NeuroCybernetic Prosthesis (NCP®) Vagus Nerve Stimulation System
SUMMARY of SAFETY and EFFECTIVENESS DATA
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SUMMARY of SAFETY and EFFECTIVENESS DATA

1. GENERAL INFORMATION

Device Generic Name:

Stimulator, Vagus Nerve

Device Trade Names:

NeuroCybernetic Prosthesis (NCP®) System

Model 100 NCP® Generator

Model 200 NCP® Programming Wand

Model 250 NCP® Programming Software

Model 300 Series NCP® Vagus Nerve Stimulation Lead

Model 400 Tunneling Tool

NCP® System Accessories

Applicant's Name and Address:

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PMA Number:	P970003
Date of Panel Recommendation:	June 27, 1997
Date of Notice of Approval to the Applicant:	July 16, 1997

2. INTENDED USE/INDICATIONS

The NCP® system is indicated for use as an adjunctive therapy in reducing the frequency of seizures in adults and adolescents over 12 years of age with partial onset seizures, which are refractory to antiepileptic medications.

3. CONTRAINDICATIONS

The NCP® system cannot be used in patients after a bilateral or left cervical vagotomy.

4. WARNINGS and PRECAUTIONS

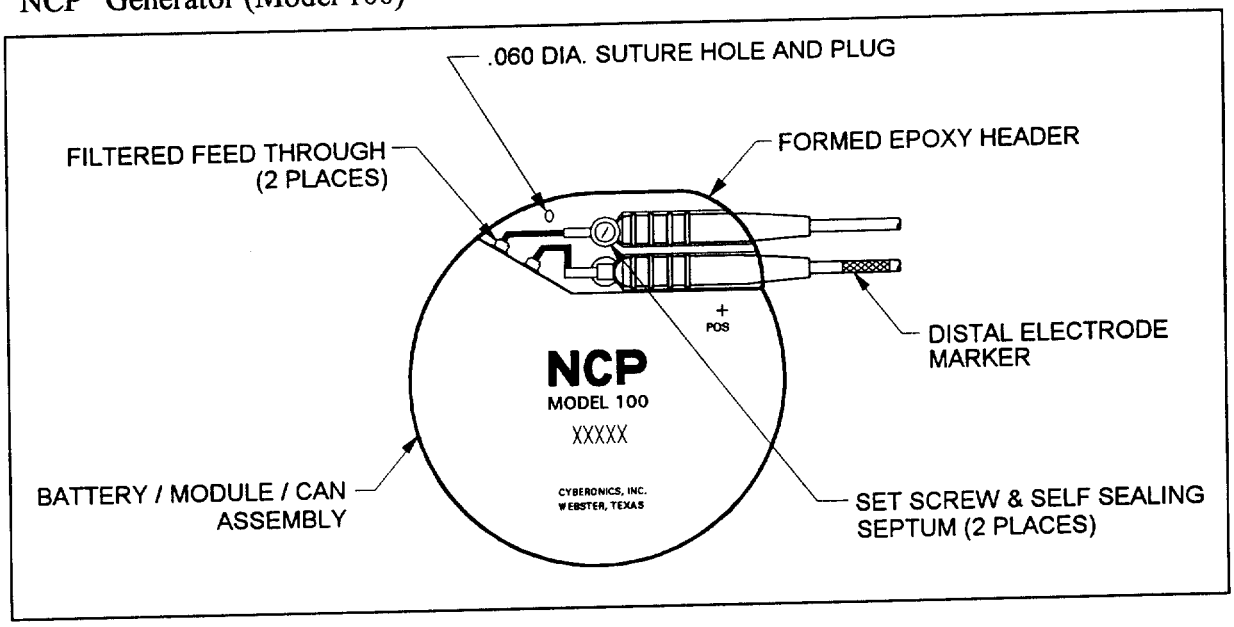
Same as final product labeling.

5. DEVICE DESCRIPTION

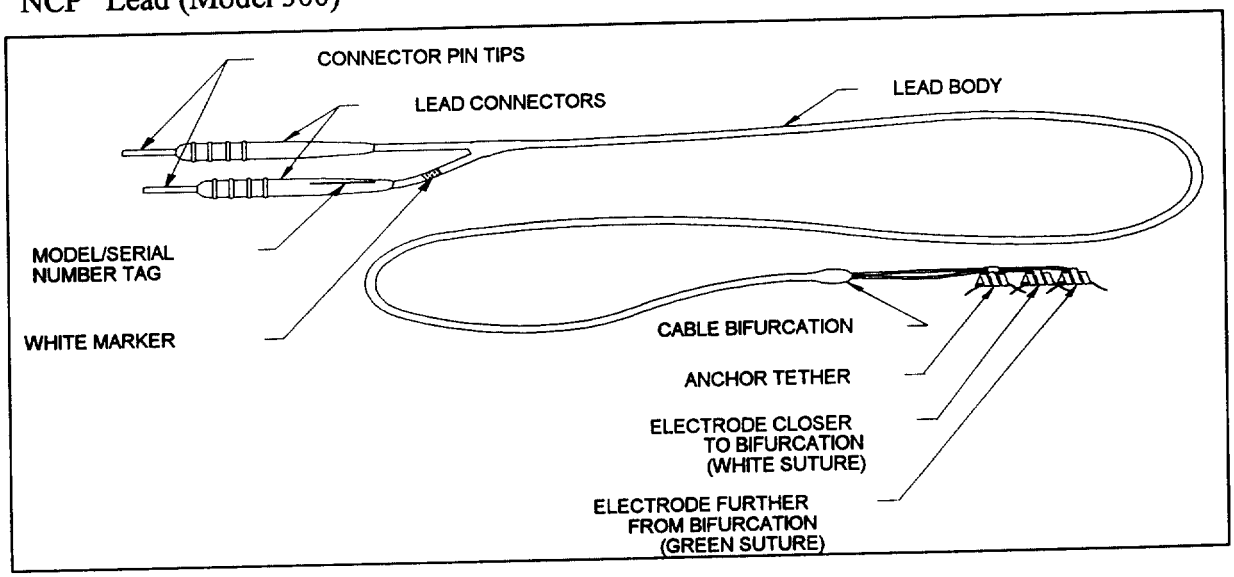
The NCP® System consists of the following components categorized into those implanted and peripheral components.

Implanted Components:

NCP® Generator (Model 100)

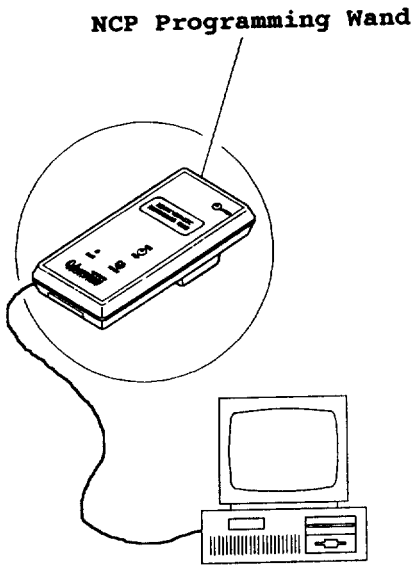


NCP® Lead (Model 300)



External Components:

NCP Programming Wand

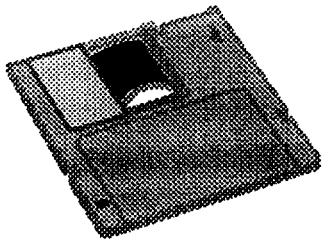


IBM Compatible Computer

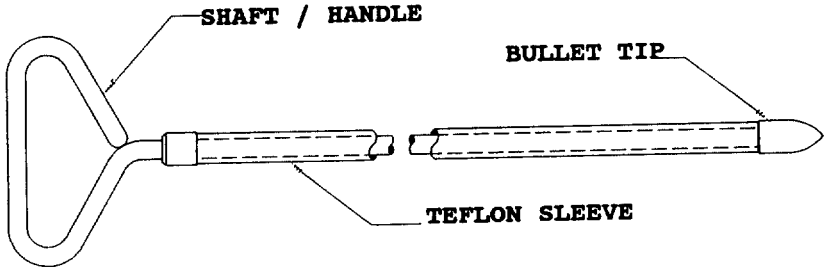
NCP Programming Wand
(Model 200)

NCP Programming Software
(Model 250)

NCP®



NCP Tuneling Tool
(Model 400)



Electrical signals are transmitted from the NCP® Generator to the vagus nerve via the Model 300 Series NCP® Lead. Peripheral components are used with an IBM-compatible personal computer to non-invasively activate, program, and retrieve information from the Generator. An NCP® Tunneling Tool (Model 400) is used during implantation to create a subcutaneous path for the Lead and is used in its placement as well.

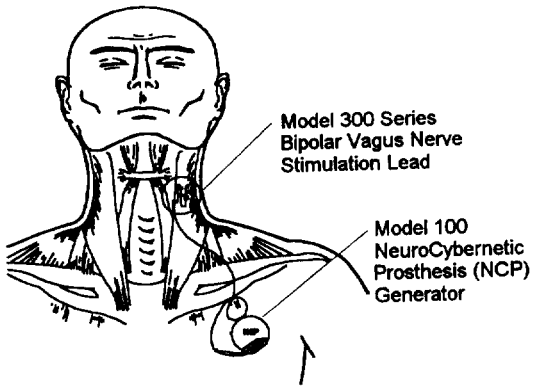


Figure 1. Placement of the Implanted Components of the NCP® System

The NCP® Generator, a device similar to a cardiac pacemaker, is surgically placed in the left chest. The NCP® Lead is connected to the Generator and attached to the left vagus nerve. Patients are provided with a hand held magnet which, by passing the magnet over the implanted NCP® Generator, can be used to manually activate the Generator to provide additional non-programmed stimulation in an effort to prevent or abort seizures and to test for battery status. Use of the magnet-activated stimulation is part of the NCP® System's prescribed treatment regimen. The magnet can also be used to deactivate (turn OFF) programmed stimulation by continuous placement of the magnet over the device. Programmed stimulation resumes when the magnet is removed.

5.1 NCP® Generator (Model 100)

The Model 100 NCP® Generator is an implantable, multiprogrammable pulse Generator that delivers electrical signals to the vagus nerve. Constant current, capacitively coupled, charge-balanced signals are transmitted from the Generator to the vagus nerve by the NCP® Lead (Model 300 Series).

