SUMMARY OF SAFETY AND EFFECTIVENESS DATA (SSED)

I. GENERAL INFORMATION

Device Generic Name:	Tumor Treatment Fields
Device Trade Name:	NovoTTF-100A System
U. S. Agent:	NovoCure Ltd. USA P.O. Box 589 Rye Beach, NH 03871
Applicant's Name and Address:	NovoCure Ltd. POB 15022 MATAM Center Haifa 31905, Israel

Date of Panel Recommendation: March 18, 2011

Premarket Approval Application (PMA) Number: P100034

Date of FDA Notice of Approval: April 8, 2011

Expedited: Granted expedited review status on April 10, 2008, because the condition the device is intended to address (for treatment of recurrent Glioblastoma Multiforme) represents a life-threatening condition and no legally marketed alternative device is currently available.

II. INDICATIONS FOR USE

The NovoTTF-100A System is intended as a treatment for adult patients (22 years of age or older) with histologically-confirmed glioblastoma multiforme (GBM), following histologically- or radiologically-confirmed recurrence in the supra-tentorial region of the brain after receiving chemotherapy. The device is intended to be used as a monotherapy, and is intended as an alternative to standard medical therapy for GBM after surgical and radiation options have been exhausted.

III. CONTRAINDICATIONS

- Do not use the NovoTTF-100A System if you have an active implanted medical device, a skull defect (i.e., missing bone with no replacement), shunt(s) or bullet fragment(s). Examples of active electronic devices include deep brain stimulators, spinal cord stimulators, vagus nerve stimulators, pacemakers, defibrillators, and programmable shunts. Use of the NovoTTF-100A System together with implanted

electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device. Use of the NovoTTF-100A System together with skull defects, shunts or bullet fragments has not been tested and may possibly lead to tissue damage or render the NovoTTF-100A System ineffective.

- Do not use the NovoTTF-100A System if you are known to be sensitive to conductive hydrogels like the gel used on electrocardiogram (ECG) stickers or transcutaneous electrical nerve stimulation (TENS) electrodes. In this case, skin contact with the electrode gel used with the NovoTTF-100A System may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

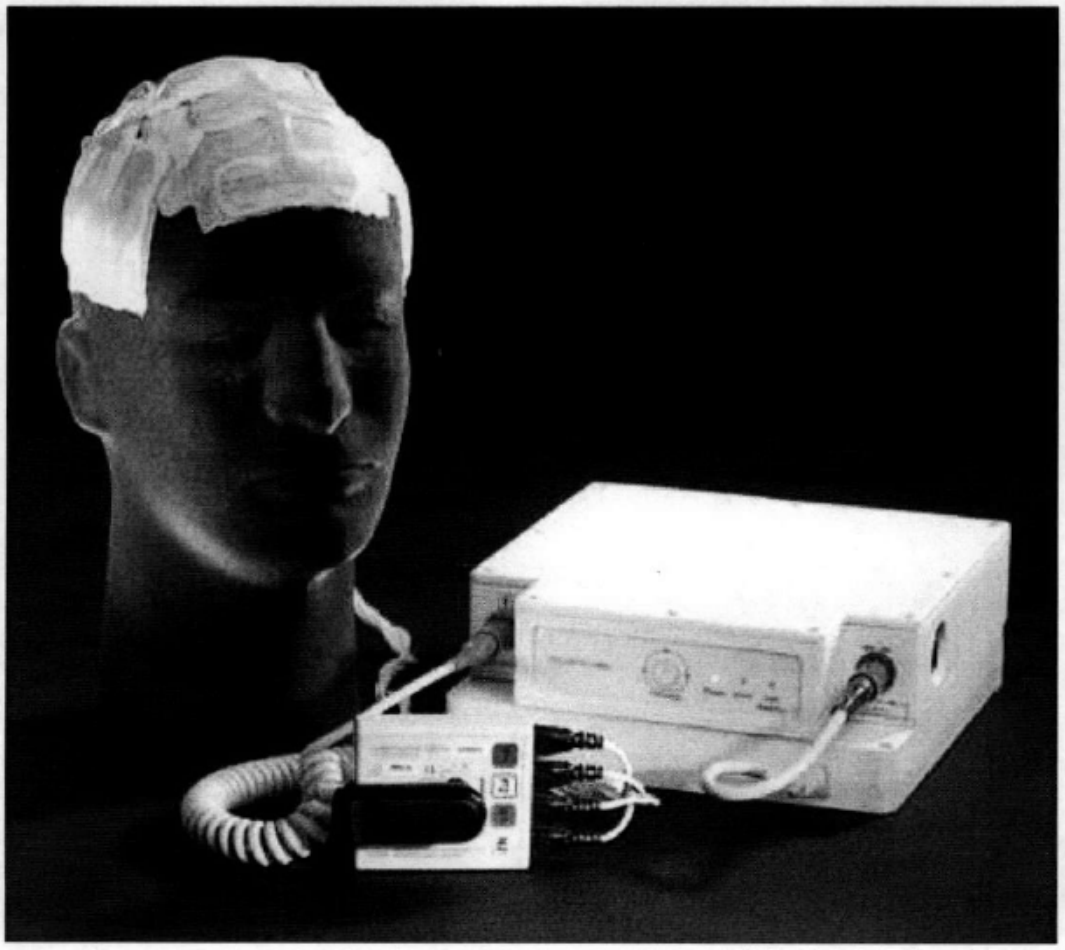
IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the NovoTTF-100A System Instructions for Use and Patient Information and Operation Manual.

V. DEVICE DESCRIPTION

The NovoTTF-100A System for the treatment of recurrent GBM is a portable battery or power supply operated device which produces alternating electrical fields, called tumor treatment fields ("TTFields") within the human body. TTFields are applied to the patient by electrically-insulated surface electrodes. Research studies demonstrate that TTFields can disrupt the rapid cell division exhibited by cancer cells.

Treatment parameters are preset by NovoCure such that there are no electrical output adjustments available to the patient. Based on detailed training provided by the physician, the patient will learn to change and recharge depleted device batteries and to connect to an external power supply overnight. In addition, the electrodes need to be replaced once to twice a week and the scalp re-shaved in order to maintain optimal contact. Patients carry the device in an over-the-shoulder bag or backpack and receive continuous treatment without changing their daily routine.



A. Technological Characteristics

The NovoTTF-100A System is comprised of two main components: (1) an Electric Field Generator; and (2) INE Insulated Electrodes.

1. Electric Field Generator ("NovoTTF-100A Device")

   The Electric Field Generator is a portable, battery- or power supply-operated device. The outputs are connected to two pairs of insulated electrode sets operated sequentially. The intensity of the field, the frequency of the waves, and the temperature of the electrodes are pre-set.

   The device status and monitored parameters are continuously stored in an internal log memory and can be transferred by trained personnel to a personal computer (PC). In addition, the device includes visual indicators for Power ON, Treatment ON, alarms and low battery.

2. INE Insulated Electrodes ("Electrodes")

Two sets of electrodes are connected to the device. Each set includes a pair of electrodes which operate together to generate one field direction. The electrodes are 'ready to use' and are supplied packaged with a gel layer, padding, medical tape and overlapping liner.

The electrodes themselves are made from high dielectric constant insulated ceramic discs soldered to a flexible circuit board. The flexible printed circuit incorporates the components required for delivering the current for each ceramic plate and for measuring the temperature. At the set parameters, the electrodes do not cause significant heating due to dielectric losses of the insulation or induced fields in the target tissue. As an additional safety feature, the temperature of the electrodes is monitored by a temperature sensor. If temperature rises beyond 41°C, the device automatically shuts off.

3. Additional Components

In addition to the Electric Field Generator and INE Electrodes, the following components, described below, are also part of the NovoTTF-100A System: power supply, portable battery, battery rack, battery charger, connection cable and carrying case.

The NovoTTF-100A device can be powered by a mains-connected power supply of 24V± 2V. The power supply connects to the power connector on the front panel of the device. Alternatively, the device can also be powered by battery using a portable, external 33V ± 2V (when fully charged) rechargeable battery. Several batteries placed in a battery rack can be recharged at the same time using a dedicated battery charger when not connected to the device. The connection between the battery and the device is through a dedicated connector on the device's front panel.

The electrodes are connected to the voltage output of the device by a spiral extension cable. Patients carry the device and the battery in a specialized over-the-shoulder bag, which allows them to receive continuous treatment without changing their daily routine.

B. Principles of Operation

The NovoTTF-100A produces alternating electrical fields within the human body that are believed to disrupt the rapid cell division exhibited by cancer cells, with the alternating electrical fields applied to the brain through electrodes placed on the scalp.

TTFields harness electric fields to arrest the proliferation of tumor cells and to destroy them. The TTField technology takes advantage of the special characteristics, geometrical shape, and rate of dividing cancer cells, which make them susceptible to the effects of the alternating electric TTFields. These special fields alter the tumor cell polarity at an intermediate frequency (on the order of 100-300 kHz). The frequency used for a particular treatment is specific to the cell type being treated (e.g., 200kHz for GBM). TTFields have been shown to disrupt mitotic spindle microtubule assembly and to lead to dielectrophoretic dislocation of intracellular macromolecules and organelles during cytokinesis. These processes lead to physical disruption of the cell membrane and to programmed cell death (apoptosis).

