SUMMARY OF SAFETY AND EFFECTIVENESS DATA
FOR A SUPPLEMENTAL PREMARKET APPROVAL APPLICATION

I. General Information

Device Generic Name: Implantable multi-programmable quadripolar deep brain stimulation system

Device Trade Name: Medtronic Activa® Parkinson's Control Therapy, consisting of:
Model 3387 DBS™ Lead
Model 3389 DBS™ Lead
Model 7482 Extension
Model 7495 Extension
Model 7426 Soletra Neurostimulator
Burr Hole Ring and Cap
Model 7432 Physician Programmer
Model 7460 MemoryMod® Software Cartridge
Model 7452 Patient Magnet
Model 3625 Test Stimulator
Model 3353/3354 Lead Frame Kit
Accessories

Applicant Name
And Address: Medtronic, Inc.
Neurological and Spinal
800 53rd Avenue NE
Minneapolis, MN 55421

PMA Supplement
Number: P960009/S7

Date Of Panel
Recommendation: March 31, 2000

Date of Notice of Approval to Applicant: January 14, 2002

The Medtronic Activa ® Tremor Control System was approved on July 31, 1997 (P960009) for unilateral thalamic stimulation to suppress tremor in the upper extremity. The system is intended for use in patients who are diagnosed with essential tremor or Parkinsonian tremor not adequately controlled by medications and where the tremor constitutes a significant functional disability. A Summary of the Safety and Effectiveness Data for this indication can be found at *http://www.fda.gov/cdrh/pdf/p960009.pdf.*

II. Indications For Use

Bilateral stimulation of the internal globus pallidus (GPi) or the subthalamic nucleus (STN) using Medtronic Activa® Parkinson's Control Therapy is indicated for adjunctive therapy in reducing some of the symptoms of advanced, levodopa-responsive Parkinson's disease that are not adequately controlled with medication.

For purposes of this document, the Medtronic Activa ® Tremor Control System and the Medtronic Activa® Parkinson's Control Therapy will be referred to as the Activa® System.

III. Contraindications

Implantation of an Activa® System is contraindicated for:

- Patients exposed to diathermy. Do not use shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy (all now referred to as diathermy) on patients implanted with a neurostimulation system. Energy from diathermy can be transferred through the implanted system and can cause tissue damage at the location of the implanted electrodes, resulting in severe injury or death.

  Diathermy is further prohibited because it can also damage the neurostimulation system components resulting in loss of therapy, requiring additional surgery for system explantation and replacement. Injury or damage can occur during diathermy treatment whether the neurostimulation system is turned "on" or "off". Patients should inform all their health care professionals that they should not be exposed to diathermy treatment.

- Patients who will be exposed to Magnetic Resonance Imaging (MRI) using a full body radio-frequency (RF) coil or a head transmit coil that extends over the chest area. Refer to the product labeling for comprehensive safety information on the use of MRI in patients with implanted Activa systems.

- Patients for whom test stimulation is unsuccessful, and

- Patients who are unable to properly operate the stimulator.

IV. Warnings/Precautions

Please refer to the device labeling for a list of warnings and precautions.

V. Device Description

The Medtronic Activa® Parkinson's Control Therapy uses an implantable neurostimulator to deliver electrical stimulation to the internal globus pallidus (GPi) or subthalamic nucleus (STN) of the brain. The device consists of a lead, a neurostimulator, and an extension that connects the lead to the neurostimulator.

A description of each of the system components follows.

Model 3387/Model 3389 DBS™ Leads

The DBS leads consist of a polyurethane protective sheath with four 1.5 mm platinum/iridium electrodes near the tip of each lead that deliver stimulation to the target site. Lead models include Model 3387, in which the 4 electrodes are spaced 1.5 mm apart and Model 3389, in which the electrodes are spaced 0.5 mm apart. The leads are stereotactically introduced into the target and fixed at the skull with a burr hole cap and ring.

Model 7495/Model 7482 Extension

The extension is a set of wires within silicone tubing that connects the lead to the neurostimulator, providing an electrical path that allows stimulation to be delivered to the target site. The extension is subcutaneously passed from the scalp area, where it connects to the lead, through to the subclavicular area or upper abdominal region, where it connects to the neurostimulator. The Model 7482 extension includes a reduced profile connector (lead end) compared to the Model 7495 extension.

Model 7426 Soletra Neurostimulator

The neurostimulator is implanted subcutaneously in the subclavicular or upper abdominal region. It is comprised of a battery and integrated circuits that are hermetically sealed within an oval-shaped titanium enclosure. The neurostimulator delivers electrical stimulation pulses with a variety of parameters, modes, and polarities. A connector assembly on the neurostimulator allows connection to the extension. Four setscrews provide electrical contact between the lead/extension and the neurostimulator.

The stimulation parameters can be non-invasively adjusted to optimize control of the symptoms of Parkinson's disease and minimize side effects. The adjustments are made via radio-frequency communication using the Model 7432 Physician Programmer with the Model 7460 MemoryMod® Software Cartridge. The neurostimulator is battery powered, and when the battery is depleted, it can be replaced surgically. The frequency of replacement is dependent upon the amount of time the neurostimulator is used each day and the stimulation parameters used.

Materials used to manufacture the neurostimulator have been widely used by Medtronic. The neurostimulator case shields are manufactured of titanium with a Parylene coating. The connector assembly is manufactured of polyurethane with titanium setscrews. Material characterizations and toxicity testing have been previously performed on all materials in accordance with applicable standards.

Burr Hole Ring And Cap

The burr hole ring is constructed of nylon and the cap is made of silicone. The ring has ridges that hold it in place within the burr hole in the skull. Troughs are machined into the ring, and when the leads are inserted, the burr hole cap secures the lead in one of the troughs.

Model 7432 Physician Programmer

The Model 7432 Physician Programmer consists of a printer, programmer, and programming head that communicates via telemetry to the neurostimulator. Clinicians use the programmer to adjust the neurostimulator's stimulation parameters and to verify current settings.

Model 7460 MemoryMod® Software Cartridge

The memorymod software cartridge is used with the Model 7432 Physician Programmer to program the neurostimulator.

Model 7452 Control Magnet

The control magnet allows the patient to turn stimulation on and off.

Model 3625 Test Stimulator

The test stimulator is used for perioperative testing. Parameters that can be adjusted include amplitude, pulse width, rate, and electrode selection.

Model 3353/3354 Lead Frame Kits

The lead frame kits (which are designed to fit Electa/Leksell and Radionics or Radionics-like stereotactic frames) are used to stabilize the lead in the insertion cannula during implantation.

VI. Alternative Practices And Procedures

Several medical and surgical alternatives are available for the symptomatic treatment of Parkinson's disease (PD). Most often medication is the first course of treatment. The standard medical therapy for PD is levodopa combined with a peripheral decarboxylase inhibitor, such as carbidopa. Other medical therapy may be used as an adjunct to levodopa. After 2 to 5 years of chronic levodopa treatment, more than 50% of patients may experience disabling motor fluctuations, as well as on-off fluctuations.

When medication is no longer effective or produces unacceptable side effects, surgery may be an alternative. Neurosurgical ablative procedures for the treatment of PD are primarily unilateral and include pallidotomy (lesion of the GPi) or subthalamotomy (lesion of the STN), although the latter is uncommon.

VII. Marketing History

The Medtronic Activa® Parkinson's Control Therapy has been commercially available in Europe since April 1998. The Medtronic Activa® Tremor Control System has been commercially available in Europe, Canada and Australia since March 1995 and in the United States (PMA P960009) since August 1997. In addition, the Model 3389 DBS Lead (PMA P960009/S3: approved September 1999), Model 7482 Extension (PMA P960009/S10: approved February 2000) and Model 7426 Soletra Neurostimulator/Model 7460 MemoryMod Software Cartridge (PMA P960009/S9: approved March 2000) are commercially available for use with the Medtronic Activa® Tremor Control System. As of May 2000, over 10,000 Activa® Systems have been sold worldwide.