The NCP® Generator is housed in a hermetically sealed titanium case. Feedthrough capacitors are used to filter electromagnetic interference from the Pulse Generator circuitry. The major components and functions of the Generator are as follows: a microprocessor, a voltage regulator, a 76.8 kHz crystal oscillator, one antenna to transmit information and another antenna to receive information, communication circuitry, DC-DC voltage generation and control circuitry, constant current control circuitry, a dual pole magnetic reed switch for manual activation of the Generator and for inhibition of the output pulses, and a lithium thionyl chloride cell to provide power for stimulation and circuit operation. The lithium thionyl chloride battery chemistry has the low impedance and high energy density characteristics required for the rapid pulsing needed in peripheral nerve stimulation, and similar batteries have been previously used in cardiac pacemakers, implantable spinal cord stimulators, and implantable drug pumps.

Therapy:

The NCP® Generator has a number of programmable settings which allow a physician to individualize the treatment for a patient. Those settings include pulse width, magnet-activated output current, normal output current, magnet-activated ON time, signal frequency, magnet-activated pulse width, signal ON time, and signal OFF time. The Applicant provides a magnet

that may be used to either manually initiate stimulation or to turn OFF the device. Device labeling instructs physicians to begin stimulation at the lowest output current settings possible (0.25 mA) and to ramp up stimulation to the desired level in 0.25 amp increments, never exceeding a level that is not tolerable to the patient.

Diagnostic and safety characteristics:

The NCP® Generator has telemetry capability which supplies information about its operating characteristics, such as parameter settings, lead impedance and history of magnet use. The Generator has a number of characteristics intended to strengthen operational reliability and safety, such as electromagnetic interference (EMI) filter capacitors, a series battery resistor to limit temperature rise in the event of short circuit, defibrillation protection diodes, direct current-blocking capacitors on both Leads that prevent direct current (DC) from being applied to the patient, a software watchdog timer to prevent continuous stimulation, and protection against voltage dips on the battery that could disrupt microprocessor memory.

5.2 NCP® Programming Wand (Model 200)

The NCP® Programming Wand (Model 200) is used with the NCP® Programming Software (Model 250) installed on a dedicated IBM-compatible personal computer to activate, program, reprogram and interrogate the NCP® Generator. The programming software is provided to the user on a 3.5-inch floppy disk. Capabilities include revision of the programmable parameters of the Generator, retrieval of telemetry data, and resetting of the Generator's microprocessor.

5.3 NCP® Programming Software (Model 250)

The NCP® Programming Software (Model 250) is a computer program which permits communication with an implanted NCP® Generator. The Programming Software is menu-driven and uses on-screen messages and prompts to assist the operator in using the system. Whenever the Programming Software is initialized, a self test is automatically run on the Software to verify checksum, file lengths, and file names. The programmed parameters and operational status can be interrogated. One or more parameters can be programmed at one time, and the programmed values are verified and displayed. The NCP® Programming System employs a strict communications protocol designed to minimize the possibility of "phantom" programming (i.e., inadvertent programming via environmental sources of electromagnetic interference or partial programming of a parameter). The Programming Software should be used on a computer dedicated only for programming the NCP® system. The Programming Software has been validated on a Compaq Contura Aero 4/25 running MS DOS 6.2 with the disk caching software disabled.

5.4 NCP® Vagus Nerve Stimulation Lead (Model 300 Series)

The Lead delivers electrical signals from the Generator to the vagus nerve. The Lead has two helical electrodes with a helical anchor tether on one end and two 5-millimeter (mm) connectors on the other end. The helix of the Lead is available in two sizes of inner diameter (2.0-mm and 3.0-mm) to allow for appropriate fit on different sized nerves. The helical design is soft, pliable, and expands or contracts with changes in nerve diameter, which may occur immediately post implant. These design features allow the 2-mm inside diameter helical electrode to fit most vagus

nerves. The Model 300 Series NCP® Lead is insulated with silicone rubber and is bifurcated at each end. The Lead wire is quadrifilar MP-35N, and the electrode is a platinum ribbon.

5.5 NCP® Tunneling Tool (Model 400)

An NCP® Tunneling Tool (Model 400) is used during implantation to create a subcutaneous path for the NCP® Lead and is used in its placement as well. The Tunneling Tool is supplied non-sterile with instruction to autoclave prior to use.

6. ALTERNATIVE PRACTICES AND PROCEDURES

A. Anti-Epileptic Drugs (AEDs)

The NCP® System clinical experience at the time of approval has been as an adjunctive treatment to anti-epileptic drug (AED) therapy. Additional anticonvulsant drugs are an alternative to treatment with vagus nerve stimulation using the NCP® System.

B. Therapeutic Resective Surgery

Epilepsy surgery may be an option for some patients. Generally less than two percent of the medically refractory patients undergo surgery each year in the U.S. The goal of resective seizure surgery is to excise a small area of brain tissue which contains a discrete seizure focus. Epilepsy surgery does have significant morbidity and mortality, including memory loss and stroke.

7. MARKETING HISTORY

On June 1, 1994, the applicant began commercial distribution of the NCP® System in Europe. The device has also been marketed in Australia, Switzerland, South Africa, Israel, China, Myanmar (Burma), Vietnam, Hungary, Hong Kong, and Canada.

The NCP® System has not been withdrawn from any country, for any reasons related to the safety or effectiveness of the device.

8. ADVERSE EVENTS

The NCP® System was implanted in 454 patients in five clinical studies involving 611 devices (some patients had Generator replacements). As of August, 1996, total NCP® exposure in these 454 patients was 901 device years. Individual patient exposure averaged 24 months with a range of 8 days to 89 months.

A total of 9 patients died during these five studies. One patient died from each: thrombotic thrombocytopenic purpura, drownings, aspiration pneumonia, pneumonia, and renal failure associated with drug and alcohol ingestion. No cause of death was apparent for the other four and they may be classified as Sudden Unexpected Death in Epilepsy (SUDEP). None of the deaths were attributed by the Investigators to the NCP® System.

8.1 Observed Adverse Events

Included among the five clinical trials were two randomized trials (Study E03 & E05) which involved 314 patients and implantation of 413 devices yielding a total NCP® System exposure

(inclusive of long term follow-up) of 591 years. These trials form the basis for the rates of observed adverse events.

Table 1 reports the adverse events from these studies during the Randomized Phase (14 week observation period) on a per patient basis. For the Extension Phase, events are reported on a per patient and per patient-year basis. The most common side effect associated with stimulation is hoarseness (voice alteration) during stimulation (hoarseness should only occur during the ON time). Most people tolerate the hoarseness well.

Table 1. Observed Adverse Events

(N=413 devices in 314 patients, 152 patients in HIGH treatment group, 591 device years)

	Randomized + Extension Phase, N= 314 patients, 591 device years				Randomized Phase, HIGH Only, N = 152 pts	
Adverse Event	**# of patients**	**% of patients**	**# of Events**	**Events per device-year**	**# of patients**	**% of patients**
Serious AEs[1]						
Surgically Related	13	4.1 %	13	0.022		
Stimulation Related	4	1.2 %	4	0.007	1	0.7 %
Non-serious AEs						
Voice Alteration	156	50%	720	1.228	91	60%
Cough Increased	129	41%	456	0.772	57	38%
Pharyngitis	84	27%	182	0.308	36	24%
Paresthesia	87	28%	377	0.638	32	21%
Dyspnea	55	18%	55	0.093	32	21%
Dyspepsia	36	12%	98	0.166	22	15%
Nausea	59	19%	154	0.261	21	14%
Laryngismus	10	3.2%	30	0.051	9	5.9%

1 - Serious AEs reported included infection, nerve paralysis, hypersthesia, facial paresis, left vocal chord paralysis, left facial paralysis, left hemidiaphragm paralysis, left recurrent laryngeal nerve injury, urinary retention, and low grade fever.

Status Epilepticus: Valid estimates of the incidence of treatment emergent status epilepticus among VNS treated patients are difficult to obtain because reporters participating in clinical trials did not all employ identical rules for identifying cases. At a minimum, 2 of 441 adult patients had episodes that could unequivocally be described as status. In addition, a number of reports of variably defined episodes of seizure exacerbation (e.g., seizure clusters, seizure flurries, etc.) were made.

Rebound after stimulation is stopped: Seizure frequency was monitored for one to four weeks after stimulation was stopped in 72 instances (68 patients) in Study E03. Seizure rate increased by greater than 1.5 standard deviations above baseline in 10% of instances (compared to 7% expected). Of these instances, 11 of 72 (15%) had a greater than 25% increase above baseline and 42 of 72 (58%) had a greater than 25% decrease in seizure rate.

8.2 Potential Adverse Events

Adverse events which may occur (including those reported in Table 1), reported in alphabetical order:

- Cough increased
- Dyspepsia, duodenal or gastric ulcer
- Dyspnea
- Facial paresis or paralysis
- Hemidiaphragm paralysis
- Hypesthesia
- Infection
- Laryngismus
- Muscle twitching during stimulation
- Nausea and vomiting
- Nerve injury
- Paresthesia
- Pharyngitis
- Voice alteration

Patients who manipulate the NCP® Pulse Generator and the Lead through the skin may damage or disconnect the Lead from the Pulse Generator and/or possibly cause damage to the vagus nerve.

Possible complications of NCP® System treatment include those related to implantation, those related to performance of the implanted Generator, and those related to long-term patient tolerance of the implant.

Except for Lead positioning, implantation of the NCP® Generator is similar to implantation of a cardiac pacemaker. In addition to the normal risks associated with a surgical procedure, complications associated with NCP® System implantation include, but may not be limited to, skin irritation; pain at the incision site; infection; extrusion or migration of the NCP® Generator and/or Lead; dislodgment, disconnection (Lead from Generator), breakage (Lead), or corrosion of the stimulating Lead; hematoma; fluid accumulation; cyst formation; inflammation; and histotoxic reactions. These phenomena may occur either acutely or chronically and may require device replacement to correct the complication.

Complications can include damage to the vagus nerve, either due to surgical trauma, compression by the electrode, or excessive stimulation. Hoarseness not associated with the stimulation suggests possible nerve irritation. Persistent hoarseness may be caused by nerve constriction, nerve fatigue, or Generator malfunction.

Normal stimulation of the vagus nerve and its branches may be associated with some side effects. In two randomized parallel controlled studies, a comparison between baseline rates of occurrence and treatment rates, for either HIGH or LOW, revealed the following adverse events (AEs) which had a statistically significant difference between periods in any study group: cough, dyspepsia, dyspnea, hoarseness/voice alteration, hypesthesia, infection, insomnia, laryngismus, non-specific pain, abdominal pain, paresthesia, pharyngitis, and vomiting.

The investigators reported that hoarseness, coughing, pharyngitis, and dyspnea were usually reported at the time of stimulation and were directly related to the strength of stimulation. Intolerable adverse events can generally be reduced or eliminated by a reduction in the output current, ON time, or increase in OFF time.

Most of the reported Study events were mild and well tolerated; very few clinical Study patients discontinued therapy due to side effects.