The TTFields have not been shown to affect cells that are not undergoing division. Since most normal adult brain cells proliferate very slowly, if at all, they are hypothesized to be minimally affected by the TTFields. Testing demonstrates no differences between treated and control animals in histology of the major internal organs (including the brain), blood examination, cardiac rhythm, body temperature, or in animal behavior. In addition, because the fields alternate so rapidly, they have no effect on normal quiescent cells nor do they stimulate nerves and muscles. Since TTFields are only applied to the brain, they are unlikely to have an effect on rapidly proliferating cells in the rest of the body. The intensities of the electric fields within the tissues are very small and do not result in any clinically meaningful increase in tissue temperature.

The above mechanisms of action are consistent with the extensive research regarding the effects of TTFields. These results demonstrate both disruption of cancer cell division up to complete cessation of the process, as well as complete destruction of the dividing cancer cells.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

There are several other alternatives for the treatment of recurrent GBM, described below. Each alternative has its own advantages and disadvantages. A patient should fully discuss these alternatives with his/her physician to select the method that best meets expectations and lifestyle.

In addition to Surgical Resection, there are currently three approved treatment options for GBM:

- Radiation therapy

- Chemotherapy, including nitrosourea-based chemotherapy, temozolomide, and bevacizumab (Avastin)
- GLIADEL® Wafer in combination with surgical resection

VII. MARKETING HISTORY

The NovoTTF-100A System has received CE mark for the treatment of both recurrent and newly diagnosed GBM. The device has been available commercially in the European Union (EU) since the fourth quarter of 2009. The device has not been withdrawn from marketing for any reason related to the safety or effectiveness of the deice in any country.

VIII. POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH

Treatment with the NovoTTF-100A is not expected to cause any serious side effects. However, it is possible that treatment may cause any of the following:

- Local warmth and tingling sensation beneath the electrodes
- Allergic reaction to the plaster or to the gel
- Medical device site reaction
- Skin breakdown / skin ulcer
- Infection at the sites of electrode contact with the skin
- Electrode overheating leading to pain and/or local skin burns
- Headache
- Fatigue / malaise
- Muscle twitching
- Falls

A detailed table of adverse events observed in the pivotal clinical study of the NovoTTF-100A System can be found in **Section X.B.5** below.

IX. SUMMARY OF PRECLINICAL STUDIES

TTFields have been shown both *in vitro* and *in vivo* to effectively inhibit cancer cell replication during mitosis without systemic side effects. At intensities of approximately 1 V/cm, TTFields can be frequency-tuned to effectively inhibit different cancer cell types (i.e., the smaller the cell, the higher the frequency needed), due to disruption of microtubule polymerization and physical disruption of cell integrity at the cleavage plane during telophase[1].

[1] Kirson, E. D., Z. Gurvich, et al. (2004). "Disruption of cancer cell replication by alternating electric fields." Cancer Res **64**(9): 3288-95.

Specifically, TTFields have been shown to inhibit glioblastoma cells *in vitro* and *in vivo* at a frequency of 200 kHz and an intensity of 0.7 V/cm. Based on realistic finite element mesh simulations and direct measurements of TTFields intensity in experimental animals, and in the human brain, NovoCure has concluded that effective TTField intensities can be generated in the brains of large animals and humans. Extensive safety studies in healthy animals (mice, rats and rabbits) have shown that TTFields are not associated with significant systemic toxicities. Neither acute nor chronic systemic toxicities were seen when TTFields were applied to the torso or head at different frequencies (100-200 kHz), different intensities or for different periods of time.

Using a model developed to simulate the growth kinetics of a malignant tumor, the minimal treatment course duration for the NovoTTF-100A device was determined to be approximately 4 weeks to reach tumor stabilization. This finding was later validated in independent animal studies and human pilot clinical studies. Stopping treatment prior to completion of a 4 week treatment course will most likely lead to continued tumor growth and appearance of symptoms within approximately 1-2 weeks.

A. In Vitro Studies

NovoCure has shown that when properly tuned, TTFields stunt the growth of tumor cells. This inhibitory effect has been demonstrated in all proliferating cell types tested; whereas, non-proliferating cells and tissues were unaffected. Different cell types showed specific intensity and frequency dependences of TTField-induced inhibition.

1. Mechanism of Action Studies

Studies assessing the mechanism of action of TTFields (Table 1) have confirmed two main processes that occur at the cellular level during exposure to TTFields: (1) arrest of proliferation, and (2) dividing cell destruction. These mechanisms of action have been studied and confirmed via NovoCure's early preclinical testing involving finite element simulations and calculations, and demonstrate no significant elevation in temperature compared to control cultures/mice.

In addition to the above early studies, NovoCure conducted studies using time-lapse microphotography, colormetric determination, staining of sub-cellular constituents, and measurements of electric fields to demonstrate the specific effects of TTFields on proliferating cancer cells grown in tissue culture, and to elucidate the mechanism of action of these effects. Based on these studies, it was determined that:

- TTFields arrest cell proliferation and result in cell death;
- the inhibitory effects of TTFields are not limited to a specific cell type;
- cell recovery can be prevented either by applying the TTFields for longer duration, or by applying fields in two directions normal to each other, that are interleaved in time; and

- the axis of division of the dividing cells in relation to the electric fields is important in effecting cell death.

Table 1. Summary of Mechanism of Action Studies

Test	Purpose	Results	Conclusions
Time-lapse microphotography of malignant cell cultures (B16F1) exposed to TTFields for 24h [1]	Identify structural changes to mitotic cells exposed to TTFields	Membrane breakdown and blebbing seen only in cells which enter telophase	"Hourglass" shape of cells during telophase leads to dielectrophoretic movement of organelles and macromolecules
Immuno-histochemical staining for Tubulin, DNA and Actin in malignant cells after 24h exposure to TTFields [1]	Identify what part of the mitotic apparatus is damaged during exposure to TTFields	Abnormal mitotic figures seen in all mitotic cells exposed to TTFields for 24h	TTFields interfere with the proper alignment of tubulin dimers and lead to the formation of ineffective mitotic spindles
Annexin staining of HeLa cells exposed to TTFields	Identify whether the mechanism of cell death due to TTFields is apoptosis versus necrosis	Annexin staining seen only in mitotic cells exposed to TTFields	TTFields-mediated cell death is through apoptosis

2. Proof of Concept Studies

NovoCure performed *in vitro* studies (Table 2) to assess the relationship between dose and frequency response using tumor cells from four of the most common types of cancer: malignant melanoma, glioblastoma, breast carcinoma and non-small cell lung carcinoma. This testing demonstrated that the optimal frequency of the fields is 200 kHz for rat glioblastoma (F-98) and human glioma (U-87), and that effective inhibition of glioma culture growth can be achieved at low field intensities (0.7-1.4 V/cm).

Finally, preclinical research both *in vitro* and *in vivo* has shown that, upon cessation of TTFields treatment, tumor growth rate does not increase beyond that seen before treatment, so that no rebound effect is expected.

3. Treatment Duration Simulations

NovoCure assessed tumor growth kinetics to evaluate optimal treatment duration and timing. Using a multi-compartmental model to simulate the growth kinetics

of a malignant tumor, NovoCure tested the time to tumor growth stabilization and reversal when exposed to TTFields using the NovoTTF-100A device. Based on the model, the minimal treatment course duration for the NovoTTF-100A device was determined to be approximately 4 weeks to reach tumor stabilization. This finding was validated in independent animal studies.

Table 2. In-Vitro Testing

Test	Purpose	Acceptance Criteria	Results	Conclusions
The number of cells in cultures exposed to TTFields for 24-72 hours was compared to heat matched controls in various cancerous cell lines [1, 2]	Test whether the antimitotic effect of TTFields has a significant impact on cancer cell replication in culture	Number of cells in TTFields-treated cultures is significantly lower than that of controls at 24h, 48h and 72h (t-test; $p<0.05$)	**Cell*/ Inhibition%** U-87 / 76% U-118 / 77% F-98 / 87% C-6 / 24% *Human and rodent GBM cell lines	GBM growth in culture is significantly inhibited by TTFields
The inhibitory effect of TTFields was tested in culture at a range of frequencies between 50-500kHz in various cultures [1, 2]	Investigate whether there is an optimal frequency for the antimitotic effect of TTFields and the main parameters that may effect dependence	None	The effect of TTFields is frequency-dependent with frequency inversely related to cell size	Optimal frequency for each cancer cell type: Glioma =200kHz Melanoma = 100kHz NSCLC = 150kHz
Cancer cell cultures were exposed to TTFields of increasing intensities and a dose-response curve constructed for each cell type [1, 2]	Test whether the effect of TTFields is intensity dependent and the threshold for inhibition of mitosis	None	The effects of TTFields are dose-dependent with effective inhibition of cell culture growth seen at intensities > 0.7 V/cm	TTField intensities > 0.7V/cm are needed in the brain to treat GBM

Direct measurements with a minimally invasive probe were performed of the intensities of TTFields in the brains of anesthetized rats, rabbits, sheep, pigs and a human volunteer	Test what the TTField intensity is within the brain	Minimal TTField intensity >0.7V/cm	TTField intensity is between 1-3 V/cm in the gray and white matter of the brain	TTField intensity of >0.7 V/cm can be generated within the brains of large animals and humans using the NovoTTF-100A device
Finite Element Mesh simulations and measurements within phantom setups of the brain	Verify that TTField distribution is homogenous within the brain	Exploratory analysis without predefined acceptance criteria	Field intensity varies by <30% using INE electrodes in a human brain model	Field distribution is highly uniform throughout the brain using INE electrodes and 200kHz TTFields
Kinetic modeling of compartmental tumor growth kinetics [3]	Test the time needed to achieve tumor growth reversal using TTFields	Exploratory analysis without predefined acceptance criteria	Tumor growth reversal is seen only if TTFields are applied continuously for several weeks	Tumor growth reversal is not immediate
Growth rate of glioma cells after stopping TTFields treatment of 24-72 hours	Test whether there is a rebound effect after TTFields are removed from a tumor	Post treatment cell growth rate less than or equal to pre-treatment growth rate	Post treatment growth rate less than pre-treatment growth rate	No "rebound" effect seen after stopping TTFields

B. In Vivo Studies

NovoCure conducted a series of early experiments in mice, rats, rabbits, sheep and pigs to verify the data that was previously obtained in prior simulations of TTField distribution. These experiments demonstrate that effective TTField intensities on the order of 0.7V/cm can be obtained within tumors in the brains of various animal models.