Since August 1997, Medtronic has conducted four field notifications regarding the Activa® System. The first notification was in response to DBS lead fractures. These fractures were a result of stress factors placed on the lead from neck movement. Product labeling allowed connection of the lead and the extension to be placed in the neck region. A notification was sent to implanting physicians cautioning them to discontinue placing the lead/extension connection in the neck and to place that connection on the head to reduce strain on the lead. Physicians were advised to follow patients who had lead/extension connections in the neck, and to use their medical judgment in determining if a revision of the system was required. Product labeling was revised to state that the lead/extension connection should be placed on the head, and not in the neck region. There have been no new lead fracture modalities to date.

The second field notification concerned the burr hole cap, which helps secure the DBS leads. It was observed that residue could form on the burr hole caps, due to insufficiently post-cured silicone, which compromises the cap. As a result, Medtronic sent notification to implanting physicians instructing them to return any unused Model 3387 or 3389 DBS Lead kits manufactured prior to April 12, 1999. The burr hole caps were contained in these lead kits. The residue was determined not to be a risk to the patient; thus no revision surgery was recommended to physicians. Manufacturing processes were checked to ensure sufficient post-cure of the silicone.

The third field notification clarified the use of the Model 7432 Physician Programmer with the Model 7460 MemoryMod Software Cartridge. While the Model 7460 MemoryMod contains software to program either the Model 7424 Itrel II[1] or the Model 7426 Soletra, the clinician must turn off the Model 7432 Physician Programmer and turn it back on before attempting to program a different neurostimulator model in succession. If the programmer is not turned off an on, the programmer will display "NO TELEMETRY, POSITION HEAD AND TRY AGAIN" and the software will not allow the different neurostimulator to be programmed.

The fourth field notification concerned revised labeling to contraindicate the use of diathermy in conjunction with implanted neurostimulation systems. In May 2001, Medtronic sent a safety alert to physicians, hospital administrators and implanted patients. The safety alert contraindicated shortwave diathermy, microwave diathermy or therapeutic ultrasound diathermy in patients implanted with any neurostimulation systems. Energy from diathermy can be transferred through the implanted system and can cause tissue damage at the location of the implanted electrodes, resulting in severe injury or death. Diathermy is further prohibited because it can also damage the neurostimulation system components resulting in loss of therapy, requiring additional surgery for system explantation and replacement. Injury or damage can occur during diathermy treatment whether the neurostimulation system is turned “on” or “off.”

Medtronic’s Activa® System has not been withdrawn from the market in any country for reasons related to its safety and/or effectiveness.

VIII. Adverse Events

For complete listing of adverse events for the Medtronic Activa® Parkinson's Control Therapy, please refer to table 3.

[1] Medtronic no longer manufactures the Model 7424 Itrel II. The Model 7426 Soletra (PMA P960009/S9: approved March 2000) replaced the Model 7424 Itrel II.

IX. Potential Adverse Events

Adverse events which may potentially occur, but were not reported in the clinical trials for the Medtronic Activa® Parkinson's Control Therapy, include:

- Allergic response to, or rejection of, the implanted material
- Random neurostimulator component failure, which can potentially result in a charge imbalance that may cause tissue damage

X. Summary Of Studies

Previous Preclinical Studies

All components of the Medtronic Activa ® Parkinson's Control Therapy have been commercially approved for the Medtronic Activa ® Tremor Control System (PMA P960009, PMA P960009/S3, PMA P960009/S9, and PMA P960009/S10). Therefore, the preclinical testing of these components provided in prior Medtronic Activa® Tremor Control System PMAs are also applicable to the Medtronic Activa® Parkinson's Control Therapy.

Additional Pre-Clinical Studies

The Medtronic Activa® System has undergone additional pre-clinical testing as follows:

Electromagnetic Compatibility/Electromagnetic Interference (EMC/EMI) Testing

The Activa® System uses EMC protective measures similar to pacemakers. In the absence of established EMC standards for neurostimulation, Medtronic has based EMC immunity testing using established standards for EMC testing of pacemakers. The pacemaker testing requirements define the EMC test frequencies and field strength levels that patients implanted with cardiac pacemakers could be exposed to. It is expected that a patient implanted with a neurostimulation system could be exposed to the same type of EMC environment.

Medtronic has tested frequencies ranging from power line (50/60 Hz) to microwave (2450 MHz), utilizing established Medtronic pacemaker protocols and the following established EMC standards: IEC 60601-1-2 2nd edition, AAMI PC69: 2000 and EN45502-1. The test results met the requirements specified.

For EMC/EMI areas of particular concern to neurostimulation patients, additional testing has been performed for electronic article surveillance/metal detector systems, shortwave diathermy systems and magnetic resonance imaging systems.

The test results from all EMC/EMI testing has dictated the necessary contra-indications, warnings and precautions and special instructions for use that have been specified and incorporated into the labeling for both the physician and patient respectively.

Clinical Studies

Introduction

The Medtronic Activa® Parkinson's Control Therapy uses an implantable neurostimulator to deliver electrical stimulation to the internal globus pallidus (GPi) or subthalamic nucleus (STN) of the brain. The device consists of a lead, a neurostimulator, and an extension that connects the lead to the neurostimulator. Neurologists and neurosurgeons have used electrical stimulation for more than 35 years as a way to locate and distinguish specific sites within the brain. In doing so, it was discovered that stimulating different areas of the brain could suppress the symptoms of Parkinson's disease (PD).

Study Design

The protocol followed a prospective open label design. Eighteen (18) centers participated in this study. Of these, 11 were in Europe (4 in Spain, 3 in Germany, 2 in France, and 1 each in Italy and Sweden); 4 were in the United States; 2 were in Australia; and 1 was in Canada. Patients received deep brain stimulators implanted bilaterally in the Gpi or the STN. Under certain circumstances, the second device system was not implanted. The study population included male and female patients, ages 30-75, diagnosed as having idiopathic Parkinson's disease as determined by clinical presence of three of the four (or two of three, as stated in the European protocol) cardinal features (tremor, rigidity, bradykinesia, and postural instability) and good levodopa response. Patients were to have a disability level due to Parkinson's disease based on the following criteria:

- Hoehn and Yahr staging 3 or worse when the patient is in the "off" state;
- Unified Parkinson's Disease Rating Scale (UPDRS) motor exam score of 30 or more in the "off" state; and
- Complications of levodopa therapy motor responses including motor fluctuations and dyskinesias.

Patients participated in the studies for 12 months; there were 2 pre-implant visits and 4 follow-up visits (1, 3, 6, and 12 months). See Figures 1 and 2 for pre-implant and follow-up assessment schedules. Each patient's dosage of antiparkinsonian medication was held constant for 1 month prior to surgery. Following surgery, physicians monitored antiparkinsonian medication status throughout the remainder of the study.

Data collected at each pre-implant and follow-up visit included the Unified Parkinson's Disease Rating Scale (UPDRS) and 2-day patient diaries recorded prior to the visit. At each visit, patients were evaluated without medication (OFF medication) and with medication (ON medication). At follow-up visits, patients were also assessed without stimulation (stimulation OFF) and with stimulation (stimulation ON).