9. SUMMARY OF PRE-CLINICAL STUDIES

Pre-clinical Studies on Leads

The helical electrode component of the Leads used in the NCP® System was developed by Huntington Medical Research Institute (HMRI) and the National Institute of Neurological Disorders and Stroke (NINDS) Neural Prosthesis Program. A number of animal studies have been performed at HMRI that showed that damage associated with peripheral nerve stimulation is of two types: mechanical and electrical. Mechanical damage, manifest as connective tissue changes in the perineurium and epineurium, is apparently caused by physical trauma to the nerve, although a chemical interaction has not been ruled out. Mechanical damage can be minimized by pliable helical electrode arrays of the appropriate size which will not compress or otherwise traumatize the nerve, and by routing and stabilizing the Lead to minimize electrode movement on the nerve. Electrical damage results in changes to myelin and the axons it surrounds. Larger, more heavily myelinated axons are most susceptible. This type of damage can be minimized by lower stimulation frequencies, less total stimulation, and lower duty cycles.

9.1 Risk Analysis

The implantable portions of the NCP® System employ known implantable materials generally considered to be biocompatable and safe for permanent implant use. The Company has conducted a risk analysis which included a system hazard analysis, fault tree analysis, component reliability analysis, drift analysis and failure modes and effects analysis. The results of these and other evaluations provide evidence of the safety of the NCP® System.

9.2 Components Testing

Integrated circuits:

Each component was subjected to qualification tests by the Applicant. These tests include 1000-hour life testing, high temperature storage, temperature shock, exposure to high temperature/high humidity, for integrated circuits. All qualification tests were successfully completed.

Battery:

The Model 8602 battery has been subjected to a series of safety and qualification tests, including vibration, temperature cycling, hermeticity, low pressure, low temperature, high temperature, mechanical shock, soldering heat, high and low temperature storage, voltage reversal, incineration, impact shock, puncture at high velocity, slow dent and puncture, crush and recharge testing. No unexpected behavior of the cells was observed. Short-circuit behavior was also characterized; the cells did not explode or vent, but the cell temperature, measured at body temperature, rose from 37 to 60 °C under an extremely low impedance discharge path. The

Applicant added a 10-ohm current limit resistor to the Generator, which limited heating during a short to a negligible amount in qualification tests.

Feedthoughs:

The feedthrough utilized in the Model 100 NCP® Generator has undergone qualification testing in accordance with applicable portions of ASTM/ANSI Standard F18, ASTM F134-85, and MIL-STD 883B, which consisted of thermal shock, mechanical shock, vacuum bake, vibration, solvent resistance (ten samples), and terminal strength. All samples passed all test requirements.

9.3 Device Testing

Qualification testing was conducted to provide adequate data to support the intended use of the device system.

"Type testing" for CE Mark approval was conducted in accordance with prEN 45502-1:1993, Active Implantable Medical Devices and the requirements of Annex 1 and Annex 3 of the Commission of the European Communities Council Directive 90/385/EEC, amended by 93/42/EEC and 93/68/EEC.

Qualification tests were largely based on commonly recognized test methods and standards, such as military standards; International Standards Organization (ISO), European Standards (EN), European Committee for Standardization (CEN/CENELEC), and International Electrotechnical Commission (IEC) standards; American Society for Testing and Materials (ASTM), National Safe Transit Association (NSTA), Medical Device Standards (MDS), and United States Pharmacopeia (USP) standards; and others. More than 130 qualification tests have been performed on the devices or their components.

Model 100 Generator

The Model 100 NCP® Generator was evaluated using electrical, mechanical, electromagnetic interference, and firmware testing.

Electrical:

The electrical qualification tests consisted of

- Electrical characterization, End of Service characterization, and Communication Distance Characterization
- Direct Current leakage / Charge Balance per EN50051:1988,
- Electrosurgery Immunity - CENELEC "Standard for the Safety of Implantable Cardiac Pacemakers" (1986) and prEN45502-1 (May 1992),
- Defibrillation Immunity - prEN45502-1 (May 1992),
- Electromagnetic Interference (EMI) - EN50061:1988/prA1:1991; MDS201-0004 with modifications to testing facility and immunity levels: tested at 20V/m for frequencies from 20 MHz to 1 GHz and high field strengths at communication
- Electromagnetic Compatibility -MDS201-0004, IEC801-2 "Electromagnetic Compatibility for Industrial Process Measurement and Control Equipment, Part 2: Electrostatic Discharge (ESD) Requirements."

- Cellular phone (digital/GSM and analog) compatibility frequencies (including Cell Phone frequencies) of 450 MHz (386 V/m), 900 MHz (206 V/m), 1.45 GHz (213 V/m), and 1.9 GHz (96 V/m).
- Magnetic Resonance Imaging (MRI) compatibility -should not be done with the MR body coil. MRI should only be done using a head coil.

Mechanical

The mechanical qualification tests consisted of the following:

- Temperature Cycle - prEN45502-1 (MAY 1992), Sec. 27.1
- Shock - prEN45502-1 (MAY 1992), Sec. 24.1
- Vibration - prEN45502-1 (MAY 1992), Sec. 24.2
- Diagnostic Ultrasound - prEN45502-1 (MAY 1992), Sec. 23.1
- Gross Leak - prEN45502-1 (MAY 1992), Sec. 26.1
- Fine Leak - Helium Leak Test performed 100% in production
- Wet Rub - prEN45502-1 (MAY 1992), Sec. 14.1
- Header Adhesion - (Header sheer test, strength exceeds 50 lb.)
- Header Seal (Isolation) - prEN45502-1 (MAY 1992), Sec. 16.1
- Shipping Shock - (NSTA - 30 inch drop onto each box corner and face)
- Shipping Vibration - (NSTA - 14,200 vibratory impacts)
- Shipping Atmosphere Pressure Changes - prEN45502-1, Sec. 12.1
- Wet Wipe - prEN45502-1 (MAY 1992), Sec. 9
- Shipping Humidity - prEN45502-1 (MAY 1992), Sec. 10.1

The Model 100 Generator performed under all conditions in accordance with its design specifications.

Model 300 Series Lead

The Model 300 Series Lead was evaluated by electrical and mechanical testing.

Electrical

- Electrode electrical characterization, V_I and dV/dt pre and post sterilization
- Lead tubing leakage current - (3 month soak at +75C in saline).

Mechanical

- Lead Dielectric - prEN45502-1, Sec, 16.2 ,
- Lead Tensile (Mandrel Wrap) - prEN45502-1, Sec, 24.3,
- Flexural Fatigue - prEN45502-1, Sec, 24.4,
- Connector Integrity - prEN45502-1, Sec, 24.5,
- Connector Insertion/Extraction Force, (5 kg force)
- Repeated Insertion, (10 cycles), Lead fatigue with tether, (10^{+7} cycles), Lead fatigue without tether, (10^{+7} cycles),
- Electrode weld pull test - (Shear pull to destruction - 310 to 540 g),
- Lead connector crimp pull test - (Pull to destruction - 0.90 to 1.05 Kg),
- Tubing bond pull test - (Pull to destruction 10 assemblies - 1.0-1.5 Kg),

- Other tests: Connector leak test - 10 psi, Lead Connector Crimp Pull Test, Connector Leak Test, Tubing Bond Pull Test, Electrode Weld Pull Test, Electrode Fatigue, Electrode Helix Force, Electrode Anchor Tether Pull-Off (90°), and Electrode Pull Test (axial)
- MRI Compatibility

The Model 300 Series Lead performed under all conditions in accordance with its design specifications. However, exposure to MRI resulted in excess heating of the electrode whenever the exposed Lead length was greater than 10 cm, when it was positioned against the outer bore of the MRI instrument and when worst case scan conditions were used. No heating was observed under worst case conditions of a fully extended Lead, when the Lead was positioned in the center of the bore, or in any position for a Lead shortened to 10 cm. Final product labeling included the following PRECAUTION:

> **Magnetic Resonance Imaging** (MRI) should not be done with the MR body coil. The heat induced in the leads by a body MRI scan can cause injury. MRI should only be done using a head coil. Conditions which have been tested include:
>
> - Transmit and Receive coil type: Head Coil Only
> - Static Magnetic Field Strength: ≤ 2.0 Tesla
> - SAR: < 1.3 W/kg for 70 kg patient
> - Time varying intensity < 10 Tesla /sec

Model 200 Programming Wand

The Model 200 Programming Wand was evaluated by electrical and mechanical testing.

Electrical:

- Electrical Characterization,
- Maximum Programming Distance,
- Evoked Potential Adapter Qualification,
- Electromagnetic Interference (EMI),
- Magnetic Field Susceptibility - 30 Hz to 100 kHz per requirements of RS101 MIL-STD 461D,
- Magnetic Field Emissions - magnetic field emissions testing per requirements of RE101 MIL-STD 461D.
- Quasi Static Electric Field - sinusoidially varying electric field at 0.5 Hz with field strengths of 500 V/m to 2000 V/m per requirements of FDA Reviewer Guidance document.
- Electric Field Susceptibility - radiated electromagnetic energy field rated at 3 V/m as specified in the requirements of IEC 801-3 and the FDA Reviewer Guidance documents.
- Fast Transient Burst - transients of 0.25, 0.50, and 1 kV coupled by way of a capacitive clamp to the signal Leads per requirements of IEC 801-4 and the Reviewer Guidance documents.
- Conducted Susceptibility - conducted electromagnetic energy as specified in CS114, of MIL-STD-461D and the FDA Reviewer Guidance documents.
- Radiated Emissions - conducted and radiated emissions testing per requirements of CISPR 11.

Mechanical:

- Temperature Cycle - prEN45502-1, Sec. 27.1, (-20 °C to 55 °C, 2 cycles)

- Free Fall Test - prEN45502-1, Sec. 24.1 (3 ft drop)
- Vibration - prEN45502-1, Sec. 24.2, Wet Wipe - prEN45502-1, Sec. 11
- Shipping Shock - (NSTA - 30 inch drop), Shipping Vibration - (NSTA - 14,200 vibratory impacts)

The Model 200 Programming Wand performed under all conditions in accordance with its design specifications.

Model 250 Programming Software

The Applicant has carried out extensive development, evaluation and testing of the software in the NCP® System.

A software development procedure which governs the creation, development, review, testing, documentation, manufacturing release, discrepancy reporting and maintenance of the software products in the NCP® System was used. The Model 250 Programming Software and the Model 100 Generator software were verified and validated to perform in accordance with their requirement specifications.

Model 400 Tunneling Tool

The Model 400 Tunneling Tool was evaluated by mechanical testing.

- non-destructive shear testing - (14 lb.)
- destructive pull testing of the bullet/shaft connection (230 lb.)

The Model 400 Tunneling Tool performed under all conditions in accordance with its design specifications.