1. Animal Effectiveness Studies

NovoCure has shown that TTFields can be applied effectively to tumors through electrodes placed on the surface of the body. Using a special type of electrically insulated electrode, significant inhibition of the growth of both intradermal melanoma (B16F1) in mice and intracranial glioma (F-98) in rats was seen after less then one week of treatment[2]. In addition, NovoCure has studied the effect of TTFields on metastatic spread of solid tumors and investigated the development of an immune response following TTField treatment[3]. Importantly, in the rabbit kidney model, TTField treatment could be extended for up to 5 weeks due to the large size of the animals being used. Analysis of the time-dependence of the effect of TTFields in tumor bearing rabbits showed that a minimum TTField treatment duration of 4 weeks is necessary in order to achieve complete arrest of macroscopic tumor growth. Thus, the extrapolated minimal treatment course duration in GBM subjects was set at 28 days. In-vivo testing is summarized in Table 3 below.

Table 3. In-Vivo Efficacy Testing

Test	Purpose	Acceptance Criteria	Results	Conclusions
TTFields applied to animals with orthotopic, syngeneic tumors inoculated in the skin or in the brain [1, 2]	Test the extent of inhibition of solid tumor models in animals (including glioma in the brain of rats)	After one week of TTFields treatment Tumor size is significantly smaller in TTFields-treated animals than in sham control animals (t-test; $p<0.05$)	Glioma: Control=107.8±70 mm^3 TTFields=61.4±50 mm^3 ($p<0.01$) Melanoma: Control=137.1±66 mm^3 TTFields=70.6±47 mm^3 ($p<0.001$)	Significant inhibition of tumor growth seen in rats with intra-cerebral GBM (200kHz) Significant inhibition of tumor growth seen in mice with intra-dermal melanoma (100kHz)
TTFields-treated versus sham-treated rabbits with deep solid tumors	Temporal profile of tumor growth	None	Tumor growth reversal was seen after 4 weeks of treatment with TTFields. 85% reduction in the growth of treated tumors compared to the control group.	Validates the findings of the in-vitro kinetic model: NovoTTF-100A should be used for a minimum duration of 4 weeks contiguously

[2] Kirson, E. D., V. Dbaly, et al. (2007). "Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors." Proc Natl Acad Sci U S A **104**(24): 10152-7.

[3] Kirson, E. D., M. Giladi, et al. (2009). "Alternating electric fields (TTFields) inhibit metastatic spread of solid tumors to the lungs." Clin Exp Metastasis **26**(7): 633-40.

(VX-2) in the kidney capsule treated for 5 weeks continuously [3]			33% increase in median overall survival.	
TTFields applied to a primary solid tumor (VX-2) in the kidney of rabbits – pathology of the lungs [4]	Test the potential of TTFields to inhibit metastatic spread and seeding in the lungs	None	Significant ($p<0.05$) decrease in the number and size of tumor metastases in the lungs	TTFields inhibit metastatic tumor spread

2. Animal Safety Studies

Extensive safety studies in healthy rabbits and rats exposed to TTFields for protracted periods of time have shown no treatment related side effects or pathologic damage to the brain. The reasons for the low toxicity of TTField treatment can be explained in light of the known passive electric properties of normal tissues within the body and the effects of electric fields applied via insulated electrodes. In both acute and chronic application of TTFields to healthy animals, no evidence of abnormal cardiac rhythms or pathologic neurological activity is seen. In addition, no treatment related toxicities were found in any of the animal safety trials performed, even when field intensities 3 times higher than the effective anti-tumoral dose were applied. Finally, these studies (as summarized in Table 4) demonstrated that hematopoietic cell replication should not be affected even with application of TTField intensities that are 10 times higher than necessary to inhibit tumor growth.

Table 4. In-Vivo Safety Testing

Test	Purpose	Acceptance Criteria	Results	Conclusions
Acute safety in rabbits	Test whether high intensity TTFields (up to 5 V/cm at 1.5 A p2p) are capable of causing	No arrhythmias for 20 minutes of continuous exposure based on EKG, continuous blood pressure	No cardiac arrhythmias were induced in any of the animals tested	Pass

	cardiac arrhythmias when applied directly to the chest	monitoring and pulse oximetry		
Chronic safety in mice (7 days) – whole body application	Assess whether the application of TTFields has any effect on mortality, internal organs, or local side effects in 50 mice treated with TTFields (1V/cm, 100kHz) compared to 46 untreated controls	Overall mortality and adverse effects on internal organs	Mortality identical in both treatment and control groups. No pathological findings in any of the following organs: brain, skin, bone, bone marrow, muscle, cardiac tissues, lungs, liver, spleen, kidney, intestine, adrenal gland.	No increase in animal mortality and no damage to internal organs.
Chronic safety in rats (7 days) – application to brain	Assess the safety of TTFields during and after chronic exposure in an additional species	Daily clinical examination by a veterinarian. Complete blood count, ECG and body weight measurements prior to treatment, after treatment termination and two weeks later before sacrificing. Overall mortality and adverse effects on internal organs.	No deaths observed. All animals behaved normally and were neurologically intact. No significant differences in blood exam results between TTFields and sham treated rats. No pathological damage to any internal organs.	The lack of treatment related toxicities after chronic exposure to TTFields is not species related
Chronic safety in rabbits (4 weeks) – application to	Assess the safety of TTFields during and after longer	Daily clinical examination by a veterinarian. Weekly complete blood	No deaths observed. All animals behaved normally and were	Chronic exposure to TTFields for 4 weeks has no significant immediate or late

the brain (100, 150 and 200kHz)	chronic exposure and at different frequencies	count, ECG and body weight measurements. Overall mortality and adverse effects on internal organs.	neurologically intact. No significant differences in blood exam results between TTFields and sham treated rabbits. No pathological damage to any internal organs.	toxicities related to the anti-mitotic effects of TTFields in the brain

C. Biocompatibility, Electromagnetic Compatibility (EMC) and Electrical Safety, Shelf-Life and Software

The NovoTTF-100A System has passed extensive hardware and software verification and validation. The system also passed testing of applicable electrical safety and electromagnetic compatibility (EMC) standards at a certified laboratory. The electrodes that contact the subject were shown to be biocompatible in dermal sensitization, cytotoxicity and delayed type hypersensitivity studies. The batteries used with the system were shown to meet their specifications after more than 100 recharge cycles. Finally, the electrodes passed shelf life and sterilization validation according to the applicable standards. All of this testing demonstrates that the NovoTTF-100A System operates per its specifications and in accordance with its intended use. These tests are summarized in Tables 5, 6, and 7.

Table 5. Biocompatibility and Sterilization Testing

Test	Methods	Acceptance Criteria	Results	Conclusions
Cytotoxicity	Mouse cell line L929 overlayed by agarose cultured for 24h in indirect contact with the INE electrodes	Vitality and membrane integrity of the cells of potential cytotoxic effects of the test system via grading of the decolorization area and assessment of the cell lysis of the cell culture	No decolorization or cell lysis under or around the test item was detectable. No leachable substances were released in cytotoxic concentrations from the test item.	The sterile INE electrodes are non-cytotoxic
Sensitization	Sterile INE electrodes were tested for	Grade of skin reactions compared to	Sensitization rate after application of the test item	The sterile INE electrodes have no sensitizing

	delayed-type hypersensitivity using the Guinea Pig Maximization Test	control animals (negative control), which were treated with the extraction medium during the induction phase and with the extract of the test item during the challenge phase	extract was 0%. Under the test conditions, the test item showed no signs of allergenic potency.	properties.
Irritation	The potential of sterile INE electrodes to produce dermal irritation in the rabbit was tested by placing them in direct contact with the skin rabbits	Four hours following application, the test item and control are removed, and dermal reactions scored and recorded at the standard time points of 1, 24, 48, and 72 hours following removal	No dermal reactions were noted in either test or control sites at any time points, with the exception of slight erythema noted at the 1hour observation on the test or control sites of 2 out of the 3 rabbits. No clinical signs in reaction to treatment were noted, nor was there any change in body weight.	Primary Irritation Index of 0.0. The irritation response caused by the sterile INE electrode was negligible.
Gamma sterilization validation	Steris IsoMedix Standard Operating Procedures	Per EN 556-1:2001/AC:2006 EN/ISO 11137-1; EN/ISO 11137-2; EN/ISO 11137-3; EN/ISO 11737-1; and EN/ISO 11737-2	Pass	Electrodes are sterile

