Food and Drug Administration

Neurological Devices Panel

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NovoCure Ltd.

NovoTTF-100A System

PMA P100034

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NovoTTF-100A System (P100034)
NovoCure Ltd.

Panel Pack
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SPONSOR EXECUTIVE SUMMARY

NOVOTTF-100A SYSTEM FOR THE TREATMENT OF RECURRENT GLIOBLASTOMA MULTIFORME (GBM)
NOVOCURE LTD.

P100034

MARCH 17, 2011

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1.0 SUMMARY

1.1 Disease Background

Glioblastoma multiforme (GBM) is the most common and devastating primary brain tumor. The disease affects more than 10,000 people annually in the US. GBM is still universally fatal despite ongoing research and the introduction of new therapies in neuro-oncology. The disease is classified as “recurrent GBM” when the tumor recurs or progresses after standard treatment. Patients with recurrent GBM have a dismal one-year survival rate of about 10% and a median overall survival time of only 3.5 months when not treated with an effective therapy. Patients who suffer from recurrent GBM experience debilitating neurological symptoms from their underlying disease while their quality of life is devastated by the side effects of the therapies used to keep them alive, none of which is curative.

1.2 Current Standard of Care

When GBM is first diagnosed, patients undergo debulking surgery, if possible, followed by concomitant radiotherapy and chemotherapy using temozolomide. Some patients have carmustine wafers (Gliadel Wafers) implanted in the resection cavity at the time of surgery. This initial treatment is then followed by monthly courses of temozolomide which are repeated for six months or until disease progression. Treatment options are limited when the disease recurs. Only 20% of GBM patients are candidates for additional debulking surgery, with or without Gliadel Wafer placement, at the time of recurrence. A small number of patients can receive an ionizing radiation boost to the area of recurrence. Most patients are treated with bevacizumab (Avastin), salvage chemotherapy or experimental treatments. These treatments are effective in extending survival by several months compared to ineffective chemotherapies (from a median of 3-4 months to a median of 6-7 months) and double the one year survival rate (from 10 to 20%). However, patients receiving chemotherapies suffer from wound healing complications, infections, diarrhea, constipation, nausea, vomiting, pain, decreased blood cell counts (and their complications), bleeding disorders and thromboembolic events (e.g., stroke). Thus, the quality of life of recurrent GBM patients is very poor due to their underlying disease symptoms together with the toxic effects of chemotherapy.

1.3 Scientific Basis of TTField Therapy

TTFields (tumor treating fields) are an electric field based loco-regional, antimitotic treatment modality, which has been shown to inhibit the growth of cancerous tumors *in vitro* and *in vivo*. These fields are intermediate frequency (200 kHz) and low intensity (1 V/cm) alternating electric fields. At this frequency and intensity, TTFields cannot stimulate nerves or muscles, nor do they lead to heating of the tumor or surrounding tissues. Since TTFields are applied using electrically insulated electrodes, there is no direct current flow into the tissue so that electrolysis and tissue damage do not occur over time. TTFields have been shown to inhibit cancer cell replication by interference with the proper formation of the mitotic spindle during anaphase and by causing dielectrophoretic intracellular dislocation of macromolecules and organelles during late telophase. Acting together, these two processes, which are specific to dividing cells only, lead to apoptosis and can result in tumor arrest or regression *in vivo*. Since most normal adult brain cells proliferate very slowly, if at all, they are hypothesized to be little 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, the antimitotic effect of TTFields has been shown to be frequency-specific to the cell type treated. Specifically, 200 kHz TTFields which inhibit the replication of GBM tumor cells do not affect the replication of other cell types (e.g., neurons).

1.4 The NovoTTF-100A Device

The NovoTTF-100A is a portable, battery or power supply operated medical device, consisting of an Electric Field Generator (the device), electrodes and accessories. The device delivers TTFields to the patient through four electrically-insulated, disposable, surface electrodes placed on the patient's shaved scalp. The electrodes can be covered with a hat or a wig for aesthetic reasons and are replaced once or twice a week in order to maintain optimal contact with the skin. The device is used continuously until clinical disease progression and is intended to be used for at least four weeks contiguously. Patients carry the device in a convenient over-the-shoulder carrying case or in a backpack. The device is fully automated and is easy to use. The patient is only required to turn the device on, change and recharge the batteries when depleted, and replace their electrodes with the assistance of a caregiver.

1.5 Pivotal Study Design

The pivotal study was a randomized, open-label, parallel-group controlled trial to evaluate the safety and efficacy of the NovoTTF-100A device as compared to best standard of care effective chemotherapies (BSC). Patients were randomized at a 1:1 ratio between treatment groups and followed until death. Clinical follow-up included monthly visits to the outpatient clinic and an MRI of the brain every second month, until disease progression. The primary efficacy endpoint was overall survival. Secondary efficacy endpoints included progression free survival rate at 6 months, one-year survival rate, radiological response rate, and time to disease progression. The trial also included an assessment of patient quality of life based on the EORTC QLQ C-30 questionnaire.

1.6 Pivotal Study Results

1.6.1 Baseline Characteristics

Two-hundred-thirty-seven (237) patients (120 NovoTTF-100A; 117 BSC) with recurrent GBM were enrolled in the study. Baseline characteristics were as follows: mean age 53.6 years; Karnofsky score 81.6±10.9%; tumor size 16.2±12.4 cm^2; progression number 1.4±0.9 (range 1-6); re-operated 26%; male 70%; previous low grade glioma 10%; prior bevacizumab failure 19%. Baseline characteristics were similar between treatment groups 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. It is important to note that the patients in this trial appear to have worse prognostic baseline characteristics than in many previous recurrent GBM trials (e.g., bevacizumab and Gliadel Wafer registration trials). More than half of the patients in the trial were at their second or subsequent recurrence and baseline tumors were very large (diameter > 5cm). In addition, patients with prior bevacizumab failure have been shown to have a poor prognosis for overall survival, which is also seen in the pivotal trial.

1.6.2 Analysis Populations

The efficacy analyses were performed on the following patient populations:

(1) Intent-To-Treat (ITT): all randomized patients regardless of whether or not they received any treatment;

(2) Modified ITT–1 (mITT1): all NovoTTF-100A patients who received at least one predefined course of NovoTTF-100A treatment (4 weeks), and all patients randomized to the BSC group regardless of whether or not they received their chemotherapy on study;

(3) Modified ITT–2 (mITT2): all NovoTTF-100A patients who received at least one predefined course of NovoTTF-100A treatment (4 weeks), and BSC patients who received at least one dose of chemotherapy on study regardless of whether or not the chemotherapy was predefined in the protocol; and

(4) Per Protocol (PP): all NovoTTF-100A patients who received at least one predefined course of NovoTTF-100A treatment (4 weeks), and BSC patients who received at least one dose of chemotherapy on study that was predefined in the protocol or bevacizumab.

All safety analyses were performed on a Safety Population, which included all patients in both treatment groups who received any treatment on study.

1.6.3 Primary Efficacy Endpoint

In the ITT population, the most conservative analysis population used for evaluation of efficacy, the OS was almost identical in the NovoTTF-100A and BSC groups (median OS=6.3 vs. 6.4 months; HR=1.0 (95% CI 0.76-1.32); p=0.98). Among the US sites, the NovoTTF-100A group showed a more favorable result compared to the BSC group, where the median OS was 6.1 and 5.3 months for NovoTTF-100A and BSC groups, respectively. Compared to literature controls, these results demonstrated that NovoTTF-100A treatment is significantly more effective than ineffective chemotherapies, and is as effective as ("non-inferior" to) BSC treatment in the ITT population. This analysis takes into consideration the upper bound of the 95% CI of HR, 1.32, which is considerably below the estimated HR (1.94) comparing the mortality risk of ineffective chemotherapies to effective chemotherapies.

To evaluate the true efficacy of the NovoTTF-100A device, NovoTTF-100A patients who did not receive a predefined treatment course (4 weeks of treatment with NovoTTF-100A) with the device were excluded from the mITT and PP populations. As shown in the table below, NovoTTF-100A patients who received a predefined treatment course had a median OS of 7.8 months, compared to 6.5 months, 6.4 months, and 6.8 months in BSC patients in the PP, mITT1, and mITT2 populations, respectively. In the PP and mITT1 analyses, the increase in OS in NovoTTF-100A patients compared to BSC patients was both clinically and statistically significant (Wilcoxon p=0.04 and 0.013, respectively). Among the US sites, the median OS was 7.3 months for the NovoTTF-100A patients vs. 5.9 months, 5.3 months, and 6.0 months for the BSC patients in the PP, mITT1, and mITT2 populations, respectively. Novocure believes that the mITT1, mITT2 and PP analyses provide a clinically and scientifically sound approach to analyzing the data because they compare patients who received similar duration of treatment in both arms of the study.

The ITT, PP and mITT results from the pivotal study data, taken together, establish that NovoTTF-100A therapy is at least as effective as best standard of care effective chemotherapies in extending overall survival.

Summary of Overall Survival Results					
Analysis Population	**NovoTTF-100A**	**BSC[1]**	**HR (95% CI) NovoTTF-100A vs. BSC**	**Logrank P-Value**	**Wilcoxon P-Value**
Intent-to-Treat					
n/N[2]	105/120	97/117			
Median OS (95% CI)	**6.3** (5.6, 7.8)	**6.4** (5.2, 7.4)	1.0 (0.76, 1.32)	0.9828	0.7152
Per Protocol					
n/N	81/93	67/79			
Median OS (95% CI)	**7.8** (6.7, 9.5)	**6.5** (5.3, 7.4)	0.84 (0.60, 1.16)	0.2792	0.0388
mITT1					
n/N	81/93	97/117			
Median OS (95% CI)	**7.8** (6.7, 9.5)	**6.4** (5.2, 7.4)	0.81 (0.60, 1.09)	0.1637	0.0133
mITT2					
n/N	81/93	79/91			
Median OS (95% CI)	**7.8** (6.7, 9.5)	**6.8** (5.7, 8.4)	0.90 (0.66,1.23)	0.5267	0.1221

[1] BSC: Best standard of care effective chemotherapy.
[2] n/N: number of events/number of patients.

1.6.4 Secondary Efficacy Endpoints and Subgroup Analyses

Secondary efficacy endpoint results support the positive findings of overall survival in patients treated with NovoTTF-100A device. The one-year survival rate is the same in the NovoTTF-100A and BSC groups in the ITT population (22%) and is higher in the NovoTTF-100A group than in the BSC group in the PP, mITT1 and mITT2 populations (28%% vs. 22% for all three). Progression free survival at 6 months (PFS6) is higher in the NovoTTF-100A group than in the BSC group in all analysis populations and significantly so in the PP (26.2% vs. 12.7%; p=0.018) and mITT1 (26.2% vs. 15.2%; p=0.0357) populations. Radiological response rate is also higher in the NovoTTF-100A group than in the BSC group in all analysis populations (ITT:14% vs. 9.6%; PP: 15.9% vs. 6.7%; mITT1: 15.9% vs. 9.6%; mITT2: 15.9% vs. 9.6%).

In addition, post-hoc analyses of OS in specific subgroups of patients of clinical interest (e.g., bevacizumab failure prior to trial entry, prior low grade gliomas) showed larger overall survival benefits for the NovoTTF-100A group compared to the BSC group (2- to 3-fold increase in median overall survival).

1.6.5 Safety

Almost all of the typical adverse events of chemotherapies are seen in a significantly higher proportion in BSC patients than in NovoTTF-100A patients: for example, gastrointestinal disorders (30% vs. 8%; p<0.0001), hematological disorders (19% vs. 4%; p=0.0009), and infections and infestations (12% vs. 4%; p=0.0376). Skin reaction beneath the device electrodes ("procedural complication") was observed in 16% of NovoTTF-100A patients. All of these cases were mild to moderate in severity, all cases resolved after discontinuing treatment, and all cases were easily treated with topical steroids and periodic shifting of electrode positions.

There was no statistically significant difference in neurological or psychiatric adverse events between treatment groups in general, or in any of the specific event terms collected in the study. Although the rates of convulsions, hemiparesis, mental status change, and headaches appear to be slightly higher in the NovoTTF-100A group than in the BSC group, the differences were not statistically significant and none of the events were assessed by the investigators as related to

NovoTTF-100A treatment. Additional analyses of the adverse events data show that none of these events appeared immediately after starting treatment with the device or reappeared upon re-challenge with the device. The majority of these events occurred in close temporal proximity to disease progression in both treatment groups, providing further evidence that they were related to the underlying disease and not the NovoTTF-100A device.

Adverse Events by Body Systems – Safety Population			
	NovoTTF-100A	**BSC**	**P-value**
System Organ Class	**(n=116)**	**(n=91)**	
Gastrointestinal disorders	*9 (7.8%)*	*27 (29.7%)*	***<.0001***
Blood and lymphatic system disorders	*5 (4.3%)*	*17 (18.7%)*	***0.0009***
Infections and infestations	*5 (4.3%)*	*11 (12.1%)*	***0.0376***
Respiratory, thoracic and mediastinal disorders	7 (6.0%)	10 (11.0%)	0.1975
Metabolism and nutrition disorders	9 (7.8%)	12 (13.2%)	0.1992
Ear and labyrinth disorders	1 (0.9%)	3 (3.3%)	0.2066
Eye disorders	3 (2.6%)	5 (5.5%)	0.2813
Musculoskeletal and connective tissue disorders	6 (5.2%)	8 (8.8%)	0.3034
Nervous system disorders	50 (43.1%)	33 (36.3%)	0.319
Renal and urinary disorders	7 (6.0%)	3 (3.3%)	0.3619
Vascular disorders	5 (4.3%)	6 (6.6%)	0.4673
Psychiatric disorders	12 (10.3%)	7 (7.7%)	0.5118
Skin and subcutaneous tissue disorders	9 (7.8%)	9 (9.9%)	0.5891
General disorders and administration site conditions	15 (12.9%)	14 (15.4%)	0.6137
Investigations	8 (6.9%)	5 (5.5%)	0.6798
Endocrine disorders	2 (1.7%)	2 (2.2%)	0.8059
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (1.7%)	2 (2.2%)	0.8059
Cardiac disorders	8 (6.9%)	6 (6.6%)	0.9313
Injury, poisoning and procedural complications	*21 (18.1%)*	*1 (1.1%)*	*<.0001*

1.6.6 Quality of Life

Patients treated with the NovoTTF-100A device reported improved quality of life compared to patients treated with BSC chemotherapy in five out of the six QLQ C-30 general scales and seven out of the nine symptom scales. Specifically, quality of life using the device was better than that of BSC chemotherapy in the following important subscale domains: vomiting, nausea, pain, diarrhea, constipation, cognitive functioning and emotional functioning, all of which are hallmarks of patient suffering while receiving chemotherapy.

1.7 Conclusions and Risk-Benefit Analysis

The results of the pivotal trial showed that the treatment effect of NovoTTF-100A on overall survival is superior to the effective best standard of care chemotherapy available in the US today when comparing NovoTTF-100A patients who completed at least one treatment course to BSC patients who received any chemotherapy on or off study (median OS 7.8 vs. 6.4 months; Wilcoxon p=0.013), or who received only protocol specified chemotherapies (median OS 7.8 vs. 6.5 months; Wilcoxon p=0.04). In the ITT population, the effect of NovoTTF-100A on overall survival was identical to BSC chemotherapies (median OS 6.3 vs. 6.4 months; HR=1.0; p=0.98).

Similar results showing comparability of NovoTTF-100A to BSC chemotherapy in the ITT population were seen in all secondary efficacy endpoints. Notably, both PFS6 and radiological response rate (RR) are higher in the NovoTTF-100A than the BSC group in all analysis populations. The NovoTTF-100A patients experienced fewer adverse events in general, significantly fewer treatment related adverse events and significantly lower gastrointestinal, hematological and infectious adverse event rates compared to BSC controls. The only clearly device-related adverse event seen was a mild to moderate skin irritation beneath the device electrodes which was easily treated with topical ointments. Finally, quality of life was superior in NovoTTF-100A patients when compared to effective BSC chemotherapy.

Especially given the devastating nature of this disease, the lack of curative therapies, and the comparable or better efficacy of the NovoTTF-100A device vs. the best standard of care effective chemotherapies, the company believes that the benefits of the NovoTTF-100A device for the treatment of patients with recurrent GBM significantly outweigh the risks. This is supported even further by the device's excellent safety profile and improved quality of life compared to BSC chemotherapies.

2.0 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

1YS – proportion of patients alive at 1 year from randomization

AE – Adverse event

BSC – Best standard of care (effective chemotherapies)

CI – Confidence interval

CPHM – Cox proportional hazards model

CR – Complete response

CRO – Clinical Research Organization

DVT – Deep vein thrombosis

GBM – Glioblastoma Multiforme (Glioblastoma, Astrocytoma grade IV) the most common and anaplastic primary brain tumor.

HR - Hazard ratio

ITT – Intent-to-Treat

kHz – kilo hertz; number of cycles per second

mITT – modified Intent-to-Treat

NovoTTF-100A (also called **TTField generator** or **NovoTTF-100A device)** – A portable battery, or power supply, operated device for delivering 200 kHz TTFields to the brain of patients with recurrent GBM.

NovoTTF-100A Treatment Kit – The TTField generator together with all associated components (batteries, charger, connection cable, power supply and carrying case)

NovoTTF-100A System – The NovoTTF-100A Treatment Kit together with the INE electrodes

OS – Overall survival

P2P – Peak-to-peak; a measure of the intensity of a sinusoidal waveform

PD – Progressive disease

PE – Pulmonary embolism

PFS – Progression free survival

PFS6 – Proportion of patients alive and progression free at 6 months from randomization

PP – Per Protocol

PR – Partial response

RMS – Root Mean Square; a measure of the intensity of a sinusoidal waveform

SAE – Serious adverse event. An adverse event of any severity (mild, moderate or severe) which leads to hospitalization, lengthening of hospitalization, permanent disability, congenital defect or death.

SD – Stable disease

Std – Standard deviation

TTFields – Tumor Treating Fields: Low intensity (1-3 V/cm), intermediate frequency (100-300 kHz), alternating electric fields, delivered using insulated electrodes to the region of the body inflicted with a solid tumor. The fields have been shown *in vitro* to arrest the replication of tumor cells by disrupting the proper formation of the microtubule spindle and by dielectrophoretic disruption of cell integrity during late telophase.

TTP – Time to progression

UADE – Unexpected adverse device event

V/cm – Volts per centimeter; the unit of intensity measurement of electric fields

3.0 RECURRENT GBM DISEASE BACKGROUND

3.1 Background and Current Therapies

Glioblastoma multiforme (GBM), a malignant form of astrocytoma, is the most common form of primary brain cancer. The incidence of GBM increases steadily above 45 years of age with a prevalence of approximately 10,000 cases in the United States. 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. The 4-year survival of these patients is only 12%, with a median survival of 14.7 months [1]. Thus, with optimal therapy, overall survival of these patients is currently less than 15 months from diagnosis and less than 7 months from first recurrence. Patients with recurrent GBM who have received maximal standard therapy and who have entered clinical trials for investigational therapies have a median survival of 25 weeks, a median progression free survival (PFS) of approximately 9 weeks and a progression free survival at 6 months (PFS6) of 15% [2]. Recurrent GBM is an end-stage condition and it is uniformly fatal with a negligible 5-year survival. Quality of life of recurrent GBM patients is poor due to the neurological deficits caused by the tumor itself together with the overwhelming side effects of the various standard chemotherapies and experimental treatments.

There are currently four principal treatment options for GBM, each with its own drawbacks and major side effects:

Surgical Resection - Treatment of patients with GBM usually begins with resection (in conjunction with biopsy or after it). Maximal debulking of the tumor is the main goal because curative resection is not possible. Surgery is principally a primary therapy; operative intervention for recurrence is possible only in selected cases. In fact, in a recent review [3] reporting the re-operation rate of patients with recurrent GBM, in a series of 13 studies carried out between 1995 and 2009, the average operation rate for recurrent GBM patients was 20.5±12.8 percent (median ± standard deviation). The effect of reoperation on disease progression and survival is controversial [4].

Radiation Therapy - Post-surgical radiation therapy has been shown to improve survival, though even with maximal treatment, survival is still limited to several months. Notably, the full standard dose of 60 Gy is typically given after primary diagnosis such that irradiation for recurrence of the disease is usually not possible. Focal radio-surgery upon recurrence of a small tumor in a single anatomic location may be possible [3].

Side effects of radiation therapy depend on the type of radiation received, the amount of the surface of the brain targeted, the site targeted, and the total dose of radiation. In general, there will be hair loss, skin irritation, possible hearing problems, nausea, vomiting, loss of appetite and neurologic effects. The most prevalent side effect is fatigue, which may last through treatment and for many months afterwards. The neurological effects most affecting patients' quality of life are permanent memory and speech problems [5].

GLIADEL® Wafer in Combination with Surgical Resection – The Gliadel Wafer delivers carmustine (BCNU) directly to the site of the recurrent brain tumor (interstitial chemotherapy). The package insert indicates that for recurrent GBM, Gliadel increased median overall survival from 20 to 28 weeks compared to placebo. Unfortunately, this approach is limited to those selected cases undergoing surgical resection for recurrent GBM, as discussed above.

Treatment with the GLIADEL® Wafer is associated with the following common side effects: fever (12%), pain (8%), wound healing abnormalities (14%), nausea and vomiting (8%), seizures (19%), brain edema (4%) and intracranial infections (4%) [6].

Chemotherapy - Chemotherapy following surgery and radiation therapy has been shown to improve survival modestly. Nitrosourea-based combination chemotherapy appears to have a small advantage over monotherapy. Recently, adjuvant temozolomide treatment has shown modest improvement in time to disease progression (TTP) (median TTP increased from 5 to 6.9 months) and overall survival (OS) (median OS increased from 12.1 to 14.6 months) [1]. In the past, temozolomide was approved for recurrent anaplastic astrocytoma [7], but not for recurrent GBM. Since temozolomide is approved for GBM at primary diagnosis, it is rarely used for recurrence.

Treatment with chemotherapy commonly (in >30% of patients) causes leucopenia, anemia, thrombocytopenia, nausea and vomiting, electrolyte disturbances, renal toxicity, pain or burning at administration site, redness of face, skin flushing (usually associated with rapid infusion rate of nitrosureas), loss of appetite, headache, fatigue and constipation. Thus, most patients suffer from combinations of unpleasant and sometimes life threatening side effects of their chemotherapeutic treatments [8].

More recently, bevacizumab (Avastin) has been approved in the US as monotherapy for patients with previously treated GBM [9] based on two single arm trials comparing bevacizumab to historical control data. Benefit was seen in radiological response rates and PFS6 compared to historical control data (based on the meta-analysis by Wong et al. 1999 [2]). Overall survival was shown to be between 8 to 9 months [10]; however an overall survival claim is not made in the approved labeling, noting the comparator arm was not a randomized control group.

In addition to the common side effects listed above, treatment with bevacizumab has other associated adverse events, including gastrointestinal perforations, surgery and wound healing complications, hemorrhage (including brain hemorrhage), non-gastrointestinal fistula formation, arterial thromboembolic events, hypertensive crisis, reversible posterior leukoencephalopathy syndrome and proteinuria [11-12].

In summary, not all of the treatment options available for newly diagnosed GBM patients are available for recurrent GBM patients. Furthermore, each presents specific issues in terms of the efficacy and safety of the treatment, and importantly, the quality of life afforded by the treatment for this very sick, end-stage patient population. Despite the immense efforts made over the years, the survival of patients with recurrent GBM is still very poor. No treatment is curative and the quality of life of these patients is significantly compromised, not only by the disease itself, but also by the side effects of the current standard treatment modalities. Thus, a new treatment modality is needed that will provide similar or better overall survival than the standard treatments, while allowing this population the benefit of reduced treatment toxicity and improved quality of life.

3.2 Effectiveness of Chemotherapies in Recurrent GBM

In order to assess the relative effectiveness of the NovoTTF-100A treatment for recurrent GBM, it is important to estimate the beneficial effect of standard chemotherapies. However, assessment of this effect is challenging because there are no placebo-controlled chemotherapy trials in recurrent GBM patients due to the general consensus that it would be unethical in this end-stage population. The only placebo-controlled trial in recurrent GBM ever performed was the Gliadel Wafer trial; however, by necessity of this treatment modality, the Gliadel trial included only surgical candidates, who are expected to have a better prognosis than patients who are not surgical candidates upon recurrence.

In this group of re-operated recurrent GBM patients, compared to sham wafers, Gliadel Wafers led to an 8-week increase in median overall survival from 20 weeks to 28 weeks [6].

In order to estimate the beneficial effect of standard chemotherapies as currently practiced in the treatment of recurrent GBM patients, which were used in the control group in the pivotal study, NovoCure performed a literature review. The objective of the review was to estimate the effect of effective chemotherapies and ineffective chemotherapies on patient outcomes from literature reports, and then use the ineffective chemotherapies as a type of "placebo control" to estimate the treatment effect of the effective chemotherapies. Based on this review, the estimated relative risk of mortality in patients who received "placebo" treatment is almost twice as high compared to patients treated with effective chemotherapies. The results of the literature review are summarized in the sections below.

3.2.1 Effective Chemotherapy

The literature review focused on recurrent GBM trials published after 1999, the year when Wong et al. published the efficacy results of a pooled analysis of 225 recurrent GBM patients from eight consecutive phase II chemotherapy trials conducted at The University of Texas M.D. Anderson Cancer Center from 1986 to 1995 [2]. The results of these studies were pooled with the results from the Wong et al. 1999 meta-analysis to assess the efficacy of the best available chemotherapies today in recurrent GBM.

The literature search identified 43 phase II-III therapeutic clinical trials that contained efficacy data for a homogenous recurrent GBM population, i.e., the reported efficacy data did not include any grade III gliomas patients, who typically have a much better outcome than the GBM patients. The reported efficacy results, including median overall survival, PFS6, radiological response rates and one year survival (1YS), of these 43 trials were abstracted and analyzed. The efficacy results reported in these trials varied widely (see **Table 1** below). The median overall survival ranged from 12–57 weeks and PFS6 ranged from 0–50%. Most of this variability appeared to be due to the small sample sizes and nonrandomized nature of most of these trials.

In order to obtain a more reliable estimate of the efficacy of chemotherapies, the analysis was limited to 9 trials with more than 50 GBM patients [2, 10, 13-20]. Among the 9 trials, the efficacy data were very similar despite the variability in the precise patient populations included in each study. The median OS of recurrent GBM patients in these trials is 7.2 months (95% CI 5.1–9.5 months), the median PFS6 is 18% (95% CI 7.7%–32.2%) and the median radiological response rate is 5.5% (95% CI 0.7%–27.2%). It should be noted that for the calculation of median PFS6 and radiological response rate, one trial [10] was excluded due to the confounding effect of anti-angiogenic agents (e.g., bevacizumab in this case) on MRI interpretation [21]. The remaining variability seen in these trials is most likely due to patient selection because of the nonrandomized nature of most of the studies. The randomized trials published by Yung et al. 2000 [13] and Wick et al. 2010 [20] both showed very similar results (median OS = 7.1 and 7.2 months for lomustine and temozolomide, respectively, versus 6.6 months and 5.8 months for enzastaurin and procarbazine, respectively.

Table 1 Summary of Historical Data on Effective Chemotherapies

Author	Year	Treatment group	Median Age	Median KPS (Range)	Progression #	Number of GBM Patients	Median Overall Survival (months)	1-year survival (%)	Median time to disease progression (weeks)	Progression-free survival at 6 months (%; PFS6)	Response rate (PR+CR) %
Wong et al.	**1999**	Meta-analysis of 8 prior chemo trials	45	80 (60-100)		225	5.83	21	9	15	6
Yung et al.	**2000**	Temozolomide	52	(70-100)	1	112	7.23		12.4	19	5.4
		Procarbazine	51	(70-100)	1	113	5.83		8.32	9	5.3
Brada et al.	**2001**	Temozolomide	54	(70-100)	1	126	5.48		9.1	18	8
Chang et al.	**2003**	Temozolomide	53	80 (≥70)		142	7.47		10	18	16
Rich et al.	**2004**	Gefitinib (Iresa)	54	(60-100)	1	57	9.19	35.6	8.1	13	0
Balmaceda et al.	**2008**	Twice daily temozolomide	53	80	71% 1st	68	9.01	35	17	35	31
Neyns et al.	**2009**	Cetuximab	53	70 (60-100)	40% 1st	55	4.99		8.1	7.3	5.5
Friedman et al.	**2009**	Avastin	54	80	81% 1st	85	9.19		18	42.6	28.2
		Avastin + Irinotecan	57	80	80.5% 1st	82	8.70		24	50.3	37.8
Perry et al.	**2010**	Dose intense temozolomide (Rescue Study)	52	ECOG 0-1	1	88	9.57	21.4	11.75	23.9	7.7
Wick et al.	**2010**	Enzastaurin	50	80	74% 1st	174	6.60		6.4	15	2.9
		Lomustine	50	80	77% 1st	92	7.09		6.9	20	4.3
Median	**1999-2010**		**53**	**80**	**1**	**92 (55-225)**	**7.23**	**28.2**	**9.1**	**16.5**	**5.75**

3.2.2 Ineffective Chemotherapy

Among the 43 trials identified from the literature that reported efficacy data for a homogenous recurrent GBM population, 7 trials reported that the drug tested was not active in recurrent GBM (see **Table 2** below) [22-28].