9.4 Biocompatability

The following testing has been conducted for all tissue contacting materials used in the Model 100 Generator and Model 300 Lead:

- Cytotoxicity (MEM elution method), Sensitization
- Intracutaneous reactivity, Systemic toxicity, acute (USP method)
- Pyrogenicity (USP method), Genotoxicity (Ames mutagenicity test) subcutaneous implant (USP method, rat model) for fourteen, thirty, and one hundred-five days duration, with investigation of histology and systemic effects

The results of these tests showed that the materials used in the Applicant's implantable products, as processed by and for them, are biocompatable, non-toxic, and non-pyrogenic.

9.5 Sterilization and Shelf Life Testing:

The ethylene oxide sterilization process was validated. Testing was performed to evaluate the effectiveness of the recommended steam autoclave sterilization method for the Model 400 Tunneling Tool. The shelf life of the sterile product was validated for a period of two years.

9.6 Animal Testing

Animal studies pertaining to vagus nerve stimulation can be divided into those dealing primarily with efficacy and those related to safety.

9.6.1 Animal Efficacy Studies

Animal models of epilepsy have been used to evaluate the efficacy of vagus nerve stimulation (VNS). A dog model was used to demonstrate the feasibility of vagus nerve stimulation to inhibit strychnine-induced seizures.

A second feasibility study, used the rhesus monkey to study the effects of vagus nerve stimulation on focal seizures induced by alumina gel. Long-term seizure frequency was reduced when the vagus nerve stimulation was delivered during a seizure in two of the four monkeys with alumina gel induced epilepsy. In the other two, seizures continued but became synchronous in time, i.e., they appeared at regular intervals. The protective effect observed during stimulation was found to be maintained for weeks when the therapy was discontinued, suggesting a carry over effect.

Three groups of investigators used rat models of epilepsy to investigate the effect of vagus nerve stimulation on seizures. One group used pentylenetetrazol (PTZ), 3-mercaptopropionic acid (3-MP), and maximal electroshock (MES) to induce seizures in rats. Another used a penicillin induced seizure model in rats to study the effects of vagus nerve stimulation on interictal spiking. The third group, used the kindling and PTZ models. These rat models are also used to evaluate potential AEDs.

Using the PTZ model, it was reported that vagus nerve stimulation affected two seizure phenomena: mild status epilepticus and discrete intense seizures. Muscle activity associated with status epilepticus was suppressed when enough current was delivered to recruit the vagus nerve C fibers and depress heart rate and respiration. Discrete seizures could be prevented by vagal stimulation, but not stopped once they started. Also using the PTZ model, another group reported that efficacy was proportionally dependent on the cumulative time of stimulation and that the inhibitory effect of stimulation decreases gradually after cessation of stimulation.

Using the MES model, it was reported that vagus nerve stimulation can abolish or reduce the tonic component of the convulsive response. The degree of inhibition was related to the fraction of C fibers stimulated and the frequency of stimulation (as measured by heart rate depression).

The effects of vagus nerve stimulation on seizures in rats produced by intraperitoneal injection of 3-MP appeared to be variable.

With penicillin induced seizures in the rat, VNS significantly reduced interictal spike frequency, and the spiking frequency remained lower for about three minutes after cessation of stimulation at levels which also reduced heart rate and respiration.

In the kindled rat model, VNS reduced seizure duration, and the amount of reduction was dependent on duration of stimulation prior to the seizure.

Overall, studies with a number of animal models for human seizure, which are also used to evaluate efficacy of AEDs, showed that the effect of vagus stimulation can be detected in various brain structures, that vagus nerve stimulation decreases the frequency and/or duration of seizures and that the effect is related to stimulation parameters and timing. These studies, however, did not determine whether these effects are specific to stimulation of the vagus nerve, and whether they are secondary to depressed heart rate and respiration.

9.6.2 Animal Safety Studies

Two safety studies were performed in monkeys and one was performed in sheep. In the first of these, the effect of a titanium cuff electrode on the vagus nerve of monkeys was examined. The effect of vagus nerve stimulation on cardiac and gastric function was also examined. Of the five animals implanted, two received 72 hours of stimulation without evidence of clinically significant effects on the stomach lining, and no pro-arrhythmic cardiac changes were observed.

In the second monkey safety study, spiral platinum electrodes were used. Six animals were exposed to electrodes for a minimum of 14 weeks and received at least 72 hours of 143 Hz, 50% duty cycle stimulation. Cardiovascular system effects included transient asystole and bradycardia. No stomach ulcerations were found. Histological analysis of the nerves indicated that stimulation with the spiral electrode did not result in electrical damage, and no mechanical damage to the nerve occurred in subjects in which proper electrode placement was achieved through adequate strain relief on the lead. Compression damage to large axons was found in 2 of the 4 experimental animals.

The effects of stimulation of the vagus nerve of sheep was studied in nine animals. Nerves from three of the animals which had been exposed to the system for at least ten months and which had received at least three months of stimulation were harvested. No evidence of nerve fiber degeneration, regeneration, or injury was present in any of the nerves analyzed, whether or not the nerve was stimulated. In all three animals studied for histology, epineural fibrosis and fatty infiltration of the nerve was found.

Overall, studies in animals indicate that stimulation of the vagus nerve may be conducted safely, with no damage to the axons of the vagus nerve. The spiral electrode design used in the NCP® System appears to be appropriate for chronic therapy.

10. SUMMARY OF CLINICAL STUDIES

Five acute phase studies were conducted. All patients that exited the acute phase studies were also followed in two long-term follow-up studies. The total stimulation exposure during these studies is greater than 900 patient years.

10.1 Design and Methods

10.1.1 Objective of studies

The overall objective of the clinical trial program was to collect clinical data regarding the NCP® System as an implantable vagus nerve stimulator indicated for use as adjunctive therapy in patients with medically refractory partial onset seizures.

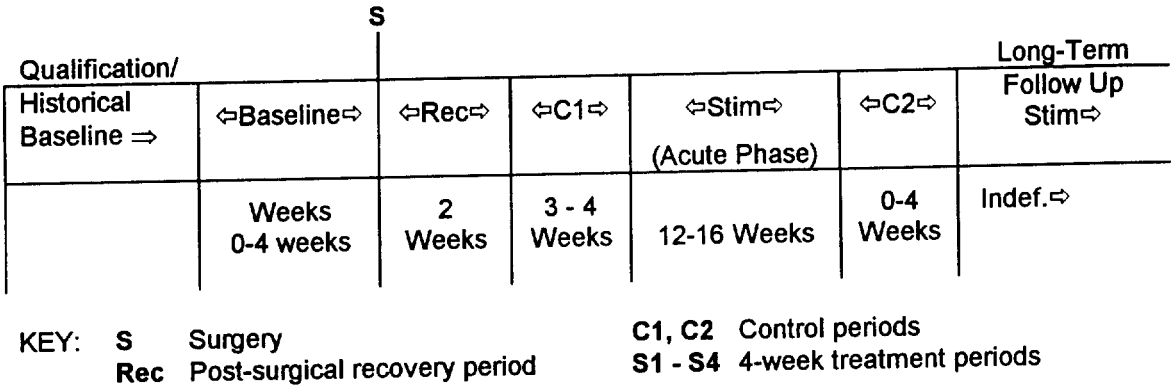
The primary objective of the studies was to demonstrate a between group difference in mean and/or median percent change in seizure frequency between patients treated with "High" stimulation (optimal stimulation for seizure reduction) and "Low" stimulation (not expected to result in as great a seizure reduction).

Secondary objectives included the effect of VNS on within group (High *vs.* Low) changes in seizure frequency, response rates, number of seizure-free days, seizure intensity and duration, global evaluations by patients, caregivers and investigators and QOL measures.

10.1.2 Design of studies

Two of the studies (E01 and E02) were multicenter pilot studies, one (E04) was an open-label controlled longitudinal study, and two of the studies (E03 and E05) were multicenter, prospectively randomized, double blinded, parallel, active control studies. In the studies, treatment was adjunctive to AEDs; in E03 and E05, AEDs were to be held constant.

Figure 2. E01, E02, E04 Study Designs and Timelines

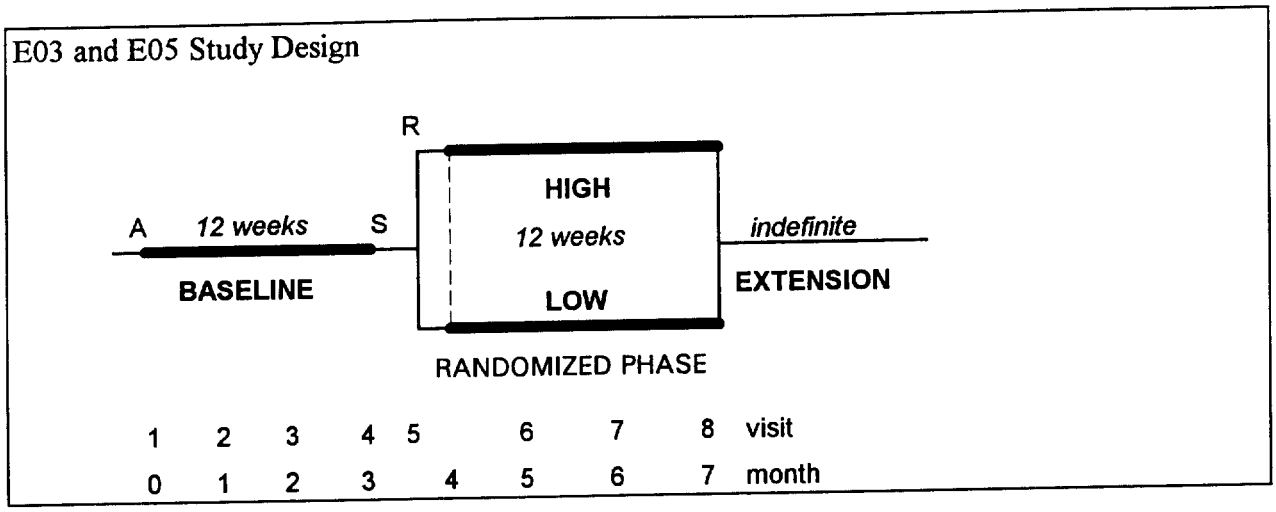


KEY: **S** Surgery
Rec Post-surgical recovery period
C1, C2 Control periods
S1 - S4 4-week treatment periods

Analysis of the E01 and E02 acute phase mean percent seizure frequency reduction was based on the average mean percent change in seizure frequency over the Acute Phase Stimulation (16 weeks) in comparison to the first placebo stimulation control period (C1). Analysis of the E04 acute phase mean percent seizure frequency reduction was based on the average mean percent change in seizure frequency over the Acute Phase Stimulation (12 weeks) in comparison to the pre-implant Baseline Period

$$\textit{Patient's \% Change} = \frac{\textit{[seizure frequency/day]treatment -[seizure frequency/day]Baseline x 100}}{\textit{[seizure frequency/day]Baseline}}$$

Figure 3. E03, E05 Study Designs and Timelines



A = Admission S = Surgery R = Randomize

For E05, V6 was after two weeks of stimulation, followed by V7, V8, and V9 corresponding to V6, V7, and V8 in E03.