Figure 1 Pre-implant Assessment Schedule

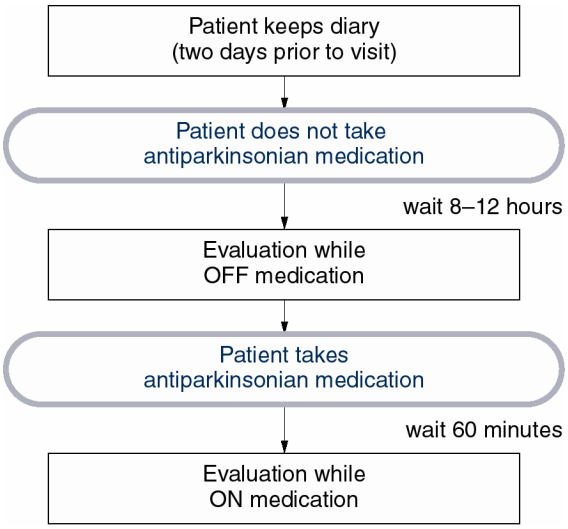
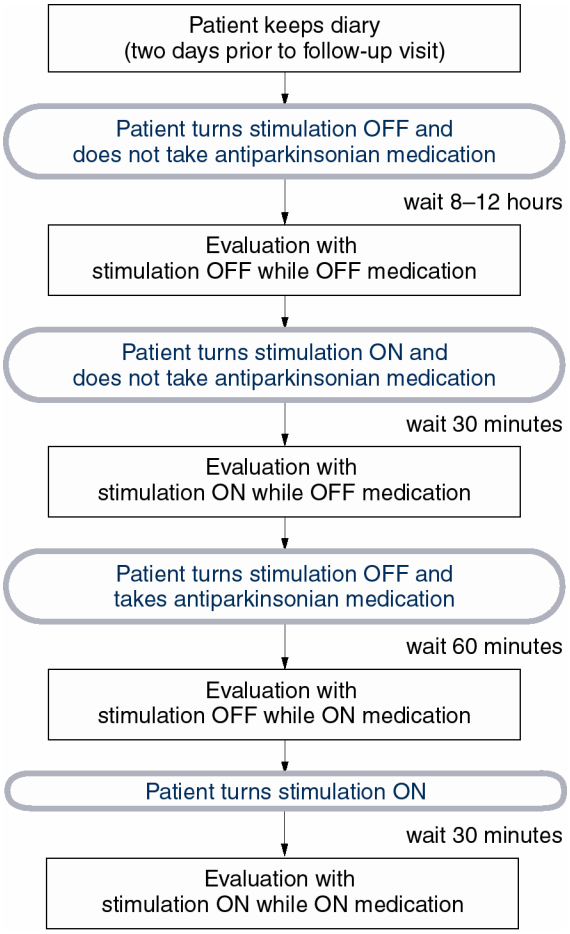


Figure 2 Follow-up Assessment Schedule



Patient Accountability

Total Patients Enrolled

A total of 160 patients were enrolled: Spain (n=30); France (n=27); United States (n=26); Canada (n=20); Germany (n=20); Sweden (n=15); Australia (n=12); and Italy (n=10).

Protocol Deviations

A total of 17/160 patients (10.6%) did not satisfy all eligibility criteria: Hoehn and Yahr Staging Scale score OFF medication <3 (n=5); UPDRS total motor examination scores OFF medication < 30 (n=4); medications adjusted during pre-implant (n=4); prior history of depression (n=1); UPDRS total motor examination score OFF medication < 30, Hoehn and Yahr Staging Scale score OFF medication <3 and prior history of depression (n=1); UPDRS total motor examination score OFF medication < 30 and Hoehn and Yahr Staging Scale score OFF medication <3 (n=1); and UPDRS total motor examination score OFF medication < 30 and medications adjusted during pre-implant (n=1).

Demographics

The majority of study patients were male (107/160; 66.9%). The mean age of disease onset was 43.9 years (range: 16.5-68.8). Definitive diagnosis occurred approximately 2 years later (mean age: 45.5 years; range 22.5-70.1) and the mean age at implant was 58.1 years (range: 32.1-75.9).

Patients Implanted by Target Site and Laterality

Patient accountability information is presented in Table 1 and Figures 3 and 4. Of the 160 enrolled patients, 106 patients (106/160, 66.3%) underwent procedures that targeted the STN (bilateral: 96, unilateral: 6, not implanted: 4) and 54 (54/160, 33.8%) underwent procedures that targeted the GPi (bilateral: 38, unilateral: 15, not implanted: 1).

All patients were intended to receive bilateral system implants that could occur in simultaneous implant procedures or in staged implant procedures. However, the target of implant (STN or GPi) and neurosurgical procedures were at the implanting physician's discretion. Upon completion of all procedures, 134 patients (134/160, 83.8%) had bilateral system implants and 21 patients (21/160, 13.1%) had unilateral system implants.

Unilateral implants were permitted if there was a satisfactory result with the unilateral implant; the patient declined the second implant; or there was a concern for patient safety. For 26/160 patients (16.3%), bilateral system implants did not occur for the following reasons: satisfied with unilateral system implant (n=11), declined second system (n=5), second system not implanted due to safety concern (n=5: intracranial hemorrhage (3), infection (2)), and no systems implanted (n=5: intracranial (2), cognitive disorder (1), hemiparesis/hemiplegia (1), no therapeutic benefit (1)).

Thirteen of the 160 (13/160, 8.1%) enrolled patients underwent neurosurgical procedures that did not follow the planned surgical course. Five of the 13 patients (5/160, 3.1%) had no systems implanted: surgical complications (n=3: intracranial hemorrhage (2), hemiparesis/hemiplegia (1)); combative behavior/cognitive disorder (n=1); and no therapeutic benefit from intraoperative test stimulation (n=1). Four patients who underwent bilateral procedures had only unilateral systems implanted (intracranial hemorrhage (3), infection (1)). Four patients underwent unsuccessful unilateral surgical procedures (positioning difficulty (1), diplopia (1), dyspnea/hypoventilation (1), intracranial hemorrhage (1)), but later were implanted successfully with bilateral systems.

Of the 160 enrolled patients, 139 patients (92 STN and 47 GPi patients) completed 12-months of follow-up. Twenty-one patients terminated before the 12-month follow-up visit: adverse events (n=6: intracranial hemorrhage (4), cognitive impairment (1), infection (1)), no systems implanted (n=5: intracranial hemorrhage (2), cognitive disorder (1), hemiparesis/hemiplegia (1), no therapeutic benefit (1)), device explant (n=4: infection (3), lead migration (1)), death (n=3: end-stage Parkinson's disease (1), esophageal neoplasia (1), myocardial infarction (1)), and lost to follow-up (n=3:patient refused 12-month visit (2), patient withdrawal (1)).

Patient Data Included in Safety and Efficacy Analyses

The product effectiveness data set excluded the results from 13 patients, because there were sufficient concerns regarding the reliability of their effectiveness data. Consequently, all clinical outcomes of these patients were excluded from study effectiveness analyses, but were included in all safety analyses. In addition, efficacy analyses presented include only the subgroup of patients whose efficacy data were verified with original source documentation. The number of patients presented in the efficacy histograms varies depending on the number of patients with verifiable data.

Table 1. Patient Accountability: Lead and System Implant Procedures

	STN (n = 106)	**GPi (n = 54)**	**Total (n = 160)**
Type of Lead Implant Procedure			
Simultaneous Bilateral*	85 (80.2%)	28 (51.9%)	113 (70.6%)
Sequential Bilateral*	14 (13.2%)	12 (22.2%)	26 (16.3%)
Median time between implants (days)	22.0	63.5	54.5
Unilateral	7 (6.6%)	14 (25.9%)	21 (13.1%)
Total Failed Procedures (no leads implanted)	**12/210 (5.7%)**	**3/94 (3.2%)**	**15/304 (4.9%)**
Systems Implanted			
Patients with Bilateral Systems	96 (90.6%)	38 (70.4%)	134 (83.8%)
Second implant within 90 days	93 (87.7%)	35 (64.8%)	128 (80.0%)
Second implant greater than 90 days	3 (2.8%)	3 (5.6%)	6 (3.8%)
Patients with Unilateral Systems	6 (5.7%)	15 (27.8%)	21 (13.1%)
Patients with no Systems	4 (3.8%)	1 (1.9%)	5 (3.1%)
Patients Undergoing Failed Procedures	**10 (9.4%)**	**3 (5.6%)**	**13 (8.1%)**
* 4 STN patients underwent attempted unilateral procedures prior to successful bilateral procedures.			

Figure 3. Flow Diagram of Total Enrolled STN Patients by Systems Implanted (n = 106).