As can be expected, these were small trials that included fewer than 50 patients. The baseline characteristics in these trials were not fully reported. The only consistent prognostic factor reported was Karnofsky Performance status, which ranged from 60 to 100 in two trials, 70 to 100 in two trials and 60 to 80 in one trial. The ranges of KPS values in these trials are similar to those of effective chemotherapy trials (60–100).

The range of median OS in these trials was 2.8 to 4.9 months. The median OS observed in these trials most likely represents the upper limit of the natural history of this disease, since limited efficacy may still be present for some of the tested agents, in addition to the possibility of a placebo effect. Thus, NovoCure believes that the median OS of these studies, 3.73 months (95% CI 2.4–4.8 months), represents a conservative (high) estimate of the median OS that could be expected in placebo-treated recurrent GBM patients. The median PFS6 reported in these trials is 9% (95% CI 0.9%–18.6%) and the one year survival 10%.

Table 2 Summary of Historical Literature on Inactive Chemotherapies

Author	Year	Agent	n	KPS	PFS(w)	PFS6(%)	OS (m)	1YS (%)
Rosenthal et al.	2000	Taxol and estramustine	20		6.0		**2.80**	
Oudard et al.	2003	Lonidamine	16	60-80	8.0	7.00%	**3.50**	
Chamberlain	2004	Cyclophosphamide	40	60-100	8.6	20.00%	**4.00**	10%
Kesari et al.	2008	Metronomic chemo X 4	28	60-100	11.0	9.00%	**4.90**	
Puduvalli et al.	2009	Fenretidine	23	70-100	6.0	9.00%	**3.73**	
Robe et al.	2009	Sulfasalazine	10		4.5	0.00%	**2.35**	0%
Quinn et al.	2009	O6-BG & TMZ	34	70-100	7.5	9.00%	**4.53**	12%
		Total	**171**	**Median=**	**7.5**	**9.00%**	**3.73**	**10.0%**

In summary, comparison of the effective chemotherapies to ineffective chemotherapies used over the past decade showed that active chemotherapy has a significant positive effect on the survival of recurrent GBM patients. On average, the median OS is 3.5 months longer in patients treated with effective chemotherapies than patients treated with ineffective chemotherapies (median OS 7.23 and 3.72 months, respectively). The estimated relative risk of mortality (based on the median OS) in patients treated with ineffective chemotherapies is almost twice as high compared to patients treated with effective chemotherapies (7.23/3.73=1.94).

4.0 DEVICE DESCRIPTION

4.1 Overview

The NovoTTF-100A System for the treatment of recurrent GBM is a portable battery or power supply operated device which produces alternating electrical fields, TTFields, within the brain by means of surface electrodes. The surface electrodes are electrically insulated, such that resistively coupled (direct) electric currents are not delivered to the patient. The electrodes, which incorporate a layer of adhesive hydrogel and a layer of hypoallergenic medical tape, are placed on the patient's shaved head. The TTFields disrupt the rapid cell division exhibited by cancer cells [29].

4.2 Indications for Use

The NovoTTF-100A System is intended as a treatment for adult patients (greater than 21 years of age) with histologically- or radiologically-confirmed glioblastoma multiforme, following recurrence in the supra-tentorial region of the brain. The device is intended to be used as a monotherapy, after surgical and radiation options have been exhausted, in place of standard medical therapy for GBM.

4.3 NovoTTF-100A System Components

As described in more detail below, and shown in **Figure 1**, the NovoTTF-100A System is comprised of two main components: (1) an Electric Field Generator (the device); and (2) INE Insulated Electrodes. In addition, the following components are also included in the NovoTTF-100A System: power supply, portable battery, battery rack, battery charger, connection cable and carrying case.

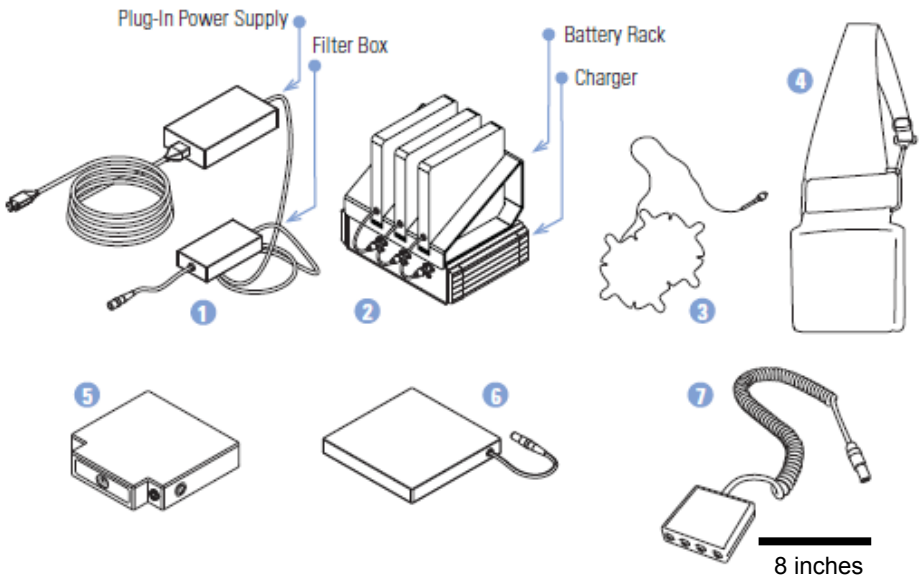
4.3.1 NovoTTF-100A Device (or "Electric Field Generator")

The Electric Field Generator delivers TTFields per the output parameters set forth in **Table 3** below. The device is connected to two pairs of insulated electrode sets, which are operated sequentially.

Table 3 NovoTTF-100A Treatment Parameters

Device Specification	**NovoTTF-100A**
Output Frequency	200kHz
Output Current	2000 mA P2P (707 mA RMS)
Treatment Field Intensity (in the center of the brain)	0.7 V/cm RMS

Figure 1 Components of the NovoTTF-100A System



1 Plug in power supply **2** Charger for portable batteries **3** Insulated electrode
4 Device & battery carrying bag **5** NovoTTF-100A electric field generator (the Device)
6 Portable battery **7** Connection cable & box

4.3.2 INE Electrodes

Two sets of INE Insulated Electrodes are connected to the Electric Field Generator. Each set includes a pair of arrays, with 9 serially interconnected single electrodes in each array. Each electrode array includes 8 thermistors. The electrodes deliver a maximal current of 50mA RMS/cm^2 of electrode surface area. The electrode surface area is 28.3 cm^2 per electrode array. Operating under such conditions ensures there is no significant heating due to the dielectric losses of the insulation or the induced fields in the skin/tissue. As an additional safety feature, the temperature of the electrodes is monitored by a temperature sensor. If temperature rises beyond 41^{o}C, the device is automatically shut off.

A layer of conductive gel ensures electric contact between the electrode and the skin. The electrodes are taped on the patient's skin with an adhesive patch. A holder made of biocompatible adhesive foam mechanically supports the electrode array. The electrodes are supplied sterile and designed for single use (up to one week).

4.3.3 Additional Components

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.

4.4 Use of the Device

The NovoTTF-100A is intended as a physician-prescribed, home-use device. All of the treatment parameters are preset by NovoCure such that there are no electrical output adjustments available to the patient. The patient only needs to connect the device to an appropriate power supply (i.e., a charged battery or connection to electrical outlet) and to turn it on and off. The patient is expected to use the NovoTTF-100A for at least 18 hours per day, with short breaks for personal needs. The minimal recommended treatment duration is four weeks contiguously.

When starting treatment at the doctor's clinic, the patient will be instructed in how to use the system (turn on and off, etc.), replace electrodes with the assistance of a caregiver, recharge and replace portable batteries, and connect to the power supply. The patient will also be taught what to do in the case of system alarms and will be provided with a telephone number to call for technical support. After this initial training period at the physician's office, the patient will be able to properly operate the NovoTTF-100A, replace rechargeable batteries, charge the rechargeable batteries and replace electrodes as needed, with the assistance of a family member or care provider.

The NovoTTF-100A is intended to be portable when operated from a battery, which allows the patient to continue normal daily activities while carrying the generator and battery in a shoulder bag or backpack. Each of the 4 rechargeable batteries will operate the system for approximately two to three hours. For sleeping or other times when the patient plans to stay in the same place for a period of time, the device can be operated on a power supply plugged into a standard wall outlet without the need to change batteries.

The disposable, insulated electrode arrays (INE electrodes) are to be replaced every 4–7 days (once or twice per week; up to 6 times per month), in order to re-shave the scalp to provide good contact between the electrode array and the scalp.

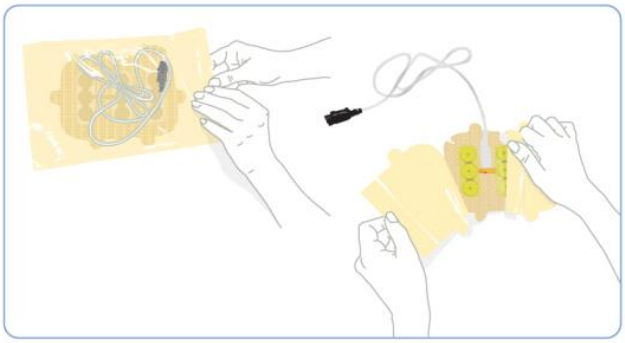
Treatment may be interrupted for personal needs such as bathing, exercise, or any situation where the device may be a distraction. For example, in order to take a shower, the patient must disconnect from the device (leaving the electrodes on the head), put on a shower cap and be cautious not to get his/her head wet. Treatment must also be stopped to replace the electrodes. When leaving the house, patients can put a wig or hat over the electrodes, if desired.

The NovoTTF-100A does not require any periodic maintenance. If the device is not operating properly, either due to a problem with the setup or an internal error, an alarm will sound to notify the patient. A simple troubleshooting guide is provided in the patient manual. In addition, around-the-clock technical support is available through NovoCure.

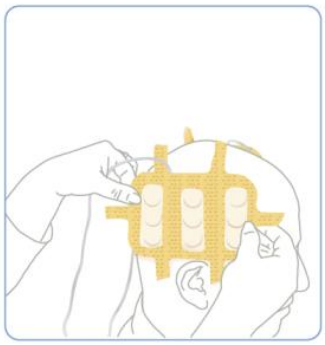
The following figure (**Figure 2**) shows the basic steps of setting up the device for use.

Figure 2 Treatment Setup Overview

1. Prepare Scalp
Shave and clean

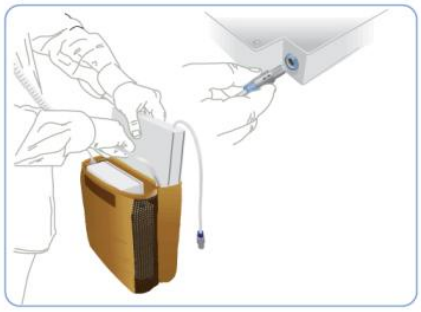


2. Remove 4 Electrodes From Package

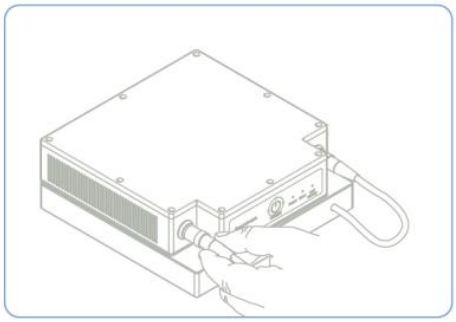


3. Place Electrodes on Scalp
Add color coded rings to indicate position; Apply based on electrode position diagram from physician

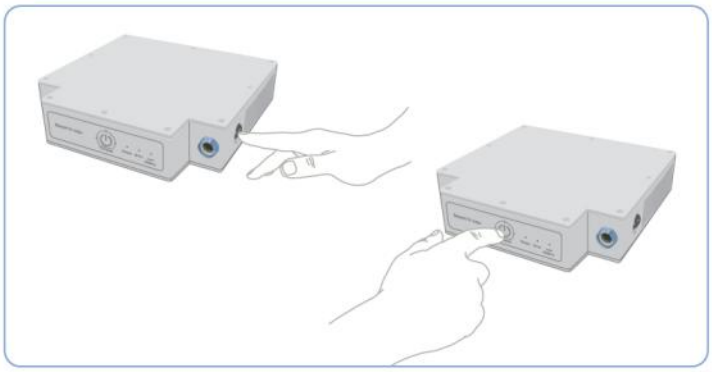
4. Connect Electrodes to Connection Cable & Box
Match colored rings to color coded sockets



5. Place Device and Battery in Bag (if applicable) and Connect Battery or Power Supply

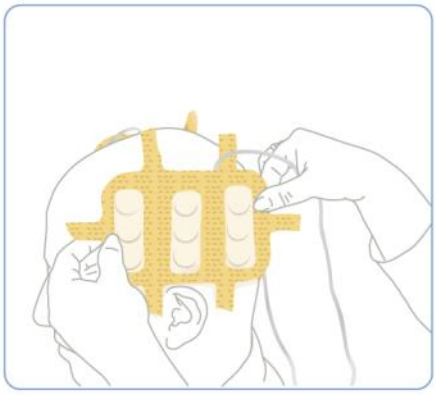


6. Connect Connection Cable to Device

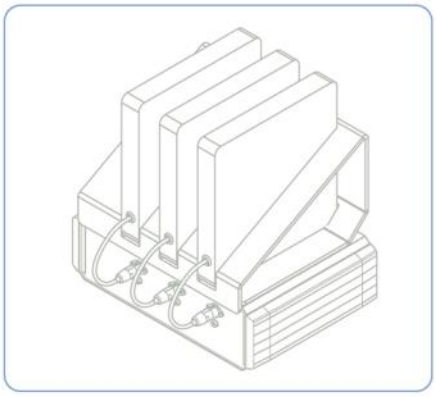


7. Start Treatment
Turn on power switch and push TTFields button

8. Place Bag Over Shoulder and Clip
If applicable



9. Replace Electrodes as Needed



10. Recharge Batteries When Not in Use

5.0 MECHANISM OF ACTION AND PRECLINICAL DATA

5.1 Introduction

Electric fields are presently used in medicine in two different modes: (1) steady or low frequency electric fields (<1 kHz); and (2) high frequency alternating fields (>10 MHz). Steady or low frequency electric fields generate action potentials in excitable cells. These fields are used therapeutically in bone and soft tissue repair, pain control (TENS), and stimulation (neurologic or cardiac). In contrast, very high frequency alternating fields generate heat in the tissues by dielectric losses. Applications in therapeutic use include ablation, diathermy and hyperthermia.

Unlike the above two modes currently used in medicine, the NovoTTF-100A uses intermediate frequency (hundereds of kHz), low intensity (single volts per cm), alternating electric fields, termed Tumor Treating Fields ("TTFields"). TTFields are delivered non-invasively to solid tumors through electrically insulated surface electrodes using the NovoTTF-100A, a portable, battery operated medical device. The intermediate frequency electric fields generated by the NovoTTF-100A alternate too fast to cause nerve-muscle stimulation and involve only minute and local dielectric losses (heating). It has been shown that when properly tuned, TTFields stunt the growth of tumor cells *in vitro* and *in vivo* [30, 31]. This inhibitory effect has been demonstrated in all proliferating cell types tested, whereas, non-proliferating cells and tissues were unaffected. Because most normal adult brain cells proliferate very slowly, if at all, they are hypothesized to be affected little 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.

As discussed in detail below, the inhibitory effect of TTFields on rapidly dividing cells was shown to be specific to two stages in mitosis: (1) spindle formation during anaphase; and (2) cytokinesis during telophase. An animation explaining the proposed mechanism of action of TTFields is shown in **Tab XI, Appendix A**. Interestingly, different cell types show specific frequency dependences of TTField inhibition. This dependence is inversely related to cell size, with smaller cells being inhibited by higher frequencies [29]. In addition, it has been shown that the damage caused by TTFields to replicating cells is dependent on the orientation of the cell division process in relation to the TTField vectors. This fact alone indicates that the effect of the TTFields is non-thermal.

5.2 Low Toxicity of TTFields

TTFields have very low toxicity. The reasons for the extremely 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, as detailed in the testing described below.

Two types of toxicities may be expected in an electric field based treatment modality: (1) acute toxicity - interference with the normal function of excitable tissues within the body; and (2) chronic toxicity - damage to the replication of rapidly dividing normal cells within the body. With regard to the former, it might be expected that the fields could interfere with the normal function of excitable tissues within the body causing, in extreme cases, cardiac arrhythmias or even seizures. However, as demonstrated in the *in vivo* testing described below, this is not a concern with TTFields due to the frequency and intensity of the TTFields. Specifically, the frequency of TTFields for the treatment of GBM is 200 kHz and their intensity is about 1 V/cm within the brain. At this frequency, neural stimulation does not occur due to the parallel resistor-capacitor nature of the plasma membrane with an electric time constant greater than 1ms [32-37]. It is well established in the literature that as stimulation pulse duration decreases (equivalent to an increase in frequency), the intensity needed

to cause supra-threshold membrane depolarization increases. In fact, at frequencies above 10 to 20 kHz it is essentially impossible to stimulate neurons [38-40]. Thus, the frequency range used by TTFields cannot scientifically lead to abnormal neuronal activity. In fact, other medical devices intended to stimulate neurons (e.g., deep brain stimulation, transcranial direct current stimulators, transcranial magnetic stimulators) all operate at a frequency range beneath 20 kHz and are most effective at frequencies beneath 1 kHz (i.e., pulse width greater than 1ms). In addition, at the frequency and intensities used, there is no heating of the brain due to the electric fields. A minor increase in skin temperature can occur beneath the electrodes; however, the NovoTTF-100A device measures the skin temperature beneath the electrodes and is designed to maintain this temperature beneath 41°C. Thus, as expected, in both acute and chronic application of TTFields to healthy animals, no evidence of abnormal cardiac rhythms or pathologic neurological activity is seen.

Second, the anti-mitotic effect of TTFields might be expected to damage the replication of rapidly dividing normal cells within the body (e.g., bone marrow, small intestine mucosa. Notably, as demonstrated in the *in vivo* testing described below, no treatment related toxicities were found in any of the animal safety trials performed by NovoCure, even when field intensities 3-fold higher than the effective anti-tumoral dose were used. Specifically, there was no histopathologic damage to the intestinal mucosa or the bone marrow in any of the animals, nor was a decrease in blood cell counts seen. The lack of damage to intestinal mucosa in TTField-treated animals is likely a reflection of the fact that the small intestine mucosal cells have a slower replication cycle than neoplastic cells and that the intestine itself most likely changes its orientation in relation to the applied field quite often, lowering the efficacy of TTField mediated mitotic disruption. Bone marrow, on the other hand, is naturally protected from TTFields by the high electric resistance of both bone and bone marrow compared to most other tissues in the body. To test the later assumption, the TTField intensity within the bone marrow of a long bone was modeled using the finite element mesh (FEM) method. It was found that the intensity of TTFields was 100-fold lower within the bone marrow compared to the surrounding tissues (including within solid tumors). Thus, hematopoietic cell replication should not be affected even when TTField intensities 10-fold higher than necessary to inhibit tumor growth are applied.

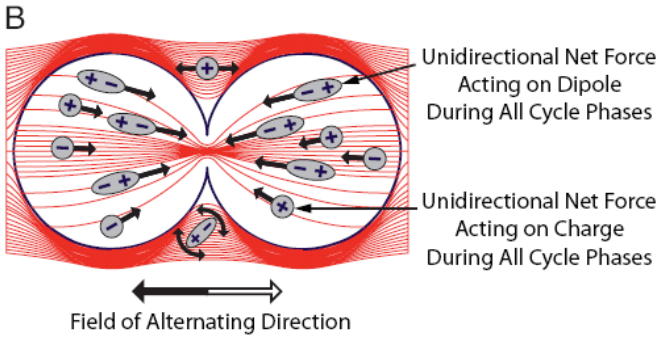
5.3 Anti-Mitotic Mechanism of Action of TTFields

As originally presented by Dbalý and Gutin at the Congress of Neurological Surgeons in 2005, TTFields are an anti-mitotic therapy which has been shown to disrupt mitotic spindle microtubule assembly and to lead to dielectrophoretic dislocation of intracellular macromolecules and organelles during cytokinesis [29, 31, 41]. These processes lead to physical disruption of the cell membrane and to programmed cell death (apoptosis). The effect of TTFields depends on the geometrical shape of dividing cells, which make them susceptible to the effects of the alternating electric TTFields. In contrast, the TTFields have no effect on cells that are not undergoing division. Because most normal adult brain cells proliferate very slowly, if at all, they are hypothesized to be affected little by the TTFields. NovoCure has condicted testing that 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.

The attached animation explains the basic science of alternating electric fields and the mechanisms of the antimitotic effect of TTFields (**Tab XI, Appendix A**). As described in detail in a study published in Cancer Research in 2004 [29], TTFields act at two stages of mitosis. First, during the formation of the microtubule spindle, tubulin dimers are known to polymerize into a spindle structure responsible for chromosome separation into the two daughter cells. Since tubulin is a highly electrically polar molecule, it aligns in the direction of an externally applied electric field, such as TTFields. The alignment in a specific field direction does not allow the tubulin dimers to orient in the correct direction for proper spindle formation, and tilts the balance of the tubulin polymerization-depolymerization process in the direction of depolymerization. Secondly, during late telophase, when the cell begins to cleave into two daughter cells, the morphology of the cell (see **Figure 3**

below – figure 1 in PNAS 2007 [42]) is such that the lines of force of the applied electric fields converge through the neck between the two interconnected daughter cells.

Figure 3 Electric Field Distribution and Dielectrophoretic Forces with a Dividing Cell During Cytokinesis



This converging electric field exerts intracellular dielectrophoretic forces in the pN range on charged and polar macromolecules (such as microtubules and chromosomes) pushing them to the bridge between the two daughter cells. This movement occurs within several minutes from the beginning of cytokinesis and leads to a physical disruption of the cell membrane at the cleavage plane (see figure 3 in Cancer Research 2004 [29], reproduced below as **Figure 4**).

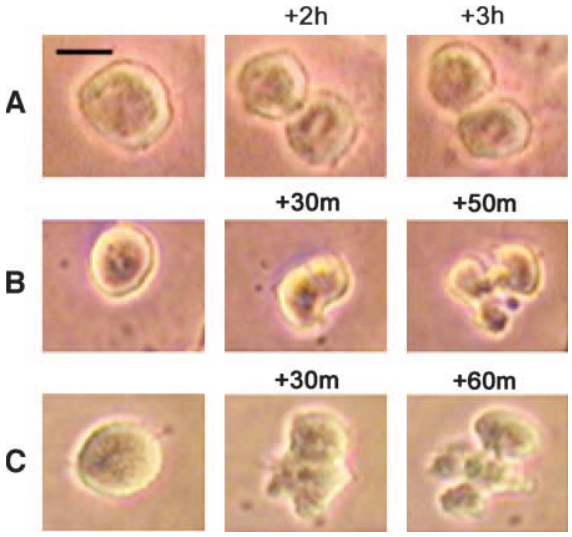
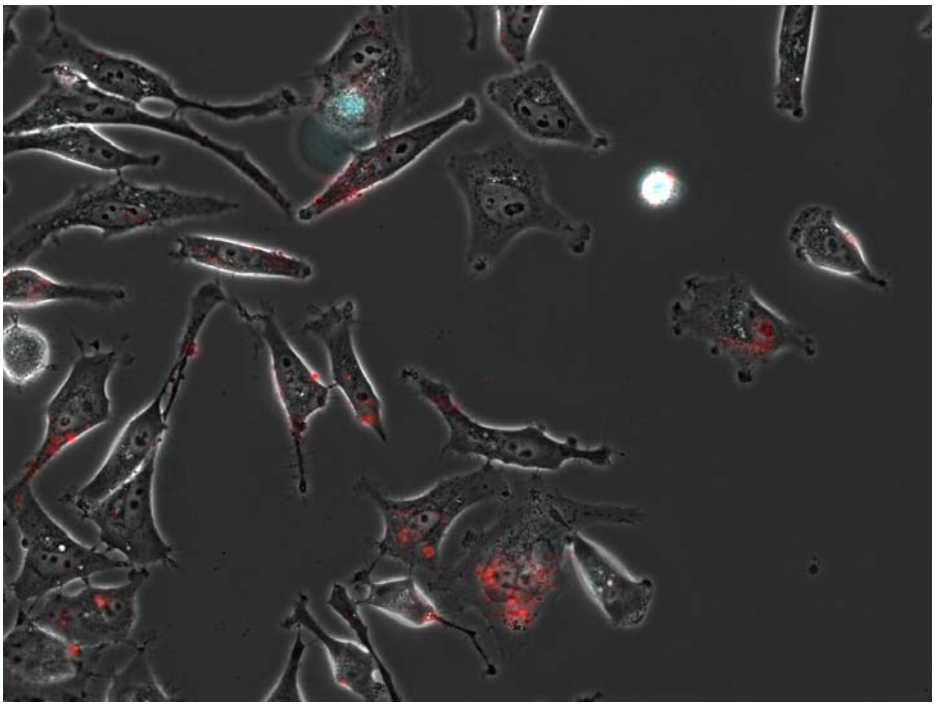


Figure 4 Mitotic Arrest and Dividing Cell Disruption by TTFields

Time-lapse microphotography of malignant melanoma cells exposed to TTFields. *A,* an example of a cell in mitosis arrested by TTFields. Contrary to normal mitosis, the duration of which is less than 1 h, the depicted cell is seen to be stationary at mid-cytokinesis for 3 h. *B* and *C,* two examples of disintegration of TTFields-treated cells during cytokinesis. Three consecutive stages are shown: cell rounding (*left*); formation of the cleavage furrow (*middle*); and cell disintegration (*right*). *Scale bar* 10 μm. (Cancer Research 2004)

Both these processes have been shown *in vitro* to lead to arrest of cell division, aberrant spindle formation, improper chromosome separation and finally apoptosis [29]. The video in **Tab XI, Appendix B** shows *in vitro* evidence of abnormal spindle formation and chromosomal separation using green fluorescent protein (GFP)-labeled microtubules followed within dividing cells using time lapse fluorescent microphotography. In addition, the video shows annexin binding and membrane blebbing in cells treated with TTFields. Both effects are classic direct evidence of apoptosis. **Figure 5** below shows an example fluorescent microphotography image of Annexin and Propidium Iodide (PI) staining of cervical cancer cells (HeLa) treated with TTFields. The staining indicates an apoptotic process is ongoing in the treated cells.

Figure 5 Annexin (red) and PI (blue) Staining of TTFields Treated HeLa Cells



Finally, as shown in a study published in PNAS in 2007 [42], the distribution of TTField intensity within the brain has been shown through finite element mesh modeling and direct measurements, in both the human brain and in large animals, to be highly homogenous. This homogeneity of TTField intensity results in a whole brain treatment, which has the potential to affect both cancer cells within the main tumor bulk and invasive cancer cells which have spread to other brain regions [31, 42].

5.4 *In Vitro* Studies Assessing the Inhibitory Effect, Optimal Frequency and Treatment Duration of TTFields

TTFields have been shown *in vitro* to effectively inhibit cancer cell replication during mitosis without any systemic side effects. This effect has been shown to be mediated by apoptosis (see video in **Tab XI, Appendix B**) and is evident in all cancer cell lines tested. Specifically, TTFields inhibit the replication of glioblastoma cell lines from human (U-87, U-118) and rat tumors (F-98, C-6), as well as malignant melanoma (B16F1), lung cancer (H1299), breast cancer (MDA-231), prostate (PC-3) and other tumor cell types (Patricia, HT-29, RG-2, VX-2).