Table 6. EMC and Electrical Testing

Test	Purpose	Standard	Results
Emission tests	Radiated RF emissions, Class B	EN/IEC 60601-1-2	Pass
Immunity tests	Immunity to electrostatic discharge (ESD)	EN/IEC 60601-1-2	Pass
	Radiated immunity to radio frequency electromagnetic field	EN/IEC 60601-1-2	Pass
	Conducted immunity to electrical fast transients/ bursts (EFT/ B)	EN/IEC 60601-1-2	Pass
	Conducted immunity to disturbances induced by radio frequency field	EN/IEC 60601-1-2	Pass
	Radiated immunity to power frequency magnetic field, 50/60 Hz	EN/IEC 60601-1-2	Pass
Safety – general requirements	Equipment when transported, stored, installed, operated in normal use and maintained according to the instructions of the manufacturer, causes no safety hazard which could reasonably be foreseen and which is not connected with its intended application in normal condition (NC) and in single fault condition (SFC)	IEC 60601-1	Pass
Safety - classification	Type of protection against electric shock Internally powered equipment	IEC 60601-1	Pass
Safety - degree of protection against electric shock	Type BF applied part	IEC 60601-1	Pass
Safety – mode of operation	Continuous operation	IEC 60601-1	Pass

Table 7. Additional Validation Testing

Test	Methods	Acceptance criteria	Results	Conclusions
NovoTTF-100A System hardware verification and validation	Validation of the device, validation of the electrodes and additional parts, and usability testing performed by independent engineers	The NovoTTF-100A will meet all of its hardware requirement specifications	The NovoTTF-100A met its mechanical specifications, hardware requirements for the Electric Field Generator, user interfaces, safety features and labeling requirements	The system functions as intended for its intended use
NovoTTF-100A System software verification and validation	Software validation was performed at the unit level, device level and integration	The NovoTTF-100A software will meet all of its software requirement specifications	Unit: Pass Device: Pass Integration: Pass	The NovoTTF-100A software was found to meet its specified performance criteria
Shelf life validation (INE Electrodes)	Test whether electrical and mechanical properties of the electrodes remain within their specifications at the end of their shelf life	Electrical and mechanical testing of the electrodes remain within their specifications after 6 months	Pass	Shelf life for INE electrodes = 6 months
Environmental testing	Test compliance with IEC TR 60721-4-2 and IEC 60529	Testing will pass when all system components are kept in their respective packaging	Pass	
Battery recharge cycle validation	After 100 charging cycles the battery complies with minimal requirements for adequate therapy	Power the system for at least 90 minutes with the NovoTTF-100A device attached to an equivalent load of 80 ohms	Pass	The NovoTTF-100A portable batteries are validated for a minimum of 100 recharge cycles

References:

1. Kirson, E.D., et al., *Disruption of cancer cell replication by alternating electric fields.* Cancer Res, 2004. 64(9): p. 3288-95.
2. Kirson, E.D., et al., *Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors.* Proc Natl Acad Sci U S A, 2007. 104(24): p. 10152-7.
3. Kirson, E.D., et al., *Modeling tumor growth kinetics and its implications for TTFields treatment planning* in *The 2010 SNO Scientific Meeting and Education Day.* 2010: Montreal, Canada.
4. Kirson, E.D., et al., *Alternating electric fields (TTFields) inhibit metastatic spread of solid tumors to the lungs.* Clin Exp Metastasis, 2009. 26(7): p. 633-40.

X. SUMMARY OF PRIMARY CLINICAL STUDIES

A summary table of the clinical studies of the NovoTTF-100A System in the treatment of recurrent GBM is presented below. These studies are discussed in detail in the following sections.

Table 8. Summary of Clinical Studies

Study Type	Study Design	Objective	Number of Sites	Number of Subjects	Accountability
Pilot	Prospective single arm study	To assess the safety and effectiveness of NovoTTF-100A treatment compared to recurrent GBM historical controls	1	10	All subjects were followed until death. Two subjects were still alive 6.5 years after starting the study.
Pivotal	Prospective, open label, best standard of care randomized control trial	To compare the overall survival (OS)of subjects treated with the NovoTTF-100A alone to subjects treated with the best standard of care chemotherapy available for recurrent GBM	28	237	207 subjects received treatment. Vital status is known for 221 (93%) of subjects. Last follow up date – June 29, 2010

A. Effect of NovoTTF-100A on Recurrent GBM Subjects - A Pilot Study

The effectiveness and safety of the NovoTTF-100A device in the treatment of GBM were first evaluated in a pilot study in 10 subjects with recurrent GBM. The study

was an open-label prospective single arm study to evaluate the safety and effectiveness of TTFields for the treatment of recurrent GBM.

The effectiveness endpoints of the study included the overall survival and time to disease progression, based on radiological assessment of disease progression by monthly magnetic resonance images (MRIs). Other outcome measures included safety and tolerability of NovoTTF-100A treatment based on the incidence and severity of adverse events and side effects (toxicities). The effectiveness results were compared to two different populations: a concurrent best standard of care (BSC) comparator group that was assembled retrospectively and an active historical comparator group that was reconstructed from the Gliadel package insert.[4]

All subjects have previously undergone surgery and radiotherapy for the primary tumor, and all had their first or second GBM recurrence at study entry. All subjects had histologically proven diagnosis of GBM. The two study groups were comparable in baseline characteristics. All NovoTTF-100A subjects were treated with TTFields as monotherapy, with continuous, 24-hour a day, 200 kHz, 0.7 V/cm TTFields. Subjects completed between 1 and 13 months of treatment. The maximal treatment duration was 14.5 months. Overall, more than 65 months of treatment were completed (6.7 months per subject on average). All subjects received at least 4 weeks of NovoTTF-100A therapy.

The treatment with the NovoTTF-100A device was well tolerated with no treatment related serious adverse events seen in any of the subjects. Compliance with treatment was high with subjects receiving treatment on average 72% of the scheduled time (range 38-91%). Mild to moderate contact dermatitis appeared beneath the electrode gel in 8 of the 10 subjects during treatment. In most cases this dermatitis appeared for the first time during the second treatment course. The skin reaction improved with use of topical corticosteroids and regular relocation of the electrode arrays.

The median time to progression (TTP) in the NovoTTF-100A subjects was 26 weeks compared to 9 weeks in historical control data (Wong et al., 1999[5]). The progression free survival at 6 months (PFS6) in the NovoTTF-100A group was 50% compared to 15% in historical control data (Wong et al., 1999[6]). Since most of the subjects in the trial were re-operated, the overall survival in NovoTTF-100A subjects was compared to that reported for Gliadel Wafers. The median overall survival was 14.7 months in NovoTTF-100A subjects compared to the 6 months reported for Gliadel Wafers. The one-year survival in NovoTTF-100A subjects was 60%. Response rate in the NovoTTF-100A treated subjects was 25% [1 complete response (CR) + 1 partial response (PR)] and only two subjects had progressive disease despite treatment. The study demonstrated the excellent safety profile of this treatment modality. Based on

[4] Gliadel Wafer Package Insert, available at http://www.gliadel.com/docs/pdf/Gliadel_PI.pdf.
[5] Wong, E. T., K. R. Hess, et al. (1999). "Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials." J Clin Oncol 17(8): 2572-8.
[6] Wong, E. T., K. R. Hess, et al. (1999). "Outcomes and prognostic factors in recurrent glioma patients enrolled onto phase II clinical trials." J Clin Oncol 17(8): 2572-8.

these pilot study results the decision was made to test the NovoTTF-100A device in a randomized pivotal study in recurrent GBM subjects.

B. Pivotal Study for Recurrent GBM

1. Study Design

The clinical study that formed the basis for determining that the NovoTTF-100A System is safe and effective for its intended use was a multicenter, randomized, controlled clinical trial designed to evaluate the safety and effectiveness of NovoTTF-100A in the treatment of recurrent GBM.

Subjects were randomized to receive either NovoTTF-100A monotherapy or the BSC chemotherapies for recurrent GBM subjects as practiced at each of the participating clinical centers. The hypothesis of this study was that NovoTTF-100A would increase the overall survival of recurrent GBM subjects compared to subjects treated with BSC. The specific aims of the study were:

- To prospectively compare the overall survival of recurrent GBM subjects treated with NovoTTF-100A to those treated with BSC.
- To prospectively determine PFS6, TTP, %1-year survival and quality of life of subjects treated with the NovoTTF-100A compared to BSC.
- To collect evidence of the safety of TTFields applied to subjects with recurrent GBM using the NovoTTF-100A System.
- To compare the median overall survival of recurrent GBM subjects treated with NovoTTF-100A to historical control data.

Subjects with previously diagnosed GBM who had relapsed or progressed despite conventional therapy (surgery and chemo-radiotherapy followed by chemotherapy) were recruited into the study at twenty-eight (28) United States (US) and outside US (OUS) clinical centers.

Immediately following screening, subjects were randomized at a 1:1 ratio to receive either NovoTTF-100A treatment or BSC. The nature of the treatment precluded blinding of subjects and their treating clinicians to the actual treatment received by the subjects. However, a central MRI review was performed by an independent neuro-radiologist blinded to the treatment group assignment of each subject. In addition, an independent Data Monitoring Committee (DMC) monitored the safety data from the study, and a Clinical Events Committee (CEC) was convened to evaluate and adjudicate, where necessary, regarding final safety and effectiveness results of the trial.

Subject accrual lasted 30 months and subject follow-up continued for at least 6 months after accrual of the last subject in each center. The final study analysis compared the OS among 120 NovoTTF-100A subjects and 117 BSC chemotherapy subjects. Subjects were treated between June 20, 2006, and

November 5, 2009. The database for this PMA reflected data collected through June 29, 2010.