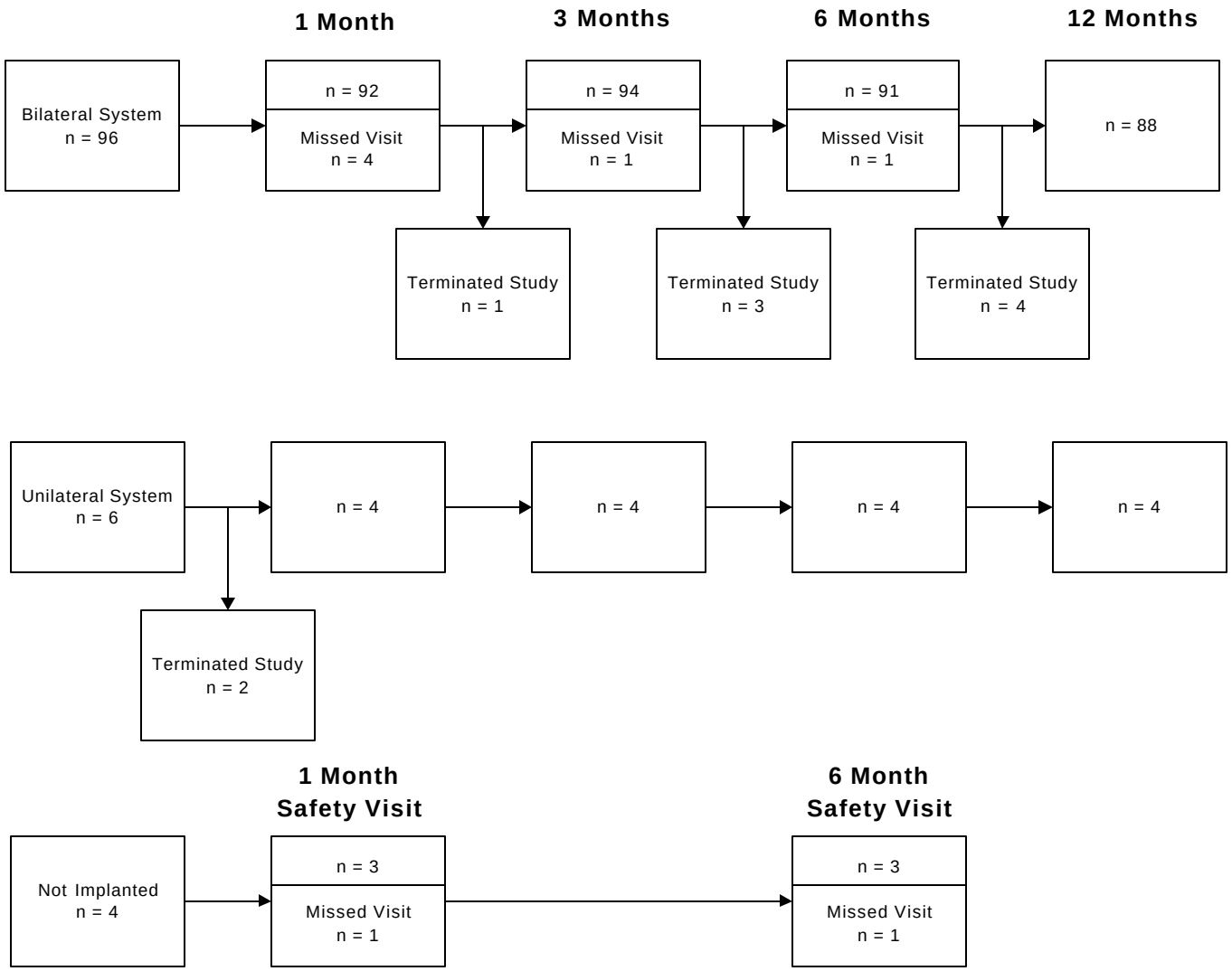
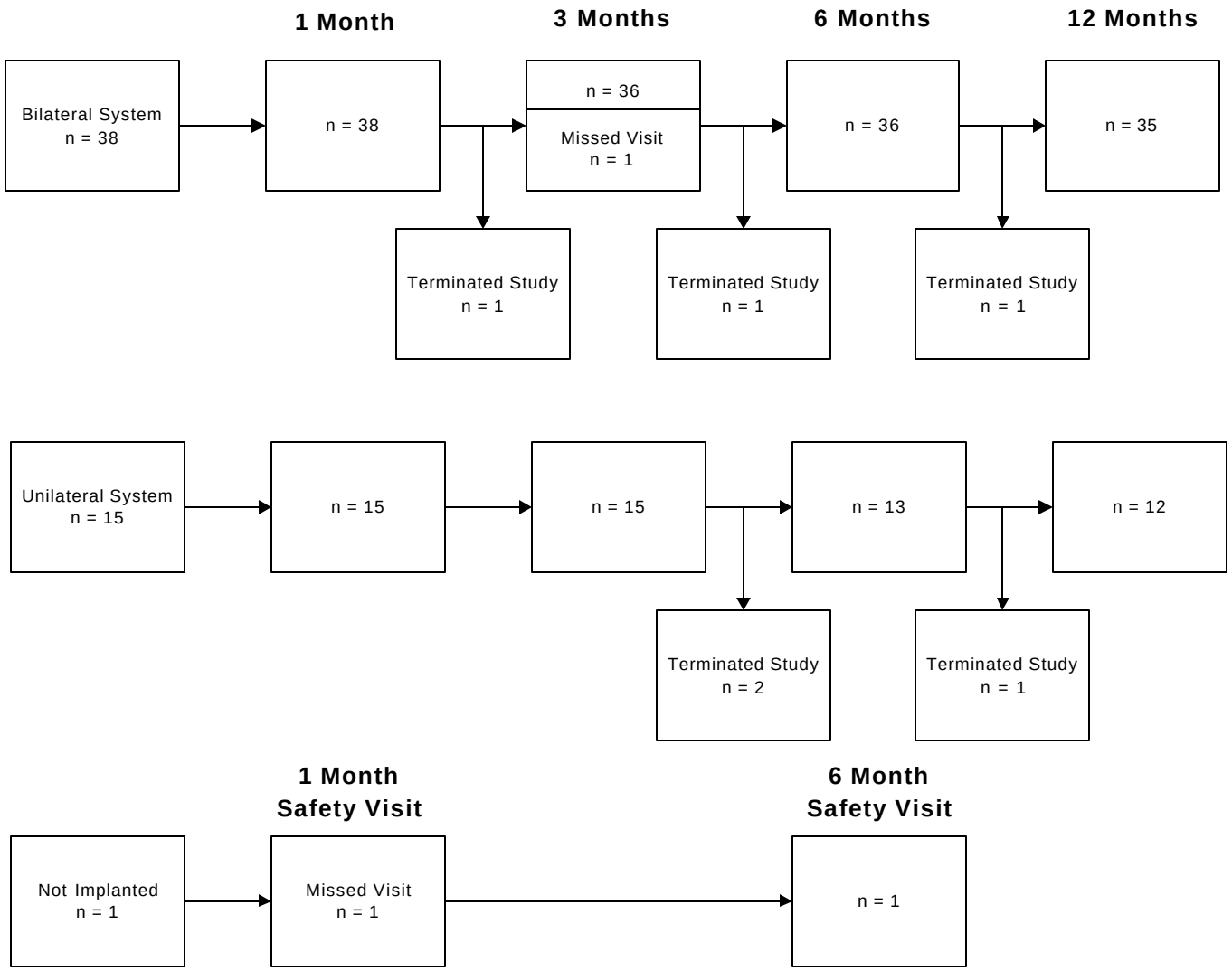


Figure 4. Flow Diagram of Total Enrolled GPi Patients by Systems Implanted (n = 54).