NovoCure performed *in vitro* studies to assess the relationship between dose and frequency response using four of the most common types of cancer: malignant melanoma, Glioblastoma, breast carcinoma and non-small cell lung carcinoma [29, 31, 41]. 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 mitosis is achieved at field intensities above 0.7 V/cm [29, 31, 41, 42]. Frequency response and intensity response curves are shown in **Figure 6** below (excerpted from figure 2 in PNAS 2007 [42]).

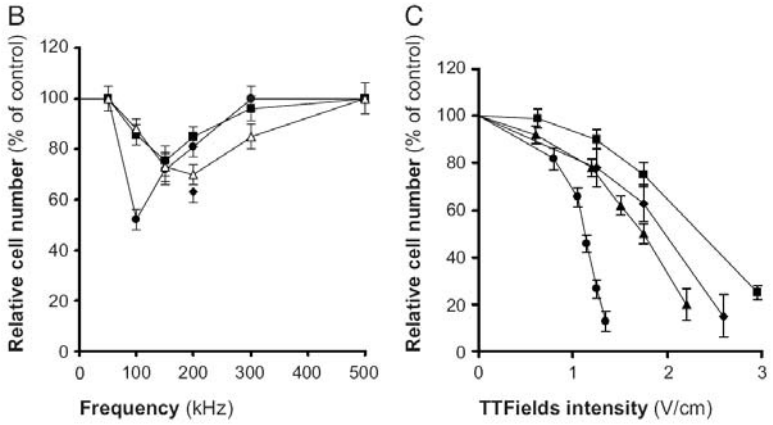


Figure 6 Frequency and intensity dependence of the Effect of TTFields in Different Cell Lines *In Vitro*

(B) The relative change in number of cells after 24 h of treatment of different frequencies (same TTFields intensity). (C) The effect of 24 h of exposure to TTFields of increasing intensities (at optimal frequencies).

● and ○, B16F1; ■ and □, MDA-MB-231; ▲ and △, F-98; ♦ and ◇, H1299.

NovoCure also assessed tumor growth kinetics to evaluate optimal treatment duration and timing. Using a 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 [43]. 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 that was later validated in independent animal studies and human pilot clinical studies. Thus, NovoCure concluded that stopping treatment prior to completion of a 4-week treatment course will likely lead to continued tumor growth and appearance of symptoms within approximately 1–2 weeks.

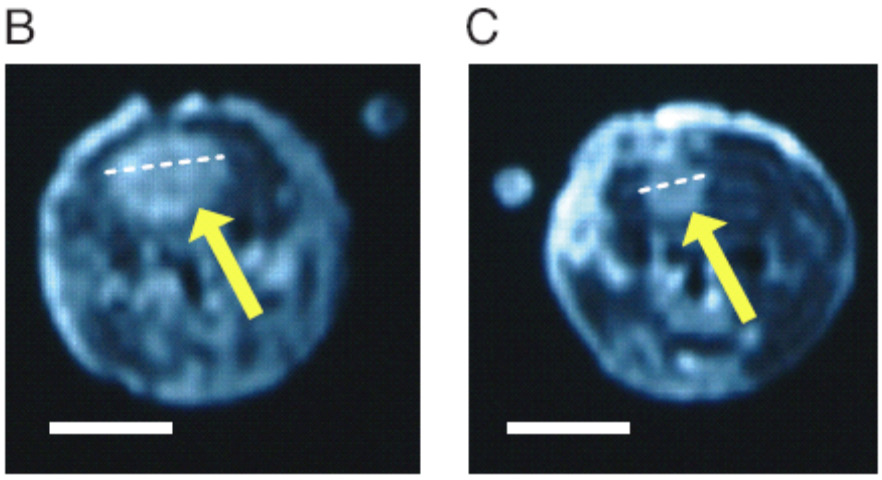
5.5 *In Vivo* Studies Establishing the Inhibitory Effect and Treatment Duration of TTFields

NovoCure conducted a series of *in vivo* experiments in mice, rats, rabbits, sheep and pigs to verify the data that was previously obtained in prior simulations of TTField distributions. These experiments demonstrate that effective TTField intensities (greater than 1 V/cm) can be obtained within tumors in the brains of various animal models.

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 [29, 42]. TTFields were shown to inhibit tumor growth in mice by 49% compared to sham-treated tumors ($P<0.01$). TTFields applied through surface electrodes placed on the scalp of rats inoculated with malignant gliomas effectively and significantly inhibited the growth of these tumors as well (by 43%; $p<0.01$) [42]. These statistically significant effects were non-thermal and due only to the effect of TTFields on tumor growth.

Figure 7 below (excerpt from Figure 3 in PNAS 2007 [42]) shows an example of contrast enhanced T1 weighted MRIs of an orthotopic F-98 glioma tumor model in a control (A) and TTFields treated (B) rat.

Figure 7 Control vs. TTFields Treated Rat Glioma



In addition, NovoCure studied the effect of TTFields on metastatic spread of solid tumors and investigated the development of an immune response following TTField treatment [44]. Based on these experiments, it was concluded that TTFields have the potential to inhibit the migration of metastases from a primary tumor, can inhibit the growth of metastases in the lungs once they have been seeded in the target organ, by the presence of the fields in the lungs themselves, and finally, TTFields may activate an anti-tumor antigen systemic immune response following treatment of a primary tumor. Together, these mechanisms significantly prolong the survival of treated animals by decreasing the metastatic load to the lungs.

In the rabbit kidney model specifically, TTField treatment could be extended for up to 5 weeks due to the large size of the animals being used. Sub-analysis of the time-dependence of the effect of TTFields in these 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, supporting the prior *in vitro* findings and leading to the recommended minimal treatment course duration of 28 days in the pivotal study. Post-treatment follow up both *in vitro* and *in vivo* demonstrated that after stopping TTFields treatment, cell replication rate and tumor growth rates do not increase beyond their pre-treatment growth rates.

5.6 *In Vivo* Safety Studies Demonstrating Low Treatment-Related Toxicity

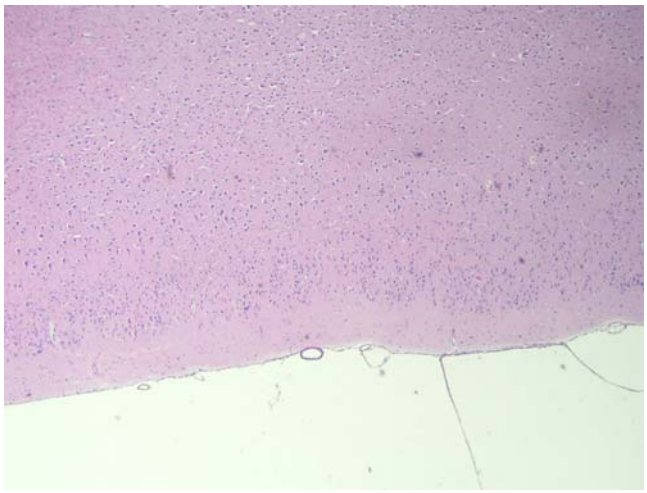
In addition to the above efficacy studies, extensive safety studies in healthy rabbits and rats exposed to TTFields for protracted periods of time have shown no systemic treatment related side effects. The reasons for the low toxicity of TTField treatment can be explained as discussed above, in light of the known passive electric properties of normal tissues within the body and the effects of electric fields applied via insulated electrodes. Insulated electrodes are used to circumvent local toxicity beneath the electrodes at the contact site, which is a phenomenon that occurs with using conducting electrodes due to electrolysis and ion concentration changes [45-49].

In both acute and chronic application of TTFields to healthy animals, no evidence of abnormal cardiac rhythms or pathologic neurological activity was seen. Histological analysis of the brains of treated animals did not show any structural damage to normal brain tissue at either the macroscopic or microscopic levels (see **Figure 8** below). In addition, no treatment related toxicities were found in any of the animal safety trials performed, even when TTField intensities 3 times higher than the effective anti-tumoral dose were applied. Finally, these studies demonstrated that hematopoietic cell

replication should not be affected even with application of TTField intensities 10-times higher than necessary to inhibit tumor growth.

In summary, the application of TTFields at 1 to 3 V/cm and 100 to 200 kHz does not result in increased animal mortality, damage to internal organs, or other systemic toxicities as compared to non-treated animals. The lack of treatment related toxicities after chronic exposure to TTFields is not species related; the same results were obtained in mice, rats and rabbits. Also, it can be concluded that chronic exposure to TTFields has no significant immediate or late toxicities related to the anti-mitotic effects of TTFields in the brain. Based on studies using different TTField frequencies, the lack of systemic toxicities can be generalized to other relevant TTFields frequencies (100, 150 and 200 kHz).

Figure 8 Example Histological Section of a Rabbit Brain Showing No Pathology Following 4 Weeks of Continuous TTFields Treatment



5.7 Engineering, EMC, Electrical Safety, Environmental and Shelf-Life, Sterilization, Biocompatibility and Software Testing

The NovoTTF-100A device has passed extensive hardware and software verification and validation. The system also passed testing of applicable electrical safety and EMC standards at a certified laboratory. The electrodes that contact the patient were shown to be biocompatible in dermal sensitization, cytotoxicity and delayed type hypersensitivity studies. Finally, the electrodes passed shelf life and sterilization validation according to the applicable standards. All of this testing demonstrates that the NovoTTF-100A operates per its specifications and in accordance with its intended use.

6.0 PILOT STUDY - EFFECT OF NOVOTTF-100A ON RECURRENT GBM PATIENTS

The efficacy and safety of the NovoTTF-100A device in the treatment of GBM were first evaluated in a single-center pilot study in patients with recurrent GBM. The study was an open-label prospective single arm study to evaluate the safety and efficacy of TTFields for the treatment of recurrent GBM.

The efficacy endpoints of the study included the overall survival and time to disease progression, based on radiological assessment of disease progression by monthly 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).

A total of 10 NovoTTF-100A patients were enrolled in this study and followed for 6 months after disease progression. All patients underwent surgery and radiotherapy for the primary tumor, and all had their first or second GBM recurrence at study entry. All patients had histologically proven diagnosis of GBM. The majority of patients received either temozolomide or other chemotherapeutic treatment as adjuvant treatment prior to recurrence. It should be noted that the patients in this study had more favorable baseline characteristics than those in past large clinical trials; six of the 10 patients in the treatment group were re-operated for their recurrence; the median Karnofsky performance score for these patients was 90; and all were followed by neurosurgeons with an aggressive re-operation approach, such that half of the patients underwent additional surgery following disease progression after using the NovoTTF-100A device.

All NovoTTF-100A patients were treated with TTFields as monotherapy, with multiple four-week treatment courses using continuous, 24-hour a day TTFields. As in the pivotal study, TTFields were applied through two sets of opposing insulated electrode arrays and alternated at a 1 second duty cycle between two perpendicular field directions through the tumor. Patients completed between 1 and 13 treatment courses. The maximal treatment duration was 14.5 months. Overall, more than 65 treatment courses were completed (6.7 courses per patient on average). All patients received at least 4 weeks of NovoTTF-100A therapy.

The treatment with NovoTTF-100A device was well tolerated with no treatment related serious adverse events seen in any of the patients. Compliance with treatment was high with patients 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 patients 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. Regular relocation of the electrode arrays was necessary in order to allow for continuous treatment. One patient had a partial seizure on treatment which resolved with clonazepam and which was not considered treatment related by the investigator. Another patient developed an unrelated metastatic adenoma to the orbit of unknown origin.

The median TTP in the NovoTTF-100A patients was 26 weeks compared to 9 weeks in historical control data (Wong et al., 1999 [2]). The PFS6 was 50% compared to 15% in historical control data (Wong et al., 1999 [2]).

Since most of the patients in the trial were re-operated, the overall survival in NovoTTF-100A patients was compared to that reported for Gliadel Wafers [6]. The median overall survival was 14.7 months in NovoTTF-100A patients compared to the 6 months reported for Gliadel Wafers. The one-year survival in NovoTTF-100A patients was 60%. Response rate in the NovoTTF-100A treated patients was 25% (1 CR + 1 PR) and only two patients had progressive disease despite treatment. The study also demonstrated the excellent safety profile of this treatment modality. Based on these

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

7.0 PIVOTAL STUDY PROTOCOL SUMMARY

7.1 Study Design and Objective

The pivotal study was a multicenter, randomized, controlled clinical trial to evaluate the safety and effectiveness of NovoTTF-100A in the treatment of recurrent GBM. Patients were randomized to receive either NovoTTF-100A monotherapy or the best standard of care effective chemotherapies (BSC) for recurrent GBM patients as practiced at each of the participating clinical centers. The hypothesis of this study was that NovoTTF-100A will significantly increase the overall survival of recurrent GBM patients compared to patients treated with BSC. The specific aims of the study were:

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

The full study protocol can be found in **Tab VI**.

7.2 Study Population

Patients 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) US and OUS clinical centers. Key eligibility criteria follow:

7.2.1 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. Patients 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 patients must sign written informed consent.

7.2.2 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 103/μL)
6) Neutropenia (absolute neutrophil count < 1 x 103/μL)
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).

7.3 Study Treatment

7.3.1 Investigational Treatment

At NovoTTF-100A treatment initiation, patients were hospitalized for 24 hours. During this period, baseline examinations were performed and NovoTTF-100A treatment was initiated under medical supervision. Patients were also instructed on the operation of the NovoTTF-100A and battery replacement. Once the patients were trained in operating the device, they were released to continue treatment at home.

Patients were to receive continuous NovoTTF-100A treatment. Treatment was to be stopped in the case of treatment-related serious adverse events or clinical disease progression. During treatment, patients were permitted to interrupt treatment for periods of up to an hour twice a day for personal needs. Any pause in treatment beyond this must have been coordinated in advance with the clinical investigator. Patients were allowed an additional 1–3 days off treatment every 4 weeks according to personal needs.

7.3.2 Control Treatment

Control patients received the best active standard of care (BSC) as practiced at each of the participating clinical centers. The treatment protocol was according to standard procedures at each of the centers. At the time of pivotal study initiation, the BSC for recurrent GBM consisted of one of the following chemotherapies:

1. Platinum based chemotherapy (Carboplatin)
2. Nitrosureas (BCNU)
3. Procarbazine
4. Procarbazine, lomustine and vincristine (PCV)
5. Temozolomide

Since 2006, bevacizumab (Avastin) has been used off-label extensively in recurrent GBM, and has become the BSC at several clinical centers. Bevacizumab was approved by FDA in May 2009 [9] as a single agent for recurrent GBM patients with progressive disease following prior therapy. Thus, bevacizumab was also included as a BSC treatment in this pivotal trial in addition to the above-mentioned agents following its FDA approval.

7.4 Randomization and Blinding

Patients who met the eligibility criteria were randomized in a 1:1 ratio to either the treatment group or to the BSC group. The randomization schedule was stratified by clinical site, and by patients who did or did not undergo re-operation for their recurrence to avoid unequal distribution of operated patients between study groups.

7.5 Study Evaluations and Visit Schedule

During treatment, and until progression for patients who stopped treatment before progression, all patients were to be seen once every month at an outpatient clinic where they would undergo medical follow-up and routine laboratory exams. An MRI was performed after 2, 4 and 6 months from initiation of treatment and subsequently according to local practice until disease progression. In the case of clinical progression, an additional MRI was to be obtained within one week of the investigator becoming aware of the clinical progression. In patients where clinical progression occurred before 6 months from treatment initiation, no additional MRIs were required after clinical progression. Medical follow-up continued for 2 months after disease progression. Since all patients had progressed already at this stage, patient mortality was to be assessed based on monthly telephone interviews with the patients' caregivers.

7.6 Study Procedure Matrix

Table 4 Schedule of Evaluations to be Performed for Each Patient

	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*			
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.

7.7 Disease Progression

The following criteria were used for determining disease progression, in cases where an MRI was available [50]:

1. Tumor growth > 25% compared to the smallest tumor area measured in this patient during the trial.
2. Appearance of one or more new tumors in the brain (diagnosed radiologically as GBM).
3. New neurological symptoms which are correlated with radiological findings on contrast MRI of the head.

In cases where an MRI was not available, clinical progression was to be diagnosed according to the following criteria:

1. Decline in functional status as indicated by a decrease in KPS of > 10, and
2. Decline in neurological function as indicated by a decrease of 2 points or more in MRC scale, and
3. ≥50% increase in steroid dose.

In order to avoid early treatment termination, guidance given to investigators included continuing treatment until known clinical progression as set forth above, even if there was a suspicion of progression according to the local MRI reading.

Determination of progression was made by the following review processes:

- *Clinical Investigator Review*

The clinical investigator review included both radiological and clinical data, based on personal knowledge of each study case, and thus is probably the most complete and accurate of the evaluations of disease progression. It is, however, non-blinded. This review was supplemented with dates of death to construct progression free survival and time to progression analyses.

- *Core Radiology Review*

The Core radiology review was based on blinded radiological review performed by an independent core lab. While Core radiology reviews are blinded, they lack clinical data to supplement the radiological picture. Hence, unblinded assessment of disease progression by the clinical investigator, including review of both radiological and clinical data, is often considered to provide a more complete assessment of progression than provided by core radiology review.

- *Clinical Events Committee (CEC) Review*

In order to remove potential bias that may be introduced by the investigators, a clinical events committee (CEC) (consisting of an independent neurosurgeon and independent neuro-oncologist) adjudicated the investigator assessment of progression. The CEC-adjudicated progression data included investigator based MRI measurements, clinical progression based on CEC judgment of investigator assessments, AEs and SAEs, and finally date of death. Thus, analysis of radiological endpoints (TTP, PFS6, radiological response rate) in the pivotal study was made using the CEC review.

7.8 Study Endpoints

The primary outcome of the study was overall survival (OS).

The secondary outcome measures of the study are listed below. The PFS6 was the only powered secondary endpoint in the study with a pre-specified hypothesis.

- 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

Safety and tolerability of NovoTTF-100A treatment were assessed based on the incidence and severity of adverse events and toxicities.

7.9 Statistical Methods Planned in the Protocol

The Statistical Analysis Plan is summarized below.

7.9.1 Analysis Populations

The following analysis populations were planned for the study. The ITT and Safety populations were specified in the study protocol, and the PP population was added in the Statistical Analysis Plan (SAP) early in the study enrollment process, and prior to the first meeting of the Data Monitoring Committee (DMC).

- *Intent-to-Treat (ITT)*

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

- *Per Protocol (PP)*

  The PP population includes:

  - Subjects who did not have any major protocol violations that would affect the endpoints being assessed, and
    - All subjects randomized to BSC treatment who received at least one protocol-specified best standard of care chemotherapy or Avastin (bevacizumab) alone or in combination with cytotoxic chemotherapy.
    - All subjects randomized to NovoTTF-100A treatment who similarly received at least one full treatment course as defined in the protocol (28 days of treatment).

  The PP population is based on patients in both treatment arms receiving the protocol specified treatment to which they were randomized and without any major protocol violations. The identification of a PP analysis population is in accordance with the ICH-E9 guidance, where the analysis is limited to a subset of patients who are more compliant with the protocol so that the opportunity for a new treatment to show additional efficacy in the analysis, and most closely reflects the scientific model underlying the protocol is maximized.

- *Safety Population*

  The Safety Population includes all subjects who received at least one dose of best standard of care therapy or any duration of treatment with the NovoTTF-100A device (even if it was just turned on and then immediately turned off). The safety analysis was to be performed by treatment group according to the treatment that the patient actually received. Only AEs occurring prior to disease progression were to be 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. All adverse events were to be included in the listing of AEs.

7.9.2 Overall Survival

The statistical hypothesis for the primary endpoint, overall survival, was as follows:

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 logrank test at an alpha of 0.05.

7.9.3 PFS6

The statistical hypothesis for the secondary endpoint, PFS6, was as follows:

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

where,

Pt and Pc are the proportions of patients 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 a significance level of 0.05.

7.10 Changes During the Course of the Study

7.10.1 Changes in the Conduct of the Study or Planned Analyses

No changes in the conduct of the study were made during the study. The only protocol change made was a modification of the UADE reporting time frame (which was overly stringent in the original protocol) to comply with the reporting requirements of 21 C.F.R. §812.150(a)(1) and 21 C.F.R. §812.150(b)(1) as well as addition of adverse events typically associated with the underlying recurrent GBM disease to the list of expected events. This change was submitted to the agency as a 5 Day Notice.

7.10.2 Changes in the Device

There was one device design modification during the conduct of the clinical trial. This change involved replacement of the overnight battery and charger for the Electric Field Generator with a medical grade overnight power supply, and was submitted to the agency. The change did not alter the electric fields delivered by the device, the intensity of these fields, the duration of treatment, or the power input specifications of the device.

7.10.3 Data Monitoring Committee (DMC)

An independent Data Monitoring Committee (DMC), comprised of a neurosurgeon, neuro-oncologist and statistician was formed to monitor the safety data from the study. DMC review was performed after 70 and 140 patients had completed the study procedures to determine if:

- there was clear evidence of unacceptably harmful side-effects of NovoTTF-100A treatment; or
- there was no likelihood of demonstrating treatment benefit or equivalence.

At both planned reviews of the data, the DMC determined the study should continue as planned without changes to the protocol.

8.0 PIVOTAL STUDY RESULTS

8.1 Enrollment and Accountability

8.1.1 Enrollment by Site

A total of 237 patients were enrolled in the study from 28 clinical centers (US-16; Europe-11; and Israel-1). The maximum number of patients recruited at one site was 21 patients, less than 10% of the total number of patients. Approximately 50% of the patients were enrolled at the US sites (US-113; Europe-103; and Israel-21). **Table 5** shows the number of patients enrolled at each center by treatment group.

Table 5 Number of Subjects Randomized by Treatment Group and Clinical Site
All Randomized Patients

				NovoTTF-100A	BSC	Total
#	**Center**	**Country/State**	**Investigator**	**(N=120)**	**(N=117)**	**(N=237)**
1	CHUV Lausanne	Switzerland	Dr. Roger Stupp	10 (8)	11 (9)	21 (9)
2	Zurich University	Switzerland	Dr. Silvia Hofer	1 (1)	1 (1)	2 (1)
3	Brno University Hospital	Czech Republic	Dr. Martin Smrjca	2 (2)	2 (2)	4 (2)
4	Na Homolce Hospital - Prague	Czech Republic	Dr. Vladimir Dbaly	7 (6)	6 (5)	13 (5)
5	Innsbruck University	Austria	Dr. Herwig Kostron	2 (2)	1 (1)	3 (1)
6	Augsburg Clinic	Germany	Dr. Volkmar Heidecke	9 (8)	11 (9)	20 (8)
7	University Graz	Austria	Dr. Franz Payer	3 (3)	3 (3)	6 (3)
9	Memorial Sloan Kettering	New York	Dr. Phillip Gutin	1 (1)	3 (3)	4 (2)
11	University of Virginia	Virginia	Dr. David Schiff	4 (3)	5 (4)	9 (4)
12	University of Illinois Chicago	Illinois	Dr. Herbert Engelhard	10 (8)	10 (9)	20 (8)
13	Northwestern Hospital	Illinois	Dr. Jeffrey Raiser	3 (3)	5 (4)	8 (3)
14	Beth Israel Deaconess	Massachusetts	Dr. Eric Wong	5 (4)	4 (3)	9 (4)
15	University of Pennsylvania Medical Center	Pennsylvania	Dr. Frank Liebermann	7 (6)	7 (6)	14 (6)
16	Evanston Northwestern	Illinois	Dr. Nina Paleologus	0 (0)	1 (1)	1 (0)
18	Columbia University	New York	Dr. Jeffrey Bruce	1 (1)	1 (1)	2 (1)
19	JFK Medical Center	New Jersey	Dr. Josef Landolfi	4 (3)	2 (2)	6 (3)
20	Allegheny Medical Center	Pennsylvania	Dr. Lara Kunschner	5 (4)	4 (3)	9 (4)
21	Cleveland Clinic Foundation	Ohio	Dr. Robert Weil	3 (3)	3 (3)	6 (3)
22	Medical College Wisconsin	Wisconsin	Dr. Mark Malkin	4 (3)	3 (3)	7 (3)
23	Boston University	Massachusetts	Dr. Lawrence Chin	3 (3)	1 (1)	4 (2)

Table 5 Number of Subjects Randomized by Treatment Group and Clinical Site All Randomized Patients						
				NovoTTF-100A	BSC	Total
#	Center	Country/State	Investigator	(N=120)	(N=117)	(N=237)
24	Lahey Clinic	Massachusetts	Dr. Rees Cosgrove	1 (1)	1 (1)	2 (1)
25	Cornell	New York	Dr. Susann Pannullo	3 (3)	2 (2)	5 (2)
26	University Hospitals	Ohio	Dr. Andrew Sloan	3 (3)	4 (3)	7 (3)
27	Tel Aviv Medical Center	Israel	Dr. Andrew Kanner	10 (8)	11 (9)	21 (9)
29	Hopital de la Pitie-Salpetriere	France	Dr. Sophie Taillibert	9 (8)	7 (6)	16 (7)
30	CHU Lyon	France	Dr. Jerome Honnorat	4 (3)	3 (3)	7 (3)
32	University of Kiel	Germany	Dr. Maximilian Mehdron	3 (3)	3 (3)	6 (3)
33	University of Hamburg	Germany	Dr. Manfred Westphal	3 (3)	2 (2)	5 (2)

8.1.2 Patient Accountability

Of the 237 patients enrolled, 120 patients were randomized to NovoTTF-100A group and 117 patients to the BSC group. Four (4) patients in the NovoTTF-100A group and 26 patients in the BSC group never received any treatment on trial (**Table 6**). There is little data available on these 30 patients who never started therapy on trial, except for the date of death, which is available for 20 of the 30 patients. The reasons for leaving the trial prior to treatment initiation were withdrawal of consent (n=18), non-compliance (i.e., patients never returned for treatment start visit) (n=7), and pre-treatment events (n=5). The great majority of patients randomized to the BSC group who did not receive any treatment on trial (20/26) either explicitly withdrew consent prior to receiving chemotherapy in the study or did not return to for the treatment start visit, after being advised they were not randomized to the NovoTTF study arm. This was also a reflection of the emerging off-label use of bevacizumab (Avastin) for recurrent GBM. Patients randomized to the BSC group were not offered bevacizumab as one of the trial chemotherapies and therefore probably preferred to receive this treatment off trial in lieu of using known treatments with serious toxicities.

Of the 207 patients who started treatment on trial, most patients (79%) discontinued from the study either due to death (n=47) or deterioration of patient conditions (e.g., patient in hospice care, too weak to travel, etc.; n=49), or because the study requirements had been completed (i.e., two additional clinical visits after disease progression) (n=68). Twenty (20) patients withdrew consent before completing two months of post-progression follow-up. Twenty (20) patients did not complete their follow-up due to adverse events. Three (3) patients did not complete their follow-up due to non-compliance. The proportions of patients who did not complete the protocol-defined follow-up due to withdrawal of consent, non-compliance, or adverse events were similar between the NovoTTF-100A group and the BSC group.

The differences in completing the study follow-up requirements between groups are mainly due to the higher number of patients who decided to leave the study before starting the assigned treatment in the BSC group compared to the NovoTTF-100A group. Vital status was available for all but 17 (7%) patients in the pivotal trial (i.e., vital status available for 220 patients out of 237 at the end of the

trial). The observed loss to follow-up is consistent with the expected loss to follow-up assumed in the protocol for the sample size assessment. The pivotal trial was planned for 236 patients to attain 220 evaluable patients.

A 7% loss to follow-up rate in the primary endpoint (i.e., vital status) of a recurrent GBM clinical trial is not unexpected, considering the debilitating nature of the disease, patient relocation and transfer of care to other medical centers, and the lack of cooperation expected in some cases due to psychosocial factors. A recent publication by Thompson et al. in 2009 [51] reviewed 10 solid tumor studies submitted to FDA and found 1 to 11% loss to follow-up of overall survival data. The authors recommend performing a sensitivity analysis of the OS endpoint for the missing data, similar to the one recommended by FDA for the pivotal trial (see OS sensitivity analysis in **Section 8.7.1.7** below).

Table 6 Patient Disposition All Randomized Patients

	NovoTTF-100A	**BSC**	**All Patients**
	(N=120)	**(N=117)**	**(N=237)**
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 patients who never started treatment)	84 (70)	55 (47)	139 (59)
Reason for Discontinuation (for patients who started therapy)	n=116	n=91	n=207
Death	31 (27)	16 (18)	47 (23)
Adverse Event (Incl. SAE)	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, patients who moved to hospice care and could not return for visits, patients 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 patient off trial without specifying a reason beyond clinical judgment, etc.