Eligibility Criteria

The inclusion and exclusion criteria for the NovoTTF-100A pivotal study are listed below:

Inclusion Criteria

a. Pathological evidence of GBM using WHO classification criteria
b. ≥ 18 years of age
c. Not a candidate for further radiotherapy or additional resection of residual tumor
d. Subjects with disease progression (by Macdonald criteria, i.e., > 25% or new lesion) documented by CT or MRI within 4 weeks prior to enrollment
e. Karnofsky scale ≥ 70
f. Life expectancy at least 3 months
g. Participants of childbearing age must use effective contraception
h. All subjects must sign written informed consent

Exclusion Criteria

a. Actively participating in another clinical treatment trial
b. Within 4 weeks from surgery for recurrence
c. Within 4 weeks from any prior chemotherapy
d. Within 4 weeks from radiation therapy
e. Pregnant
f. Significant co-morbidities within 4 weeks prior to enrollment:
    1) Significant liver function impairment - AST or ALT > 3 times the upper limit of normal
    2) Total bilirubin > upper limit of normal
    3) Significant renal impairment (serum creatinine > 1.7 mg/dL)
    4) Coagulopathy (as evidenced by PT or APTT >1.5 times control in patients not undergoing anticoagulation)
    5) Thrombocytopenia (platelet count < 100 x $10^3/\mu L$)
    6) Neutropenia (absolute neutrophil count < 1 x $10^3/\mu L$)
    7) Anemia (Hb < 10 g/L)
    8) Severe acute infection
g. Implanted pacemaker, defibrillator or deep brain stimulator, or documented clinically significant arrhythmias
h. Infra-tentorial tumor
i. Evidence of increased intracranial pressure (midline shift > 5mm, clinically significant papilledema, vomiting and nausea or reduced level of consciousness)

Treatment Arm

At treatment initiation, subjects were hospitalized for 24 hours. During this period, baseline examinations were performed and NovoTTF-100A treatment was initiated by the investigator under continuous medical supervision. The subjects were also instructed by the investigator on the operation of the NovoTTF-100A System and battery replacement. Once the subjects were trained in operating the device, they were released to continue treatment at home. The subjects received continuous NovoTTF-100A treatment. Treatment was discontinued in the case of non-compliance or clinical disease progression.

Control Arm

All subjects had baseline examinations performed prior to treatment initiation. Subjects received the BSC chemotherapy practiced at each of the participating centers. The BSC treatments used in the study were comprised mainly of the following chemotherapies:

1. Platinum based chemotherapy (Carboplatin)
2. Nitrosureas (BCNU)
3. Procarbazine
4. Procarbazine, lomustine and vincristine (PCV)
5. Temozolomide
6. Avastin
7. Imatinib, erlotinib, irinotecan (mainly in Europe)

Chemotherapeutic treatment protocol was according to standard procedures at each of the participating centers.

Follow Up

During treatment, and until progression for subjects who stopped treatment before progression, all subjects were seen once a month at an outpatient clinic where they underwent medical follow up and routine laboratory exams. An MRI was performed every 2 months until disease progression. Central MRI review was performed by a neuro-radiologist blinded to the treatment group of each subject. Medical follow-up continued for 2 months following disease progression. Subject survival was assessed based on monthly follow up visits, monthly telephone interviews with the subjects' caregivers, and by review of hospital records. Table 9 below provides the full schedule of evaluations in the study.

Table 9. Schedule of Evaluations to be Performed for Each Subject

	T=0 (baseline)	T=1 month (±7 days)	T=2 months (±7 days)	T=3 months (±7 days)	T=4 months (±7 days)	T=5 months (±7 days)	T=6 months (±14 days)	T=monthly until progression+	T=Progression	T=1 month From progression+	T=2 months From progression+	Monthly thereafter+
MRI of the head	X*		X*		X*		X*		X*			
Electrocardiogram (ECG)	X	X	X	X	X	X	X	X	X	X	X	
Physical examination	X	X	X	X	X	X	X	X	X	X	X	
Neurological status	X	X	X	X	X	X	X	X	X	X	X	
Complete blood count (CBC) and differential	X	X	X	X	X	X	X	X	X	X	X	
Chemistry panel (SMAC)	X	X	X	X	X	X	X	X	X	X	X	
Coagulation study	X	X	X	X	X	X	X	X	X	X	X	
Quality of life questionnaire	X			X			X	X&				
Telephone interview												X

* MRI of the head was performed routinely at baseline and again after 2, 4 and 6 months. An MRI of the head was obtained in the event of clinical signs of progression.
& Every third month until progression.
+ Visit window of ± 7 days if visit occurs prior to the 6 month follow-up window, ± 14 days if visit occurs on or after the 6 month follow-up window.

Endpoints

Primary Safety Endpoint

The safety endpoint was the safety and tolerability of NovoTTF-100A treatment based on the incidence and severity of adverse events and toxicities.

Primary Effectiveness Endpoint

The primary outcome of the study was overall survival (OS), as assessed by the Log-Rank test in the intent-to-treat population.

Secondary Effectiveness Endpoints

The secondary outcome measures of the study were:

- Progression free survival rate at 6 months (PFS6)
- Time to progression (TTP)
- One year survival rate (%1-year survival)
- Quality of life (EORTC QLQ-C30 questionnaire)
- Radiological response rate

2. Statistical Analysis Plan and Analysis Populations

Sample Size

The sample size of 237 subjects for the study was designed to test the superiority hypothesis that NovoTTF-100A would significantly increase the overall survival of recurrent GBM subjects compared to subjects treated with best standard of care chemotherapies. This sample size took into consideration missing vital status data on 7% of subjects.

Statistical Analysis

The statistical hypothesis that was to be tested for the primary endpoint of overall survival was:

$H_0: \beta=0$ versus $H_A: \beta\neq0$

where, $\exp(\beta)=h_1(t)/h_2(t)$ and $h_1(t)$ is the hazard at time t for the treatment arm and $h_2(t)$ is the hazard at time t for the control arm. This hypothesis was to be tested using the log-rank test at an alpha of 0.05 (after waiving an interim analysis).

PFS6 was to be compared between groups. The statistical hypothesis that was to be tested was:

$H_0: P_t\text{-}Pc \leq 0$ versus $H_A: P_t\text{-}Pc > 0$

where, P_t and Pc are the proportions of subjects with progression free survival at 6 months in the treatment and control groups, respectively. Since PFS6 was the only secondary endpoint with a formal hypothesis test, the endpoint was to be tested at significance level of 0.05 if and only if the pre-specified superiority test for the primary endpoint (i.e., log-rank test for overall survival) was to show $p < 0.05$.

Analysis Populations

The following analysis populations were used to evaluate the study results:

- **Intent-to-Treat (ITT)**

  The ITT population includes all subjects who were randomized to the trial. The analysis was performed by the treatment group to which the subject was randomized.

- **Safety Population**

  The Safety Population includes all subjects who received at least one dose of BSC therapy or at least one treatment with the NovoTTF device. The safety analysis was performed by treatment group according to the treatment that the subject actually received. Only adverse events (AEs) occurring prior to disease progression were included in the summary tables because of the obvious confounding of the safety analysis that may result from the disease condition and/or subsequent therapy.

  See **Figure 1** below showing the analysis populations for the NovoTTF-100A trial.

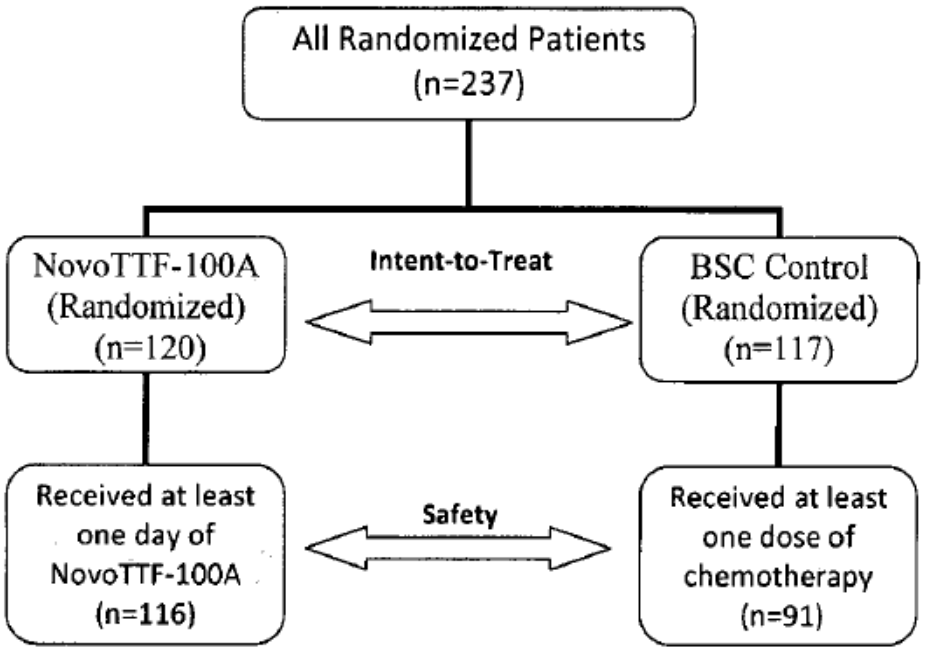


Figure 1. Analysis Populations

3. Subject Accountability

237 subjects (120 NovoTTF-100A; 117 BSC) with progressive or recurrent GBM were enrolled in the study. One-hundred-twenty subjects (120) were randomized to NovoTTF-100A group and 117 subjects to the BSC group. Four (4) subjects in the NovoTTF-100A group and 26 subjects in the BSC group never received any treatment on study. The date of death is available for 20 of the 30 subjects who never started therapy on trial.