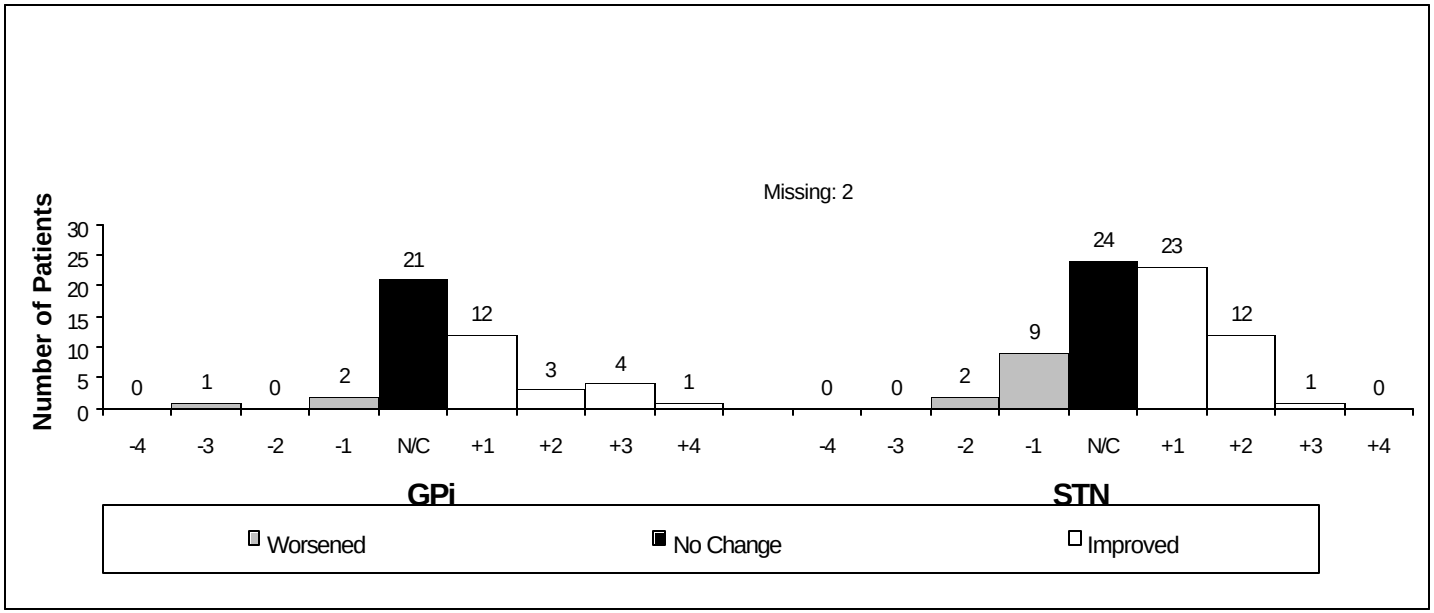
Efficacy results

A number of parameters were evaluated in the study including the following:

- To evaluate PD symptoms, the Unified Parkinson's Disease Rating Scale (UPDRS) total motor examination score (Section III) at follow-up was compared to pre-implant. The UPDRS total motor examination includes 14 items, including separate questions for axial and peripheral symptoms, to evaluate speech, facial expression, tremor at rest, action or postural tremor of hands, rigidity, finger taps, hand movements, rapid alternating movement of hands, leg agility, arising from chair, posture, gait, postural stability, and body bradykinesia and hypokinesia. Each item is scored on a scale from 0 (normal) to 4 (severe), with the total possible score ranging from 0 to 108. At each visit, patients were evaluated both with medication (ON medication) and without medication (OFF medication). At follow-up, patients were also assessed with stimulation (stimulation ON) and without stimulation (stimulation OFF). (See figures 5 and 6)

- To evaluate "on" time and "on" time with dyskinesia, patients recorded two-day diaries before each visit. During these two days, patients recorded the amount of time they experienced "on" time (good motor function, relief from PD symptoms) and "on" time with dyskinesia (good motor function and relief from PD symptoms, but troubled by abnormal involuntary movements). (See figures 7 and 8)

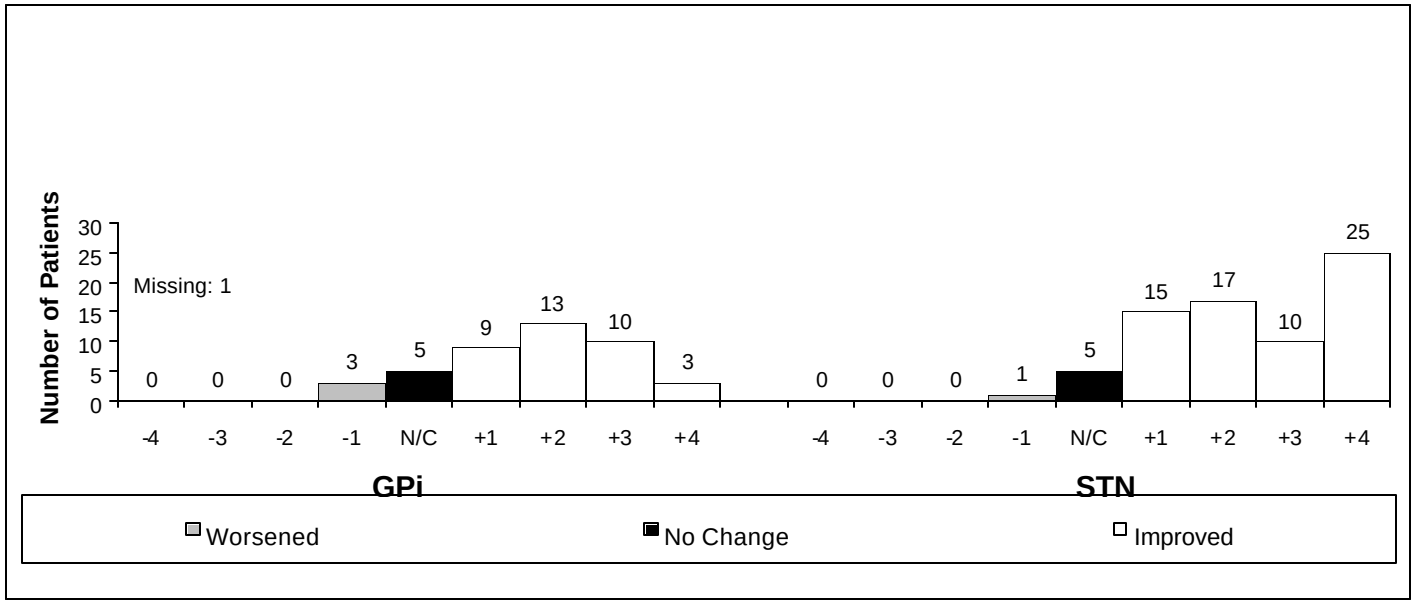
Figure 5 Absolute change in UPDRS TME scores while ON medication by target: pre-implant to 12 months (GPi N=44, STN N=73)*



Definition of Histogram Ranges									
Histogram Label	-4	-3	-2	-1	N/C (no change)	+1	+2	+3	+4
TME Score Change	> 35	>25 and ≤ 35	>15 and ≤ 25	>5 and ≤ 15	>-5 and ≤ 5	>-15 and ≤ -5	>-25 and ≤ -15	>-35 and ≤ -25	≤ -35

*Data presented include 117 of 160 total patients who had verifiable source documentation for this efficacy measure.