Based on **Table 6** it may appear that a slightly higher proportion of patients in the NovoTTF-100A group discontinued from the study due to death than in the BSC group; however, it should be noted that the patient disposition categories used in **Table 6** are for the purpose of study administration and patient accountability, and thus are not appropriate for comparison of death rates or any other study endpoints between the study groups. Specifically, if the two patient disposition categories, i.e., "completion of study requirements" and "discontinuation due to death" are combined, the proportion of patients discontinued from the study due to having reached an "administrative" study endpoint are

similar between the two study groups, 54% (63/116) in the NovoTTF-100A group and 57% (52/91) in the BSC group. In addition, very few patients discontinued from the study while on treatment (i.e., premature withdrawal) due to death or adverse events in either treatment group (6.9% in the NovoTTF-100A group and 5.5% in the BSC group).

In response to an agency question on this topic, the company analyzed the AEs leading to discontinuation of the study treatment in patients that discontinued due to an AE. The time from randomization to adverse event which led to discontinuation was significantly longer for NovoTTF-100A than BSC patients (166±41 days versus 31±4 days; mean ± SEM; t-test p=0.017) indicating that patients were at a much later stage of their disease when discontinuing treatment and thus likely to discontinue due to symptoms of disease progression. In line with this finding, the AE term leading to discontinuation was predominantly a symptom of disease progression ("neurological", "psychiatric", "clinical progression" or "disease progression") both in the NovoTTF-100A group (12 of 13) and in the BSC group (5 out of 7 patients

8.2 Study Administration Issues (Protocol Deviations, Minor Administrative Issues)

The number of deviations in the pivotal trial was relatively low considering the number of patients in the study (n=237) and the severe nature of the symptoms of the underlying disease. Also, as seen in **Table 7** below, the number of deviations in the study were well balanced between the NovoTTF-100A and BSC groups.

Table 7 Number of Deviations by Category and Treatment Group

Deviation	NovoTTF-100A	BSC Chemotherapy	All Patients
Eligibility Criteria	16	16	32
Randomized to Wrong Strata	6	6	12
Wrong ICF version date	2	2	4
SAE Report timing	2	2	4
Bevacizumab (Avastin) used as BSC	0	14	14
Non-Protocol chemotherapy as BSC	0	11	11
Less than 4 weeks NovoTTF-100A treatment	27	0	27
Visit Not Done	19	20	39
MRI Not Done	2	5	7
Total	**74**	**76**	**140**

Eligibility Criteria Deviations

The same number of eligibility criteria deviations was seen in both groups (n=16).

The only eligibility deviation that could reasonably impact the study efficacy assessment was one patient in the BSC group with a screening KPS of 60 where the inclusion criterion was a minimum KPS of 70. Because KPS is a known predictor of overall survival in recurrent GBM patients [2, 4, 52, 53], this deviation is considered a major protocol deviation and the patient was excluded from the Per Protocol analysis. The remaining eligibility criteria deviations, discussed below, are considered minor since they do not impact the efficacy or safety analysis of the study.

About half of the eligibility deviations in each group (n=7) were patients who entered the study just less than 4 weeks after their last chemotherapy dose. The purpose of the 4-week limit since last

chemotherapy in the study inclusion criteria was to allow patients to fully recuperate from the toxicities of prior therapies before entering the study, in order to avoid misinterpretation of these toxicities as AEs in the study. The 14 patients enrolled within 4 weeks of their last chemotherapy were all for administrative reasons (the next possible date for a baseline visit would have been at least a week later). All of these patients also had normal organ function at baseline and had therefore recuperated from prior therapies. [4, 54]

Two patients did not have their baseline KPS recorded in their file; however, both patients were independent in activities of daily life, thus indicating their KPS was at least 70.

The other eligibility deviations were laboratory values marginally out of the normal range, without any clinical significance according to the investigators' assessment. These included slightly elevated bilirubin in most cases (6), one case of mild thrombocytopenia (70,000/µl), and one case of neutropenia due to a concomitant viral illness. In addition, PT (prothrombin) and differential were not done at screening in individual patients. Elevated bilirubin is a normal finding in patients receiving anti-epileptic drugs (AEDs). All these patients had either received AEDs in the past or were currently receiving AED treatment. PT was part of the eligibility criteria in order to rule out significant bleeding disorders which could affect patient safety outcomes in the trial. However, all of these patients had normal PT values on subsequent testing, ruling out any effect on safety assessment in the trial.

One patient in each treatment group had a screening MRI more than 4 weeks before randomization, making the determination of increase in intracranial pressure (possible exclusion criteria) less accurate. However, both these patients' baseline MRIs did not show any evidence of increased ICP.

One patient with midline shift greater than 5mm (increased ICP) was started on systemic steroids with a subsequent decrease in midline shift (<5mm) at baseline.

Randomization Errors

The pivotal study used a stratified randomization design where patients who underwent surgery for their current progression (prior to trial entry) were randomized separately from patients who did not undergo surgery for their recent progression. The intent of the stratified randomization was to avoid imbalance in the proportion of re-operated patients between the treatment groups, since re-operation may be a predictor of improved survival in recurrent GBM [2, 5]. Six patients in each treatment group were randomized into the wrong strata (all 12 patients were incorrectly randomized in the re-operated strata instead of non-re-operated strata). All stratification errors occurred early in the study (within the first 6 months of patient recruitment) and were administrative in nature. The errors occurred due to individual investigators in both the US and Europe misunderstanding the definition of re-operation for recurrence for purposes of randomization strata. These 12 patients all had surgery in the past for recurrence, but they did not have surgery for the latest recurrence which made them eligible for the trial; thus, they should have been randomized in the non-operated strata. The patient allocation to re-operation strata was subsequently corrected for analysis purposes, and patients were allocated to the correct group for efficacy analysis. Moreover, since the number of patients randomized in the wrong strata was balanced between treatment groups and the total number of re-operated patients was the same in both treatment groups (28% vs. 25%; p=0.64; NovoTTF-100A vs. BSC, respectively), these deviations do not impact the assessment of efficacy in the study.

Administrative

Four administrative deviations were seen in each group (wrong ICF version signed and SAE report timing beyond specified).

Follow Up Visit Schedule

The number of follow up visits not performed was slightly lower in the NovoTTF-100A group than in the BSC group. A minimum of 1,242 visits were to be performed in the study (screening, baseline, month 1, month 2, post progression visit 1, post progression visit 2 at minimum for all 207 patients who actually started treatment). Only 39 visits (3%) in the study were not done as expected (1.5% in each group). Since survival data was collected until death on all patients, this deviation has no impact on the efficacy assessment in the study.

In line with the MRI accountability analysis performed in the PMA (Section 13.5.6.2.2.2), more patients in the BSC group missed an MRI (n=5) than in the NovoTTF-100A group (n=2). These were all cases where a progression MRI was performed and thus had no impact on the assessment of PFS6 or radiological response rate in the trial.

Non-Protocol Specified Therapies

The 14 patients in the BSC group who were treated with bevacizumab (Avastin) as BSC and the 11 patients who received other chemotherapies not defined in the protocol were reported as protocol deviations. The protocol defined a recommended list of BSC chemotherapies to be used in the trial as an active control group. Although Avastin was not one of the listed therapies (since it was not approved at the time the pivotal study protocol was approved by FDA), more and more patients insisted on receiving this treatment off-label during the study. Since Avastin was approved in 2009 for recurrent GBM, these patients were included in all the company's analyses in the PMA.

Ten of the 11 patients who received other chemotherapies were recruited in European centers. This reflects slightly different trends in the choice of chemotherapies in Europe compared to the US (e.g., Avastin was not approved in Europe for recurrent GBM, whereas in the US it was approved by FDA in 2009; also other chemotherapies such as CPT11 without Avastin are used in Europe which are not common practice in the US). As seen in the overall survival analyses in the PMA, the results seen in US and OUS centers were very similar. In order to fully balance the types of chemotherapies used in US and European centers, these 11 patients were excluded from the BSC control in the Per Protocol analysis.

Twenty seven (27) patients in the NovoTTF-100A group received less than the minimal protocol pre-specified treatment duration of 28 days (1 course), where the duration of a single course was determined based on preclinical evidence as described in the PMA. Furthermore, TTFields are a real-time, physical modality, and thus have no half life. The moment the treatment is interrupted, the anti-mitotic effect of the fields stops and the tumor is free to resume growth. Chemotherapy, on the other hand, whether oral or intravenous, has a tissue half life in the order of several weeks; thus, after receiving even one dose, an anti-mitotic effect can be expected to continue for about 4 weeks. In order to balance the amount of effective therapy received in both treatment groups in the study, these 27 patients were excluded from the Per Protocol analysis.

Visits Out of Window

Given the debilitating nature of recurrent GBM, not surprisingly there were a number of study visits which were performed slightly outside of the protocol specified visit windows. However, all such visits were completed within one week of the pre-specified windows. Moreover, the number of out of

window visits was essentially the same in both study groups. None of the out of window visits impact the trial endpoints, especially since OS is assessed independent of visit window.

Conclusion

The company concludes that a relatively low number of deviations were seen in the trial and that they were balanced in number and type of deviation between groups. The majority of the deviations were administrative in nature and did not impact the safety and efficacy analyses of the study.

8.3 Analysis Populations

As described above, there are six groups of patients who together comprise the ITT population:

1. NovoTTF-100A patients who never started therapy (n=4)
2. NovoTTF-100A patients who received less than 4 weeks of therapy (n=23)
3. NovoTTF-100A patient treated Per Protocol (n=93)
4. BSC patients who never started therapy on study (n=26)[1]
5. BSC patients with protocol violations (n=12)
6. BSC patients treated Per Protocol (n=79)

Figure 9 shows the number of patients available for analysis in the Intent-to-Treat (ITT), Per Protocol (PP), first modified ITT (mITT1), second modified ITT (mITT2), and Safety Populations. At the request of FDA, the company analyzed the Safety Population for the effectiveness endpoints of OS, PFS6 and TTP.

- **ITT**: The ITT population includes all 237 randomized patients. This includes 120 patients in the NovoTTF-100A group and 117 patients in the BSC group. The ITT population includes groups 1-6 above.

- **PP**: The PP population includes 93 patients in the NovoTTF-100A group and 79 patients in the BSC group (groups 3 and 6 above). In the NovoTTF-100A group, 4 patients who did not receive any NovoTTF-100A treatment and 23 patients who received less than one course (4 weeks) of NovoTTF-100A treatment were excluded from the PP population. Three of the four untreated patients withdrew consent and 1 patient had a pre-treatment AE which did not allow treatment to start. The 23 patients who did not complete one course (4 weeks) of treatment did so due to non-compliance with the treatment protocol and withdrawal of consent.

  In the BSC group, 26 patients who did not receive any treatment on study, 11 patients who received non-protocol specified chemotherapy or supportive care only, and 1 patient who had a major protocol violation (KPS 60%) were excluded from the PP population. There were no other major protocol deviations requiring removal from the PP population.

- **mITT1**: The mITT1 (first modified ITT) population comprises groups 3, 4, 5 and 6 above for a total of 93 NovoTTF-100A patients who received at least one course of treatment and all 117 patients randomized to the BSC group regardless of whether or not they received any chemotherapy as part of the study.

- **mITT2**: The mITT2 (second modified ITT) population comprises groups 3, 5 and 6 above for a total of 93 NovoTTF-100A patients who received at least one course of treatment and 91 BSC

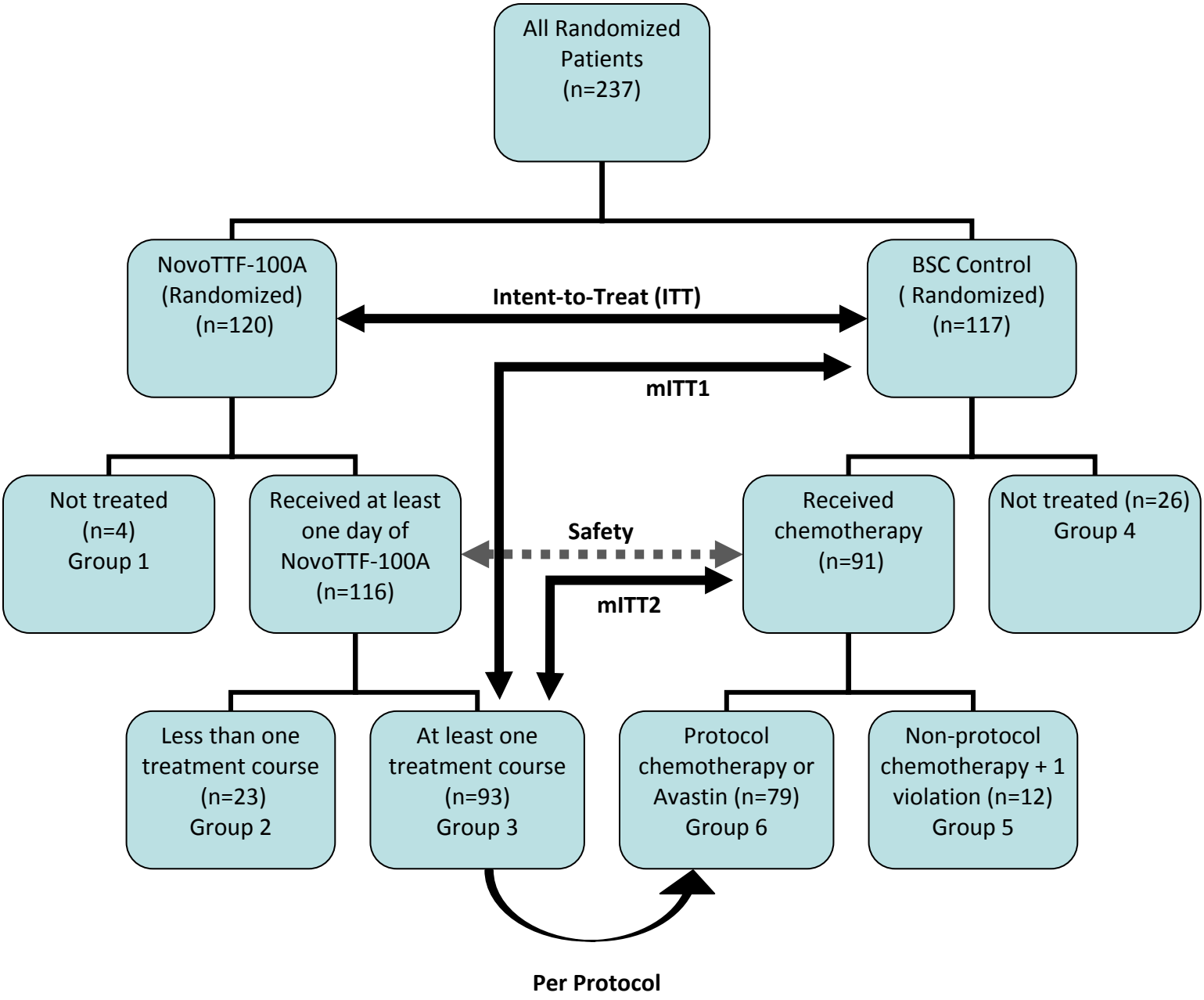
patients who received at least one course of chemotherapy on trial regardless of whether or not the chemotherapy used was defined in the protocol.

- **Safety**: The Safety Population comprises groups 2, 3, 5 and 6 above for a total of 116 NovoTTF-100A and 91 BSC patients who received any treatment on trial. Note that data used for the safety analyses are limited to events occurring until disease progression, in order to minimize the capturing of events clearly related to disease progression or additional post-progression experimental treatments.

  At FDA's request, certain efficacy analyses were also performed on the Safety Population. Please note that the company believes that the efficacy analyses based on the Safety Population and the ITT population are less robust in assessing the true effect of the NovoTTF-100A device compared to BSC chemotherapy due to the inclusion of patients who received very limited therapy with the device (less than 4 weeks; n=23). Based on the preclinical data submitted in the PMA, these patients are not expected to have any efficacy benefit from the device.

It should be noted that the patients who did not receive the full course of BSC chemotherapy are only those patients excluded from the mITT2 and Safety Populations (i.e.. the patients who withdrew consent from the study). The remainder of the patients received at least one course of chemotherapy.

Figure 9 Pivotal Study Analysis Populations



8.3.1 NovoTTF-100A Per Protocol and mITT Populations

The purpose of the PP and mITT analyses is to evaluate the potential of the treatment effect of NovoTTF-100A in patients with recurrent GBM if the device is used properly according to the instructions for use [55].

In the NovoTTF-100A group, 27 patients who did not receive at least 4 weeks of TTF treatment were excluded from the PP and mITT populations because 4 weeks was the predefined single treatment course duration for NovoTTF-100A in the study protocol (**Tab VI**). The 4-week course duration was based on preclinical evidence that if less than 4 weeks of TTFields therapy is provided, arrest of tumor growth is not possible.

Furthermore, TTFields are a real-time, physical modality, and thus have no half life. The moment the treatment is interrupted, the anti-mitotic effect of the fields stops and the tumor is free to resume growth. Chemotherapy, on the other hand, whether oral or intravenous, has a tissue half life in the order of several weeks[2], thus, after receiving even one dose, an anti-mitotic effect can be expected to continue for about 4 weeks. . Note that it is expected that all BSC patients in the PP and mITT populations received therapy whether on study or not (patients who withdrew from the study probably received either Avastin off-label or experimental chemotherapies outside of the study). Thus, it is important to compare the treatment effect of NovoTTF-100A in patients who received at least one full NovoTTF-100A treatment course, i.e., 4 weeks, to patients who received chemotherapy for the PP and mITT analyses, where such a comparison standardizes the *amount of treatment* in terms of biological efficacy each group received.

It should be noted that the reasons for treatment discontinuation reported by the study investigators were primarily non-compliance and withdrawal of consent, and were typically not due to serious adverse events (SAE) or progression in these patients.

8.3.2 BSC Per Protocol Population

For patients assigned to the BSC group, in addition to the 26 patients who did not receive any BSC treatment on protocol (withdrew consent immediately after randomization), 1 patient who violated the KPS inclusion criteria and 11 patients who did not receive a protocol defined chemotherapy were also excluded from the PP population (patients who received bevacizumab were included in the PP BSC population). It should be noted that the majority of patients who received non-protocol defined chemotherapies were recruited in the OUS sites (10 of 11 patients). **Table 8** shows the various types of BSC chemotherapies used in the trial.

8.3.3 BSC mITT1 Population

Based upon the company's best information, the 26 BSC patients who withdrew consent prior to treatment initiation may well have done so due to disappointment from not receiving the study device,

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[2]Pharmacokinetics of approved GBM therapies:

a. Based on a population pharmacokinetic analysis of 491 patients who received 1 to 20 mg/kg of Avastin weekly, every 2 weeks, or every 3 weeks, the estimated half-life of bevacizumab was approximately 20 days (range 11−50 days). The predicted time to reach steady state was 100 days. The accumulation ratio following a dose of 10 mg/kg of bevacizumab every 2 weeks was 2.8 [*Avastin package insert.*].
b. About 38% of the administered temozolomide total radioactive dose is recovered over 7 days [Temozolomide Package Insert], thus Temozolomide and its active metabolites are likely to be present in the brain for at least 3-4 weeks after the 5 day course of maintenance temozolomide given according to the Stupp protocol.

knowing that bevacizumab was not yet approved for recurrent GBM (all trial patients were recruited prior to the FDA approval of bevacizumab) and thus not available on the BSC arm of the study at the time. The study investigators believe that the majority of BSC patients who withdrew consent from the study received bevacizumab "off–label". Thus, the sponsor believes that comparison of NovoTTF-100A patients who received at least one course of treatment (n=93) to all randomized BSC patients (n=117), is the most scientifically sound comparison to test the efficacy of NovoTTF-100A versus the best available active chemotherapy today (including bevacizumab).

8.3.4 BSC mITT2 Population

Based on a request from FDA, the company has also defined a modified ITT population including all patients who received any chemotherapy on study, whether predefined in the protocol or not. Thus, the mITT2 BSC population excludes the 26 BSC patients who withdrew consent prior to receiving any therapy on study, despite the fact that it is likely that most, if not all of these patients received standard of care chemotherapies off-trial (probably bevacizumab).

Table 8 Type of Chemotherapies BSC Patients Received by Analysis Population

Treatment/Regimen	ITT and mITT1	mITT2	PP
	(N=117)	(N=91)	(N=79)
Nitrosureas (BCNU)	27 (23)	27 (30)	27 (34)
Platinum Based Chemotherapy	16 (13)	16 (18)	16 (20)
Procarbazine	1 (1)	1 (1)	1 (1)
Procarbazine, Lomustine and Vincristine	8 (7)	8 (9)	8 (10)
Temozolomide	14 (12)	14 (15)	13 (16)
Avastin	14 (12)	14 (15)	14 (18)
Other (e.g., Etoposide, Imatinib, Irinotecan)	11 (9)	11 (12)	0 (0)
Withdrew Prior to Receiving Treatment on Study (most likely received bevacizumab)	26 (22)	0 (0)	0 (0)

8.4 Demographics and Baseline Characteristics

The distributions of baseline characteristics of patients are well balanced between the two treatment groups, as seen in **Table 9** below. The only significant differences between groups in the ITT population were gender, tumor location (frontal versus non-frontal) and Karnofsky Performance Status (KPS). Gender is not known to be associated with outcomes in recurrent GBM patients. A frontal tumor location is generally considered to lead to a better outcome in brain tumors due to a lower incidence of difficult and debilitating neurological deficits. The percentage of patients with frontal tumor location was significantly higher in the BSC group than in the NovoTTF-100A group (50% vs. 32%), leading to a possible bias in favor of the control group with regard to overall survival. A higher KPS is associated with better outcome in GBM. The mean KPS was significantly higher in the NovoTTF-100A group than in the BSC group (83±11 vs. 80±11), leading to a possible bias in favor of the NovoTTF-100A group with regard to overall survival. Thus, the statistical analysis of overall survival difference between groups in the ITT population was adjusted for these differences in baseline characteristics and other predefined, clinically significant covariates using a Cox proportional hazards model (see **Section 8.7.1.11**).

NovoCure has performed an analysis of demographics and baseline covariates of the PP population to assess potential bias in the PP analysis. The major prognostic baseline characteristics for GBM patients, age and Karnofsky performance scale, remained balanced between treatment groups in the PP population (even more so than in the ITT population). The only significant differences

between groups in the PP population were frontal tumor location and gender. In the PP population, there remained more patients with frontal tumor location in the BSC group than in the Novo-TTF group (48% vs. 28%). There were also more men in the NovoTTF-100A group than in the BSC group (80% vs. 59%).

Table 9 Demographics and Baseline Characteristics by Treatment Group Intent-to-Treat Population

Characteristics	NovoTTF-100A (N=120)	BSC (N=117)	P-Value
Race			
Caucasian	111 (93)	106 (91)	0.0865
African American	2 (2)	5 (4)	
Asian	0	3 (3)	
Hispanic	7 (6)	2 (2)	
Other	0	1 (1)	
Gender			
Male	92 (77)	73 (62)	0.0169
Female	28 (23)	44 (38)	
Region			
OUS	63 (53)	61 (52)	0.9554
US	57 (48)	56 (48)	
Tumor Position			
Frontal	38 (32)	58 (50)	0.0018
Non-Frontal	77 (64)	50 (43)	
Tumor Location			
Left	42 (35)	46 (39)	0.5796
Right	49 (41)	45 (38)	
Bilateral	23 (19)	17 (15)	
Prior Avastin Use			
Yes	24 (20)	21 (18)	0.6873
No	96 (80)	96 (82)	
Re-operation for Recurrence Status			
Yes	33 (28)	29 (25)	0.6346
No	87 (73)	88 (75)	
Prior Low-grade Glioma			
Yes	12 (10)	11 (9)	0.8764
No	108 (90)	106 (91)	
Age (years)			
N	120	117	0.3783

Table 9 Demographics and Baseline Characteristics by Treatment Group Intent-to-Treat Population

Characteristics	NovoTTF-100A (N=120)	BSC (N=117)	P-Value
Mean (Std)	54.2 (10.3)	53 (10.77)	
Weight (kg)			
N	111	104	0.8060
Mean (Std)	83.06 (18.136)	82.46 (17.817)	
Prior GBM Recurrences			
N	120	117	0.2115
Mean (Std)	1.5 (0.92)	1.3 (0.83)	
Karnofsky Performance Score			
N	120	114	0.0456
Mean (Std)	83 (10.84)	80.1 (11.01)	
Median	80	80	
Tumor Area (mm^2)			
N	115	108	0.8542
Mean (Std)	1629.3 (1125.21)	1598.8 (1347.29)	
Time from GBM Diagnosis to Randomization (days)			
N	120	117	0.7835
Mean (Std)	456.5 (387.96)	449.8 (357.28)	
Median	334.5	340	
Time from last RT dose to Randomization (Months)			
N	117	116	0.641
Mean (Std)	13.71 (19.627)	13.93 (19.392)	
Median	8.57	7.83	

8.4.1 Prior Therapies

During their review of the PMA, the FDA requested that NovoCure further analyze the use of concomitant radiotherapy and temozolomide ("RT+TMZ") to ensure that pseudoprogression was not mistaken for progression, and to analyze time from last radiation therapy ("RT") to randomization to ensure that radionecrosis was not mistaken for recurrence in patients in the study. These analyses are presented below.

8.4.1.1 Pseudo-Progression

As described in detail below, the use of concomitant RT+TMZ was well balanced between groups and, if at all, there was a slightly higher chance of pseudo-progression in individual BSC patients than in NovoTTF-100A patients (which in turn would lead to longer survival times and better outcomes in the BSC group).

In GBM patients, pseudo-progression is a term used for the first transient tumor growth in the 3 following concomitant radiotherapy and temozolomide according to the Stupp protocol [56-59]. As such, pseudo-progression is seen only in newly diagnosed GBM patients. After the first disease recurrence, pseudo-progression, per definition, is no longer a possibility. Therefore, pseudo-progression can be mistaken only for the first recurrence of disease in GBM patients. In the NovoTTF-100A trial, only 12 and 17 patients were enrolled at first recurrence in the NovoTTF-100A and BSC groups, respectively. Of these patients, only 3 and 6 patients were within 3 months from end of RT in the NovoTTF-100A and BSC groups, respectively. Since pseudo-progression is seen in about 20% of GBM patients at first recurrence, and is usually seen in the first three months following RT, the expected maximum number of patients who might be expected to have been misdiagnosed as having recurrent disease due to pseudo-progression in the current trial is 1 patient in each treatment group.

In order to assess whether an imbalance in the incidence of chemo-radiotherapy between the treatment and control groups could cause bias in the risk of misdiagnosis of pseudo-progression as recurrent disease, a review of each patient history (for all patients in the study) was performed. A similar percentage of patients received RT+TMZ prior to entering the trial in the BSC group compared to the NovoTTF-100A group (ITT – 87% vs. 84%; PP – 86% vs. 85%, respectively). This analysis shows that RT+TMZ use was well balanced between groups.

It should be noted that when looking specifically at the subset of patients (n=29) who were enrolled at first recurrence, *i.e.*, those who were at risk of being misdiagnosed due to pseudo-progression, no imbalance favoring the NovoTTF group was seen in the patients receiving RT+TMZ prior to trial entry in the ITT population (9% vs. 14% in NovoTTF-100A and BSC patients, respectively) or the PP population (9% vs. 16% in NovoTTF-100A and BSC patients, respectively). These results show that it is very unlikely that the study results could be biased in favor of the NovoTTF group due to potential enrollment of patients with pseudo-progression.

In conclusion, the maximum number of patients who might reasonably be expected to have been misdiagnosed as having recurrent disease due to pseudo-progression in the current trial is about 1 patient in each group. Because the use of RT+TMZ was well balanced between groups, it is expected that the minimal risk of diagnosis of pseudo-progression as recurrence would be the same between groups, and therefore that the study conclusions would not be affected.

8.4.1.2 Radiation Necrosis

Radionecrosis is the phenomenon of immediate or delayed brain tissue death following ionizing radiation therapy. The tissue can appear as swelling (edema) on an MRI and, rarely, even as an increase in the contrast enhancing area of the tumor. The study inclusion criteria were designed to ensure patients at study entry had recurrent disease by using the Macdonald criteria [50] to define recurrence – thus edema alone or changes in non-contrast enhancing portions of the tumor were not sufficient to define recurrent disease. The clinical investigators in the NovoTTF-100A study were well-aware of the issue of radionecrosis, were trained to recognize it clinically, and would have excluded patients they identified with this condition from the NovoTTF-100A trial. The clinical investigators did not identify any cases of radiation necrosis based on their clinical judgment. Moreover, it is not possible to diagnose radionecrosis based on MRI alone. The only way to conclusively distinguish between true GBM recurrence and radionecrosis is to perform a brain biopsy, which is not practically feasible for the majority of patients. Therefore, it is not possible to definitively identify which patients in the NovoTTF-100A trial, if any, had radionecrosis.