Subject disposition and follow-up is shown in the table below.

Table 10. Subject Disposition All Randomized Subjects

	NovoTTF-100A	**BSC**	**All Subjects**
	(N=120)	**(N=117)**	**(N=237)**
	n (%)	n (%)	n (%)
Number of Subjects Randomized	120 (100)	117 (100)	237 (100)
No. Subjects not Receiving Study Treatment	4 (3)	26 (22)	30 (13)
Withdrawal of Consent	3 (3)	15 (13)	18 (8)
Non-Compliance	0 (0)	5 (4)	5 (2)
Pre-treatment Adverse Event	1 (1)	3 (3)	4 (2)
Other	0 (0)	3 (3)	3 (1)
No. Subjects Receiving Treatment/Therapy	116 (97)	91 (78)	207 (87)
Number of subjects completing 2 months post progression follow-up	32 (27)	36 (31)	68 (29)
Number of subjects discontinued from the study prior to completing 2 months post progression follow-up (excluding subjects who never started treatment)	84 (70)	55 (47)	139 (59)
Reason for Discontinuation (for subjects who started therapy)	n=116	n=91	n=207
Death	31 (27)	16 (18)	47 (23)
Adverse Event (including Serious AEs)	13 (11)	7 (8)	20 (10)
Non-Compliance	1 (1)	2 (2)	3 (2)
Withdrawal of Consent	10 (9)	10 (11)	20 (10)
Other*	29 (25)	20 (22)	49 (24)

* "Other" includes different definitions which most likely correspond to one of the three previous categories, but did not precisely fit any one CRF category. For example, subjects who moved to hospice care and could not return for visits, subjects with general clinical decline who stopped coming for visits due to transportation limitation, individual cases where the investigator thought it would be better to take the subject off trial without specifying a reason beyond clinical judgment, etc.

4. Demographics and Baseline Characteristics

Baseline characteristics of the overall study population were as follows: mean age: 53.6 years; Karnofsky score: 81.6±11%; tumor size (cm^2): 16.1±12.4; progression number: 1.4±0.9; re-operated: 26%; male: 70%; previous low grade: 10%; prior bevacizumab (Avastin) failure: 19%. Baseline characteristics were similar between treatment groups (Table 4) with slightly more men in the NovoTTF-100A group than in the BSC group (77% vs. 62%), a lower incidence of frontal lobe tumors in the NovoTTF-100A group than in the BSC group (32% vs. 50%), and a slightly higher mean KPS in the NovoTTF-100A group than in the BSC group (83% vs. 80%), though the median KPS was 80% in both groups. Adjusted analyses for all pre-specified or all statistically significant baseline covariates for overall survival did not change the outcome of the trial.

Table 11. Demographics and Baseline Characteristics by Treatment Group Intent-to-Treat Population			
	NovoTTF-100A	**BSC**	
Characteristics	**(N=120)**	**(N=117)**	**P-Value**
	n (%)*	n (%)	
Race			
Caucasian	111 (93)	106 (91)	ns**
African American	2 (2)	5 (4)	
Asian	0	3 (3)	
Hispanic	7 (6)	2 (2)	
Other	0	1 (1)	
Female Gender	28 (23)	44 (38)	0.0169
Frontal Tumor Position	38 (32)	58 (50)	0.0018
Bilateral or Midline Tumor Location	23 (19)	17 (15)	ns
Prior Avastin Use	24 (20)	21 (18)	ns
Re-operation for Recurrence	33 (28)	29 (25)	ns
*(n/N)(100) = %			
Prior Low-grade Glioma	12 (10)	11 (9)	ns
Median Age (years) (min, max)	54 (24, 80)	54 (29,74)	ns
Median Weight (kg)	80	80.5	ns
Mean # of Prior GBM Recurrences	1.5	1.3	ns
Mean Karnofsky Performance Score (min, max)	83±10.84	80.1±11.01	0.0456
Median Tumor Area (mm^2)	1440	1391	ns
Median Time from GBM Diagnosis to Randomization (days)	334.5	340	ns
Mean Time from last RT dose to Randomization (months)	13.71	13.93	

*(n/N)(100) = % ** ns = non-significant or $p < 0.05$

5. Study Results

Safety Results

The analysis of safety was based on the safety population including 116 NovoTTF-100A subjects and 91 BSC chemotherapy subjects followed for 6 months since the inclusion of the last subject in the trial. The key safety outcomes for this study are presented below in Tables 12 to 14.

Treatment with the NovoTTF-100A device is not expected to cause any serious side effects. However, the following adverse events were seen in ≥2% of subjects treated with the device in the pivotal study, or in ≥2% of subjects treated with BSC chemotherapy:

Table 12. Percentage of Subjects with AEs in the NovoTTF-100A versus BSC groups (Including incidence of severe AEs) ≥ 2%

	NovoTTF-100A (N=116)		BSC Chemotherapy (N=91)	
System Organ Class	**Subjects n (%)***		**Subjects n (%)**	
Preferred Term	**All AEs**	**Severe**	**All AEs**	**Severe**
Percentage of Subjects with >=1 AE	64 (55)	18 (16)	54 (59)	17 (19)
Blood and lymphatic system disorders	5 (4)	1 (1)	17 (19)	4 (4)
Anaemia	2 (2)	0 (0)	2 (2)	0 (0)
Leukopenia	1 (1)	0 (0)	6 (7)	1 (1)
Lymphopenia	2 (2)	1 (1)	3 (3)	1 (1)
Neutropenia	2 (1)	0 (0)	2 (2)	0 (0)
Thrombocytopenia	3 (3)	0 (0)	11 (12)	2 (2)
Cardiac disorders	8 (7)	1 (1)	6 (7)	0 (0)
Oedema peripheral	6 (5)	1 (1)	3 (3)	0 (0)
Tachycardia	1 (1)	0 (0)	3 (3)	0 (0)
Ear and labyrinth disorders	1 (1)	0 (0)	3 (3)	0 (0)
Ear pain	0 (0)	0 (0)	2 (2)	0 (0)
Endocrine disorders	2 (2)	0 (0)	2 (2)	0 (0)
Cushingoid	2 (2)	0 (0)	1 (1)	0 (0)
Eye disorders	3 (3)	0 (0)	5 (5)	0 (0)

Table 12. Percentage of Subjects with AEs in the NovoTTF-100A versus BSC groups (Including incidence of severe AEs) ≥ 2%				
	NovoTTF-100A (N=116)		BSC Chemotherapy (N=91)	
System Organ Class	Subjects n (%)*		Subjects n (%)	
Preferred Term	**All AEs**	**Severe**	**All AEs**	**Severe**
Dry eye	2 (2)	0 (0)	0 (0)	0 (0)
Vision blurred	1 (1)	0 (0)	2 (2)	0 (0)
Gastrointestinal disorders	9 (8)	1 (1)	27 (30)	3 (3)
Abdominal pain	0 (0)	0 (0)	6 (7)	0 (0)
Aphthous stomatitis	0 (0)	0 (0)	2 (2)	0 (0)
Constipation	2 (2)	0 (0)	4 (4)	0 (0)
Diarrhoea	0 (0)	0 (0)	11 (12)	2 (2)
Nausea	3 (3)	0 (0)	15 (16)	0 (0)
Vomiting	3 (3)	0 (0)	6 (7)	0 (0)
General disorders and administration site conditions	15 (13)	1 (1)	14 (15)	1 (1)
General physical health deterioration	2 (2)	0 (0)	1 (1)	0 (0)
Malaise	11 (9)	1 (1)	10 (11)	0 (0)
Pyrexia	2 (2)	0 (0)	1 (1)	0 (0)
Infections and infestations	5 (4)	0 (0)	11 (12)	1 (1)
Candidiasis	4 (3)	0 (0)	3 (3)	0 (0)
Ear infection	0 (0)	0 (0)	2 (2)	0 (0)
Urinary tract infection	0 (0)	0 (0)	3 (3)	1 (1)
Injury, poisoning and procedural complications	21 (18)	0 (0)	1 (1)	0 (0)
Fall	5 (4)	0 (0)	0 (0)	0 (0)
Medical device site reaction (rash under electrodes)	18 (16)	0 (0)	0 (0)	0 (0)
Investigations	8 (7)	2 (2)	5 (5)	1 (1)
Blood lactate dehydrogenase increased	2 (2)	0 (0)	1 (1)	0 (0)
Hepatic enzyme abnormal	1 (1)	0 (0)	2 (2)	1 (1)
Weight increased	1 (1)	0 (0)	2 (2)	0 (0)
Metabolism and nutrition disorders	9 (8)	1 (1)	12 (13)	3 (3)