Analysis of the E03 and E05 acute phase seizure frequency reduction was based on the difference in the average mean and median percent change in seizure frequency for the HIGH Group vs. the LOW Group over the first three stimulation periods (12 weeks) in comparison with the 12 week baseline period.

Analysis of the Long Term Follow-up Study (for Studies E01 through E04) and XE5 Study seizure frequency was based on the difference in the average mean and median percent change in seizure frequency over the three stimulation periods ending at 6, 9 (XE5 only), 12, 18, 24, and 36 months in comparison with the control period used in the respective acute phase studies.

The following stimulation parameters were used in the Studies.

Table 2. Protocol Stimulation Parameters

Parameter	STUDY						
	E01	E02	E04	E03 HIGH (LOW)	E05 HIGH (LOW)	XE1-4	XE5 3 mo. (Longer)
CURR (mA)	1 - 6	0.5 to 5	≤ 1	0.5 - 3.0	3.5	0-12	0-3.5
FREQ (Hz)	≤ 50	20 to 50	30	20 - 50 (1 to 2)	30 (1)	1-143	20 (1-30)
PW (μsec)	250	250 to 500	500	500 (130)	500 (130)	130-1000	750 (130-1000)
ON (sec)	60	30 to 60	30	30 - 90 (30)	30 (30)	7-270	30 (7-60)
OFF (min)	60	5 to 20	10	5 (90)	5 (180)	0.2-180	1.8 (1.1-180)

The parameters used in Studies E03, E04, and E05 were similar, whereas Studies E01 and E02 used higher frequencies, longer OFF times and shorter pulse widths.

10.1.3 Statistical methods

Standard statistical tests were used in comparing changes in seizure frequency between stimulation and control or baseline periods for Studies E01, E02, and E04 between and within HIGH and LOW stimulation groups for E03 and E05. The statistical test employed most extensively in E03 was the Student's t-test with the Wilcoxon rank-sum test used as a corroborative non-parametric test. Fisher's exact test was used to compare equality of proportions between HIGH and LOW stimulation groups. All tests were two-tailed and normality assumptions were checked as required.

E05 was analyzed in essentially the same manner as E03, with the exception that different statistical tests were applied. The null hypothesis that the two treatment percent changes are equal was tested using an extended Mantel-Haenszel test with modified ridit scoring of this ordinal outcome. The ranking for the modified-ridits is done for all patients from all sites after adjustment for investigative site through the subtraction of the means for the sites.

As a supplementary parametric analysis, analysis of variance (ANOVA) techniques were carried out to analyze between-treatment group comparisons of percent change in mean seizure frequency. One ANOVA model had treatment, investigative site, and treatment-by investigative site as independent variables. A second model additionally included baseline seizure frequency as a covariate and a baseline seizure frequency-by-treatment interaction term. Treatment-by investigative site interaction was addressed in the ANOVA models even though the primary method for comparing treatments is a non-parametric extended Mantel-Haenszel test.

All hypothesis tests were two-sided with an alpha of 0.05. Statistical significance was determined by p-values less than 0.05. A p-value between 0.05 and 0.10 was considered marginally statistically significant.

10.1.4 Patient Population and Collection Criteria

The final Inclusion and exclusion criteria were similar for each study.

Table 3. Inclusion Criteria

INCLUSION CRITERIA	E01	E02	E03	E04	E05
Age	18-60	18-60	12-60	2*-60	12-65
Seizure type	SPS, CPS	SPS, CPS, 2ND	SPS, CPS, 2ND	ALL TYPES	SPS, CPS, 2ND
# AED's	1-2	1-2	0-3	Not Specified	1-3
Good physical and health	yes	yes	Not Specified	Not Specified	Yes
Mental ability	IQ>80	IQ>80	Ability to understand IC, patient or guardian	Ability to understand IC, patient or guardian	Ability to understand IC, patient or guardian
Steady state serum levels	Yes	Yes, 1 month prior to study	Yes, +/- 20% over 3 months	Not Required	Yes, +/- 20% over 3 months
Seizure rate	6/mo.	6/mo	6/mo	1/mo	6/mo with AOC
Max seizure free interval	14 days	14 days	14 days	None Specified	21 days
Women with acceptable birth control	Not Specified	Not Specified	Yes	Not Specified	Yes
Ability of patient or caregiver to accurately record seizures	Implied	Implied	Implied	Implied	Yes

Table 4. Exclusion Criteria

Exclusion Criteria	E01	E02	E03	E04	E05
Living alone	Yes	Yes	Not Specified	Not Specified	Not Specified
Ulcers	Yes	Yes	Not Specified	Not Specified	Yes, peptic
Diabetic	Yes	Yes	Not Specified	Not Specified	Not Specified
Prior cervical vagotomy	Yes	Yes	Yes	Yes	Yes
Significant heart, lung or chronic bowel	Yes (heart and lung)	Yes	Yes (heart and lung)	Not Specified	Yes (heart and lung)
Medical condition likely to deteriorate	Yes	Yes	Yes	Yes	Yes
Investigational drugs	Not Specified	Not Specified	within 2 wk. + 5X half life	Not Specified	Within 2 wk. + 5X half life
History of pseudo seizures	Implied	Implied	Implied	Not Specified	Yes

E05 patients were excluded for prior VNS treatment or any other stimulation treatment for epilepsy, as well as prior resective surgery for epilepsy. E05 patients were also excluded if they had experienced more than two episodes of status epilepticus within the last year.

* E04: Patients under 12 years old had to meet the following additional criteria:

    1. During the last five years (or over lifetime if younger) at least three anticonvulsants must have been tried (alone or in combination) to control seizures.
    2. The Investigator and family must be of the opinion (and Investigator must so document in the chart) that seizures and/or drug side effects are detrimental to the patient.
    3. Admission must first be discussed with the Applicant's staff and approval given on a case by case basis. The purpose of this condition is to provide Investigators and family with all current information, so that the best risk/benefit decision can be made for the patient.

The important differences in the inclusion/exclusion criteria are:

- E05 excluded patients with resective surgery and required patients to have at least 6 seizures/month with AOC.
- E04 included patients with all types of seizures and allowed children down to 2 years of age.

10.2 Description of Patients Studied and analyses for Gender Bias

10.2.1 Patients Studied

Overall the populations across Studies was comparable as displayed in Table 4.

Table 5. Description of Study Patients

Study No.	Group	Number of Patients	Gender	Average Age, Range	Average Years with Epilepsy, Range	Seizures/ Day	Ave. No. AEDs
E01	—	11	7 M, 4 F	31.6 (20-58)	22.2 (13-32)	2.95 mean 0.70 median	1.0
E02	—	5	3 M, 2 F	33.0 (18-42)	20.3 (5-36)	0.44 mean 0.44 median	1.0
E04	—	124	67 M, 57 F	23.9 (3.6-63)	17.4 (0.8-48)	25.2 mean 0.65 median	2.2
E03	HIGH	57	35 M, 22 F	32.9 (20-57)	22.4 (6-47)	1.45 mean, 0.7 median	2.1
	LOW	57	36 M, 21 F	33.7 (13-50)	20.5 (4-44)	1.76 mean, 0.85 median	2.1
E05	HIGH	95	49 M, 46 F	32.1 (13 - 54)	22.1 (2 - 52)	1.59 mean, 0.58 median	2.2
	LOW	103	44 M, 59 F	34.2 (15 - 60)	23.7 (2 - 48)	0.97 mean, 0.51 median	2.1

Table 6. Description of Clinical Studies

All patients enrolled in all clinical studies, N=537

Study	E01	E02	E04	E03	E05	Total
Type of Study	Pilot Longitudinal	Pilot Longitudinal	Open Longitudinal	Randomized Parallel High/Low	Randomized Parallel High/Low	-
Patients Enrolled	11	5	133	126	262	537
# Centers [a]	3	2	24	17	20	45
Reference (baseline) period	Weeks 2 through 4	Weeks 3 through 6	Weeks -4 through 0	Weeks -12 through 0	Weeks -12 through 0	-
Seizure Type	Partial	Partial	All types	Partial	Partial	-
Num. AEDs	1 to 2	1 to 2	not specified	0 to 3	1 to 3	-

a Total includes OUS centers (Canada, Holland, Germany 2, and Sweden), several US centers participated in more than one study

10.2.2 Gender Bias

Inclusion and exclusion criteria were designed and carried out to avoid gender bias in patient enrollment. Of all patients enrolled 254 of 454 (54%) were male. This proportion (254/210 =1.21) of males is consistent with the male to female incidence (1.1 to 1.7) for nonfebrile epilepsy.[1]

Separate analyses of safety and effectiveness data for males and females indicated no differences between the genders; hence, the results presented in the following analyses are representative for both men and women.

10.3 Results – Effectiveness and Safety

10.3.1 Effectiveness

The following table provides efficacy data for all studies. The mean percent reduction in seizure frequency is consistent across all studies except E04. E03, E04 and E05 studies established efficacy with statistical significance, however, two interim analyses were performed on the E03 data.

The median reduction in seizure frequency in the trials consistently improved over time. However, this data is uncontrolled and may be due to changes in drug therapy, rather than VNS.

Study E03 enrolled 115 patients, one patient dropped out prior to randomization/stimulation of the device and is not included in the efficacy tables below leaving an N=114. Study E05 enrolled 254 patients and had 55 baseline failures. In addition, 1 patient was explanted prior to randomization/stimulation of the device, 1 patient was excluded due to unreliable seizure diary counts, and 1 patient dropped from the study prior to collection of any effectiveness data leaving an N=196. All randomized/stimulated patients are included in the safety tables which follow.

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[1] page 16 in: Hauser WA, Hesdorffer DC: Epilepsy: Frequency, Causes and Consequences. Demos Publications, New York, 1990, 378 pages.

There was no statistically significant change in seizure intensity or seizure duration in either the E03 or E05 Studies.