However, if patients with radionecrosis were enrolled in the trial, the number of affected patients would be expected to be very low, and to be balanced between treatment groups. The incidence of radionecrosis in brain tumor patients has been reported to be in the range of 2.5-4.9% [60]. Radionecrosis being mistaken for recurrence could theoretically mean that non-recurrent patients were included in the trial. These patients might be expected to have longer survival times. For the NovoTTF-100A trial, if, of the patients who received radiation therapy (117 NovoTTF, 116 BSC) at any time point (up to a maximum of 12.5 years prior to randomization), the highest reported percentage (5%) in fact had radionecrosis, this condition would affect a maximum of 5 or 6 patients per group. Furthermore, due to the randomized nature of the trial, it is expected that the incidence of radionecrosis would be the same between groups. Therefore, since only a minority of patients in both groups could have been mistaken as recurrent at trial entry, the between-group comparisons detailed in this section would not be impacted.

The company also performed an analysis of the time from last radiation therapy ("RT") dose to randomization, which was a mean of approximately 14 months in each group (see **Table 9**). Radionecrosis has been shown in the past to appear after a mean latent period from last RT of 11.6 months [61]. In fact, the literature suggests that at one year, 66% of cases of radionecrosis have already occurred. Thus, the company believes it is very likely that the majority (>70%) of the small number of potential cases of radiation necrosis would have occurred well before 14 months from end of radiation and would thus have been identified prior to the study.

Since the time from last RT to randomization was balanced in the trial (both in the ITT and PP populations), the chance that radionecrosis occurred, small as it is, would likely be balanced between NovoTTF-100A and BSC patients. Theoretically, small differences between regions in the time from RT to randomization, might have led to a slightly different incidence of radionecrosis between the groups, if it occurred, in the different regions. In order to rule out that such differences may have led to differences in survival, we tested the treatment effect of NovoTTF-100A compared to BSC on overall survival ("OS") adjusting for time from last RT to randomization using a Cox proportional hazards model. Since the adjusted and unadjusted results are nearly identical, the company concludes that there is no effect of time to RT on OS.

In summary, the NovoTTF-100A pivotal trial included criteria intended to ensure that patients were correctly diagnosed with recurrent GBM. Despite this, it is possible that a very small number of patients included in the study may have had radionecrosis, although it might be difficult, if not impossible, to conclusively identify these patients. If it occurred, it is expected that the very low incidence of radionecrosis would be the same between groups, and therefore that the study conclusions would not be affected.

8.5 Study Treatment

The NovoTTF-100A patients in the study were treated for 1.6 months longer on average than the BSC chemotherapy patients (4.2 vs. 2.6 months, respectively, in the ITT population; **Table 10**). Since standard practice in oncology is to change treatments when a therapy is no longer working (i.e., the patient is deteriorating clinically or radiologically under treatment), this indicates that the investigators in the pivotal trial assessed NovoTTF-100A patients as clinically stable for a longer period of time on average compared to patients on BSC chemotherapies. NovoTTF-100A patients were treated in the pivotal trial for a total of 553 months cumulatively.

Table 10 Duration (Months) of Treatment Received by Treatment Group Intent-to-Treat Population

	NovoTTF-100A	**BSC**
	(N=120)	**(N=117)**
N	120	117
Mean (Std)	4.2 (5.59)	2.6 (3.68)
Median	2	2
Min, Max	0.0, 35.8	0.0, 23.0

8.6 Device Failures and Replacements

The NovoTTF-100A System was allocated to 116 patients in the pivotal trial (4 patients withdrew consent prior to starting therapy). These patients were treated for a total of 553 months, or 4.2 months per patient on average during which there was a total of 404 device or additional part failures which required service. The majority of failures were the result of wear and tear of the device cables and plastic casings due to the portable nature of the device. None of the device failures led to adverse events, and loss of treatment was negligible. On average, each patient lost less than 0.7% of the total treatment time due to device and additional part failures. Almost all failures were disconnected wires or connectors in the device, connection cable, batteries or chargers. All device and connection cable failures were detected by the device as intermittent or continuous disconnects leading to a system alarm and immediate shutdown. The battery and charger failures were obvious to the patients since the batteries did not charge or did not maintain the device for the expected amount of time (at least 1.5 hours).

8.7 Efficacy Results

As described in the protocol summary in **Section 7.0** above, the primary efficacy endpoint of the pivotal trial was overall survival. The trial was designed to show superiority of NovoTTF-100A treatment compared to best standard of care effective chemotherapies, and was sized based on the highly promising results seen in the small OUS open-label prospective single arm pilot study in recurrent GBM described in **Section 6.0** above.

In addition, the following efficacy endpoints were defined as secondary:

- PFS6 – subject to a formal hypothesis test with a one-sided alpha of 0.05
- TTP – Time to progression
- 1-Year Survival
- Radiological response rate
- Quality of life (EORTC QLQ-C30)

8.7.1 Primary Efficacy Endpoint – Overall Survival

8.7.1.1 Vital Status Patient Accountability

Patient death in the pivotal study was determined based on the following sources: hospital records, death certificates, telephone interviews with family members, and public records. All death dates were from source data verified at periodic monitoring visits performed by the study CROs. Patients with no known date of death were censored in the overall survival analysis at their last face-to-face or telephone contact date.

Vital status is known for 221 (93%) patients at the end of the study; 202 patients were known to have died and 19 patients (TTF=9; BSC=10) were still alive at the end of the study (6 months after last patient randomized). Sixteen (7%) (TTF=6; BSC=10) patients were lost to vital status follow-up. The majority of patients lost to follow-up were patients who withdrew from the study after randomization and before receiving any treatment on study (n=9; TTF=8; BSC=1) (censored at day 1). The remaining 7 patients (TTF=5; BSC=2) were lost to follow-up during the study due to non-compliance with the follow-up protocol; the average follow-up duration for these patients was 3.1 months (range 1.5 to 6.3 months). Most of the patients with unknown vital status are BSC patients who never started treatment; 9 of the 16 patients lost to follow-up in the trial were in the BSC group.

The patient accountability for the analysis of overall survival is seen in the life table beneath **Figure 10**. At 24 months, 18 patients (15%) in the BSC group were censored and 11 patients (9%) in the NovoTTF-100A group were censored. This trend towards higher censoring in the BSC group compared to the NovoTTF-100A group was seen from the beginning of the study and is most likely due to the lack of motivation of patients assigned to the BSC group to complete their follow-up since they were not receiving the experimental treatment. Most of the patients censored for OS after day 1 were censored due to administrative censoring (patient was alive at the end of the trial). It is clear from the life table that after 12 months, the number of patients at risk is very small (20%) and identical between groups. Thus, comparisons between the survival curves beyond 12 months are not reliable.

It should be noted that the majority (28/35) of censored observations were censored either before receiving any study treatment or at the end of the study (administrative censoring). This type of censoring is most likely to be non-informative thus should not bias the study results. Furthermore, the key baseline characteristics, including gender, age, KPS, tumor area, tumor location, tumor position, prior Avastin use, of the censored patients were comparable ($p>0.05$) between the NovoTTF-100A and the BSC groups, suggesting the censoring is also non-differential in terms of prognosis between the two treatment groups; this is true for all analysis populations (ITT, PP, mITT1, and mITT2).

8.7.1.2 Overall Survival – Intent-to-Treat Analysis

In the pivotal trial, patients assigned to the NovoTTF-100A group had a median overall survival (OS) nearly identical to those assigned to the best standard of care effective chemotherapy (BSC) group. The median OS is 6.3 months (95% CI 5.6-7.8) in the NovoTTF-100A group and 6.4 months (95% CI 5.2-7.4) in the BSC group (logrank p=0.98; Wilcoxon p=0.72) The hazard ratio is 1.0 (95% CI=0.76, 1.32) (test for proportional hazards p=0.45). (**Table 11**).

The Kaplan-Meier survival curves for the two treatment groups show a trend towards a survival advantage for NovoTTF-100A patients during the first 12 months of follow-up, where 80% of the

events occurred in both groups (**Figure 10**). The number of patients remaining at risk beyond 12 months may be too small to reliably estimate the long term survival outcome.

When compared to the literature data discussed in **Section 3.2**, the median OS observed in both treatment groups is not only consistent with the OS data presented for effective chemotherapies (median OS 7.2 months; 95% CI 5.1-9.5 months) but also superior to that for the ineffective chemotherapies. Specifically, the 95% CIs for the median OS in the NovoTTF-100A and BSC groups (5.6-7.8 months and 5.2-7.4 months, respectively) are overlapping with the 95% CI for the median OS for effective chemotherapies (5.1-9.5 months) and completely above the 95% CI for the median OS for ineffective chemotherapies (2.4-4.8 months).

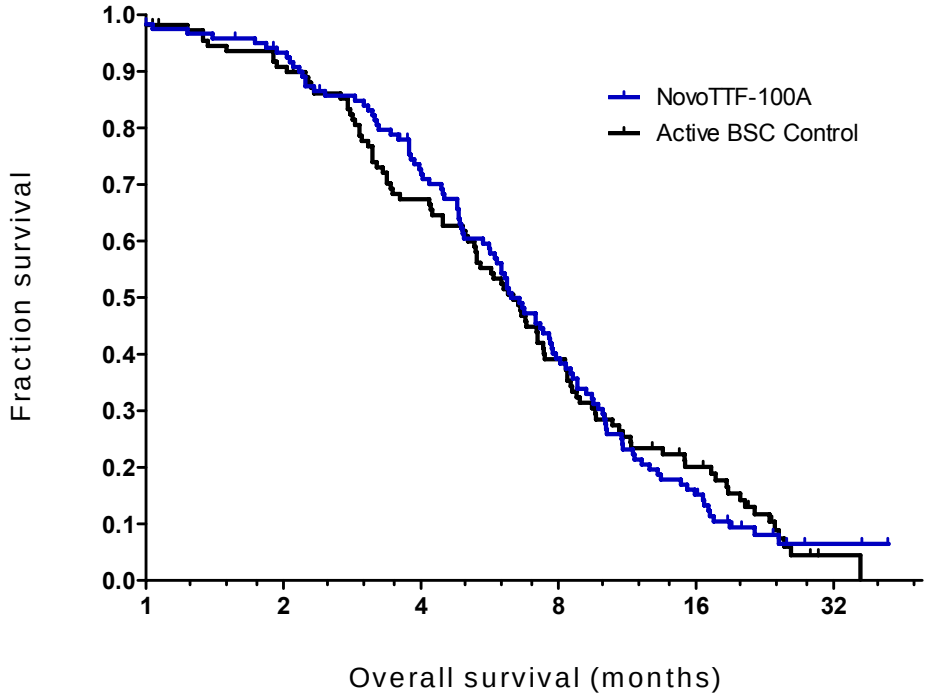
The slightly lower median OS (point estimate) seen in the NovoTTF-100A pivotal trial as compared to the literature data may be in part due to the differences in disease severity at baseline. Both the recurrence number and baseline tumor size are higher in patients enrolled in the pivotal trial than those enrolled in previous trials. Most of the trials reported in the literature accepted either patients with single small lesions or mainly patients with first recurrence. In addition, the majority (74%) of patients enrolled in the pivotal trial are non-re-operated patients, who have a slightly worse outcome than the re-operated patients (see **Section 8.7.1.9.1** below).

Based on the literature review presented in **Section 3.2** above, the estimated excess risk of mortality for the ineffective chemotherapies relative to the effective chemotherapies is 94% based on the estimated median OS (7.23/3.73=1.94). The hazard ratio (NovoTTF vs. BSC) in the ITT population observed in the pivotal trial is 1.0 with a 95% CI of 0.76 to 1.32. Since the upper 95% CI 1.32 is less than 1.94, consistent with the conclusion reached using the median OS, the company concludes that NovoTTF-100A treatment is superior to ineffective chemotherapies in reducing the mortality risk.

For a non-inferiority analysis, it is reasonable to consider a 50% non-inferiority margin as conservative, considering the end-stage nature of this disease and in light of the benign safety profile of the NovoTTF-100A device, as described below, and the quality of life benefit to these patients compared to those receiving chemotherapy. In order to maintain this margin, the upper bound of the HR 95%CI should be beneath 1.47 (1 + 0.5 x 0.94). Since the upper bound of the HR 95%CI in the ITT analysis is 1.32, it is reasonable to conclude that NovoTTF-100A is non-inferior to effective chemotherapies with a non-inferiority margin of 50%.

Thus, the NovoTTF-100A treatment is effective in extending overall survival in recurrent GBM patients compared to ineffective chemotherapies. NovoTTF-100A treatment is not only superior to ineffective chemotherapies but also equivalent to the effective BSC chemotherapies in this ITT analysis. Additional discussion of the non-inferiority of the NovoTTF-100A device can be found in **Section 8.7.1.8** below.

Figure 10 Kaplan-Meier Curves for Overall Survival - Intent-to-Treat Population



	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

*Note that due to the logarithmic distribution of survival times, overall survival is presented graphically on a logarithmic time scale.

Table 11 Overall Survival
Intent-to-Treat Population

	NovoTTF-100A (n=120)	BSC (n=117)
Summary of Censored and Uncensored Value		
Number of Patients	120	117
Number of Deaths	105	97
Number Censored	15	20
Descriptive Statistics for OS (Months)		
Median (95% CI)	6.3 (5.6, 7.8)	6.4 (5.2, 7.4)
Minimum, Maximum	0.77, 42.03	0.03, 36.67
Statistical Analysis		
Logrank p-value	0.9828	
Wilcoxon p-value	0.7152	
Hazard Ratio (95% CI)	1.00 (0.76,1.32)	
Test for proportional hazards p-value	0.45	

8.7.1.3 Overall Survival – Per Protocol Analysis

The Per Protocol analysis is intended to compare patients receiving the same *amount of biologically effective* treatment using two different modalities. NovoTTF-100A, a physical modality, has no half life while chemotherapies have a biological half life of several weeks.

When the overall survival is compared between NovoTTF-100A and best standard of care effective chemotherapies in this population, NovoTTF-100A is also clearly non-inferior to chemotherapy. In fact, utilizing the appropriate statistical analyses, NovoTTF-100A is superior to chemotherapy by 20% in median overall survival (7.8 vs. 6.5 months, respectively; logrank p=0.28; Wilcoxon p=0.04). The hazard ratio is 0.84 (95% CI 0.60, 1.16) comparing NovoTTF-100A treatment to BSC treatment (**Table 12**). Kaplan-Meier curves of the overall survival in both groups are presented in **Figure 11** below.

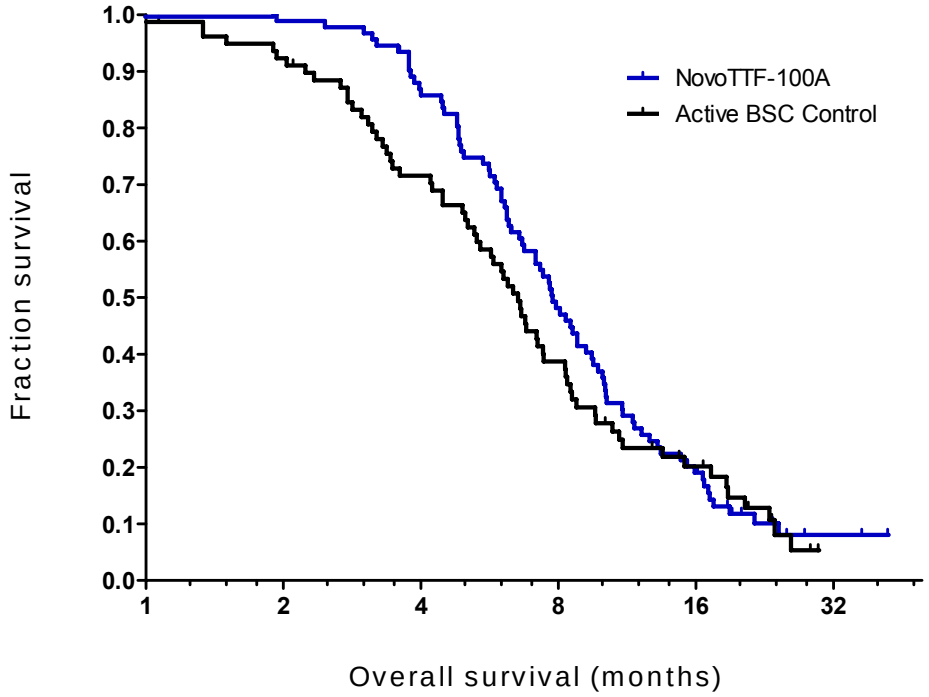
The prospectively defined statistical test for the primary endpoint was the logrank test. However, when examining the survival curves, particularly for the PP analysis, it can be seen that the logrank test may not be the most powerful or the most appropriate test for detecting survival differences in the study population. Specifically, in the PP population, the survival in the NovoTTF-100 group is consistently higher than in the BSC group during the first 12 months of the study, but there is little difference after 12 months. Moreover, the test for proportional hazards is highly statistically significant (p=0.0095), indicating a significantly greater difference in hazards between the two study groups during the early part of the study. From a statistical perspective, the Wilcoxon test is a more powerful test for detecting early survival differences whereas the logrank test is more powerful with proportional hazards. Accordingly, the Gehan-Breslow weighting method was used for the Wilcoxon test, where the weight used is the number of patients at risk at each event time. Thus, this method is most powerful for detecting early survival differences.

From a clinical perspective, since the patients in this trial have a very poor prognosis even compared to other recurrent GBM trials (high recurrence, large tumors, many patients after Avastin failure), it is expected that despite effective treatment, they all have relatively short life expectancy. Thus, the latter part of the survival curve is most likely dictated by the underlying disease. Given that the expected survival in the study population is very short (median survival of less than 7 months), a test such as the Wilcoxon test that is more sensitive to early survival differences (i.e., the test gives higher weights to early differences in survival) is thus more appropriate as compared to the logrank test that weighs event time equally and is more sensitive to later survival differences.

Because the use of the Wilcoxon test is both statistically and clinically justified, we believe the Wilcoxon test accurately characterizes the survival benefit of the NovoTTF-100A over BSC chemotherapy in this Per Protocol analysis.

In addition, even if the log-rank test is chosen for this analysis, the hazard ratio is below 1.0, 0.84 (95% CI 0.60, 1.16). The upper bound of the 95% CI (1.16) is much below the threshold of 1.47 for demonstrating that the NovoTTF-100A device is non-inferior to the effective BSC chemotherapy.

Figure 11 Kaplan-Meier Curves for Overall Survival - Per Protocol Population



	Months	0	3	6	9	12	15	18	21	24
NovoTTF-100A (N=93)	At Risk	93	89	61	37	24	19	11	7	5
	Events	0	3	30	53	66	71	78	79	80
	Censored	0	1	2	3	3	3	4	7	8
BSC (N=79)	At Risk	79	63	42	22	16	13	10	6	3
	Events	0	14	35	53	58	59	61	64	66
	Censored	0	2	2	4	5	7	8	9	10

*Note that due to the logarithmic distribution of survival times, overall survival is presented graphically on a logarithmic time scale.

Table 12 Overall Survival Per Protocol Population

	NovoTTF-100A (n=93)	BSC (n=79)
Summary of Censored and Uncensored Value		
Total Number of Patients	93	79
Total Number of Events	80	67
Total Number Censored	13	12
Descriptive Statistics for OS (Months)		
Median (95% CI)	7.8 (6.7, 9.5)	6.5 (5.3, 7.4)
Minimum, Maximum	1.90, 39.00	0.93, 29.63
Statistical Analysis		
Logrank p-value	0.2359	
Wilcoxon p-value	0.03	
Hazard Ratio (95% CI)	0.82 (0.59,1.14)	
Test for proportional hazards p-value	0.0095	

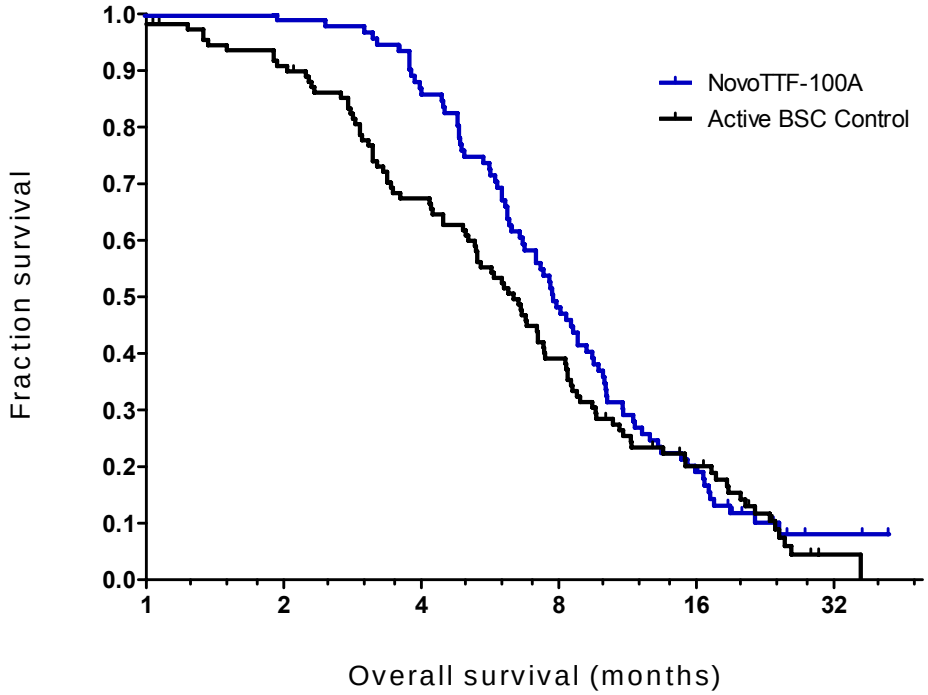
8.7.1.4 Overall Survival – mITT1 Analysis

In the mITT1 population, the median OS in patients who received at least one course of NovoTTF-100A treatment is six weeks longer than patients who received any BSC treatment, whether on study or not. As in the PP population, NovoTTF-100A is superior to chemotherapy by 20% in median overall survival where the median OS is 7.8 months (95% CI 6.7-9.5) in the NovoTTF-100A group and 6.4 months (95% CI 5.2-7.4) in the BSC group (logrank p=0.16; Wilcoxon p=0.01). The Kaplan-Meier survival curves are shown in **Figure 12**. The survival curves beyond 12 months are unreliable due to only a small number of patients surviving past this time point.

In addition, even if the log-rank test is chosen for this analysis, the hazard ratio of NovoTTF-100A treatment versus BSC chemotherapy is below 1.0; HR=0.81 (95% CI 0.60-1.09) (**Table 13**). The upper bound of the 95% CI (1.09) is much below the threshold of 1.47 for demonstrating that the NovoTTF-100A device is non-inferior to the effective BSC chemotherapy.

Thus, in the mITT1 analysis, NovoTTF-100A treatment leads to longer OS and is clearly non-inferior to effective BSC chemotherapy.

Figure 12 Kaplan-Meier Curves for Overall Survival – mITT1 Population



	Months	0	3	6	9	12	15	18	21	24
NovoTTF-100A (N=93)	At Risk	93	89	61	37	24	19	11	7	5
	Events	0	3	30	53	66	71	78	79	80
	Censored	0	1	2	3	3	3	4	7	8
BSC (N=117)	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

*Note that due to the logarithmic distribution of survival times, overall survival is presented graphically on a logarithmic time scale.

Table 13 Overall Survival
mITT1 Population

	NovoTTF-100A (n=93)	BSC (n=117)
Summary of Censored and Uncensored Value		
Total Number of Patients	93	117
Total Number of Events	81	97
Total Number Censored	12	20
Descriptive Statistics for OS (Months)		
Median (95% CI)	7.8 (6.7, 9.5)	6.4 (5.2, 7.4)
Minimum, Maximum	1.90, 42.03	0.03, 36.67
Statistical Analysis		
Logrank p-value	0.1637	
Wilcoxon p-value	0.0133	
Hazard Ratio (95% CI)	0.81 (0.60-1.09)	

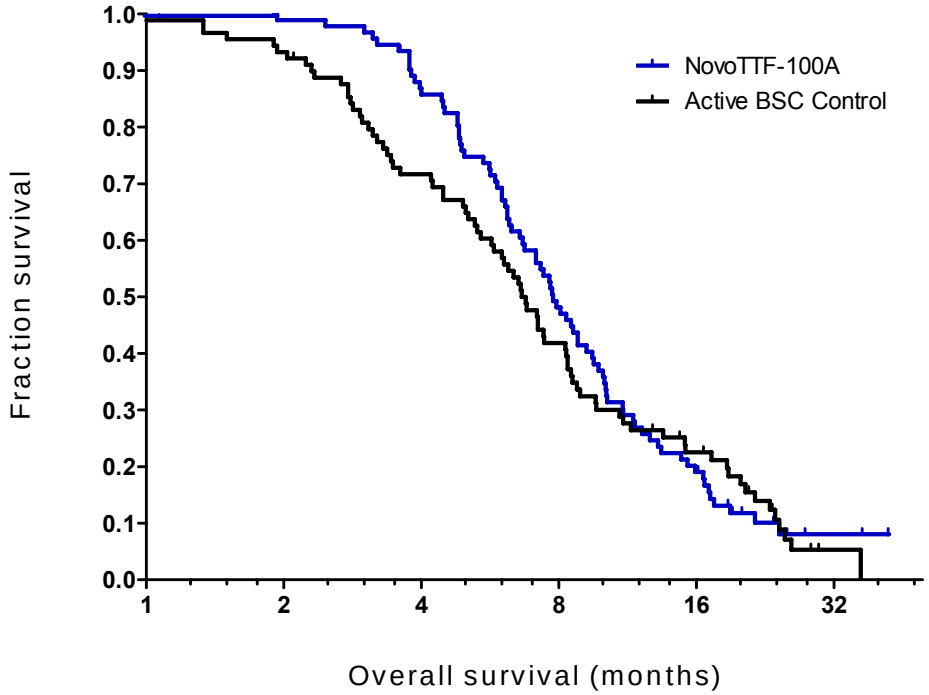
8.7.1.5 Overall Survival – mITT2 Analysis

In the mITT2 population, the median overall survival (OS) in patients who received at least one course of NovoTTF-100A treatment is one month longer than patients who received any BSC treatment on study, whether pre-specified or not. The median OS is 7.8 months (95% CI 6.7-9.5) in the NovoTTF-100A group and 6.8 months (95% CI 5.7-8.4) in the BSC group (logrank p=0.53; Wilcoxon p=0.12) (**Table 14**). The Kaplan-Meier survival curves are shown in **Figure 13**. Please note that the survival curves beyond 12 months are unreliable due to only a small number of patients surviving past this time point.

In terms of the relative efficacy of NovoTTF-100A treatment versus BSC chemotherapy, the hazard ratio is below 1.0, HR=0.90 (95% CI 0.66-1.23). The upper bound of the 95% CI (1.23) is much below the threshold of 1.47 for demonstrating that the NovoTTF-100A device is non-inferior to the effective BSC chemotherapy.

Thus, in the mITT2 analysis, NovoTTF-100A treatment shows a trend towards longer OS and is clearly non-inferior to effective BSC chemotherapy.

Figure 13 Kaplan-Meier Curves for Overall Survival – mITT2 Population



	Months	0	3	6	9	12	15	18	21	24
NovoTTF-100A (N=93)	At Risk	93	89	61	37	24	19	11	7	5
	Events	0	3	30	53	66	71	78	79	80
	Censored	0	1	2	3	3	3	4	7	8
BSC (N=91)	At Risk	91	72	52	28	23	20	16	11	7
	Events	0	17	37	59	63	64	67	71	74
	Censored	0	2	2	4	5	7	8	9	10

*Note that due to the logarithmic distribution of survival times, overall survival is presented graphically on a logarithmic time scale.