Table 12. Percentage of Subjects with AEs in the NovoTTF-100A versus BSC groups (Including incidence of severe AEs) ≥ 2%				
	NovoTTF-100A (N=116)		BSC Chemotherapy (N=91)	
System Organ Class	Subjects n (%)*		Subjects n (%)	
Preferred Term	**All AEs**	**Severe**	**All AEs**	**Severe**
Anorexia	0 (0)	0 (0)	4 (4)	1 (1)
Diabetes mellitus	2 (2)	0 (0)	0 (0)	0 (0)
Hyperglycaemia	2 (2)	0 (0)	2 (2)	1 (1)
Hypokalaemia	2 (2)	0 (0)	4 (4)	1 (1)
Musculoskeletal and connective tissue disorders	6 (5)	0 (0)	8 (9)	0 (0)
Back pain	2 (2)	0 (0)	3 (3)	0 (0)
Muscular weakness	0 (0)	0 (0)	3 (3)	0 (0)
Pain in extremity	0 (0)	0 (0)	2 (2)	0 (0)
Neoplasms benign, malignant and unspecified	2 (2)	2 (2)	2 (2)	1 (1)
Neoplasm progression	2 (2)	2 (2)	2 (2)	1 (1)
Nervous system disorders	50 (43)	8 (7)	33 (36)	5 (5)
Amnesia	3 (3)	0 (0)	0 (0)	0 (0)
Balance disorder	2 (2)	0 (0)	0 (0)	0 (0)
Brain oedema	1 (1)	0 (0)	2 (2)	0 (0)
Cognitive deterioration	2 (2)	1 (1)	2 (2)	0 (0)
Cognitive disorder	2 (2)	0 (0)	2 (2)	0 (0)
Convulsion	11 (9)	3 (3)	4 (4)	2 (2)
Coordination abnormal	2 (2)	0 (0)	4 (4)	0 (0)
Cranial nerve disorder	3 (3)	0 (0)	1 (1)	0 (0)
Difficulty in walking	1 (1)	0 (0)	2 (2)	0 (0)
Dizziness	3 (3)	0 (0)	2 (2)	0 (0)
Dysaesthesia	2 (2)	0 (0)	1 (1)	0 (0)
Dysphasia	4 (3)	0 (0)	2 (2)	0 (0)
Headache	18 (16)	2 (2)	9 (10)	0 (0)
Hemianopia	2 (2)	0 (0)	4 (4)	1 (1)
Hemiparesis	11 (9)	0 (0)	4 (4)	1 (1)
Hyperreflexia	3 (3)	0 (0)	2 (2)	0 (0)
Hypoaesthesia	2 (2)	0 (0)	3 (3)	0 (0)
Hyporeflexia	0 (0)	0 (0)	2 (2)	0 (0)
Memory impairment	2 (2)	0 (0)	0 (0)	0 (0)
Nervous system disorder	3 (3)	1 (1)	3 (3)	0 (0)
Neuropathy peripheral	2 (2)	1 (1)	1 (1)	0 (0)

Table 12. Percentage of Subjects with AEs in the NovoTTF-100A versus BSC groups (Including incidence of severe AEs) ≥ 2%				
	NovoTTF-100A (N=116)		BSC Chemotherapy (N=91)	
System Organ Class	Subjects n (%)*		Subjects n (%)	
Preferred Term	**All AEs**	**Severe**	**All AEs**	**Severe**
Tremor	2 (2)	0 (0)	2 (2)	0 (0)
Psychiatric disorders	12 (10)	0 (0)	7 (8)	0 (0)
Agitation	2 (2)	0 (0)	0 (0)	0 (0)
Depression	2 (2)	0 (0)	5 (5)	0 (0)
Insomnia	2 (2)	0 (0)	2 (2)	0 (0)
Mental status changes	6 (5)	0 (0)	1 (1)	0 (0)
Renal and urinary disorders	7 (6)	1 (1)	3 (3)	0 (0)
Pollakiuria	2 (2)	0 (0)	0 (0)	0 (0)
Urinary incontinence	4 (3)	1 (1)	2 (2)	0 (0)
Respiratory, thoracic and mediastinal disorders	7 (6)	0 (0)	10 (11)	1 (1)
Cough	4 (3)	0 (0)	4 (4)	0 (0)
Dyspnea	2 (2)	0 (0)	4 (4)	1 (1)
Nasopharyngitis	0 (0)	0 (0)	2 (2)	0 (0)
Skin and subcutaneous tissue disorders	9 (8)	0 (0)	9 (10)	0 (0)
Alopecia	0 (0)	0 (0)	3 (3)	0 (0)
Rash	5 (4)	0 (0)	0 (0)	0 (0)
Swelling face	2 (2)	0 (0)	1 (1)	0 (0)
Vascular disorders	5 (4)	2 (2)	6 (7)	2 (2)
Hypertension	1 (1)	0 (0)	3 (3)	0 (0)
Pulmonary embolism	1 (1)	1 (1)	2 (2)	2 (2)

*(n/N)(100) = %

The following serious adverse events (SAEs) were seen during the pivotal trial:

Table 13. Treatment Emergent SAEs by Body System and Preferred Term				
	NovoTTF-100A (N=116)		BSC Chemotherapy (N=91)	
System Organ Class	**Events n**	**Subjects n (%)***	**Events n**	**Subjects n (%)**
Preferred Term				
Number with ≥1 SAE	16	15 (13)	11	10 (11)
Blood and lymphatic system disorders	**0**	**0 (0)**	**1**	**1 (1)**
Febrile neutropenia	0	0 (0)	1	1 (1)
Cardiac disorders	**2**	**2 (2)**	**0**	**0 (0)**
Oedema peripheral	2	2 (2)	0	0 (0)
Gastrointestinal disorders	**0**	**0 (0)**	**1**	**1 (1)**
Intestinal perforation	0	0 (0)	1	1 (1)
General disorders and administration site conditions	**1**	**1 (1)**	**0**	**0 (0)**
General physical health deterioration	1	1 (1)	0	0 (0)
Infections and infestations	**0**	**0 (0)**	**3**	**2 (2)**
Cellulitis	0	0 (0)	1	1 (1)
Pneumonia	0	0 (0)	1	1 (1)
Urinary tract infection	0	0 (0)	1	1 (1)
Injury, poisoning and procedural complications	**1**	**1 (1)**	**0**	**0 (0)**
Cerebrospinal fluid leakage	1	1 (1)	0	0 (0)
Metabolism and nutrition disorders	**1**	**1 (1)**	**1**	**1 (1)**
Anorexia	0	0 (0)	1	1 (1)
Dehydration	1	1 (1)	0	0 (0)
Neoplasms benign, malignant and unspecified (incl cysts and polyps)	**2**	**2 (2)**	**2**	**2 (2)**
Neoplasm progression	2	2 (2)	2	2 (2)

Table 13. Treatment Emergent SAEs by Body System and Preferred Term				
	NovoTTF-100A (N=116)		BSC Chemotherapy (N=91)	
System Organ Class	**Events n**	**Subjects n (%)***	**Events n**	**Subjects n (%)**
Preferred Term				
Nervous system disorders	**5**	**5 (4)**	**1**	**1 (1)**
Convulsion	3	3 (3)	0	0 (0)
Headache	2	2 (2)	0	0 (0)
Nervous system disorder	0	0 (0)	1	1 (1)
Psychiatric disorders	**1**	**1 (1)**	**0**	**0 (0)**
Mental status changes	1	1 (1)	0	0 (0)
Respiratory, thoracic and mediastinal disorders	**1**	**1 (1)**	**0**	**0 (0)**
Dyspnoea	1	1 (1)	0	0 (0)
Vascular disorders	**2**	**2 (2)**	**2**	**2 (2)**
Cerebral hemorrhage	1	1 (1)	0	0 (0)
Pulmonary embolism	1	1 (1)	2	2 (2)

*n/N)(100) = %

The following adverse events were assessed as possibly to definitely related to NovoTTF-100A treatment:

Table 14. Device-Related AEs

	NovoTTF-100A
Adverse Event	**[N=116]**
	# (%)
Medical device site reaction	18 (16)
Headache	4 (3)
Malaise	2 (2)
Muscle twitching	1 (1)
Fall	1 (1)
Skin ulcer	1 (1)

