatment for patients and to evaluate adverse events of patients with drug-refractory gastroparesis who did not meet the entry criteria of the WAVESS study.

[1] The Model 7425G Neurostimulator is identical to the Model 7425 Neurostimulator used in the clinical study. The Model 4351 Lead is similar to the Model 4300 Lead used in the clinical study. The Model 4351 Lead has a fixed electrode length of 10 mm, whereas the Model 4300 Lead had an adjustable electrode length.

WCU entry criteria

Candidates eligible for the WCU study consisted of those subjects who did not meet the complete entry criteria for the WAVESS study, but who had documentation of drug-refractory gastroparesis.

The study entry criteria were:

- Did not meet the entry criteria of the WAVESS study
- Were likely to die within the next few weeks if they did not receive this therapy
- Signed an informed consent form relevant to this study

This WAVESS Compassionate Use study required:

- Documentation of life-threatening situation by an independent physician
- IRB (or IRB chairperson) approval on a case-by-case basis
- An additional informed consent form relevant to the applicable patient's condition was approved by the clinical investigator and the IRB or IRB chairperson (this varied depending on the reason(s) why the patient did not qualify for the WAVESS study)

WCU study demographics

A total of 24 subjects were enrolled in the WCU study. The demographic information on these subjects is presented in Table 3.

Table 3. Patient demographics

	Diabetic	Idiopathic	Post-surgical
N	6	17	1
Gender (M/F)	1M / 5F	17 F	1 F
Age, mean	36.4	35.7	69.0
BMI, mean	20.5	23.1	18.4
Baseline:			
Vomiting Severity (mean)	3.5	3.6	4.0
Nausea Severity (mean)	3.3	3.6	4.0
GET 2 Hr (median)	74.0	67.0	18.0
GET 4 Hr (median)	34.0	22.0	2.0

WCU study design

Subjects satisfying entry criteria received gastric stimulation systems which included an implanted neurostimulator connected to two unipolar leads which were implanted in the muscle wall of the stomach on the greater curvature at the limit of the corpus-

antrum. All subjects received a Model 7425 implantable neurostimulator and a pair of Model 4300 leads. The stimulation parameters used in the study were: Intensity: 5 mA, Pulse Width: 330 µsec, Frequency: 14 Hz. The neurostimulator was set to deliver a pair of pulses at these parameters every five seconds continuously 24 hours per day. The stimulation parameters could be adjusted at any time by the physician to optimize treatment therapy.

Compassionate Use Electrical Stimulation study (CUESS)

The Compassionate Use Electrical Stimulation study was an open label, non-randomized study that included a total of 51 subjects. This study was designed to provide gastric stimulation safety information.

CUESS study objective

The purpose of the Compassionate Use Electrical Stimulation study was to treat patients with drug-refractory gastroparesis who had no other medical treatment alternative.

CUESS entry criteria

The inclusion criteria for the study were:

- Symptomatic gastroparesis ≥ 1 year, as documented by an initial gastric emptying test (GET)
- Refractory or intolerant to at least two antiemetic and prokinetic drug classes
- On stable medical therapy during the month prior to enrollment
- Frequency of vomiting > 7 vomiting or nausea episodes per week, as documented with a baseline patient diary
- Delayed gastric emptying, defined by greater than 50% retention at two hours and > 6% retention at four hours, as measured by standardized gastric emptying testing

The exclusion criteria were:

- Organ transplant
- Organic obstruction
- Pseudo-obstruction
- Scleroderma
- Amyloidosis
- Peritoneal or unstable dialysis
- Chemical dependency
- Pregnancy
- Primary eating or swallowing disorders
- Psychogenic vomiting

- Implanted electronic medical devices
- Age < 18 or > 70 years

CUESS study demographics

A total of 50 subjects were enrolled, screened, and qualified in the Compassionate Use Electrical Stimulation Study. The demographic information on these subjects is presented in Table 4.

Table 4. Patient demographics

	Diabetic	Idiopathic	Post-surgical[a]
N	22	19	9
Gender (M/F)	10 / 12 F	1 / 18 F	1 / 8 F
Age, mean	39.8	44.5	48.8
BMI, mean	23.5	22.4	23.5
Gastric retention (median)%			
@ 2 hours	79.5	51.0	73.5
@ 4 hours	39.5	21.0	33.5

[a] Enterra Therapy System is not indicated for postsurgical gastroparesis

CUESS study design

Subjects satisfying entry criteria received gastric stimulation systems which included an implanted neurostimulator connected to two unipolar leads which were implanted in the muscle wall of the stomach on the greater curvature at the limit of the corpus-antrum. All subjects received a Model 7425 implantable neurostimulator and a pair of Model 4300 leads.