Table 14 Overall Survival mITT2 Population		
	NovoTTF-100A	**BSC**
	(n=93)	(n=91)
Summary of Censored and Uncensored Value		
Total Number of Patients	93	91
Total Number of Events	81	79
Total Number Censored	12	12
Descriptive Statistics for OS (Months)		
Median (95% CI)	7.8 (6.7, 9.5)	6.8 (5.7, 8.4)
Minimum, Maximum	1.90, 42.03	0.93, 36.67
Statistical Analysis		
Log-Rank P-Value	0.5267	
Wilcoxon P-Value	0.1221	
Hazard Ratio (95% CI)	0.90 (0.66,1.23)	

8.7.1.6 Overall Survival – Safety Population

Although not specified in the protocol, the company performed an (efficacy) analysis of OS in the Safety Population at the request of FDA. In the Safety Population, the median overall survival (OS) in patients who received any NovoTTF-100A treatment is almost identical to patients who received BSC treatment. The median OS is 6.6 months (95% CI 5.7-7.8) in the NovoTTF-100A group and 6.8 months (95% CI 5.7-8.4) in the BSC group (logrank p=0.51; Wilcoxon p=0.67).

In terms of the relative efficacy of NovoTTF-100A treatment versus BSC chemotherapy, the hazard ratio is 1.1 (95% CI 0.82-1.48). The HR is just above 1 and the upper bound of the 95% CI 1.48 is almost exactly the threshold of 1.47 for demonstrating that the NovoTTF-100A device is non-inferior to the effective BSC chemotherapy.

As noted above, the safety analysis population includes many NovoTTF-100A patients who did not receive one course of treatment, thus underestimates the true effectiveness of NovoTTF-100A therapy. Nevertheless, in this biased comparison, the observed median OS is almost identical in the NovoTTF-100A and the BSC groups, and the NovoTTF-100 device remains non-inferior to effective BSC chemotherapy.

8.7.1.7 Sensitivity Analysis

In order to assess the sensitivity of the survival advantage of NovoTTF-100A treatment compared to BSC seen in the PP population to the definitions used to choose the PP population, 5 sensitivity analyses were initially performed. In analyses 1 to 4, one of the following groups was censored at their last known follow-up:

1. Patients who withdrew consent prior to any therapy on NovoTTF-100A (n=4)

2. Patients who received less than 4 weeks of NovoTTF-100A treatment (n=23)

3. Patients who withdrew consent prior to receiving any BSC chemotherapy (n=26)

4. Patients who received chemotherapies not approved in the protocol and one patient with a major eligibility criteria violation (n=12).

In analysis 5, all the above groups were censored together (n=65) at their last known follow-up.

At the request of the agency, two additional sensitivity analyses were performed by censoring the patients excluded from the mITT2 and the Safety Populations at their last known follow up. The following patients were censored in each group:

- In analysis 6, patients from groups 1, 2 and 3 were censored together (n=53) at their last known follow-up.

- In analysis 7, patients from groups 1 and 3 were censored together (n=30) at their last known follow-up.

Table 15 summarizes the median OS results by group for the various sensitivity analyses.

	Table 15 Overall Survival – Sensitivity Analysis				
Analysis	**NovoTTF-100A Median (95%CI) (months)**	**BSC Median (95%CI) (months)**	**Hazard Ratio (95%CI)**	**Logrank p-value**	**Wilcoxon p-value**
1	6.6 (5.7, 7.8)	6.4 (5.2, 7.4)	0.99 (0.75,1.31)	0.9498	0.6470
2	7.8 (6.7, 9.5)	6.4 (5.2, 7.4)	0.81 (0.61,1.09)	0.1660	0.0098
3	6.3 (5.6, 7.8)	6.8 (5.8, 8.5)	1.14 (0.85,1.53)	0.3794	0.5221
4	6.3 (5.6, 7.8)	6.5 (5.3, 8.3)	1.12 (0.84,1.49)	0.4444	0.9577
5	7.8 (6.7, 9.5)	7.2 (6.0, 8.6)	1.04 (0.75,1.44)	0.8002	0.2575
6	7.8 (6.7, 9.5)	6.8 (5.8, 8.5)	0.96 (0.70,1.31)	0.7852	0.1666
7	6.6 (5.7, 7.8)	6.8 (5.8, 8.5)	1.2 (0.89,1.61)	0.2230	0.3175

The ITT OS result is mainly affected by censoring patients who received less than 4 weeks of NovoTTF-100A (sensitivity analyses 2, 5 and 6). The reason for this is that the patients who withdrew consent in both groups prior to starting any treatment most likely continued to receive some form of treatment (either experimental or "off–label", e.g., bevacizumab) (sensitivity analyses 3, 6 and 7). The reason that censoring patients on non-protocol approved chemotherapy does not make a large change to the BSC survival curve is likely that, although these chemotherapies were not specifically approved in the protocol, they may have similar clinical benefit to the protocol specified chemotherapies (albeit unproven to date in this patient population; see sensitivity analysis 4). In sensitivity analysis 5, with all the above groups censored together, the median OS is higher in both groups compared to the ITT analysis. The HR for this analysis is similar to the HR in the ITT analysis; HR=1.04 (95% CI 0.75-1.44).

Sensitivity analysis 6, censoring patients excluded from the mITT2 population shows that the NovoTTF-100A group is consistently non-inferior to BSC chemotherapy. However, the company believes that sensitivity analysis 7, censoring patients excluded from the Safety Population, is overly conservative. Specifically, it includes patients in the NovoTTF-100A group who did not receive a single full course of treatment, thus underestimating the OS in the NovoTTF-100A group. At the

same time, it assumes that patients in the BSC group who withdrew consent ("non-compliant" patients) have the same OS experience as patients who remained in the trial, thus overestimating the OS in the BSC group.

8.7.1.8 Demonstration of Non-Inferiority

In order to establish the equivalence, or non-inferiority, between Novo-TTF treatment and best standard of care effective chemotherapies in increasing overall survival in recurrent GBM patients, NovoCure used two measures with point estimates and 95% confidence intervals (CIs): (1) the estimated median overall survival (OS) in each treatment group, and (2) the hazard ratio comparing the mortality risk of the two treatment groups. Using median OS to establish the non-inferiority of NovoTTF-100A to effective chemotherapies was the methodology suggested by the agency.

The literature review of ineffective chemotherapies ("historical placebo control" – see **Section 3.2.2** above) showed a median OS of 3.73 months (95% CI 2.4-4.8 months). The median OS for NovoTTF-100A patients in the ITT population of the pivotal trial is 6.3 months (95% CI 5.6-7.8 months). Since the 95% confidence intervals of the median OS in the NovoTTF-100A group and the historical "placebo" control data presented above do not overlap, we conclude that in the ITT population, NovoTTF-100A treatment increases OS significantly compared to the ineffective chemotherapies with $p < 0.025$.

The following graph (**Figure 14**) shows the median OS in months with 95% CI for the different analyses of the study primary endpoint, including the intent to treat (ITT) analysis, the per protocol (PP) analysis, the two additional modified ITT (mITT) populations, the Safety Population requested by FDA and the seven sensitivity analyses (labeled "Sens 1" to "Sens 7") (see **Section 8.7.1.7** above). The graph also presents the median and 95% CIs of ineffective chemotherapies and effective chemotherapies based on the above mentioned literature review. The vertical dashed line represents the upper limit of the 95% confidence interval of ineffective chemotherapies. Note that this line is below the lower confidence interval of all NovoTTF-100A analyses of OS, as well as below the lower confidence intervals of the majority of the sensitivity analyses.

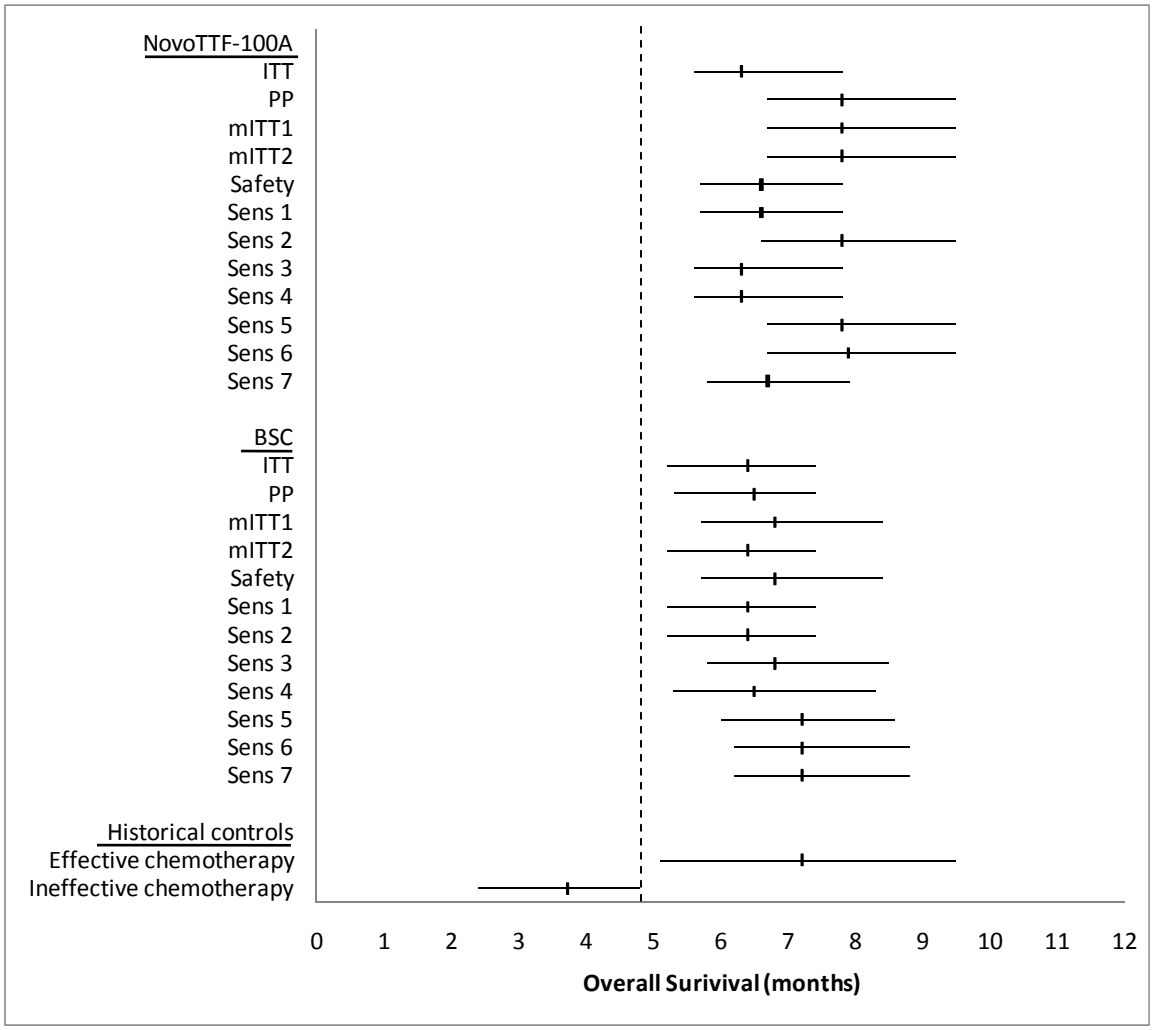
In order to be able to establish non-inferiority using historical controls, it is important that the active control group in the study be as effective as the active controls used for determination of their effectiveness ("constancy assumption"). As seen in **Table 11** above, the 95% CI of the BSC control group in the ITT population of the pivotal trial (5.2–7.4 months) is fully contained within the 95% CI of the historical control data in the literature for effective chemotherapies (5.1–9.5 months). Thus, the company concludes that the constancy assumption is maintained in the BSC control group in the pivotal study.

As presented in **Section 3.2.2** above, the estimated excess risk of mortality for the ineffective chemotherapies relative to the effective chemotherapies is 94% based on the estimated median OS (7.23/3.73=1.94). The hazard ratio (NovoTTF vs. BSC) in the ITT population observed in the pivotal trial is 1.0 with a 95% CI of 0.76 to 1.32. Since the upper 95% CI (1.32) is less than 1.94, consistent with the conclusion reached using the median OS, the company concludes that NovoTTF-100A treatment is superior to ineffective chemotherapies in reducing the mortality risk.

The following graph (**Figure 15**) shows the hazard ratio for death with the NovoTTF-100A device compared to effective BSC chemotherapies used in the pivotal study. A HR of 1.0 (left-most vertical dashed line) reflects an equal hazard of death in the two groups. The higher the HR, the higher the risk of death using the device compared to chemotherapy. As explained above, based on the literature review, the estimated HR of death with ineffective chemotherapies versus effective chemotherapies is 1.94 (right-most vertical dashed line). The middle vertical dashed line represents the point where NovoTTF-100A is superior to the ineffective chemotherapies and also maintains at

least 50% of the efficacy of the effective chemotherapies, which corresponds to a clinically justified non-inferiority margin (Δ).

Figure 14 Comparison of Median Survival and 95% CIs in the Pivotal Trial and in Historical Controls

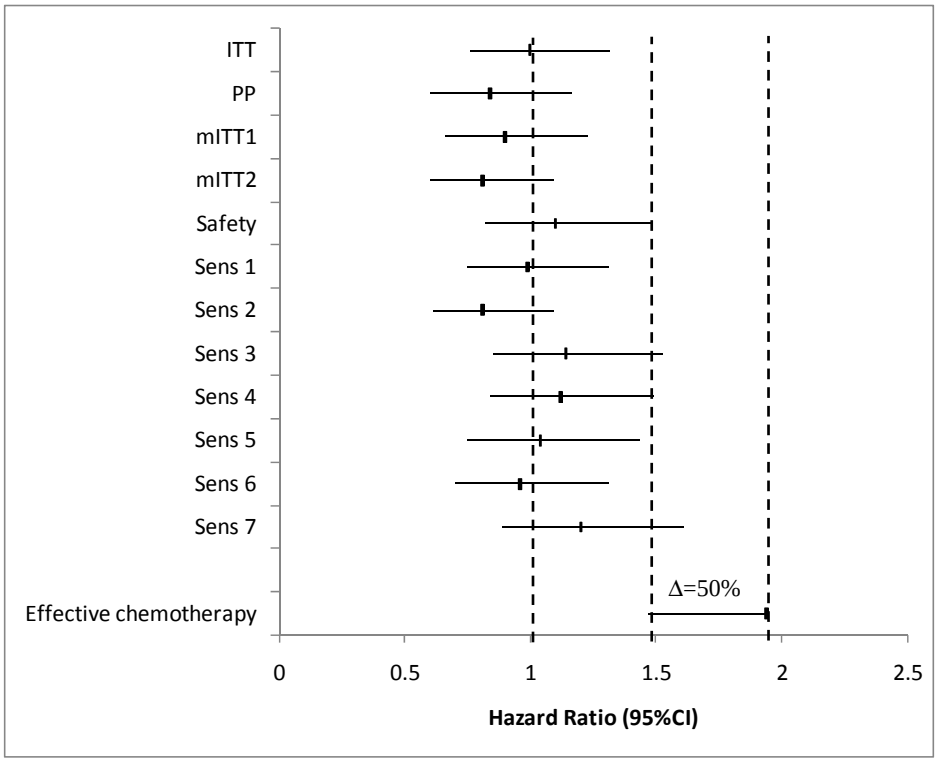


We believe that the 50% non-inferiority margin chosen in this analysis is conservative, considering the end-stage nature of this disease and in light of the benign safety profile of the NovoTTF-100A device and the quality of life benefit to these patients compared to those receiving chemotherapy, described below. Note that the upper confidence limits of the HR in the ITT, PP, mITT1 and mITT2 analyses are below the non-inferiority margin.

Furthermore, in the context of non-inferiority studies, the ITT analysis is usually considered anti-conservative and thus the PP analysis is regularly requested to ensure valid conclusion of non-inferiority (see Section 5.2.3 of the *ICH Harmonised Tripartite Guideline E9: Statistical Principles for Clinical Trials*). It is noteworthy that the PP and both mITT analyses give a hazard ratio below 1.0 with an upper confidence interval below the non-inferiority margin. In addition, the majority of

sensitivity analyses performed have upper confidence intervals below the non-inferiority margin. It should be noted that the company believes that the Sensitivity 3, Sensitivity 4, Sensitivity 7 and the Safety Population analyses have limited value for efficacy assessment, since they are not balanced between groups with regard to treatment exposure. These four analyses exclude (or censor) BSC patients who received no therapy during the trial while including NovoTTF-100A patients regardless of how much treatment they received (even patients who received a single day of therapy, which cannot be expected to be effective).

Figure 15 HRs with 95% CI of NovoTTF-100A Compared to BSC Are Non-inferior to Effective Chemotherapy



Using both the estimates of OS with 95% CIs as proposed by the agency and a non-inferiority margin approach based on hazard ratios with a conservative non-inferiority margin, the NovoTTF-100A device is non-inferior to the best available chemotherapy today for the treatment of recurrent GBM.

Note that covariate adjusted results of the OS analyses and sensitivity analyses are included in **Sections 8.7.1.7** and **8.7.1.11**.

8.7.1.9 Subgroup Analysis

8.7.1.9.1 Overall Survival by Re-Operation Status

Since re-operation may extend overall survival, the randomization in the pivotal study was stratified by re-operation status (yes or no) to balance the proportion of re-operated patients assigned to each study group. In the pivotal study, overall, 26% of the patients were re-operated for their recurrence immediately before randomization. The re-operation rate is the same in the two study groups (28% in the NovoTTF-100A group and 25% in the BSC group; p=0.63).

The re-operation rate observed in the pivotal study is consistent with that reported in the literature. In a recent review [3] reporting the re-operation rate of patients with recurrent GBM in a series of 13 studies carried out between 1995 and 2009, the average re-operation rate for recurrent GBM patients was 20.5±12.8 percent (median ± standard deviation). As expected, patients who were re-operated prior to randomization lived longer than those who were not re-operated in the pivotal trial, regardless of treatment assignment. It is still controversial whether this effect is due to the debulking operation itself or is due to a selection bias, i.e., patients who are candidates for surgery for recurrence are in better clinical shape, have smaller and more confined tumors in more easily accessible locations and are younger.

In the ITT population, in the re-operated patients, the overall survival was essentially the same in NovoTTF-100A patients and BSC patients (median OS 7.3 vs. 7.5 months, respectively). The between-group difference in OS was not statistically significant (logrank p=0.18; Wilcoxon p=0.51). In the non-re-operated patients (75% of patients in the trial), the results in NovoTTF-100A and BSC patients are very similar to those seen for the entire cohort (median OS 6.2 vs. 5.8 months, respectively). There is no significant difference in overall survival between the treatment groups in this analysis (logrank p=0.55; Wilcoxon p=0.47). In the PP population, consistent with the overall results for OS, the median OS is higher in NovoTTF-100A patients compared to BSC patients, regardless of whether they were re-operated (median OS 8.5 vs. 6.5 months in NovoTTF-100A and BSC patients, respectively; logrank p=0.71; Wilcoxon p=0.42) or not (median OS 7.6 vs. 6.6 months; logrank p=0.17; Wilcoxon p=0.06) prior to randomization.

Based on the above results, we conclude that the treatment effect of NovoTTF-100A compared to BSC on the overall survival is not affected by the re-operation status of patients at baseline.

8.7.1.9.2 Overall Survival by Region

Differences in disease outcome can differ in different parts of the world due to differences in local medical practice, differences in approved treatment regimens and differences in end-of-life supportive care. We performed separate analyses of the overall survival endpoint in the pivotal study for patients recruited in the US and for patients recruited in OUS sites.

Approximately half of the patients in the study were recruited in the US and half out of the US in highly respectable European and Israeli oncology centers (OUS). While the median OS is somewhat longer in the OUS patients than in the US patients, the comparative results of NovoTTF-100A treatment vs. BSC chemotherapy treatment in the US and OUS sites are similar, and consistent with the overall results.

In the US, the median overall survival was 6.1 vs. 5.3 months for NovoTTF-100A vs. BSC chemotherapy, respectively, in the ITT population and 7.3 vs. 5.9 months in the PP population.

In OUS sites, the median overall survival was modestly longer for both the NovoTTF-100A and BSC chemotherapy patients. The median overall survival was 7.1 vs. 7.2 months for NovoTTF-100A vs. BSC chemotherapy respectively in the ITT population and 8.3 vs. 6.8 months in the PP population.

These results and statistical comparisons between the groups by region and analysis population are shown below in **Table 16**.

Although some differences in local supportive care may exist between OUS and US centers, leading to a modest increase in the OS of patients treated in OUS centers, the equivalence of NovoTTF-100A to BSC chemotherapy in the ITT population and trend towards superiority in the PP population is identical in both regions. In fact, there is a small trend towards higher OS in the NovoTTF-100A compared to BSC chemotherapy in the US vs. OUS sites in the ITT analysis. Comparison of the

treatment arms in the PP population by region does not meet statistical significance due to halving of the number of patients in each region.

Table 16 Overall Survival by Region

	NovoTTF-100A	BSC	HR (95% CI)	Logrank P-Value	Wilcoxon P-Value
Intent-to-Treat					
US					
n/N	49/57	41/56			
Median OS (95% CI)	6.1 (4.0, 7.7)	5.3 (3.6, 7.2)	1.02 (0.67, 1.55)	0.9158	0.6957
OUS					
n/N	56/63	56/61			
Median OS (95% CI)	7.1 (5.6, 8.6)	7.2 (5.4, 8.5)	1.00 (0.69, 1.45)	0.9930	0.9434
Per Protocol					
US					
n/N	38/43	32/41			
Median OS (95% CI)	7.3 (6.0, 10.2)	5.9 (4.2, 7.4)	0.91 (0.57, 1.46)	0.7042	0.1975
OUS					
n/N	43/50	35/38			
Median OS (95% CI)	8.3 (6.7, 9.5)	6.8 (5.4, 8.5)	0.77 (0.49, 1.20)	0.2415	0.1199

*n/N: number of events/number of patients.

8.7.1.9.3 Overall Survival by Maximal Compliance

The NovoTTF-100A device has an internal log file which allows the calculation of patient compliance with treatment. This parameter “treatment time evaluation” was collected during the trial for each 4 week treatment course as the percent of the entire course in which the device delivered TTFields to the patient. Treatment time evaluation was always calculated from the first day a patient started treatment until the last day (regardless of disease progression). When patients did not complete a full course, the percentage reported is of the total number of days that treatment was received. Thus, this percentage is a reflection of patient compliance with treatment, and it represents the average daily “dose” of TTFields the patient received.

In the ITT population, most of the patients received treatment ≥75% of the time. Overall survival of NovoTTF-100A patients with a maximal monthly compliance rate ≥75% was significantly longer than patients who received treatment <75% of the time (median OS = 7.7 months vs. 4.5 months, respectively; logrank p=0.042; Wilcoxon p=0.016). In the PP population, overall survival of NovoTTF-100A patients with a maximal monthly compliance rate ≥75% was also longer than patients who received treatment <75% of the time, though this difference did not reach statistical significance (median OS = 8.1 months vs. 7.1 months, respectively; logrank p=0.51;Wilcoxon p=0.64). The non-significant difference in the PP population is a reflection of the fact that by excluding patients who received less than 4 weeks of treatment with the device from the PP population, several patients with very poor outcomes were excluded from the <75% compliance group and thus the difference between the two NovoTTF-100A groups decreased.

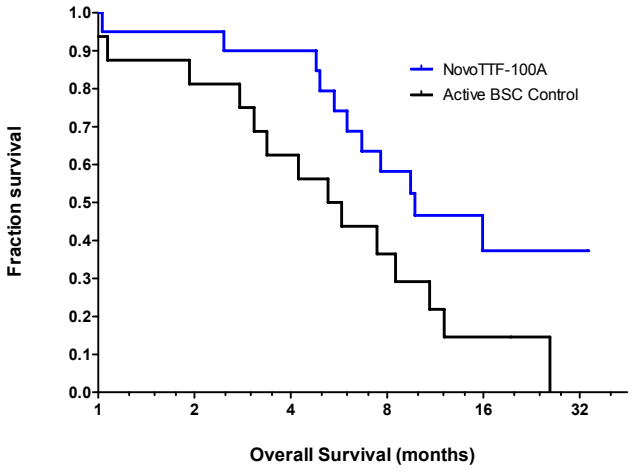
The results of this analysis are suggestive of a dose-response to NovoTTF-100A treatment, whereby the more treatment the patient receives each month, the longer s/he lives.

8.7.1.9.4 Overall Survival in Specific Patient Populations

While NovoTTF-100A treatment is at least as effective as active chemotherapies in all recurrent GBM patients (non-inferior in the ITT and mITT2 populations and superior in the PP and mITT1 populations using the Wilcoxon test), as shown above, it is possible that specific subgroups of patients will benefit from NovoTTF-100A treatment even more than the general recurrent GBM population. In order to assess the maximal benefit of NovoTTF-100A treatment when used as intended (i.e., for at least 4 weeks), the company performed several analyses of overall survival in specific patient sub-populations of clinical interest. Due to the post-hoc nature of these analyses and the small number of patients in each analysis, these results should be treated as exploratory.

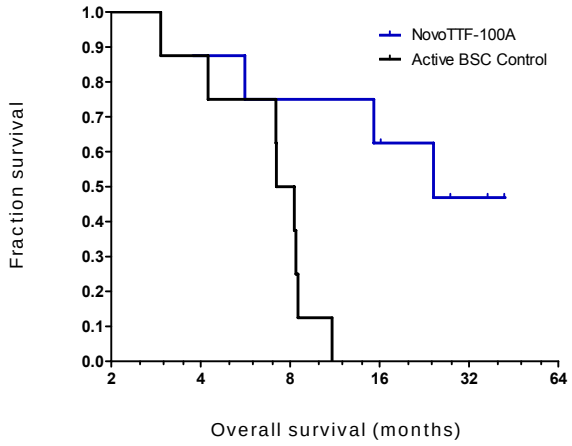
Patients who had biopsy only (surgery naïve), i.e., never had any debulking surgery for their primary disease or any recurrence, are thought to have a worse prognosis than patients who undergo debulking surgery [3, 62, 63]. Consistent with this, the surgery naïve BSC patients in the study had a median OS more than a month shorter than the general BSC control group (5.2 vs. 6.4 months, respectively). Interestingly, when NovoTTF-100A was used as intended, surgery naïve patients lived twice as long as patients treated with BSC chemotherapy (10.7 vs. 5.2 months, respectively; logrank p=0.0261; see **Table 17** and **Figure 16** below).

Figure 16 NovoTTF-100A versus BSC Control in Surgery Naïve Patients



Patients with prior low grade glioma which later transformed to GBM are known to have a more favorable prognosis than patients with *de novo* GBM [2, 4, 52, 64, 65]. Consistent with this, the prior low grade glioma BSC patients in the study had a median OS more than a month longer than the general BSC control group (7.7 vs. 6.4 months, respectively). Interestingly, when NovoTTF-100A was used as intended, prior low grade glioma patients lived three times as long as patients treated with BSC chemotherapy (24.3 vs. 7.7 months, respectively; logrank p=0.008; see **Table 17** and **Figure 17** below).

Figure 17 NovoTTF-100A versus BSC Control in Patients with Previous Low Grade Glioma



Finally, patients who progress on bevacizumab have been reported to have a worse prognosis than patients who progress on other therapies [66-68]. Consistent with this, patients after bevacizumab failure in the study had a median OS more than three months shorter than the general BSC control group (3.2 vs. 6.4 months, respectively). Interestingly, when NovoTTF-100A was used as intended, patients after bevacizumab failure lived twice as long as patients treated with protocol specified BSC chemotherapy (6.3 vs. 3.2 months, respectively; logrank p=0.0142; see **Table 17** and **Figure 18** below). This result is not surprising since the effect of NovoTTF-100A is not dependant on an intact blood supply to the tumor, whereas BSC chemotherapies are dependent on the blood supply to reach the tumor. Since bevacizumab acts by inhibition angiogenesis, it is not unexpected that NovoTTF-100A is as effective in patients who failed bevacizumab as in patients who recurred after cytotoxic chemotherapies.