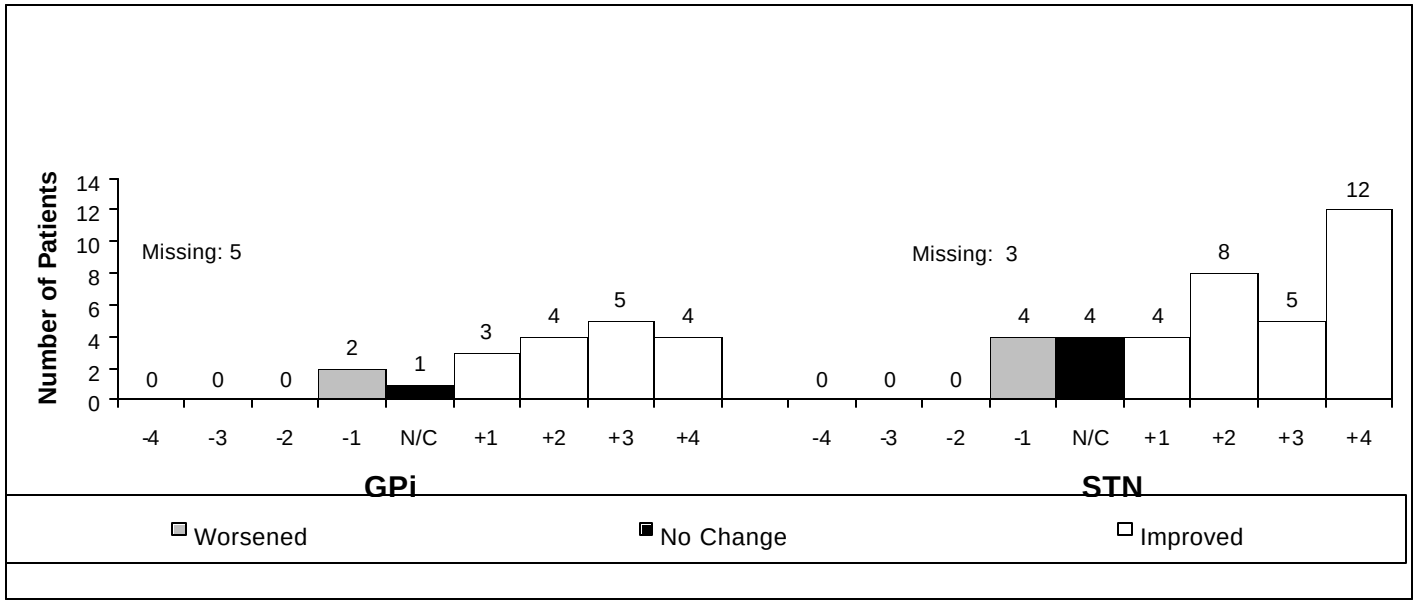
Figure 6 Absolute change in UPDRS TME scores while OFF medication by target: pre-implant to 12 months (GPi N=44, STN N=73)*



Definition of Histogram Ranges									
Histogram Label	-4	-3	-2	-1	N/C (no change)	+1	+2	+3	+4
TME Score Change	> 35	>25 and ≤ 35	>15 and ≤ 25	>5 and ≤ 15	>-5 and ≤ 5	>-15 and ≤ -5	>-25 and ≤ -15	>-35 and ≤ -25	≤ -35

* Data presented include 117 of 160 total patients who had verifiable source documentation for this efficacy measure

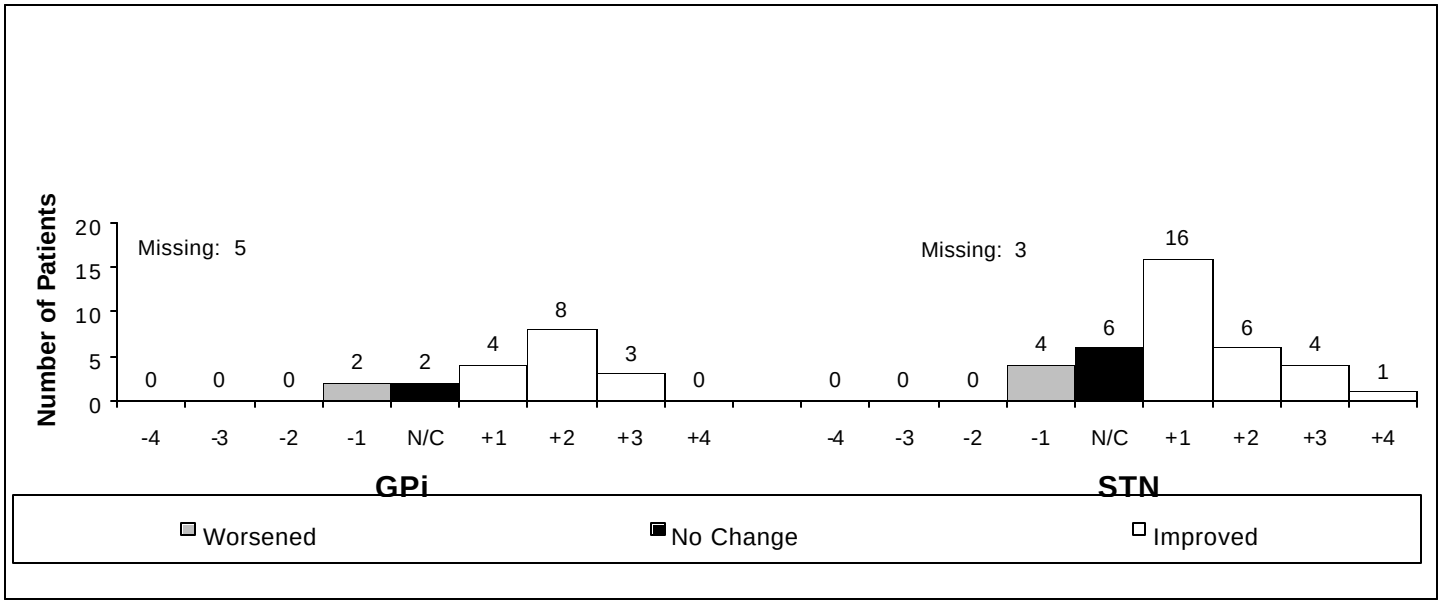
Figure 7 Absolute change in "on" time by target: pre-implant to 12 months (GPi N=24, STN N=40)*



Definition of Histogram Ranges									
Histogram Label	-4	-3	-2	-1	N/C (no change)	+1	+2	+3	+4
Change in ON Time: hours	≤ -10	≤ -7 and > -10	≤ -4 and > -7	≤ -1 and > -4	> -1 and < 1	≥ 1 and < 4	≥ 4 and < 7	≥ 7 and < 10	≥ 10

***** Data presented include 64 of 160 total patients who had verifiable source documentation for this efficacy measure.

Figure 8 Absolute change in "on" time with dyskinesia by target: pre-implant to 12 months (GPi N=24, STN N=40)*



Definition of Histogram Ranges									
Histogram Label	-4	-3	-2	-1	N/C (no change)	+1	+2	+3	+4
Change in ON w/ Dysk Time: hours	≥ 10	≥ 7 and < 10	≥ 4 and < 7	≥ 1 and < 4	< 1 and > -1	≤ -1 and > -4	≤ -4 and > -7	≤ -7 and > -10	≤ -10

* Data presented include 64 of 160 total patients who had verifiable source documentation for this efficacy measure.

Safety results

The Activa® Parkinson's Control Therapy was implanted in 155 of 160 enrolled patients involving 289 implanted systems. A total of 134 patients were implanted bilaterally and 21 patients were implanted unilaterally.

Of the 289 systems implanted, 8 systems were removed and of these 8, 3 systems were replaced during the clinical study. A total of 293 leads were implanted and 30 leads were removed during the clinical study. Of these leads, 20 were replaced. One bilaterally implanted patient had both leads replaced twice. No leads were left in place while a second lead was implanted on the same side. See Table 2.

Three patients died during the 12-month study period. Causes of death included esophageal neoplasia, myocardial infarction and end-stage Parkinson's disease.