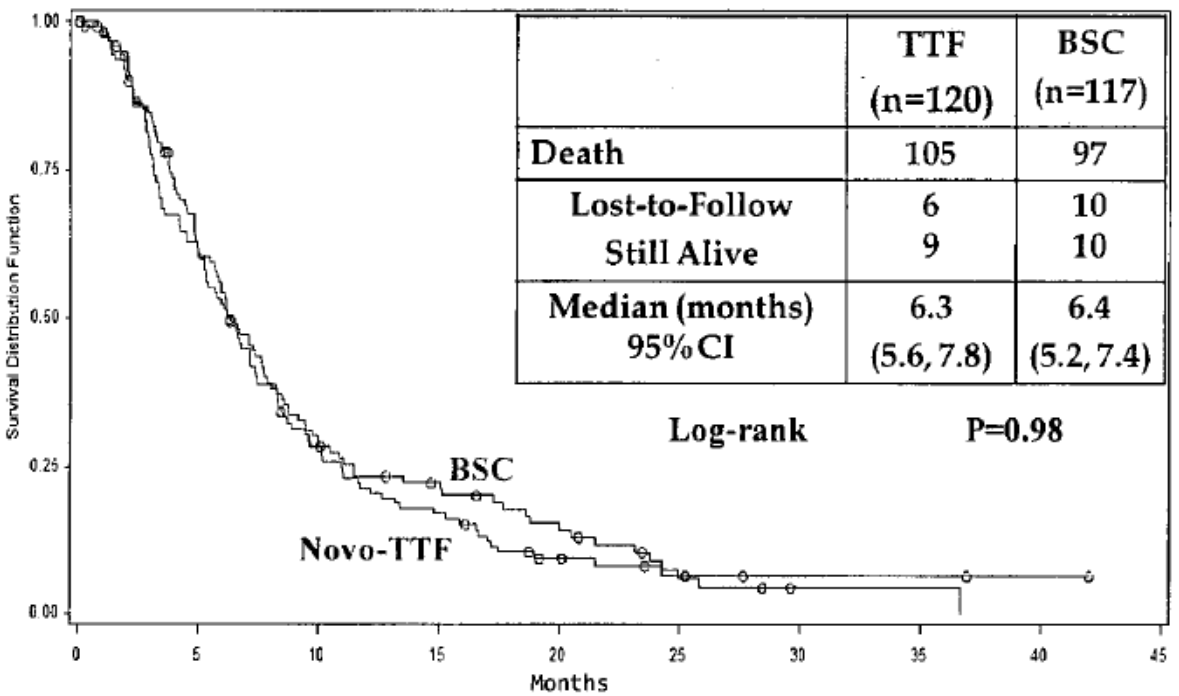
Effectiveness Results

Primary Effectiveness Endpoint – Overall Survival

Vital status is known for 221 (93%) subjects at the end of the study; 202 subjects were known to have died and 19 subjects (Novo-TTF=9, BSC=10) were still alive at the end of the study (6 months after the last subject had been randomized). Sixteen (7%) subjects (Novo-TTF=6, BSC=10) were lost to vital status follow-up. The majority of subjects lost to follow-up were subjects who never started the assigned treatment after randomization (Novo-TTF=1, BSC=8). The remaining 7 subjects (Novo-TTF=5, BSC=2) were lost to follow-up during the study due to non-compliance with the follow up protocol.

In the ITT population including all randomized subjects (Novo-TTF=120, BSC=117), there was no significant difference in overall survival (OS) between the two treatment groups (median OS Novo-TTF=6.3 vs. BSC=6.4 months; Log-rank p=0.98, Hazard Ratio (HR) = 1.0, 95% Confidence Interval of HR: 0.76, 1.32). The Kaplan-Meier survival curves (Fig. 2) for the two treatment groups appeared to be very similar during first 12 months of follow-up, where 80% of the events occurred in both groups. Between 12 and 24 months, the survival curves separated in favor of the BSC control group. After 24 months, the number of subjects remaining may be too small to reliably estimate the long term survival outcome.

Figure 2. Primary Effectiveness Endpoint Analysis: ITT population



	TTF (n=120)	BSC (n=117)
Death	105	97
Lost-to-Follow	6	10
Still Alive	9	10
Median (months)	6.3	6.4
95% CI	(5.6, 7.8)	(5.2, 7.4)

	Months	0	3	6	9	12	15	18	21	24
NovoTTF-100A	At Risk	120	98	62	38	24	19	11	7	5
	Events	0	19	53	76	90	95	102	103	104
	Censored	0	3	5	6	6	6	7	10	11
BSC	At Risk	117	83	56	32	23	20	15	10	6
	Events	0	24	51	73	81	82	86	90	93
	Censored	0	10	10	12	13	15	16	17	18

Secondary Effectiveness Endpoints

The secondary effectiveness endpoints for the NovoTTF-100A trial support the primary endpoint results, in that they show the NovoTTF-100A device is clinically comparable to the BSC control among the evaluable subjects (Table 15). One-year-survival in the NovoTTF-100A group (evaluable number of subjects = 114) was very similar to that in the BSC chemotherapy group (evaluable = 104) 21.9% vs. 22.1%, respectively. According to the Clinical Events Committee's (CEC) adjudication of the investigator's assessment of tumor progression, which considered both clinical and radiological information, progression free survival at 6 months (PFS6) was 21.4% for the Novo-TTF-100A group (evaluable = 103) vs. 15.2% for the BSC group (evaluable = 92) and median time to progression (TTP) was 9.3 weeks for NovoTTF-100A vs. 9.6 weeks for BSC. Based on the unblinded investigator's assessment, radiological response rates were reported as 14% for the NovoTTF-100A group (evaluable = 100) compared to 9.6% for the BSC group (evaluable = 73).

However, based on core radiology review, limited to MRI review, PFS6, radiological response rate and median TTP appeared to be better among the evaluable subjects in the BSC group than in the NovoTTF-100A group.

Table 15. Summary of Secondary Endpoints (except Quality of Life)

Secondary Endpoints	**Treatment Group**	
	NovoTTF-100A	**BSC**
Total Number of Patients	120	117
	% (n/N)	% (n/N)
One-Year Survival	21.9% (25/114)	22.1% (23/104)
PFS6		
CEC adjudicated	21.4% (22/103)	15.2% (14/92)
Core radiology review	17.0% (17/100)	19.4% (13/67)
Radiological Response Rate		
Investigator assessment	14.0% (14/100)	9.6% (7/73)
Core radiology review	4.1% (4/97)	6.8% (5/73)
Median TTP (weeks)		
CEC adjudicated	9.3	9.6
Core radiology review	9.9	12.1

Finally, quality of life based on QLQ C-30 and BN-20 questionnaires was consistently higher in NovoTTF-100A than in BSC chemotherapy subjects (5 out of 6 general scales and of 9 symptom 7 scales including, nausea, vomiting, diarrhea, constipation and pain)

XI. PANEL MEETING RECOMMENDATION AND FDA'S POST-PANEL ACTION

A. Panel Meeting Recommendation

At an advisory meeting held on March 17, 2011, the Neurological Devices Advisory Panel recommended that the data included in the NovoCure Ltd. PMA for the NovoTTF-100A System demonstrated that:

- There is a reasonable assurance that the NovoTTF–100A System is safe for use in patients who meet the criteria specified in the proposed indication.
- There is a reasonable assurance that the NovoTTF–100A System is effective for use in patients who meet the criteria specified in the proposed indication.
- The benefits of the NovoTTF–100A System for use in patients who meet the criteria specified in the proposed indication outweigh the risks of the NovoTTF–100A System for use in patients who meet the criteria specified in the proposed indication.

B. FDA's Post-Panel Action

Following the Neurological Devices Advisory Panel meeting, we revised the indications for use (IFU) statement to address concerns expressed by members of the panel and to incorporate specific recommendations conveyed by members of the panel. Specifically, the age restriction was modified to reflect a population "22 years of age or older" and that the patients had to have received chemotherapy prior to receiving treatment with the NovoCure device ("...after receiving chemotherapy").

XII. CONCLUSIONS DRAWN FROM PRECLINICAL AND CLINICAL STUDIES

A. Safety Conclusions

In general, the NovoTTF-100A System was well tolerated by subjects during the study. Localized skin reactions on the scalp at the site of device contact were observed in 16% of subjects. A slightly higher rate of neurological adverse events (e.g., convulsion, hemiparesis, headache) was observed in NovoTTF-100A treated subjects (43.1% or 50/116 subjects) compared to BSC-treated subjects (36.3% or 33/91 subjects). However, BSC subjects, as anticipated, experienced a much higher rate of chemotherapy associated adverse events (e.g., hematological, gastrointestinal, infectious).

B. Effectiveness Conclusions

The pivotal trial failed to demonstrate the superiority of the NovoTTF-100A System over BSC with respect to the primary endpoint (i.e., overall survival). Because there was no prespecified statistical analysis plan to assess non-inferiority of the device-treated group compared to BSC, and the questionable validity of post-trial identified historical control of ineffectively treated subjects, it is difficult to draw a sound statistical conclusion regarding the non-inferiority from the effectiveness data. However, Kaplan-Meier survival curves for the two treatment groups appeared to be very similar in the first 12 months of follow up. Between 12 and 24 months, the survival curves separated slightly in favor of the BSC control group while being aware that after 12 months, the number of subjects remaining may be too small to reliably estimate the long term survival outcome. Secondary effectiveness endpoints including one year survival, progression free survival at 6 months, radiological response rate, and time to tumor progression also appeared comparable between the two treatment groups.

C. Overall Conclusions

Recurrent GBM is a fatal, end-stage, disease with a 1-year survival of less than 20% and a negligible 5-year survival. The outcome of patients with this disease has not improved significantly in the past decade despite the introduction of temozolomide, Bevacizumab and the use of Gliadel wafers. Quality of life of recurrent GBM patients is compromised due to the neurological deficits caused by the tumor itself together with the considerable side effects of the various standard chemotherapies and experimental treatments. Treatment options for recurrent GBM are very limited, and all have limitations, including severe potential side effects. These options include tumor resection in a minority of cases (with or without Gliadel Wafer implantation), additional radiotherapy boost in selected cases and chemotherapy using bevacizumab.

Compared to previous chemotherapy approvals for recurrent GBM, the current pivotal trial was generally well designed and conducted (e.g., randomized superiority study, multi-center, half of the subjects from the US, data poolable between countries, and minimal loss to follow-up). Although the pivotal study failed to show that NovoTTF-100A is superior to BSC in overall survival and secondary effectiveness endpoints, NovoTTF-100A treatment exhibits minimal toxicity, clinically comparable primary and secondary effectiveness, and better quality of life compared to the chemotherapies used in the control arm of the study.

XIII. CDRH DECISION

CDRH issued an approval order on April 8, 2011.
The final conditions of approval cited in the approval order are described below.

The applicant's manufacturing facilities were inspected and found to be in compliance with the device Quality System (QS) regulation (21 C.F.R. 820).

XIV. APPROVAL SPECIFICATIONS

Directions for use: See device labeling.

Hazards to Health from Use of the Device: See Indications, Contraindications, Warnings, Precautions, and Adverse Events in the device labeling.

Post-approval Requirements and Restrictions: See approval order.

XV. REFERENCES

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