Figure 18 NovoTTF-100A versus BSC Control in Patients Who Failed Bevacizumab

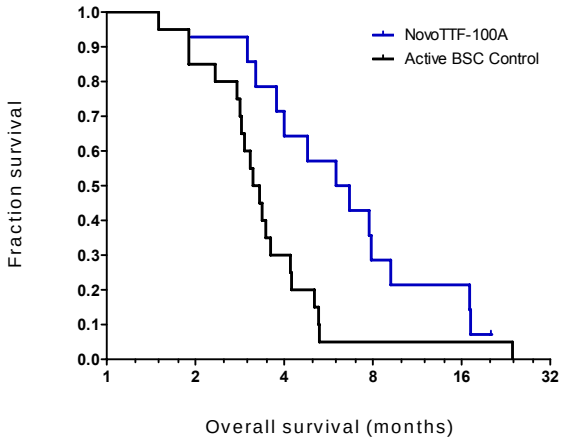


Table 17 Subgroup Analyses Showing Superior Overall Survival in NovoTTF-100A Patients Treated According to Protocol				
	NovoTTF-100A	**BSC**	**HR (95% CI)**	**Logrank P-Value**
Prior Bevacizumab Failure				
Number of Patients	14	21		
Median OS	6.3	3.2	0.39 (0.19 to 0.83)	0.0142
Prior Low Grade Glioma				
Number of Patients	8	9		
Median OS	24.3	7.7	0.17 (0.05 to 0.63)	0.0080
Surgery Naive Patients				
Number of Patients	16	11		
Median OS	10.7	5.2	0.37 (0.15 to 0.90)	0.0261
Bevacizumab On Study or W/D Consent				
Number of Patients	93	40		
Median OS	7.8	4.9	0.51 (0.30 to 0.86)	0.0115

8.7.1.10 Homogeneity of OS by BSC Treatment

In order to test the homogeneity of the treatment effect of the different BSC chemotherapies used in the trial (see **Table 8** above), we used a Cox proportional hazards model to test for the significance of the BSC chemotherapy interaction with overall survival. In the ITT population, this analysis led to a p-value of 0.66 and in the PP population to a p-value of 0.53. We conclude that the different chemotherapy regimens used in the pivotal trial are poolable.

8.7.1.11 Covariate Analysis

In order to rule out a confounding effect of prognostically important covariates on the comparison of NovoTTF-100A to effective BSC chemotherapies in the trial, the company performed adjusted analyses of the treatment effect on overall survival. The adjustments were performed for the prespecified analysis populations in the study (ITT and PP) and for analysis populations specified by FDA (mITT2 and Safety). Logrank tests were adjusted using a Cox Proportional Hazards Model (CPHM) as described in the protocol. Based on a request from FDA, Wilcoxon tests were adjusted as well by defining covariates as categorical strata.

The following four models were used for covariate adjustment:

1. **Full Model**: The following covariates were specified in the protocol and adjusted for using a Cox Proportional Hazards Model of OS by treatment group:

    a. Age (Years) – Continuous variable
    b. Karnofsky Performance Status (0-100) – Categorical variable
    c. Baseline Tumor Area as per Core radiology review (mm^2) – Continuous variable
    d. Tumor Location (Hemispheric versus bilateral or midline) – Dichotomous variable
    e. Tumor Position (Frontal and non frontal lobe locations) – Dichotomous variable
    f. Number of Prior Recurrence – Continuous variable

g. Prior surgery – Dichotomous variable

All of these parameters are known clinically significant predictors of overall survival in the general clinical trial GBM population [2, 52, 53, 62, 63]. In addition, the increasing use of bevacizumab in recurrent GBM patients during the years the pivotal trial was performed led to a significant number of patients who had failed bevacizumab entering the trial. Prior bevacizumab failure is a significant predictor of survival [68] and was thus included in the adjusted analysis as a dichotomous variable.

2. **Reduced Model ($p<0.05$)**: The company also performed an alternative analysis based on standard statistical methodology that adjusts only for those covariates with a significant correlation with overall survival in the CPHM (i.e., prior bevacizumab use and baseline tumor area; $p < 0.05$).

3. **Reduced Model ($p<0.15$)**: Based on a request from FDA, the company also performed adjustments only for those covariates with an arbitrarily, post-hoc selected p-value of 0.15 (baseline tumor area, prior bevacizumab use and prior surgery; $p<0.15$).

4. **Adjusted for differences in baseline characteristics**: Based on a request from FDA, the company also performed adjustments only for baseline covariates that showed an imbalance between the treatment groups (i.e., gender, tumor position and KPS in the ITT analysis, and gender and tumor position in the PP analysis)..

As seen in **Table 18** below, adjustment in the full model or the reduced models had no effect on the p-value or hazard ratio of the treatment effect of NovoTTF-100A compared to BSC chemotherapy for ITT, mITT and PP analyses. Even after adjustment, the HR 95% confidence interval upper bound remains below 1.47, fully supporting the non-inferiority analyses presented in **Section 8.7.1.8** above.

Table 18 Covariate Adjusted Analyses of Treatment Effect on Overall Survival			
	HR (95% CI)	**Logrank P-Value**	**Wilcoxon P-Value**
Intent-to-Treat			
Full model	1.10 (0.79, 1.45)	0.66	Not Valid*
Reduced model (p<0.05)	1.02 (0.77, 1.36)	0.87	0.75
Reduced model (p<0.15)	1.10 (0.83, 1.47)	0.51	0.20
Adjusted for differences in baseline covariates only	1.22 (0.90, 1.64)	0.20	Not Valid
Per Protocol			
Full model	0.88 (0.62, 1.25)	0.47	Not Valid
Reduced model (p<0.05)	0.86 (0.62, 1.20)	0.37	0.34
Reduced model (p<0.15)	0.91 (0.65, 1.27)	0.57	0.85
Adjusted for differences in baseline covariates only	0.94 (0.67, 1.33)	0.72	Not Valid
mITT2			
Full model	1.04 (0.74, 1.47)	0.83	Not Valid
Reduced model (p<0.05)	0.90 (0.66, 1.24)	0.51	0.60
Reduced model (p<0.15)	0.96 (0.69, 1.33)	0.80	0.83
Safety			
Full model	1.31 (0.95, 1.81)	0.10	Not Valid
Reduced model (p<0.05)	1.18 (0.87, 1.60)	0.30	0.11
Reduced model (p<0.15)	1.18 (0.87, 1.60)	0.30	0.04

As stated in **Section 8.7.1.6** above, the company believes that efficacy analyses using the Safety Population are of limited value. In addition, the company believes that adjustment only for baseline covariates that show an imbalance between treatment groups ignores other prognostically important covariates which may affect the outcome of the study.

In response to an agency question regarding adjustment of the Wilcoxon test for baseline covariates, the company believes that it is not statistically valid to partially adjust the Wilcoxon test (e.g., tumor position, gender) for covariates that have not been shown to be significant predictors of survival based on the results of the Cox proportional hazards model (P>0.05). Although when the Wilcoxon test is adjusted for tumor position or gender alone, it leads to a p-value >0.05, selecting other important covariates for adjustment of the Wilcoxon test maintains the significance of this test (e.g., US vs. OUS p=0.044; Operation vs. no operation for recurrence p=0.0430). Other important covariates such as baseline tumor area and KPS, have very little influence on the significance of this test.

8.7.2 Secondary Efficacy Endpoints

8.7.2.1 One-Year Survival Rate

Generally, in cancer, 5 and 10 year survival rates are used as measures of overall survival to which patients and oncologists can refer easily in order to define the patient's chance of being a long-term survivor. However, in patients with recurrent GBM the 1 year survival rate is used, since most recurrent GBM patients do not survive into their second year. The review of historical control data presented in **Section 3.2** above demonstrates that without effective chemotherapy, only 10% of recurrent GBM patients are expected to live one year.

The one-year survival rate was analyzed in patients who died ≤351 (365 – 14 day window) days after randomization or who survived beyond 351 days after randomization as determined by telephone follow-up questionnaires or any other dates of patient assessment. Patients lost to follow-up for whom there is no survival information beyond 351 days post-randomization are not included in this analysis.

In the ITT population, 114 of 120 (95%) NovoTTF-100A patients and 104 of 117 (89%) BSC patients were evaluable for one year survival. This is in line with the percentage of patients lost to follow-up in each group before the one year assessment (5% and 11%, respectively – see ITT population survival life table beneath **Figure 10**). **Table 19** below shows that in the ITT population, the 1-year survival rate is the same, approximately 22%, in both the NovoTTF-100A and BSC treated patients. This rate is more than twice the expected 1-year survival rate had the patients not been treated with an effective chemotherapy (10%).

In the PP population, 90 of 93 (97%) NovoTTF-100A patients and 74 of 79 (94%) BSC patients were evaluable for one year survival. This is in line with the percentage of patients lost to follow-up in each group before the one year assessment (3% and 6%, respectively). **Table 19** below demonstrates that in the PP population, the 1-year survival rate is higher in the NovoTTF-100A patients than in the BSC patients (27.8% vs. 21.6%, respectively).

We conclude that the 1-year survival results in the pivotal study support the conclusion that the treatment effect of NovoTTF-100A is equivalent to best standard of care effective chemotherapies in the ITT population, and is superior to BSC chemotherapy in the PP population.

Table 19 One-Year Survival Rate

	NovoTTF-100A	BSC
Intent-to-Treat		
One-Year Survival	25/114 (21.9%)	23/104 (22.1%)
95% CI	14.33%, 29.53%	14.14%, 30.09%
Per Protocol		
One-Year Survival	25/90 (27.8%)	16/74 (21.6%)
95% CI	18.52%, 37.03%	12.24%, 31.00%

8.7.2.2 Progression Free Survival Rate at 6 Months

8.7.2.2.1 Definition of Progression-Free Survival at 6 Months

PFS6 was defined as follows: [69]

- Success: Alive and progression-free at 6 months, defined as any patient with at least one valid tumor response at the 6-month visit (or later) showing no signs of clinical or radiological progression, and with no tumor assessments of progressive disease at any point from baseline to that visit.
- Failure: Dead or progressive disease at 6 months, defined as any patient with a radiological tumor response or clinical assessment of progressive disease at the 6-month visit or earlier, or any patient that has died for any reason ≤166 days (180 days – 2 weeks exam window) after the date of randomization, as long as the patient was not discontinued from the trial prior to failure.
- Indeterminate: Defined as any patient with no tumor assessments at the 6-month visit or later who cannot be classified into either of the two preceding categories. Indeterminate patients are not included in the denominator for the calculation of the rate of PFS at 6 months.

8.7.2.2.2 PFS6 Patient Accountability

Based on MRI review alone, in the ITT population, 100 of 120 NovoTTF-100A patients (83%) were evaluable for PFS6 (i.e., were not indeterminate). In contrast, only 67 of 117 BSC patients (57%) were evaluable for PFS6 based on MRI alone. The following section discusses the reasons for this difference. It should be noted that when clinical progression was added to the MRI data by an independent CEC review, the number of evaluable patients was more balanced between groups: 86% of NovoTTF-100A patients and 79% of BSC patients were evaluable in the ITT population.

Progression free survival is an inherently problematic and subjective endpoint in GBM [70, 71], and is used sometimes as a surrogate endpoint for survival in expedited approval of drugs for GBM [72]. There are several reasons for the problematic nature of PFS analysis in recurrent GBM:

1. The tumor is infiltrative in nature and not all portions enhance on MRI.
2. The tumor is rarely spherical so measuring diameters as recommended in the Macdonald criteria [50] is inconsistent and difficult.
3. Patients can deteriorate neurologically before MRI evidence of progression is seen. This leads to patients stopping therapy prior to MRI confirmation of progressive disease and sometimes to non-compliance with MRI scheduling.

To address these issues, the company performed the following analyses:

1. The number of subjects censored for PFS6 at day 1, between 1 day and 6 months, and after 6 months was compared between NovoTTF-100A and BSC chemotherapy patients to assess possible follow-up bias between the groups. This analysis showed that more than double the number of patients were censored prior to reaching the 6 month follow-up in the BSC group than in the NovoTTF-100A group.

2. The reasons for censoring in each time interval were summarized and compared between groups. Patients censored at day 1 were censored due to withdrawal of consent or AE prior to starting treatment in approximately 20% vs. 3% of BSC vs. NovoTTF-100A patients, respectively. Censoring after performing the first follow-up MRI, but prior to 6 months was due mainly to study discontinuation based on local MRI assessment of progressive disease (PD) without PD assessment by Core radiology review. Many more cases of discrepancy

between local and central MRI assessment before 6 months were seen in the BSC group than in the NovoTTF-100A group. This may have been due to investigator familiarity with the radiological patterns seen with the BSC chemotherapies used in the trial, whereas NovoTTF-100A is a completely new modality. Finally, the number of patients censored after 6 months was the same between groups. The main reasons for censoring after 6 months were similar and due to patients reaching the end of the study (administrative censoring) or not complying with follow-up.

As seen in the number of evaluable patients in both the ITT and PP analyses, the balance between treatment groups was improved dramatically by adding clinical assessment to the MRI review (by an independent CEC). This is most likely because, for many BSC patients who were indeterminate for PFS6 based on MRI alone, it could now be determined as to whether they had progressive disease. Thus, the number of indeterminate cases in the BSC group is reduced from 50 to 25 patients in the ITT population and from 27 to 8 in the PP population, by using a composite of clinical and radiological data.

The utility of Core radiology review in general has been the center of debate in the literature [73]. This is due to the fact that, as discussed above, MRI interpretation in recurrent GBM is difficult without also taking into consideration the patient's clinical condition. Also, in the Core radiology review alone, without CEC assessment, there is differential informative censoring between groups (e.g., more local MRI assessment of progressive disease (PD) without PD assessment by Core radiology review in the BSC group than in the NovoTTF-100A group). Thus, although Core radiology review lessens some potential biases, it can raise others instead in the evaluation of treatment effectiveness. It may introduce bias because of informative censoring, which results from having to censor unconfirmed locally determined progressions. In a publication by Dodd et al. from the National Cancer Institute in 2008 [73], the final recommendation is that if a trial cannot be conducted in a double blind fashion, as is the case in the current pivotal study, Core radiology review may introduce more bias due to informative censoring than it does by blinding the radiology reader.

Accordingly, all the following radiological analyses presented (unless stated otherwise) are based on a composite of clinical and radiological data as determined by an independent CEC.

Table 20 Reasons for Censored Observations for PFS Analysis by Time Period Intent-to-Treat Population				
Censored at day 1	**NovoTTF-100A**		**BSC**	
	N	**%**	**N**	**%**
Reason				
Treatment never started	4	3.3%	26	22.2%
Withdrawal of consent before 1st MRI	6	5.0%	3	2.6%
Discontinued d/t AE[3] before 1st MRI	***2***	***1.7%***	***4***	***3.4%***
Clinical deterioration before 1st MRI	***1***	***0.8%***	***1***	***0.9%***
Total	13		34	
Censored <6 months	**NovoTTF-100A**		**BSC**	
	N	**%**	**N**	**%**
Reason				
Investigator PD[4] w/o Core radiology PD[5]	***3***	***2.5%***	***10***	***8.5%***
Discontinued d/t AE before 6m MRI	***2***	***1.7%***	***2***	***1.7%***
Discontinued before Progression MRI	***2***	***1.7%***	***2***	***1.7%***
Progression free at end of study	0	0.0%	1	0.9%
Discontinued d/t[6] Investigator decision before 6mo MRI	0	0.0%	***1***	***0.9%***
Total	7		16	
Censored ≥6 months	**NovoTTF-100A**		**BSC**	
	N	**%**	**N**	**%**
Reason				
Progression free at end of study	7	5.8%	3	2.6%
No MRIs performed after post 6mo stable disease	0	0.0%	3	2.6%
Investigator PD without Radpharm PD	0	0.0%	1	0.9%
Total	7		7	

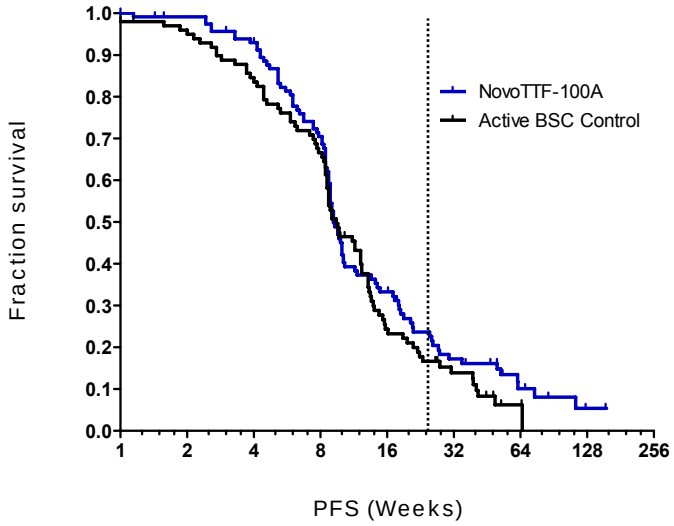
8.7.2.2.3 PFS6 – CEC Assessment

Based on the discussion in **Section 8.7.2.2.2** above regarding PFS accountability, CEC Review was used as the primary analysis for radiological endpoints in the study. Based on this analysis, in the ITT population, 21.4% of NovoTTF-100A patients were alive and progression free at 6 months whereas only 15.2% of BSC patients were alive and progression free at 6 months. This difference was not statistically significant (p=0.13; one-sided chi–square test; **Table 21** and **Figure 19**; the dashed vertical line represents the lower end of the 6 month window used for PFS6 assessment).

[3] d/t AE – Due to an adverse event
[4] PD – Radiological assessment of progressive disease
[5] PD – Radiological assessment of progressive disease
[6] d/t – Due to

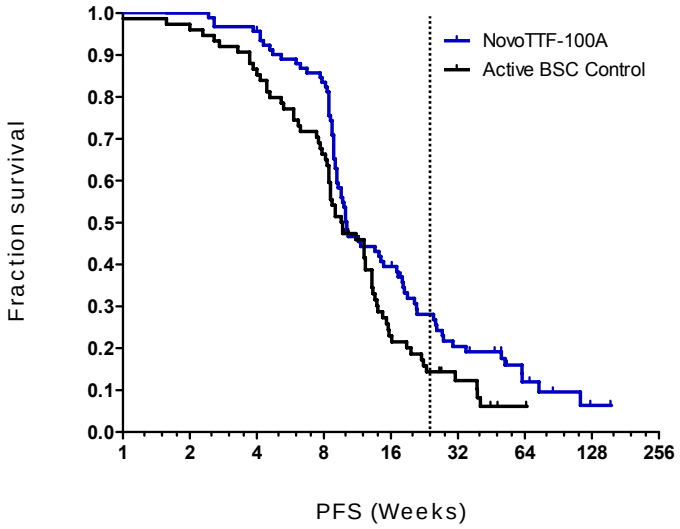
Table 21 Progression Free Survival at 6 Months Intent-to-Treat Population		
	NovoTTF-100A	**BSC**
	(n=120)	**(n=117)**
PFS6 Status		
Indeterminate/Censored	17 (14.2)	25 (21.4)
PFS6 determined	103 (85.8)	92 (78.6)
Alive and Progression Free at 6 Months		
Yes	22 (21.4)	14 (15.2)
No	81 (78.6)	78 (84.8)
Radiographic Progression by MRI	64 (79)	46 (59.0)
Clinical Progression	17 (21.0)	31 (12.8)
Death	0 (0)	1 (1.3)
95% CI for PFS6	(13.44, 29.27)	(7.88, 22.56)
P-value (one-sided chi-square test)	0.1349	
Kaplan-Meier Estimate of PFS at 6 Months (%)	23.7 (15.3, 32.0)	16.6 (9.0, 24.2)

Figure 19 PFS Kaplan Meier Curve – ITT population



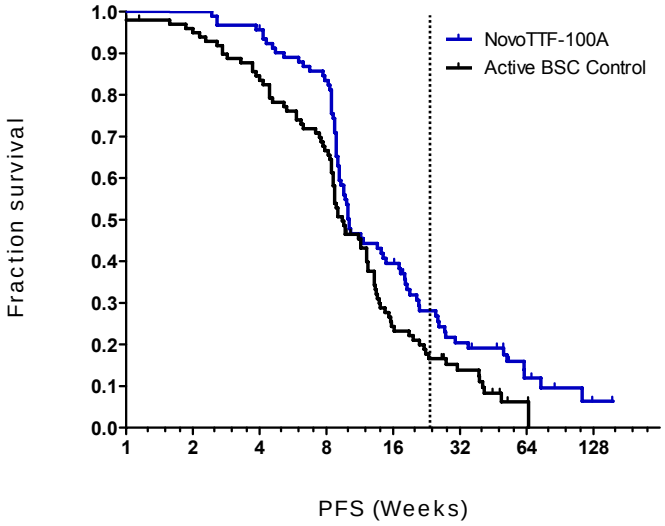
In the PP population, PFS6 was significantly higher in the NovoTTF-100A group than in the BSC chemotherapy group (26.2% vs. 12.7%, respectively, p=0.02; see **Table 22** and **Figure 20** below; the dashed vertical line represents the lower end of the 6 month window used for PFS6 assessment).

Figure 20 PFS Kaplan Meier Curve – PP population



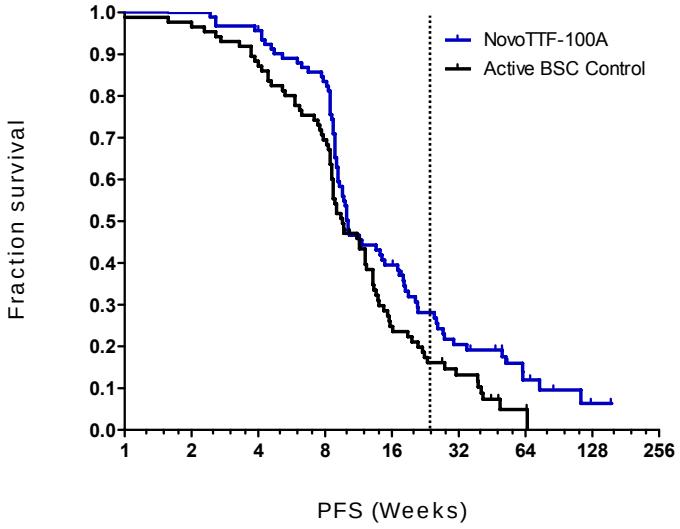
In the mITT1 population, 26.2% of NovoTTF-100A patients were alive and progression free at 6 months whereas only 15.2% of BSC patients were alive and progression free at 6 months (see **Table 22** and **Figure 21** below; the dashed vertical line represents the lower end of the 6 month window used for PFS6 assessment). This difference was statistically significant (p=0.0357; one-sided chi–square test).

Figure 21 PFS Kaplan Meier Curve – mITT1 population



In the mITT2 population, 26.2% of NovoTTF-100A patients were alive and progression free at 6 months whereas only 15.7% of BSC patients were alive and progression free at 6 months (see **Table 22** and **Figure 22** below; the dashed vertical line represents the lower end of the 6 month window used for PFS6 assessment). This difference was statistically significant (p=0.047; one-sided chi–square test).

Figure 22 PFS Kaplan Meier Curve – mITT2 population



In the Safety Population, PFS6 was higher in the NovoTTF-100A group than in the BSC chemotherapy group, albeit not significantly (21.4%% vs. 15.7%, respectively, p=0.16).

Table 22 Progression Free Survival at 6 Months by Analysis Population

	NovoTTF-100A		BSC		
Analysis Population	**n/N (%)**	**95% CI for PFS6%**	**n/N (%)**	**95% CI for PFS6%**	**One sided Chi Square p-value**
Per Protocol	22/84 (26.2)	17.2, 36.9	9/71 (12.7)	4.94, 20.4	0.0181
mITT1	22/84 (26.2)	17.2, 36.9	14/92 (15.2)	7.88, 22.6	0.0357
mITT2	22/84 (26.2)	17.2, 36.9	13/83 (15.7)	8.60, 25.3	0.0473
Safety	22/103 (21.4)	13.9, 30.5	13/83 (15.7)	8.60, 25.3	0.1615

n/N: number of patients alive and progression free at 6 months/total number of evaluable patients.

8.7.2.2.4 PFS6 - Core Radiology Assessment

The Core radiology review was based on blinded radiological review performed by an independent core lab. As discussed in **Section 8.7.2.2.2** above regarding MRI accountibility, imbalance in informative censoring between the treatment groups limits the utility of Core radiology review. The Core radiology review assessment of PFS6 showed PFS6 values for NovoTTF-100A slightly lower than for BSC chemotherapy in the ITT and Safety Populations. In the PP, mITT1 and mITT2 populations, the PFS6 was slightly higher for NovoTTF-100A than for BSC chemotherapy. The differences were not significant in any of the populations.

8.7.2.3 Time to Progression (TTP)

For determination of progression for TTP analysis, disease progression can be radiological progression, and/or clinical progression (as determined by the investigator in the absence of an MRI). The main difference between TTP and PFS is that, for TTP, deaths without disease progression as defined above are censored at the time of death, whereas, for determination of PFS, any death (regardless of cause) within the predefined evaluation time frame (i.e., two months from last assessment) is considered an event.

In the pivotal trial, there was only one death in the NovoTTF-100A group (at 42 days) that was censored at time of death in the TTP analysis. This single event has negligible impact on the Kaplan-Meier curves presented above for PFS, such that these curves are also essentially TTP curves.

Table 23 summarizes the median TTP, based on Kaplan-Meier curves, by treatment group for the ITT, PP, mITT1, mITT2 and Safety Populations. As seen in **Table 23**, median TTP in the NovoTTF-100A and BSC chemotherapy groups is consistent with prior efficacy endpoints for all analysis populations.

Table 23 Time to Progression by Analysis Population

	NovoTTF-100A		BSC			
Analysis Population	**N**	**Median TTP (95% CI)**	**N**	**Median TTP (95% CI)**	**HR (95% CI)**	**Logrank P-Value**
Intent-to-Treat	120	9.3 (8.9, 10.1)	117	9.6 (8.6, 12.3)	0.84 (0.62,1.13)	0.2444
Per Protocol	93	10.1 (9.1, 14.9)	79	9.7 (8.4, 13.1)	0.70 (0.50,0.98)	0.0359
mITT1	93	10.1 (9.1, 14.9)	117	9.6 (8.6, 12.3)	0.69 (0.50, 0.95)	0.0224
mITT2	93	10.1 (9.1, 14.9)	91	9.7 (8.7, 13.1)	0.73 (0.53,1.00)	0.0508
Safety	116	9.1 (8.9, 10.1)	91	9.7 (8.7, 13.1)	0.88 (0.65,1.20)	0.4155

8.7.2.4 Radiographic Response

Radiological response rate in cancer is a useful tool in managing patient treatment. However, in the age of anti-angiogenic agents, such as bevacizumab [70, 71], which modify vascular permeability and change MRI enhancement pattern regardless of anti-tumor effect, radiological response is a highly problematic clinical trial endpoint. Assessment of radiological response is often difficult in recurrent GBM without the benefit of a clinical examination and anamnesis. Thus, Core radiology review of radiographic response, although blinded, is inherently inaccurate. Investigator assessment, on the contrary, is highly accurate, but suffers from the appearance of bias of being unblinded.

As seen in **Table 24**, investigator assessment of radiological response in the ITT population showed that NovoTTF-100A treatment led to a higher response rate than seen for BSC chemotherapy (14.0% vs. 9.6%, respectively; p=0.19). In the PP population, NovoTTF-100A treatment led to a significant increase in the response rate over that seen for BSC chemotherapy (15.9% vs. 6.7%, p=0.046).

Core radiology review in both populations identified considerably fewer radiological responses in both groups compared to investigator assessment (4.1% vs. 6.7% in NovoTTF-100A and BSC groups, respectively; p=0.77 in the ITT population and 4.7% vs. 4.8% (p=0.52) in the PP population).

Note that radiological response rate was not analyzed in the mITT1, mITT2 or Safety Populations, as the FDA did not request such analyses.

Table 24 Objective Best Overall Response Rate

Intent-to-Treat Population	**NovoTTF-100A**	**BSC**
	(n=120)	**(n=117)**
Tumor Response, n (%)		
Complete Response	3 (3.0)	0 (0)
Partial Response	11 (11.0)	7 (9.6)
Stable Disease	26 (26.0)	25 (34.2)
Progressive Disease	59 (59.0)	41 (56.2)
Not Evaluable	1 (1.0)	0 (0)
Not Available	20	44
Objective Tumor Response Rate, n (%)**	**(n=100)**	**(n=73)**
(CR + PR)	14 (14.0)	7 (9.6)
(SD + PD + NE)	86 (86.0)	66 (90.4)
Chi-Square Test*	0.1901	
Fisher's Exact Test*	0.2628	
Per Protocol Population	**NovoTTF-100A**	**BSC**
	(n=93)	**(n=79)**
Tumor Response, n (%)		
Complete Response	3 (3.4)	0 (0)
Partial Response	11 (12.5)	4 (6.7)
Stable Disease	26 (29.5)	22 (36.7)
Progressive Disease	48 (54.5)	34 (56.7)
Not Evaluable	0 (0)	0 (0)
Not Available	5	19
Objective Tumor Response Rate, n (%)**	**(n=88)**	**(n=60)**
(CR + PR)	14 (15.9)	4 (6.7)
(SD + PD + NE)	74 (84.1)	56 (93.3)
Chi-Square Test*	0.0456	
Fisher's Exact Test*	0.0732	

*P-value based on one-sided test.
**Objective tumor response rate is calculated by dividing the number of all partial and complete response by the total number of available MRIs (PR+CR)/(PR+CR+SD+NE). This calculation excludes unavailable MRIs from the denominator.