The stimulation parameters used in the study were: Intensity: 5 mA, Pulse Width: 330 µsec, Frequency: 14 Hz. The neurostimulator was set to deliver a pair of pulses at these parameters every five seconds continuously 24 hours per day.

The stimulation parameters could be adjusted at any time by the physician to optimize treatment therapy. In contrast to the WAVESS study design, Compassionate Use Electrical Stimulation study was an unblinded open label study. Upon implantation of the device within each patient, the stimulation therapy was immediately initiated without a randomized on/off crossover period.

WAVESS results

The effectiveness results described below were obtained from the WAVESS study.

Primary endpoint evaluations

Weekly vomiting frequency was determined for each patient diary. These data were further analyzed by Wilcoxon signed-rank test. For the combined patient group, median weekly vomiting frequency declined 49.6% in the on period vs. the off period ($p < 0.05$), see Table 5. Before breaking the blind at the end of Phase I, 21 patients (10 diabetic, 11 idiopathic) preferred stimulation on, while 7 (4 diabetic and 3 idiopathic) preferred stimulation off, and 5 (3 diabetic and 2 idiopathic) had no preference.

These results were analyzed by the Mainland-Gart test and were statistically significant for the idiopathic and the combined group ($p < 0.05$). At the end of Phase I, subjects were unblinded and given the option of having the device programmed on or off. At the six month follow-up, all subjects had the device programmed on. Each patient had the option of having stimulation turned off or on at any time during the Phase II period.

Table 5. Vomiting Frequency, WAVESS Phase I, All Subjects (N=33)

Vomiting episodes per week	Baseline	On	Off	Difference (off-on)	% Difference
Mean (N ± SD)	37.3 ± 45.1	15.9 ± 25.0	23.6 ± 35.6	7.7	32.6
Median (N)	17.3	6.8	13.5	6.7	49.6

Although 33 patients completed the two-month crossover period of the study (through Phase I), data at six months is provided for only 27 patients. Of these 27 patients, some patients had the device turned to the on mode immediately at the end of the Phase I period, while others had the device turned on later. By the end of the fourth month postrandomization, all 27 patients had the device turned on. As a result, the vomiting frequency at six months was obtained from patients who received continuous stimulation for at least two months, see Table 8.

Vomiting frequency results at 6 and 12 months post-implantation are shown in Table 6, Table 7, and Table 8. Table 6 includes data for all subjects, while Table 7 and Table 8 include data for the idiopathic and diabetic gastroparesis groups, respectively. The vomiting frequency at 6 and 12 months was significant compared to baseline.

Table 6. Vomiting frequency, WAVESS phase II, all subjects

All patients combined	Baseline	6 months	% difference	Baseline	12 months	% difference
(N)	33	27	—	33	24	—
Mean number of episodes ± SD	37.3±45.1	13.7±30.2	-63	37.3±45.1	8.5±16.3	-77
Median number of episodes	17.3	2.6	-85	17.3	4.8	-72

Table 6. Vomiting frequency, WAVESS phase II, all subjects (continued)

All patients combined	Baseline	6 months	% difference	Baseline	12 months	% difference
Patients with > 50% vomiting reduction vs baseline, N(%)	—	16/27 (59)	—	—	18/24 (75)	—
Patients with > 80% vomiting reduction vs baseline, N(%)	—	13/27 (48)	—	—	13/24 (54)	—

Table 7. Vomiting frequency, WAVESS phase II, idiopathic gastroparesis subjects

All patients combined	Baseline	6 months	% difference	Baseline	12 months	% difference
(N)	16	14	—	16	13	—
Mean number of episodes ± SD	44.3±55.5	12.1±25.1	-73	43.3±55.5	11.8±21.2	-73
Median number of episodes	26.8	3.0	-88	26.8	4.5	-83
Patients with > 50% vomiting reduction vs baseline, N(%)	—	9/14 (64)	—	—	10/13 (77)	—
Patients with > 80% vomiting reduction vs baseline, N(%)	—	8/14 (57)	—	—	7/13 (54)	—

Table 8. Vomiting frequency, WAVESS phase II, Diabetic gastroparesis subjects

All patients combined	Baseline	6 months	% difference	Baseline	12 months	% difference
(N)	16	13	—	16	11	—
Mean number of episodes ± SD	30.3±31.9	15.7±36.4	-48	30.3±31.9	4.2±3.9	-87

Table 8. Vomiting frequency, WAVESS phase II, Diabetic gastroparesis subjects (continued)

All patients combined	Baseline	6 months	% difference	Baseline	12 months	% difference
Median number of episodes	13.4	2.6	-80	13.4	4.9	-63
Patients with > 50% vomiting reduction vs baseline, N(%)	—	7/12 (58)	—	—	8/11 (73)	—
Patients with > 80% vomiting reduction vs baseline, N(%)	—	5/12 (42)	—	—	6/11 (55)	—

WAVESS secondary endpoint evaluations

The results of secondary endpoint evaluations indicate that many patients experienced improvements in quality of life (73%) and ability to tolerate solid meals (73%). Additionally, there was a trend in improvement for gastric retention, subjective symptoms, and hypoglycemic attacks.