Table 7. Seizure Rate Changes

ACUTE CHANGE IN SEIZURE FREQUENCY					EXTENSION PHASE FOLLOW-UP N, MEDIAN PERCENT SEIZURE REDUCTION				
Study	N	Mean % Seizure Reduc-tion	Median % Seizure Reduc-tion	Between Group Means p Value	6 MO	12 MO	18 MO	24 MO	36 MO
E01	10	24.3%	31.6%	N/A	10 41.90	10 43.43	10 46.19	8 58.69	4 64.84
E02	4	39.9%,	48.1%	N/A	4 3.01	4 30.04	3 67.64	2 60.32	2 31.88
E04	116	7%	21.8%	N/A	107 32.46	86 26.81	72 41.41	34 32.18	Insufficient data
E03 HIGH	57	23.6%	22.6%	0.0175	108 26.84	102 32.51	71 45.79	51 40.74	49 40.42
E03 LOW	57	6.4%	6.3%						
E05 HIGH	94	27.9%	23.4%	0.0396	89 32.5	40 34.2 (9 mo.)	N/A N/A	0	0
E05 LOW	102	15.2%	20.5%						
E01 E04 Pooled	244	11.8%	17.1%	N/A	229 29.75%	202 31.31%	156 44.25%	95 40.74%	55 40.42%
Total N for effic calcula tion	440	N/A	N/A	N/A	318	242	156	95	55

NS = Not Significant *N/A = Not Applicable*

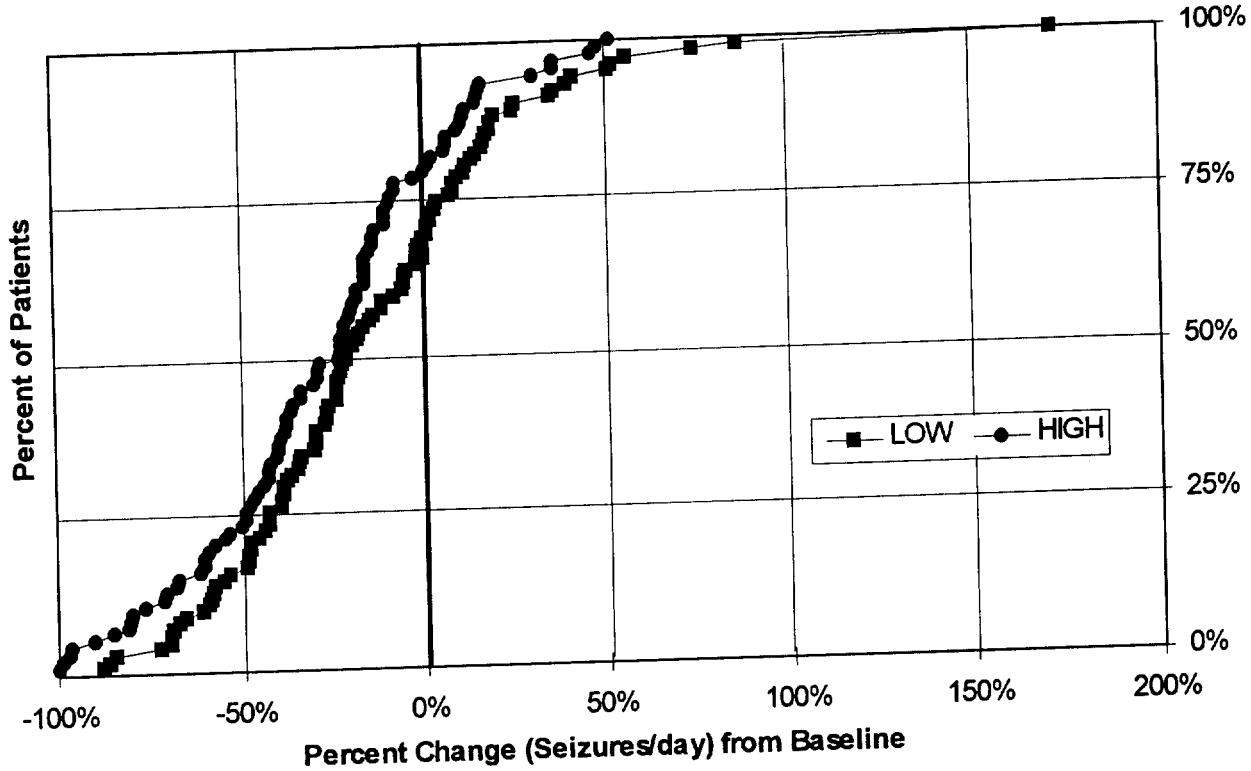
Table 8. Responder Rates

ACUTE Responder Rate (% pts >50% Reduction)				LONG TERM FOLLOWUP Responder Rate (% pts >50% Reduction)				
Study	N	Responder Rate	Betw'n Group p Value	6 MO	12 MO	18 MO	24 MO	36 MO
E01	10	30%		20% (2/10)	30% (3/10)	50% (5/10)	63% (5/8)	50% (2/4)
E02	4	50%	NA	25% (1/4)	25% (1/4)	67% (2/3)	100% (2/2)	0% (0/2)
E04	116	29.3%		37% (40/107)	31% (27/86)	39% (28/72)	35% (12/34)	na
E03HIGH	57	29.8%	0.042	26% (28/108)	31% (32/102)	45% (32/71)	39% (20/51)	39% (19/49)
E03LOW	57	14.0%		NA	NA	NA	NA	NA
E05HIGH	94	23.4%	0.171	39.3%	40%	NA	NA	NA
E05LOW	102	15.6%			(9 mo.)			
E01E04 Pooled	244	25%	NA	31.4%	31.2%	42.9%	41.1%	38.2%

N/A = Not Applicable

Figure 4. Change in Seizure Frequency, Patient Distribution

All Patients Completing Effectiveness Evaluation, N=196



	Percent Change (seizures/day) from Baseline		
	HIGH	LOW	Difference
N	94	102	196
Median	-23%	-21%	n/a
25%, 75% Quartiles	-8.9%, -49%	4.0%, -43%	n/a
95% Confidence Intervals	-35%, -21%	-23%, -7.7%	-23%, -2.3%
Range (min, max)	-100%, 52%	- 89%, 171%	-23%, -2.3%
Mean ± SD	-28% ± 34%	-15% ± 39%	-13%* ± 37%

* Difference statistically significant ($p<0.05$) by Analysis of Variance ($p=0.032$) and by Cochran-Mantel-Haenszel Aligned Ranks ($p=0.040$)

Table 9. Patient Summary Chart:
Patients Continuing Treatment as of August 22, 1996

STUDY PERIOD	E01	E02	E03	E04	Total
Patients Randomized/Stimulated (N)	10	5	114	123	253
Patients (N) Entering Extension Phase	10	5	113	123	251
Total continuing patients being treated for up to one year (N)	10/10	5/5	111/115	112/121[4]	238/251
Continuing patients being treated for up to two years (N)	9/10	4/5	71/87[1]	58[2]/70	142/173
Continuing patients being treated for up to three years (N)	7/10	3/5	57/87	21[3]/24	88/127

(1) Twenty eight (N=28) commercial European patients were excluded from follow-up after one year of treatment due to the commercial release of the NCP® system in those countries.

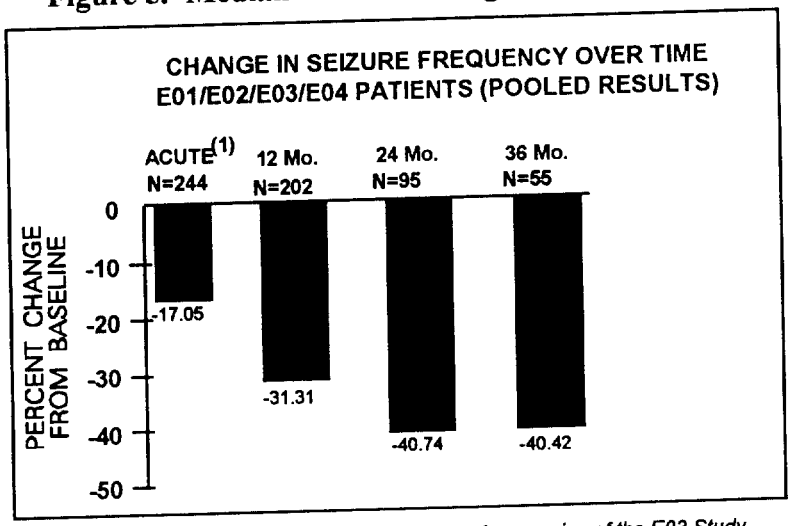
(2) As of 8/22/96. Only 70 patients had been implanted long enough to reach the 2 year treatment period; only 58 of the 70 were continuing.

(3) As of 8/22/96, Only 24 patients had been implanted long enough to reach the 3 year treatment period; only 21 of the 24 were continuing.

(4) Two of the original 123 patients entering the extension phase had been implanted for less than one year as of 8/22/96.

A total of 238 out of a possible 251 completed one year of therapy (95%); 142 out of 172 completed two years of therapy (83%); and 88 out of 126 completed three years of therapy (70%). Although these numbers of patients remained in the study, only those patients who had completed the annual follow up visits are represented in the above efficacy calculations. NCP® System treatment did not cause changes in AED plasma concentrations as measured during studies E03 and E05.

Figure 5. Median Percent Change in Seizure Frequency



(1) Note: The acute phase results include seizure frequencies of the E03 Study LOW stimulation group, which includes one-half of the E03 patients, N=57

Patients were permitted to change their AEDs during these studies and these changes may have contributed to the change in seizure frequency.

Pediatric Patients

Study E05 allowed patients as young as 12 years to enter the study. There were 20 patients in the E05 Study between 12 and 18. Their response during the Study was a 22.5% median reduction and a 26.2% mean reduction in seizures compared to baseline.

Global Rating

Global ratings by Investigators and patients support the conclusion that HIGH stimulation is associated with an improved quality of life, although improvements were seen in both groups. Patients, companions, and Investigators who were blinded to the treatment were asked to give a global rating of the patient's overall condition at each visit. A visual analog scale consisting of a 100 mm line was use. All Global scores for the Investigator, Patient and Companion are significantly improved over baseline. In the E05 study, the Investigators and Patients rated the HIGH group significantly improved over the LOW group.

Quality of Life and Cognitive Functioning

The E03 and E05 Studies used several instruments to measure QOL and cognitive functioning, with those used in the E05 Study being more comprehensive. Observed changes in the health related quality of life (HQL) and psychosocial scale scores were generally more favorable in the HIGH VNS group. There were few significant correlations between changes in cognitive tests and changes in global ratings of patient's overall well-being and seizure activity.

Other secondary endpoints

There was a statistically significant difference in mean % change in seizure frequency for within group stimulation compared to baseline. There was no statistically significant difference between groups for the number of responders (≥50% seizure reduction), number of seizure free days, seizure intensity or duration.