Table 2. Summary of Implanted, Internalized, Replaced, and Explanted Device Components

	STN	GPi	All Patients
Number of Systems			
Implanted (all components)	198	91	289
Replaced (all components)[1]	3	0	3
Total Implanted and Replaced (all components)	201	91	292
Explanted, not Replaced (all components)[2]	4	1	5
Total Number of Patients Successfully Implanted with a Bilateral System	96	38	134
Total Number of Patients with Bilateral Systems at 12-month Follow-up	85	35	120
Total Number of Patients with Bilateral Systems in Use at 12-month Follow-up	84	35	119
Number of DBS Leads			
Implanted	200	93	293
Replaced[3]	13	7	20
Total Implanted and Replaced	213	100	313
Repositioned	2	4	6
Explanted, not Replaced[4]	6	4	10
Number of Neurostimulators			
Internalized	198	91	289
Replaced[5]	4	3	7
Total Internalized and Replaced	202	94	296
Explanted, not Replaced[6]	6	2	8
Number of Extensions			
Internalized	198	91	289
Replaced[7]	5	6	11
Total Internalized and Replaced	203	97	300
Explanted, not Replaced[8]	6	3	9

[1] Systems replaced due to: infection (n=2), lead migration (n=1)
[2] Systems explanted (not replaced) due to: infection (n=4), headache/infection (n=1)
[3] DBS leads replaced due to: positioning difficulties (n=5), increased Parkinson's disease symptoms (n=5), lead breakage (n=4), infection (n=3), migration (n=1), lead breakage/migration (n=1), intermittent continuity (n=1)
[4] DBS leads explanted (not replaced) due to: infection (n=5), migration (n=2), lead dislodgement (n=1), intracranial hemorrhage (n=1), headache (n=1)
[5] Neurostimulators replaced due to: infection (n=3), infection/abnormal healing (n=1), battery failure, normal (n=2), migration (n=1)
[6] Neurostimulators explanted (not replaced) due to: infection (n=8)
[7] Extensions replaced due to: infection (n=6), lead breakage (n=2), increased PD symptoms (n=1), conductor wire broken (n=1), migration (n=1)
[8] Extensions explanted (not replaced) due to: infection (n=9)

Adverse Events

All 160 enrolled patients were evaluated for the occurrence of adverse events. One hundred and fifty-four (154/160, 96.3%) of the enrolled patients experienced one or more adverse events. Table 3 lists adverse events for all patients reported during the clinical investigation by major category and subcategories.

Over the entire study duration, 12/160 patients (7.5%) had intracranial hemorrhage; 17/160 patients (10.6%) had device-related infection; 16 patients (10.0%) had paresis/asthenia; and 13/160 patients (8.1%) had hemiplegia/hemiparesis.

The rate of stimulation-related adverse events was 51.9% (83/160 patients) and the rate of ongoing stimulation-related events was 22.5% (36/160 patients). The rate of serious stimulation-related adverse events was 9.4% (15/160) and the rate of ongoing serious stimulation related adverse events was 3.1% (5/160) patients. Ongoing serious stimulation-related adverse events included: worsening of motor impairment/PD symptoms (dyskinesia), sensory impairment (pain); and speech/language (dysarthria, hypophonia, and speech disorder). Other stimulation related adverse events included: worsening of motor impairment/PD symptoms (worse motor fluctuations, incoordination, abnormal gait, akinesia/bradykinesia, tremor, rigidity, myoclonus and dysphagia); sensory impairment (paresthesia, sensory disturbance, hypesthesia, hearing [tinnitus] and headache); speech/language (voice alteration); eye (visual disturbances [diplopia, abnormal vision and visual field defect] and eye disorders [twitching]); cognitive (thinking abnormal, confusion, alteration of mentation [dizziness]); general (respiratory [laryngismus], musculo-skeletal [abnormal posture], gastrointestinal [vomiting], urogenital [urinary incontinence], metabolic/nutritional [weight loss], skin and appendages [sweating] and systemic [accidental injury]; sleep [somnolence and insomnia]; neuropsychological (psychiatric disturbances [manic reaction and neurosis]); general paresis/asthenia; internal system events (shock/jolt, positioning difficulties); cardiovascular (cerebrovascular accident); hemiplegia/hemiparesis (asthenia) and depression.

The rate of device-related adverse events was 36.9% (59/160 patients) and the rate of ongoing device-related events was 10.0% (16/160 patients). The rate of serious device-related adverse events was 17.5% (28/160 patients) and the rate of ongoing serious device-related adverse events was 6.3% (10/160 patients). Ongoing, serious device-related adverse events included: internal DBS system events (intermittent continuity, electromagnetic interference, and lead breakage); infection, worsening of motor impairment/PD symptoms (worse motor fluctuations, and incoordination) due to loss of effect; and skin and appendages (erosion). Other device-related adverse events included: internal DBS system events (shock/jolt, dislodged, migration, normal battery failure, malfunction, current leak, wire breakage, kinked electrode, electrode problem, positioning difficulties, impedance low); external system events (difficult to program, printer problem); sensory impairment (pain, sensory disturbance, paresthesia and headache); speech/language (hypophonia); skin and appendages (skin disorder); subcutaneous hemorrhage/seroma (seroma); paresis/asthenia; metabolic/nutritional (edema); and cerebral spinal fluid abnormality (pneumocephalus).

One patient experienced manic symptoms (manic reaction) and attention and cognitive deficits (thinking abnormal) concurrent with exposure to an electronic article surveillance (electromagnetic interference) device.

Table 3. Summary of Adverse Events for All Patients Reported in the Parkinson's Disease Clinical Trial

Adverse Event All Patients (n=160)				
Major Category	**# of Events (serious)**	**Study Related**	**# (%) of Patients**	**95% CI****
Intracranial Hemorrhage*	13 (8)	13	12 (7.5)	3.4, 11.6
Device-Related Infection*	32 (23)	31	17 (10.6)	5.9, 15.4
Infection with Explant*	15 (15)	15	9 (5.6)	2.1, 9.2
Infection without Explant*	17 (8)	16	12 (7.5)	3.4, 11.6
Paresis/Asthenia*	16 (1)	6	16 (10)	5.4, 14.7
Hemiplegia/Hemiparesis*	15 (8)	10	13 (8.1)	3.9, 12.4
Worsening of Motor Impairment/ PD Symptom*	357 (48)	130	110 (68.8)	61.6, 75.9
Dyskinesia*	131 (22)	64	60 (37.5)	30.0, 45.0
Worse Motor Fluctuations*	85 (15)	23	56 (35)	27.6, 42.4
Abnormal gait*	38 (4)	10	30 (18.8)	12.7, 24.8
Incoordination*	33 (3)	14	29 (18.1)	12.2, 24.1
Tremor*	22 (0)	4	18 (11.3)	6.4, 16.2
Akinesia/Bradykinesia*	20 (0)	9	19 (11.9)	6.9, 16.9
Dysphagia*	13 (3)	2	12 (7.5)	3.4, 11.6
Rigidity*	13 (1)	3	12 (7.5)	3.4, 11.6
Myoclonus	1 (0)	1	1 (0.6)	0, 1.9
Therapeutic Response, decreased	1 (0)	0	1 (0.6)	0, 1.9
Sensory Impairment*	148 (14)	59	79 (49.4)	41.6, 57.1
Pain*	71 (5)	15	50 (31.3)	24.1, 38.4
Paresthesia*	37 (1)	23	29 (18.1)	12.2, 24.1
Sensory Disturbance*	18 (2)	11	16 (10)	5.4, 14.7
Headache*	16 (4)	8	14 (8.8)	4.4, 13.1
Neuralgia	3 (2)	0	3 (1.9)	0, 4.0
Hearing*	2 (0)	1	2 (1.3)	0, 3.0
Neuropathy	1 (0)	1	1 (0.6)	0, 1.9
Cognitive*	142 (21)	61	72 (45)	37.3, 52.7
Confusion*	56 (5)	27	44 (27.5)	20.6, 34.4
Thinking abnormal*	39 (3)	16	33 (20.6)	14.4, 26.9
Hallucinations	15 (2)	1	11 (6.9)	3.0, 10.8
Alteration of Mentation*	16 (5)	9	14 (8.8)	4.4, 13.1
Amnesia*	9 (2)	6	8 (5.0)	1.6, 8.4
Delusions*	5 (4)	0	4 (2.5)	0, 4.9
Dementia	2 (0)	2	2 (1.3)	0, 3.0
DBS System*	93 (33)	80	57 (35.6)	28.2, 43.1
Internal*	86 (33)	74	55 (34.4)	27.0, 41.7
External*	7 (0)	6	6 (3.8)	0.8, 6.7
Speech/Language*	77 (15)	48	59 (36.9)	29.4, 44.4
Dysarthria*	47 (6)	32	42 (26.3)	19.4, 33.1
Speech/Language*	30 (9)	16	23 (14.4)	8.9, 19.8