Adverse events

The adverse events information (Table 9) was obtained from the WAVESS study (N=27), the WAVESS Compassionate Use study (N=24), and the CUESS study (N=49). Adverse events were reported at each follow-up visit or at interim periods as appropriate in both studies. Table 9 summarizes those system related adverse events reported through May 22, 2003.

Table 9. Summary study of system related adverse events[a]

Event description	WAVESS N=27			WAVESS compassionate use N=24			CUESS N=49		
	Events	Patients	% of patients	Events	Patients	% of patients	Events	Patients	% of patients
Device infections	10	7	26	4	4	17	5	5	10
Device erosion	1	1	4	0	0	0	0	0	0
Extrusion of neurostimulator through incision	1	1	4	0	0	0	0	0	0
Hematoma at pocket	1	1	4	0	0	0	1	1	2
Infection in wound incision/abdominal wall	1	1	4	0	0	0	0	0	0
Neurostimulator migration	1	1	4	2	1	4	1	1	2
Lead penetration	4	4	15	1	1	4	0	0	0
Lead revision	1	1	4	0	0	0	0	0	0
Lead impedance out of range	3	3	11	5	5	21	3	2	4
Irritation/ inflammation over neurostimulator site	5	4	15	5	5	21	3	2	4
Pain at neurostimulator site	5	4	15	0	0	0	2	2	4

Table 9. Summary study of system related adverse events[a] (continued)

Event description	WAVESS N=27			WAVESS compassionate use N=24			CUESS N=49		
	Events	Patients	% of patients	Events	Patients	% of patients	Events	Patients	% of patients
Concomitant stimulation of abdominal rectus muscle	1	1	4	0	0	0	2	2	4
Seroma at pocket	2	2	7	1	1	4	0	0	0
Surgical removal of system due to discomfort	0	0	0	2	2	8	0	0	0
Inability to program device/programming difficulty	0	0	0	1	1	4	1	1	2
Tingling sensation	0	0	0	1	1	4	0	0	0
Failure of wound healing	0	0	0	0	0	0	1	1	2
Extra-abdominal pain	0	0	0	0	0	0	4	4	8
Epigastric pain	0	0	0	0	0	0	1	1	2
Surgical removal of IV access	0	0	0	0	0	0	1	1	2
Electrical shocks with discomfort	0	0	0	0	0	0	1	1	2

Table 9. Summary study of system related adverse events[a] (continued)

Event description	WAVESS N=27			WAVESS compassionate use N=24			CUESS N=49		
	Events	Patients	% of patients	Events	Patients	% of patients	Events	Patients	% of patients
Patient "Can't eat as well as before therapy."	0	0	0	0	0	0	1	1	2
Left side nerve rib pain	0	0	0	0	0	0	1	1	2
Uncomfortable neurostimulator location	0	0	0	0	0	0	2	2	4
Fluid collection at neurostimulator site with erythema over RLQ	0	0	0	0	0	0	1	1	2

[a] Refer to the notes following this table for more information.

Adverse event table notes

The decline in the rate of device-related adverse events from the WAVESS to the CUESS protocols may be related to several factors:

- During patient enrollment in the WAVESS study, the protocol was modified to require intraoperative endoscopy to ensure that neither stimulating lead perforated the stomach.
- During the WAVESS study, the physicians were encouraged to administer perioperative antibiotics to minimize the potential for infections at the implant site.
- At one center, the majority of the 39 total cases implanted in the three protocols were done by one surgeon, and 4 infections (10.3%) were reported.
- At another center, 11 systems were implanted in the three protocols and 5 infections (45.5%) were reported. All implant procedures in the WAVESS study and WAVESS Compassionate Use study were done by laparotomy, whereas 5 (10.2%) of the 49 in CUESS were done by laparoscopy.

CUESS (N=49): Two diabetic patients who were implanted but did not qualify for the CUESS protocol were excluded from this summary table.

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M954480A001