10.3.2 Safety

In each of the studies, the system was safe and well tolerated. The following treatment emergent signs and symptoms were observed in the Studies. Almost all were mild or moderate and anecdotally reported by Investigators to occur when the stimulator was ON and the intensity of the AE's were related to the strength (output current) of the stimulation. Symptoms that decreased or disappeared are not included in this analysis. In the E05 Study a symptom check list was used to prompt patients for adverse event reporting to ensure complete reporting of all events. Use of the checklist is likely the cause of slightly higher adverse event reporting rates in E05 Study as compared to E03.

Table 9. Observed Adverse Events

(n=413 devices in 314 patients, 152 in HIGH (optimal stimulation) treatment group, 591 device years)

	Randomized + Extension Phase, N= 314 patients, 591 device years				Randomized Phase, HIGH Only, N = 152 pts	
Adverse Event	**# of patients**	**% of patients**	**# of Events**	**Events per device-year**	**# of patients**	**% of patients**
Serious AEs1						
Surgically Related	13	4.1 %	13	0.022		
Stimulation Related	4	1.2 %	4	0.007	1	0.7 %
Non-serious AEs						
Voice Alteration	156	50%	720	1.228	91	60%
Cough Increased	129	41%	456	0.772	57	38%
Pharyngitis	84	27%	182	0.308	36	24%
Paresthesia	87	28%	377	0.638	32	21%
Dyspnea	55	18%	55	0.093	32	21%
Dyspepsia	36	12%	98	0.166	22	15%
Nausea	59	19%	154	0.261	21	14%
Laryngismus	10	3.2%	30	0.051	9	5.9%

1 - Serious AEs reported included infection, nerve paralysis, hyperesthesia, facial paresis, left vocal chord paralysis, left facial paralysis, left recurrent laryngeal nerve injury, urinary retention, and low grade fever

Table 10. Adverse Events Reported During Baseline or Stimulation

Test of Difference between Baseline (12 Weeks) and Stimulation (14 Weeks)

Adverse Event	E05					
	HIGH			LOW		
	Baseline	Treatment	p-value[C]	Baseline	Treatment	p-value[C]
Cough	28.4	52.6	<0.0001	23.3	51.5	<0.0001
Dyspepsia	5.3	21.1	0.0011	13.6	15.5	0.6171
Dyspnea	4.2	27.4	<0.0001	6.8	14.6	0.0114
Infection	4.2	14.7	0.0184	8.7	15.5	.1615
Pain, nonspecific	20.0	33.7	0.0124	19.4	37.9	0.0030
Paresthesia	1.1	24.2	<0.0001	4.9	33.0	<0.000
Throat pain[D]	15.8	42.1	<0.0001	16.5	29.1	0.0236
Voice alteration/hoarseness	6.3	72.6	<0.0001	8.7	32.0	<0.0001
Vomiting	8.4	17.9	0.0389	6.8	14.6	.0325

Adverse Event	E03					
	HIGH			LOW		
	Baseline	Treatment	p-value[C]	Baseline	Treatment	p-value[C]
Cough	0.0	12.3	0.008	3.5	10.5	.157
Dyspepsia	na	na	na	na	na	na
Dyspnea	1.8	10.5	*0.059*	0.0	0.0	na
Infection	0.0	3.5	0.157	1.8	3.5	.564
Pain, nonspecific	na	na	na	na	na	na
Paresthesia	0.0	15.8	0.003	0.0	7.0	0.046
Throat pain[D]	0.0	7.0	0.046	0.0	5.3	0.083
Voice alteration/hoarseness	0.0	38.6	<0.0001	0.0	14.0	0.005
Vomiting	1.8	1.8	ns	1.8	1.8	ns

A As reported or observed

[B] As elicited using Symptoms Checklist, reported or observed

[C] Within group analysis

[D] Throat pain is specifically reported as an AE in E03 but not E05. For comparative purposes a separate analysis of E05 data, aggregating neck pain, Pharyngitis and Laryngismus, was done and is presented here

Statistically significant <0.05

Marginally significant 0.05< p < 0.10

Table 11. Treatment Emergent Adverse Events By Severity

Adverse Event	AE's Reported During Baseline and Stimulation			Treatment Emergent AE's by Severity (% of reports)		
	E05 HIGH Group			Severity Ratings		
	Baseline [A]	Treatment [A]	pvalue [c]	Mild	Moderate	Severe
Cough	28.4%	52.6%	.0001	74%	23%	3%
Dyspepsia	5.3%	21.1%	.0011	76%	24%	0%
Dyspnea	4.2%	27.4%	<.0001	46%	54%	0%
Hypesthesia	0.0%	5.3%	.0253	100%	0%	0%
Infection	4.2%	14.7%	.0184	70%	30%	7%
Insomnia	1.1%	5.3%	.0455	75%	25%	0%
Pain, NonSpecific	20.0%	33.7%	.0124	63%	33%	4%
Paresthesia	1.1%	24.2%	<.0001	82%	18%	0%
Throat Pain & Laryngismus/Pharyngitis	15.8%	42.1%	<.0001	55%	43%	2%
Voice Alteration/Hoarseness	6.3%	72.6%	<.0001	73%	27%	0%
Vomiting	8.4%	17.9%	.0389	76%	24%	0%

AE's that are > 10% in the E05 HIGH stimulation group and were statistically significantly different from baseline are included.

Since the E03 and E05 Studies were active controlled studies as opposed to the traditional placebo controlled studies, a comparison of adverse events to baseline is required in order to obtain a more complete understanding of the differential effects of VNS therapy. A within group analysis of AEs for both HIGH and LOW groups in the E03 and E05 Studies in comparison to baseline AE rates is shown in the table above. Ninety nine percent of the side effects were rated as mild or moderate.

Table 12. Treatment Emergent Signs and Symptoms (>2%)

Study Number	E01	E02	E04	E03		E05		XE01 04		XE5
Group				HIGH [1]	LOW [2]	HIGH	LOW	1 YR	2 YR	9 MO
N	11	5	123	57	57	95	103	244	166	41
BODY AS A WHOLE										
Asthenia						7.4	1.9			12.2
Chills										2.4
Cyst						1.1	1.0			4.9
Edema Face						0.0	1.0			2.4
Fever			7.3	3.5	1.8	11.6	18.4	0.8	1.2	2.4
Flu Syndrome						1.1	3.9			2.4
Headache	60	20	8.9	5.3	7.0	24.2	23.3	4.5	1.8	17.1
Infection				3.5	3.5	11.6	11.7	2.1	1.2	4.9
Injury Accident			5.7			12.6	12.6	2.1	1.2	14.6
Malaise						1.0	0.0			4.9
Overdose						0	2.9			
Pain	30			8.8	1.8	28.4	30.1	0.4	1.2	31.7
Pain Abdominal	20		4.1	3.5	3.5	6.3	6.8	2.1	0	9.8
Pain Back				0	1.8	0	3.9	0	0	9.8
Pain Chest	20			1.8	0	9.5	12.6	0.8	0	4.9
Pain Neck	30					3.2	1.0			4.9
CARDIOVASCULAR SYSTEM										
Arrhythmia								0	0	2.4
Arrhythmia Vent										2.4
Fibrillate Atria										2.4
Hemorrhage						3.2	3.9			
Hypertension						4.2	1.0	0	0	7.3
Phlebitis						2.1	0			
Tachycardia						2.1	2.9	0.4	0	
DIGESTIVE SYSTEM										
Appetite Increase	10									
Anorexia	10					1.1	1.9	1.2	0	4.9
Constipation		20	2.4	0	0	2.1	7.8	0.4	0	2.5
Diarrhea	20		4.1	3.5	0	6.3	24.3	1.2	1.2	12.2
Dyspepsia						17.9	12.6			9.8
Dysphagia	20	60	4.9	3.5	0	2.1	6.8	2.1	1.2	2.4
Gingivitis						2.1	1.9			
Nausea	10		2.4	7.0	1.8	14.7	20.4	0.8	1.2	2.4
Vomit	10		4.9	0	1.8	17.9	13.6	1.6	1.8	4.9
HEMIC AND LYMPHATIC SYSTEM										
Anemia						0.0	1.0			2.4
Ecchymosis						3.2	3.9			7.3
METABOLIC AND NUTRITIONAL DISORDERS										
Cyanosis						0	2.9			

Table 12. Treatment Emergent Signs and Symptoms (>2%)

Study Number	E01	E02	E04	E03		E05		XE01 04		XE5
Group				HIGH [1]	LOW [2]	HIGH	LOW	1 YR	2 YR	9 MO
N	11	5	123	57	57	95	103	244	166	41
Edema						3.2	6.8			2.5
Edema Periph						0.0	1.0			2.4
Weight Decrease						1.1	2.9			2.4
MUSCULO SKELETAL SYSTEM										
Arthralgia						2.1	1.0	0.4	0	
Bone Fract Spontan						5.3	2.9			4.9
Myalgia	30		6.5			2.1	1.0	1.2	0	4.9
Myasthenia										2.4
NERVOUS SYSTEM										
Agitation				0	1.8	1.1	2.9	1.6	0	
Anxiety	10					1.1	1.0			2.4
Ataxia	10			0	0	4.2	3.9	0.4	0.6	9.8
Coordination Abnormality		20								
Convulsions						2.1	3.9			
Depression	10		0.8	1.8	1.8	3.2	0	0	0.6	12.2
Diplopia						5.3	2.9	0.4	0.6	
Dizziness				0	3.5	5.3	3.9	3.3	0.6	4.9
Dream Abnormality	10					1.1	0.0			
Emotional liability			2.4			1.1	1.9	1.2	0	
Euphoria	20									
Gait Abnorm										2.4
Hallucin								0.4	0	2.4
Hostility						1.1	1.0			2.4
Hypesthesia						2.1	0			2.4
Insomnia	10	20	2.4	5.3	1.8	4.2	4.9	0	0.6	2.4
Movement Dis						1.1	0.0			2.4
Neuralgia										2.4
Nervousness			3.3			1.1	1.9	1.6	0	2.4
Neurosis										2.4
Paresthesia			5.7	5.3	3.5	17.9	25.2	0.8	2.4	41.5
Person Disorder						1.1	0.0			2.4
Somnolence				5.3	3.5	2.1	1.9	1.2	0	2.4
Tremor			2.4	1.8	1.8	3.2	2.9	0	1.2	2.4
Twitch	50	20	3.3	1.8	0	3.2	1.0	0.8	0	9.8
Vertigo										2.4
RESPIRATORY SYSTEM										
Asthma						2.1	3.9			2.4
Cough Increased			17.1	8.8	8.8	45.3	42.7	2.9	3.0	17.1
Dyspnea	30	20	3.2	7.0	0	25.3	10.7	2.5	0	9.8

Table 12. Treatment Emergent Signs and Symptoms (>2%)