Adverse Event All Patients (n=160)				
Major Category	**# of Events (serious)**	**Study Related**	**# (%) of Patients**	**95% CI****
Neuropsychological*	55 (18)	6	31 (19.4)	13.3, 26.0
Psychiatric Disturbances*	25 (8)	4	14 (8.8)	4.4, 13.1
Personality Disorder	12 (4)	1	9 (5.6)	2.1, 9.2
Hostility	6 (2)	0	5 (3.1)	0.4, 5.8
Manic Reaction*	5 (2)	2	3 (1.9)	0, 4.0
Neurosis*	1 (0)	1	1 (0.6)	0, 1.9
Paranoid Reaction	1 (0)	0	1 (0.6)	0, 1.9
Anxiety*	25 (7)	2	20 (12.5)	7.4, 17.6
Apathy	4 (2)	0	4 (2.5)	0, 4.9
Suicide Attempt	1 (1)	0	1 (0.6)	0, 1.9
Depression*	41 (10)	4	35 (21.9)	15.5, 28.3
Sleep*	45 (1)	8	37 (23.1)	16.6, 29.7
Eye*	48 (6)	25	39 (24.4)	17.7, 31.0
Visual Disturbance*	33 (6)	20	30 (18.8)	12.7, 24.8
Eye Disorder*	10 (0)	5	9 (5.6)	2.1, 9.2
Eye Infection	5 (0)	0	4 (2.5)	0, 4.9
Subcutaneous Hemorrhage/Seroma*	15 (6)	10	14 (8.8)	4.4, 13.1
Convulsions	7 (6)	5	7 (4.4)	1.2, 7.5
Death	3 (3)	0	3 (1.9)	0, 4.0
Cerebral Spinal Fluid Abnormality	5 (1)	5	5 (3.1)	0.4, 5.8
General*	312 (52)	40	110 (68.8)	61.6, 75.9
Systemic*	75 (14)	7	49 (30.6)	23.5, 37.8
Gastrointestinal*	55 (5)	9	41 (25.6)	18.9, 32.4
Urogenital*	53 (7)	3	43 (26.9)	20.0, 33.7
Respiratory	43 (10)	8	30 (18.8)	12.7, 24.8
Metabolic/Nutritional*	36 (4)	6	29 (18.1)	12.2, 24.1
Musculo-Skeletal*	21 (7)	2	19 (11.9)	6.9, 16.9
Skin and Appendages*	25 (5)	5	22 (13.8)	8.4, 19.1
Ecchymosis	1 (0)	0	1 (0.6)	0, 1.9
Erosion*	3 (3)	2	3 (1.9)	0, 4.0
Infection, fungal	2 (0)	0	2 (1.3)	0, 3.0
Lymphedema	1 (0)	0	1 (0.6)	0, 1.9
Petechia	1 (0)	0	1 (0.6)	0, 1.9
Psoriasis	1 (1)	0	1 (0.6)	0, 1.9
Rash	7 (0)	0	7 (4.4)	1.2, 7.5
Skin Disorder	6 (1)	2	6 (3.8)	0.8, 6.7
Sweating*	3 (0)	1	3 (1.9)	0, 4.0
Ear	4 (0)	0	4 (2.5)	0, 4.9
Cardiovascular*	64 (14)	24	32 (20)	13.8, 26.2

* *Includes adverse events related to the system components.*

** *Note: Exact 95% confidence intervals were used when the # (%) of patients was 0 (0%) because the normal approximation to the binomial does not provide a confidence interval. In every other case, the normal approximation to the binomial was used to calculate confidence intervals.*

XI. Conclusions Drawn From Studies

The preclinical and clinical testing provide a reasonable assurance that the Activa® Parkinson's Control Therapy is safe and effective when used in accordance with its labeling. A summary of conclusions regarding safety and effectiveness are as follows:

Safety Summary

All 160 enrolled patients were evaluated for the occurrence of adverse events. One hundred and fifty-four (154/160, 96.3%) of the enrolled patients experienced one or more adverse events. Table 3 lists adverse events for all patients reported during the clinical investigation by major category and subcategories.

Over the entire study duration, 12/160 patients (7.5%) had intracranial hemorrhage; 17/160 patients (10.6%) had device-related infection; 16 patients (10.0%) had paresis/asthenia; and 13/160 patients (8.1%) had hemiplegia/hemiparesis.

In addition to the adverse events collected through the 12 months of study follow-up, the sponsor has provided adverse event information for 100 patients at 2 years (60 STN and 40 GPi), 82 patients at 3 years (47 STN and 35 GPi), 38 patients at 4 years (17 STN and 21 GPi), and 16 patients at 5 years (4 STN and 12 GPi).

FDA review of the safety data concluded that the probable benefits to health outweigh the probable risks.

Effectiveness Summary

UPDRS TOTAL MOTOR EXAMINATION (TME) SCORES

TME scores improved between pre-implant and 12 months for both GPi and STN patients when assessed while ON medication with stimulation ON and when assessed while OFF medication with stimulation ON (Figures 5 and 6).

For the subset of patients whose data were verified against medical records:

- Symptoms of Parkinson's disease (TME scores) improved for 56/117 patients while ON medication;
- Symptoms of Parkinson's disease (TME scores) improved for 102/117 patients while OFF medication.

PATIENT DIARY RESULTS

"On" time improved between pre-implant and 12 months for GPi and STN patients (Figure 7). "On" time with dyskinesia decreased between pre-implant and 12 months for GPi and STN patients (Figure 8).

For the subset of patients whose data were verified against medical records:

- The duration of "on" time increased by an average of 6.7 hours in GPi patients and 6.1 hours in STN patients; and

- The duration of "on" time with dyskinesias decreased by an average of 4.2 hours in GPi patients and 2.8 hours in STN patients.

XII. Panel Recommendation

The FDA Neurological Device Advisory Panel held on March 31, 2002 recommended that Medtronic's PMA for the Activa® Parkinson's Control Therapy be approved with the following conditions:

- Provide physicians with instructions for use to assist in programming patients, including how to program and what parameters and electrode settings to program.
- Modify the indication statement to state "…advanced, levodopa-responsive Parkinson's disease that are not adequately controlled…".
- Conduct a three-year, long-term clinical follow-up study that includes assessment of cognitive and neuropsychological status.
- Revise wording in claims to replace "patient" with "advanced, levodopa-responsive Parkinson's disease patient".
- Delete the proposed claim #5 (reduction of medications in STN patients).
- Modify Claim #4 with the word "many", i.e., Activa Parkinson's Control Therapy allows ***many*** patients with Parkinson's disease to regain their independence and functional ability. (Note: This claim was deleted prior to approval).
- Add to labeling that the safety and effectiveness has not been demonstrated for patients with dementia or coagulopathies.
- Add to labeling that specific physician training on this procedure is recommended.

XIII. FDA Decision

Although there were a number of serious adverse events experienced by patients in this study, Parkinson's disease can be very disabling, both because of the "off" periods and also the dyskinesias patients can experience, related to medication treatment. Both of these components of the disease may worsen over time. The patients treated in this study had a Hoehn and Yahr stage 3 or worse in the "off" state; Unified Parkinson's Disease Rating Scale (UPDRS) motor exam score of 30 or more in the "off" state; and complications of levodopa therapy motor responses including motor fluctuations and dyskinesias. These patients have symptoms of advanced, levodopa-responsive Parkinson's disease that are not adequately controlled with medication. For this group of patients, FDA believes that the benefits outweigh the risks.

The FDA worked with Medtronic to modify the device labeling. These modifications incorporated the panel recommendations regarding indications and target population. The labeling included instructions for use as recommended by the panel. Labeling also indicates the need for physician training and experience. In addition, Medtronic has agreed to conduct a three-year post-approval study of the system to assess its long-term clinical results including cognitive and neuropsychological assessments.

In addition to addressing the panel issues, FDA worked with Medtronic to address all outstanding pre-clinical, clinical, and labeling concerns not addressed during the March 31, 2000 panel meeting. FDA has completed their review of the pre-clinical data, clinical data and the product labeling submitted to the PMA supplement as a result of the panel recommendations and additional FDA concerns. FDA has issued an approval order on January 14, 2002.

XIV. Approval Specifications

Directions For Use: See product labeling.

Hazards To Health From Use Of The Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the product labeling.

Post-Approval Requirements And Restrictions: See Approval Order