Study Number	E01	E02	E04	E03		E05		XE01 04		XE5
Group				HIGH [1]	LOW [2]	HIGH	LOW	1 YR	2 YR	9 MO
N	11	5	123	57	57	95	103	244	166	41
Hiccup	10					3.2	0			
Hyperventilate						2.1	1.0			
Laryngismus						7.4	1.0			2.4
Lung disorder						1.1	3.9			4.9
Pharyngitis	10	40	4.9	12.3	10.5	34.7	25.2	4.1	1.2	19.5
Respiratory Disorder						2.1	0			
Rhinitis			11.4	0	3.5	7.4	14.6	1.6	1.2	4.9
Sinusitis						3.2	2.9			4.9
Voice Alteration	100	80	13	36.8	10.5	66.3	30.1	7.8	5.4	75.6
SKIN AND APPENDAGES										
Application Site Reaction						1.1	2.9			2.4
Alopecia						0.0	1.0			2.4
Pruritis										4.9
Rash	10					5.3	1.9	0	0	4.9
Rash Vesis Bull						2.1	1.0			
SPECIAL SENSES										
Amblyopia						2.1	1.9	0.4	0.6	
Conjunctivitis						1.1	1.0			2.4
Glaucoma										2.4
Pain Ear		20		0	1.8	4.2	3.9	1.2	0.6	
Parosmia										2.4
Taste Pervers								0	0	2.4
Tinnitus				3.5	1.8	4.2	5.8	0	0	
UROGENITAL SYSTEM										
Dysmenorrhea						2.1	3.9			
Dysuria						0	2.9	0.4	0	
Hematuria						0.0	1.0			2.4
Incontin Urine						1.1	0.0			2.4
Infection, Urin Tract						2.1	6.8			
Menstrual Disorder				3.5	0	1.1	0	0	0	
Merorrhagia						2.1	1.9			
Urination Frequency						0.0	1.0			4.9

*1 = **HIGH** Stimulation parameters generally believed to provide maximum efficacy*

*2 = **LOW** Stimulation parameters generally believed to provide sensation of stimulation but less effective.*

Cardiac monitoring: For Study E05 all patients had 24 hour Holter monitoring twice during baseline and five times during stimulation. Data from the Holter monitoring showed no difference between either of the Treatment groups, and/or Baseline periods on cardiac endpoints. Some patients in all acute and long term studies were monitored at baseline and stimulation with EKG

or Holter recording. None of the monitoring showed any statistically significant differences between baseline and stimulation.

Pulmonary monitoring: Patients in the E05 Study were monitored once during baseline and twice during stimulation for FVC and FEV1. There was no statistical difference between the treatment groups, and/or baseline periods pulmonary endpoints. Although dyspnea was statistically significantly increased over baseline, no effect was detected with pulmonary function monitoring.

Gastric monitoring: All patients in E05 were monitored for serum gastrin levels and some patients in the other acute and long term studies were monitored for gastrin or gastric acid output. No clinically meaningful changes were observed.

DEATHS AND OTHER SERIOUS ADVERSE EVENTS

A total of 17 deaths have been reported in 950 clinical and commercial patients followed for 1650 patient-years. Nine of the deaths were judged to be possible/probable/definite Sudden Unexpected Death in Epilepsy (SUDEP). Additionally, one patient died of SUDEP during the preimplant baseline period, and two patients have died after discontinuation of treatment.

Based on the 17 deaths, there was a mortality of 10.3/1000 patient-years and a SUDEP incidence of 3.0/1000 patient-years for definite/probable and 5 for definite/probable/possible SUDEPs.

Table 13. Deaths and Other Serious Adverse Events

Study	N	No. of Deaths [1]	Other Serious AEs
E01	11	0	1 vocal cord paralysis due to surgery, resolved.
E02	5	0	0
E03	114	1 preimplant	1 vocal cord paralysis, permanent, device failure 1 infection, hospitalization complete recovery 1 MI
E04	123	0	2 Infections; 1 hospitalization for transient increase in seizures; 1 poor appetite; 1 fever; 1 coughing.
E05	198	0	Surgery & device related 3 infections which ultimately were explanted; 1 vocal cord paralysis; 1 left facial paralysis; 1 post operative fever; 1 localization of fluid around generator; and 1 left recurrent laryngeal nerve injury. Therapy related: 1 near syncope; 1 Cheyenne Stokes respiration, and 1 bleeding duodenal ulcer.
XE14	229	7	Definitely related: 1 respiratory distress; 1 obstructive bronchitis; 3 voice alteration; 1 choking Probably related: 1 Change of seizure type Possibly related: 1 Fall; 1 pulmonary congestion; 1 obstructive bronchitis.
XE5 (6 mo.)	41	2	1 probable left hemidiaphragm paralysis, 1 hospitalization for seizures, 1 institutionalized for selfabusive behavior

1 = Table does not include patients who died using a commercially available product, N = 8

10.3.3 DEVICE PERFORMANCE

DEVICE COMPLICATIONS AND OBSERVATIONS

For the purposes of this report, a device complication is an event which cannot be treated or resolved by reprogramming the device and requires intervention other than reprogramming. A device observation is an adverse event which can be corrected by reprogramming and which does not require surgical intervention

Table 14. Device Complications and Observations

Study	N	NCP® System Complications	Description
E01	11	2 Lead	1 high impedance, 1 broken wire
E02	5	None	None
E03	114	3 Lead 2 Generator	1 cut by surgeon, 1 Lead not fully inserted in Generator 1 Electrode not on nerve, but reduced seizures 1 Internal short, DC on electrode 1 Premature battery depletion, excessive drain from circuit
E04	123	0	None
E05	198	0	None
XE14		54 Lead 5 Generator	24 Lead breaks, 24 High lead impedance, 1 insulation, 1 infection, 1 patient discomfort, 1twiddler, 4Infection (explanted), 1 user error
XE5 (6 mo.)	41	1 Lead	1 Lead high impedance, Lead was twisted, no strain relief or tie down. Replaced Lead
Study	N	Observations	NCP® System Observations
E01	11	0	0 NCP® System
E02	5	0	0 NCP® System
E03	114	3 Generator 4 System 1 Programming Software	2 reset, 1 communication 4 infections treated with antibiotics 1 exited to DOS, program was modified
E04	123	3 Lead 3 Generator Several Programming 4 Programming Software	1 high impedance, unverified, 2 helix stuck together 1 pt discomfort, 2 erratic stim, unverified Programming difficulties Resolved by repositioning or turning off other equipment in the room 2 Operator error, 1 corrupted history file, 1 background program interfered with printing
E05	198	3 Generator 1 Lead 1 System 12 Communication	2 Pain during diagnostic tests, User error, explained in Manual 1 Programmer operator error, explained in Manual 1 "Malformed" Lead at implant, used backup Lead returned Lead within specs. 1 infection Resolved by repositioning Wand or turning off electrocautery equipment. Discovered disk caching routines on certain computers may interfere, instructed users to disable this function.

Table 14. Device Complications and Observations

Study	N	NCP® System Complications	Description
XE14 8 yr. total	229	23 Lead	11 high impedance, 4 break, 3 user error, 2 connector, 2 helix stuck together, 1 dislodged
		36 Generator	10 erratic stim (not duplicated), 8 reset, 8 user errors, 5 communication, 1 each: infection, magnet effectiveness, package anomaly, set screw, other
		8 Wand	6 communication, 2 user error
		14 Programming Software	7 communication, 3 software difficulties, 4 user error
XE5 6 mo.	89	2 Generator	2 reports of erratic stimulation; not verified
		2 Communication	2 communication difficulties resolved by repositioning

Two Generator complications have occurred related directly to device performance. One Generator malfunction caused by an internal short circuit and DC current on the ground electrode resulted in patient injury, and although the patient's nerve was believed to be permanently damaged the patient's voice fully recovered. The second was premature battery depletion due to a transient high current drain.

Over fifty Leads have been verified to have broken or developed high impedance. Design changes have been made as a result of these failures. Over 500 of the redesigned leads have reportedly been implanted, with no reported complications, other than one case where a suture was tied directly around the lead.

There have been a number of reported programming communication problems. These problems are related, in part, to a strict communication protocol which ensures reliable data transfer and programming, and in part to the use of electrocautery and other electrically noisy equipment in the vicinity of the programmer. The noise immunity of the receiver circuitry in the Programming Wand was improved, and disk caching routines in some computers was identified as a source and corrected.

11. CONCLUSIONS DRAWN FROM STUDIES

Valid scientific evidence is necessary to establish that there is reasonable assurance the NeuroCybernetic Prosthesis (NCP®) System is safe and effective for its intended use. The *in vivo* and in vitro nonclinical laboratory studies together with the clinical investigations provide reasonable assurance that the NeuroCybernetic Prosthesis (NCP®) System is safe when used as indicated in the labeling.

The results of clinical studies of the NCP® system for seizure reduction in patients with partial onset seizures support the effectiveness of the device. The mean seizure reduction experienced by the HIGH treatment groups (the group on whom labeling is based) was statistically significant as compared to the active LOW treatment control group. The HIGH group in both studies had a statistically significant mean seizure reduction as compared to baseline.

The safety of the NCP® System has been demonstrated in clinical trials with reported side effects being negligible in relationship to the severity of the disorder being treated. The most common

side effects reported are generally a function of the device's programmed stimulation setting which can be altered or adjusted to lessen the effect or discontinue it altogether.

12. PANEL RECOMMENDATIONS

On June 27, 1997, the Neurological Devices Panel recommended that the Premarket Approval Application for the NeuroCybernetic Prosthesis (NCP®) System be approved with some specific labeling recommendations. The approved labeling followed those recommendations. The panel also recommended that post approval studies will be conducted to examine the morbidity and mortality associated with the device and to develop a method to assess, prior to implant if possible, a means to determine which patients would respond to the therapy and which would not.

13. FDA DECISION

FDA and the applicant worked out conditions of approval including post-approval studies which were formally agreed to in the applicant's amendment received July 16, 1997.

In addition to the general conditions of approval, the applicant must conduct the studies outlined in the amendment dated July 16, 1997, ("Description of the Postapproval Studies - P970003"). The information to be collected for five years will include:

- continued reporting on a cohort of E05 patients;
- characterization of the long-term morbidity and mortality; and
- development of an approach to identifying responders and non-responders.

If appropriate, the results of the long-term data must be reflected in the labeling (via a supplement) when the post-approval study is completed.

FDA performed an inspection and found the applicant in compliance with the Good Manufacturing Practices (GMP) regulation (21 CFR, Part 820).

FDA concurred with the recommendations of the Neurological Devices Panel of June 27, 1997, and issued an approval order to Cyberonics on July 16, 1997

14. APPROVAL SPECIFICATIONS

- Directions for use: See the labeling.
- Hazards to health from use of the device: See indications, contraindications, warnings, precautions and adverse events in the labeling.
- Post Approval Requirements and Restrictions: See approval order.