Representative post contrast T1 weighted MRI images for each of the 14 NovoTTF-100A patients with a radiological response assessed as partial or complete response by the investigators are presented in **Tab XI, Appendix C**.

8.7.2.4.1 Steroid Use

At the request of FDA, the company analyzed whether an imbalance in steroid dose could have had the potential to affect the radiological response in the NovoTTF-100A trial. However, average daily steroid dose (dexamethasone equivalent dosages) was found to be slightly lower in NovoTTF-100A patients than in BSC patients in both the ITT and PP populations (6.3 mg vs. 6.8 mg in ITT, 5.0 mg vs. 6.8 mg in PP) (see **Table 25**). Thus, there was no increased steroid use in the NovoTTF-100A arm of the study. Consequently, NovoCure concludes that there is no evidence of bias favoring the NovoTTF group with regard to assessment of imaging studies.

Table 25 Daily Steroid Use (mg) by Treatment Group				
	NovoTTF-100A		BSC	
	N	Mean (Std)	N	Mean (Std)
Intent-to-Treat				
Overall	120	6.3 (6.5)	101	6.8 (6.4)
By Region				
US	57	6.1 (4.9)	48	5.8 (5.5)
OUS	63	6.5 (7.6)	53	7.7 (7.1)
Per Protocol				
Overall	93	5 (4.7)	77	6.8 (6.8)
By Region				
US	43	5.5 (4.9)	39	5.6 (5.4)
OUS	50	4.7 (4.5)	38	8.1 (7.8)

8.7.2.5 Quality of Life

Quality of life (QOL) was assessed as part of the pivotal trial as a secondary efficacy endpoint. Assessment was performed using the EORTC QLQ C-30 questionnaire which has been validated in many languages for cancer related quality of life, together with the BN-20 supplement (for brain tumor patients). The 30 questions in the QLQ-C30 were coded according to the EORTC guidelines into a general health scale, 5 functional scales and 9 symptom scales. The BN-20 questionnaire was similarly coded into 4 subscale domains and 7 single symptom items.

In order to compare the effect of NovoTTF-100A treatment to that of BSC chemotherapy on patient QOL, the percentage change from baseline (CFB) of the QOL scores was calculated in the ITT population for the NovoTTF-100A and BSC chemotherapy groups. QOL data over all follow-up visits was combined for all patients owing to the diminishing number of patient visits over time due to the devastating nature of the disease. The average CFB (in percent) for NovoTTF-100A and BSC patients is shown in **Table 26** below. For ease of comparison between the multiple scales used in the QLQ C-30 questionnaire, the difference in CFB results between NovoTTF-100A and BSC chemotherapy groups was calculated and is presented graphically in **Figure 23** and **Figure 24** below.

For all the symptom scales and domains, an increase in value represents a decrease in QOL, whereas for the general health and 5 functional scales, an increase in value represents an increase in QOL. As seen below in **Table 26**, patients treated with the NovoTTF-100A device had a higher quality of life in Global Health, 4 of the 5 Functional Scales (**Figure 23**), 7 of the 9 Symptom Scales (**Figure 24**), 3 of the 4 BN-20 Subscale Domains and 5 of the 6 relevant Single Items (hair loss was not a relevant question for NovoTTF-100A patients since they all shaved their heads) than patients treated with BSC chemotherapy.

Large differences between groups (>20% difference) were almost all in favor of NovoTTF-100A patients as well and included: Cognitive functioning, Appetite loss, Constipation, Diarrhea, Nausea and Vomiting, Pain, Bladder Control, Headaches and Itchy Skin. In both groups, there was a large decrease (>20%) from baseline in the negative effect of seizures on QOL; however, this decrease was more prominent in BSC patients than in NovoTTF-100A patients.

Table 26	Quality of Life (Change from Baseline)		
		NovoTTF-100A	**BSC**
		(n=120)	**(n=117)**
QLQ - C30	**Global Health Scale**	3.6%	2.6%
	Functional scales		
	Cognitive functioning	14.4%	-7.5%
	Emotional functioning	6.3%	0.7%
	Physical functioning	-7.0%	-4.8%
	Role functioning	-1.6%	-4.0%
	Social functioning	-6.3%	-7.5%
	Symptom Scales		
	Appetite Loss	0.0%	35.2%
	Constipation	-31.7%	76.8%
	Diarrhea	-30.5%	49.9%
	Dyspnea	6.4%	-5.7%
	Fatigue	-7.5%	21.9%
	Financial difficulties	7.6%	-10.4%
	Insomnia	-3.2%	5.2%
	Nausea and Vomiting	17.9%	62.6%
	Pain	-3.2%	63.3%
BN20	**Subscale Domains**		
	Communication deficit	-24.3%	-24.8%
	Future Uncertainty	-28.7%	-27.0%
	Motor Dysfunction	-21.2%	-16.9%
	Visual Disorder	-15.2%	1.1%
	Single Items		
	Bladder Control	-16.4%	48.6%
	Drowsiness	-4.9%	7.1%
	Headaches	-24.3%	24.4%
	Itchy Skin	11.8%	67.2%
	Seizures	-19.2%	-49.7%
	Weakness of legs	18.2%	34.3%

Figure 23 QLQ C-30 Functional Scales

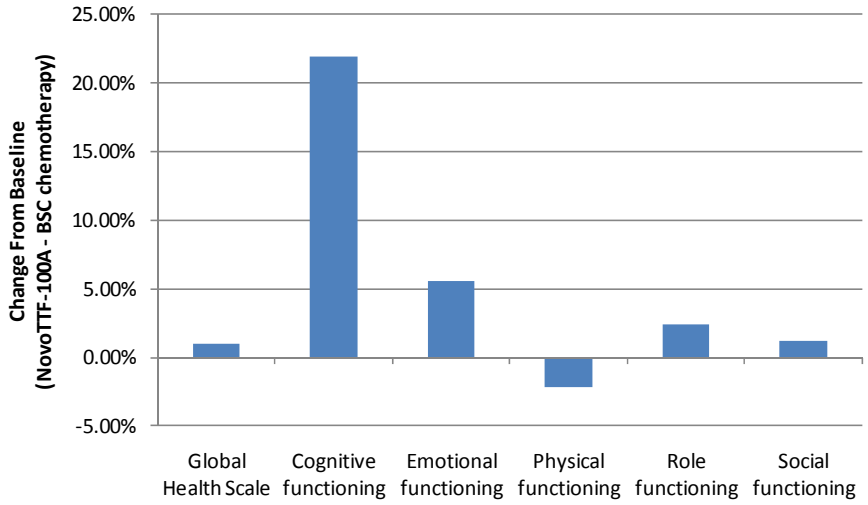
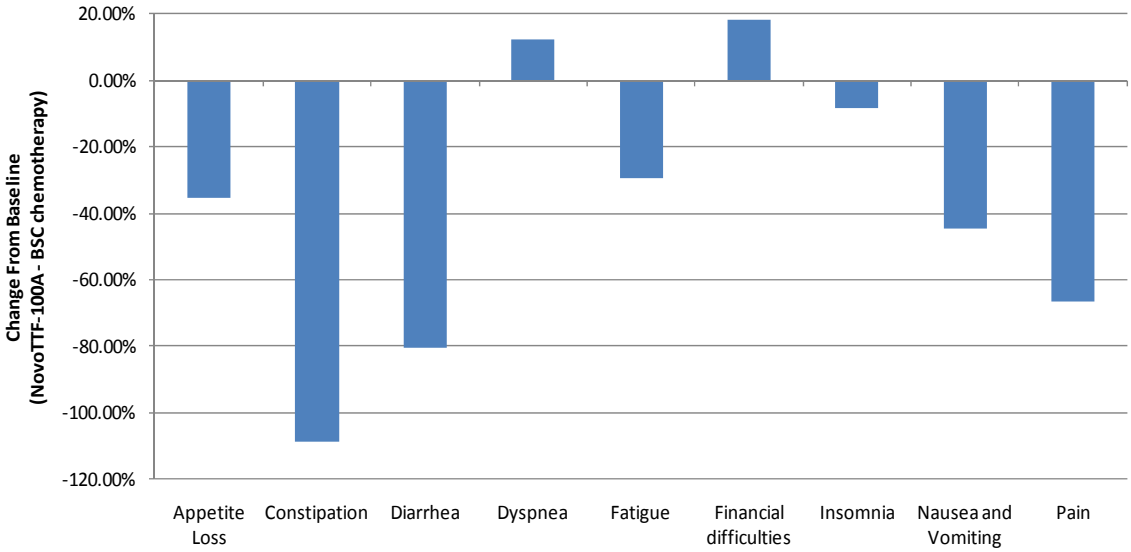


Figure 24 QLQ C-30 Symptom Scales



8.7.2.5.1 Patient Testimonials

In order to supplement the quality of life analysis, NovoCure has collected patient testimonials on video of subjects enrolled in the NovoTTF-100A pivotal clinical trial. Sample testimonials are included in **Tab XI, Appendix D**. This video provides the patients' perspective and their assessment of the impact of the NovoTTF-100A device in the treatment of their recurrent GBM. It also provides their perspective on their quality of life with the NovoTTF-100A device, as well as the side effects they experienced when using the NovoTTF-100A device and when previously on chemotherapy.

Please note that all of the patients participating in the video testimonials signed a consent form allowing their image and voice to be used.

8.7.3 Efficacy Discussion and Conclusion

The NovoTTF-100A device, which delivers TTFields to patients with recurrent GBM, was tested here for the first time in a randomized clinical trial. The prospectively defined primary endpoint in the trial was overall survival. In the ITT population, which included all randomized patients, NovoTTF-100A treatment was shown to be equivalent in overall survival to the best available chemotherapy today for recurrent GBM (including the recently approved Avastin). In the PP population, which excluded patients who received less than one course of treatment in both arms and excluded patients who received non-protocol-specified treatments, the overall survival was superior in patients treated with NovoTTF-100A device compared to patients treated with BSC chemotherapies.

The equivalence in the overall survival results between NovoTTF-100A and best standard of care effective chemotherapies is consistently observed in specific subgroups, including US vs. OUS sites, re-operated and non-re-operated patients, and across different countries in which the trial was conducted. It is worth noting that in the US, the OS data in the ITT population showed a slight trend towards better survival in the NovoTTF-100A patients compared to BSC patients (median OS 6.1 vs. 5.3 months for US NovoTTF-100A and BSC patients, respectively).

Table 27 Overall Survival Summary

		Treatment Group	
	Population	**NovoTTF**	**BSC**
N	ITT PP	120 93	117 79
Median OS (months)	ITT PP	6.3 **7.8**	6.4 **6.5**
Logrank p	ITT PP	0.98 0.28	
Wilcoxon p	ITT PP	0.72 **0.04**	
HR (95% CI)	ITT PP	1.00 (0.76 – 1.32) 0.84 (0.60 – 1.16)	

The secondary endpoints for the NovoTTF-100A trial support the primary endpoint results in that they show the NovoTTF-100A device to be comparable to or better than the BSC control. One-year-survival was virtually identical in the NovoTTF-100A group versus the BSC chemotherapy group in the ITT population (21.9% vs. 22.1%, respectively) and higher in the PP population (27.8% vs. 21.6%, respectively). PFS6 was higher in NovoTTF-100A patients than in BSC chemotherapy patients in the ITT population (21.4% vs. 15.2%) and significantly so in the PP population (26.2% vs. 12.7%; chi-square p = 0.02). Radiological response rate for NovoTTF-100A patients was higher than for BSC chemotherapy patients in the ITT population (14.0% vs. 9.6%) and significantly so in the PP population (15.9% vs. 6.7%; chi-square p=0.046). Median TTP for both groups was essentially the same in all analysis populations.

Finally, quality of life based on QLQ C-30 and BN-20 questionnaires was consistently higher in NovoTTF-100A than in BSC chemotherapy patients. A summary of the secondary efficacy endpoints of the trial can be found in **Table 28** below.

Table 28 Summary of Secondary Endpoints			
Secondary Endpoints		**Treatment Group**	
	Population	**NovoTTF**	**BSC**
Number of patients (n=)	ITT PP	120 93	117 79
One-Year Survival (%)	ITT PP	21.9 27.8	22.1 21.6
PFS6 (%)	ITT PP	21.4 **26.2**	15.2 **12.7**
Chi-square p-value	ITT PP	0.13 **0.02**	
Radiological Response Rate (%)	ITT PP	14.0 **15.9**	9.6 **6.7**
Median TTP (weeks)	ITT PP	9.3 10.1	9.6 9.7

Analysis of overall survival, PFS6 and TTP in the additional analysis populations requested by the agency (modified ITT and Safety Populations) fully supports superiority of NovoTTF-100A treatment over ineffective chemotherapies and its non-inferiority compared to effective BSC chemotherapy (whether predefined in the protocol or not). Also, as in the PP population, in the mITT1 population, which excluded patients who received less than one course of treatment in the NovoTTF-100A group and included all patients in the BSC group (assuming they all received chemotherapy, whether on study or not), the overall survival, PFS6 and TTP were all superior in patients treated with NovoTTF-100A device compared to patients treated with BSC chemotherapies.

Interestingly, in certain clinically relevant subpopulations (e.g., patients with prior bevacizumab failure, surgery naïve patients, prior low-grade glioma patients), NovoTTF-100A may be even more effective than in the overall population compared to active BSC chemotherapies.

We conclude that when the NovoTTF-100A is used as intended, that is, treatment is maintained for at least one treatment course of 4 weeks, this novel therapy increases the overall survival of recurrent GBM patients significantly compared to best standard of care effective chemotherapies (HR=0.84 in the PP population). Even in the ITT population, which includes many patients who did not undergo a full treatment course, the overall survival in the NovoTTF-100A group is comparable to that of patients receiving the best chemotherapies available to patients in the US today (HR=1.0). In addition, NovoTTF-100A treatment was shown to be non-inferior to BSC chemotherapy in all analysis populations, while maintaining a conservative non-inferiority margin. Taken together with the supportive secondary endpoint results seen in NovoTTF-100A patients compared to BSC controls, the company has shown that treatment with the NovoTTF-100A device is at least as effective as the best available chemotherapy today while affording these end-stage patients with recurrent GBM a better quality of life.

8.8 Safety Results

8.8.1 Adverse Events

The primary safety endpoint of the pivotal trial was the incidence of patients with adverse events, and serious adverse events (defined as leading to hospitalization, lengthening of hospitalization, permanent disability, death or congenital defect). All AEs and SAEs in the trial were assessed for severity based on the Common Terminology Criteria V3.0 as is the standard methodology in oncology trials.

Modern management of oncology patients in general and recurrent GBM patients, specifically, makes the incidence of serious adverse events (e.g., leading to hospitalization) very low. The primary toxicities related to chemotherapies are gastrointestinal, infectious and hematological. These range from mild to severe in severity. Thus, most AEs can be managed on an outpatient basis without requiring hospitalization. This fact does not reduce the importance of chemotherapy related AEs, since they contribute significantly to patient morbidity and mortality [74-76]. For instance, even a relatively "insignificant" side effect of chemotherapy such as dysgeusia (loss of the sense of taste) can have a significant impact on patient quality of life and lead to substantial suffering [77]. Treatment with chemotherapy commonly (in >30% of patients) causes leucopenia, anemia, thrombocytopenia, nausea and vomiting, electrolyte disturbances, renal toxicity, pain or burning at administration site, redness of face, skin flushing (usually associated with rapid infusion rate of nitrosureas), loss of appetite, headache, fatigue and constipation. Thus, most patients suffer from combinations of unpleasant and sometimes life threatening side effects of their chemotherapeutic treatments [8]. Treatment with bevacizumab is associated with gastrointestinal perforations, surgery and wound healing complications, hemorrhage (including brain hemorrhage), non-gastrointestinal fistula formation, arterial thromboembolic events, hypertensive crisis, reversible posterior leukoencephalopathy syndrome and proteinuria [11].

Finally, it is important to note the unblinded study design. Patients and physicians knew who was receiving the NovoTTF-100A device and therefore, may have been biased in the reporting of neurological or other AEs.

We first evaluated the incidence of AEs by body system (see **Table 29**), and then assessed adverse events within body system by severity and relationship to treatment (**Table 30**), as well as by outcome.

In the pivotal trial, the classic chemotherapy related toxicities were seen at various levels of relatedness and severity in the BSC group; relatedness ranged from possible to definite and severity from mild to severe. In the NovoTTF-100A group, the only device-related adverse event seen was a local reaction of skin beneath the device electrodes. This reaction did not lead to treatment discontinuation in the trial, nor was it considered severe in any of the cases. The skin irritation ranged from mild skin redness or rash in about a quarter of the device patients to moderate blistering or ulceration in individual cases. The skin irritation seen beneath the electrodes resolved in all cases once NovoTTF-100A treatment was stopped. In addition, headaches were assessed by the investigators as possibly related to NovoTTF-100A treatment in four patients, although headaches are an expected symptom of GBM patients in general.

It is important to note that most AEs in the pivotal trial and almost all SAEs (leading to hospitalization) in NovoTTF-100A patients were related to the underlying recurrent GBM disease. The basic symptoms of recurrent GBM are such that they are captured in clinical trials as AEs and SAEs. Most of the symptoms related to the disease itself are neurological and psychiatric in nature. Some common neurological symptoms of the disease are headaches, seizures, focal neurologic signs (e.g., hemiparesis, visual disturbances, mental status change, speech disturbances, etc.) and general

neurologic and or functional deterioration. In addition, there are many disease symptoms which are secondary to the primary neurological deficits. These include, among others, DVT and PE due to decreased mobility, falls and orthopedic damage due to balance disturbances and pyramidal tract deficiency related muscular contractions.

Significant between-group differences ($p<0.05$) were found in the following systems:

1. Gastrointestinal – significantly more AEs in the BSC group
2. Blood and Lymphatic – significantly more AEs in the BSC group
3. Infections – significantly more AEs in the BSC group
4. Procedural complications – significantly more AEs in the NovoTTF-100A group (due to rash under the electrodes)

Table 29 Adverse Events by Body Systems Safety Population[1]

	NovoTTF-100A	**BSC**	**p-value**
System Organ Class	**(n=116)**	**(n=91)**	
Blood and lymphatic system disorders	*5 (4.3%)*	*17 (18.7%)*	*0.0009*
Cardiac disorders	8 (6.9%)	6 (6.6%)	0.9313
Ear and labyrinth disorders	1 (0.9%)	3 (3.3%)	0.2066
Endocrine disorders	2 (1.7%)	2 (2.2%)	0.8059
Eye disorders	3 (2.6%)	5 (5.5%)	0.2813
Gastrointestinal disorders	*9 (7.8%)*	*27 (29.7%)*	*<.0001*
General disorders and administration site conditions	15 (12.9%)	14 (15.4%)	0.6137
Infections and infestations	*5 (4.3%)*	*11 (12.1%)*	*0.0376*
Injury, poisoning and procedural complications	*21 (18.1%)*	*1 (1.1%)*	*<.0001*
Investigations	8 (6.9%)	5 (5.5%)	0.6798
Metabolism and nutrition disorders	9 (7.8%)	12 (13.2%)	0.1992
Musculoskeletal and connective tissue disorders	6 (5.2%)	8 (8.8%)	0.3034
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (1.7%)	2 (2.2%)	0.8059
Nervous system disorders	50 (43.1%)	33 (36.3%)	0.319
Psychiatric disorders	12 (10.3%)	7 (7.7%)	0.5118
Renal and urinary disorders	7 (6.0%)	3 (3.3%)	0.3619
Respiratory, thoracic and mediastinal disorders	7 (6.0%)	10 (11.0%)	0.1975
Skin and subcutaneous tissue disorders	9 (7.8%)	9 (9.9%)	0.5891
Vascular disorders	5 (4.3%)	6 (6.6%)	0.4673

1 - Systems with significant differences are marked in italic font.

As seen in **Table 30** below, fewer NovoTTF-100A patients had any AE compared to BSC patients (55% vs. 59%, respectively). NovoTTF-100A patients suffered significantly less from treatment-related AEs than BSC patients (22% vs. 48%, respectively), where the difference between the

incidence of related AEs in NovoTTF-100A versus BSC patients was statistically significant (chi-square p-value<0.00001) **Figure 25** below shows the percentage of patients with AEs related to treatment (assessed by the investigators as “possibly”, “probably” or “definitely” related to therapy) by body system.

Please note that **Table 30** is an abbreviated adverse event table, which includes only events seen in ≥ 2% of patients. Therefore, only major categories of events with an incidence ≥ 2%, and subcategories of events with an incidence ≥2% are listed in the table. Since subcategories with an incidence less than 2% are not listed, the totals for all of the subcategories may not add up to the total for the major category. A system oriented discussion of selected AEs observed in the pivotal trial is provided in the following sections.

Table 30 Percentage of Patients with AEs in the NovoTFF-100A versus BSC Groups (Including incidence of severe and of related AEs) ≥ 2%

	NovoTTF-100A			BSC Chemotherapy		
	(N=116)			(N=91)		
System Organ Class	% of patients			% of patients		
Preferred Term	**All AEs**	**Severe**	**Related**	**All AEs**	**Severe**	**Related**
Percentage of Patients with >=1 AE	55	16	22	59	19	48
Blood and lymphatic system disorders	4	1	0	19	4	16
Anemia	2	0	0	2	0	2
Leukopenia	1	0	0	7	1	4
Lymphopenia	2	1	0	3	1	2
Neutropenia	1	0	0	2	0	2
Thrombocytopenia	3	0	0	12	2	10
Cardiac disorders	7	1	0	7	0	2
Peripheral edema	5	1	0	3	0	2
Tachycardia	1	0	0	3	0	0
Ear and labyrinth disorders	1	0	0	3	0	2
Ear pain	0	0	0	2	0	2
Endocrine disorders	2	0	0	2	0	0
Cushingoid	2	0	0	1	0	0
Eye disorders	3	0	0	5	0	1
Dry eye	2	0	0	0	0	0
Vision blurred	1	0	0	2	0	1
Gastrointestinal disorders	8	1	0	30	3	30
Abdominal pain	0	0	0	7	0	3
Aphthous stomatitis	0	0	0	2	0	2
Constipation	2	0	0	4	0	2
Diarrhea	0	0	0	12	2	11
Nausea	3	0	0	16	0	14

Table 30 Percentage of Patients with AEs in the NovoTFF-100A versus BSC Groups (Including incidence of severe and of related AEs) ≥ 2%

	NovoTTF-100A			BSC Chemotherapy		
	(N=116)			(N=91)		
System Organ Class	% of patients			% of patients		
Preferred Term	**All AEs**	**Severe**	**Related**	**All AEs**	**Severe**	**Related**
Vomiting	3	0	0	7	0	7
General disorders and administration site conditions	13	1	2	15	1	9
General physical health deterioration	2	0	0	1	0	0
Malaise	9	1	2	11	0	8
Pyrexia	2	0	0	1	0	0
Infections and infestations	4	0	0	12	1	0
Candidiasis	3	0	0	3	0	0
Ear infection	0	0	0	2	0	0
Urinary tract infection	0	0	0	3	1	0
Injury, poisoning and procedural complications	18	15	16	1	0	0
Fall	4	0	1	0	0	0
Medical device site reaction (rash under electrodes)	16	0	16	0	0	0
Investigations	7	2	0	5	1	2
Blood lactate dehydrogenase increased	2	0	0	1	0	1
Hepatic enzyme abnormal	1	0	0	2	1	2
Weight increased	1	0	0	2	0	0
Metabolism and nutrition disorders	8	1	0	13	3	3
Anorexia	0	0	0	4	1	3
Diabetes mellitus	2	0	0	0	0	0
Hyperglycemia	2	0	0	2	1	0
Hypokalaemia	2	0	0	4	1	1
Musculoskeletal and connective tissue disorders	5	0	1	9	0	0
Back pain	2	0	0	3	0	0
Muscular weakness	0	0	0	3	0	0
Pain in extremity	0	0	0	2	0	0
Neoplasms benign, malignant and unspecified	2	2	0	2	1	0
Neoplasm progression	2	2	0	2	1	0
Nervous system disorders	43	7	3	36	5	3
Amnesia	3	0	0	0	0	0

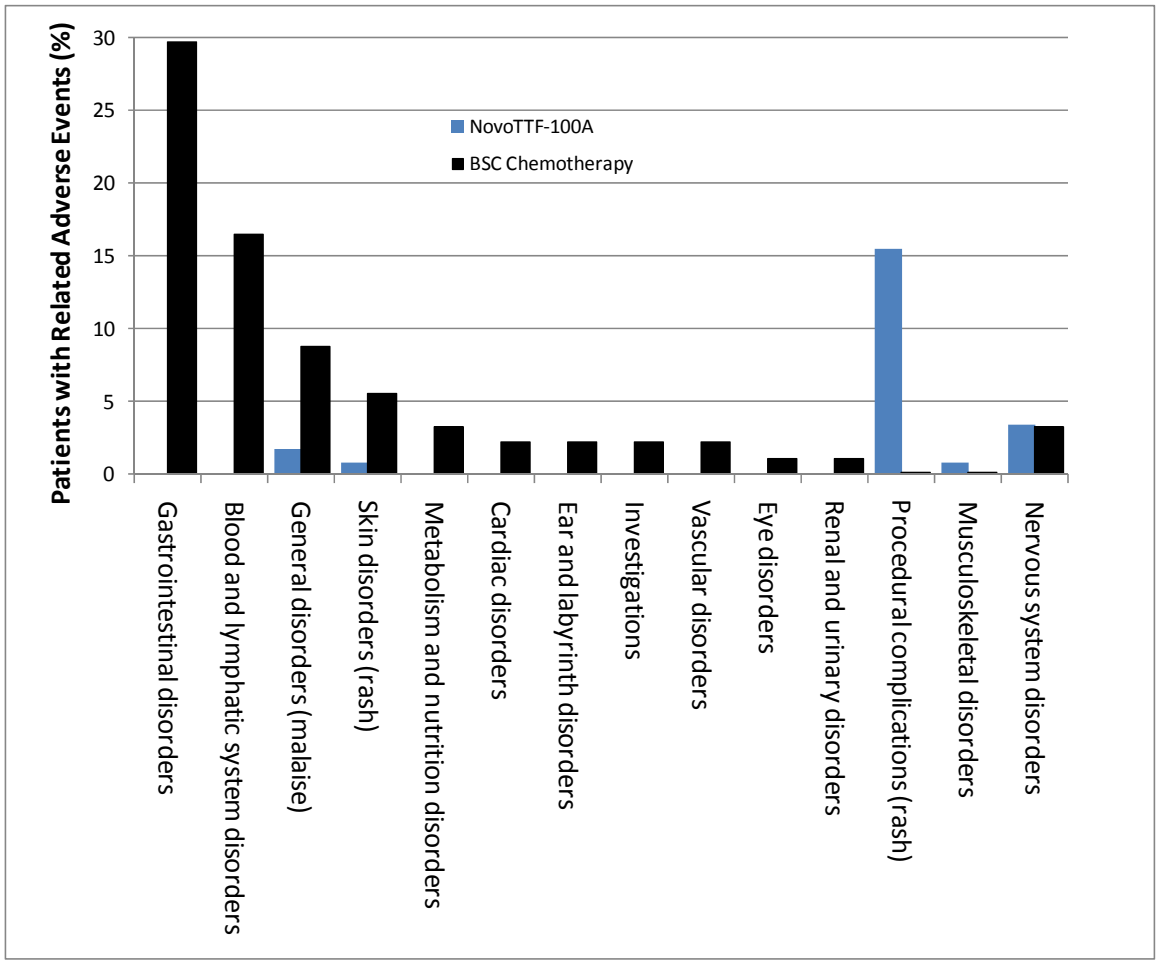
Table 30 Percentage of Patients with AEs in the NovoTFF-100A versus BSC Groups (Including incidence of severe and of related AEs) ≥ 2%

	NovoTTF-100A			BSC Chemotherapy		
	(N=116)			(N=91)		
System Organ Class	% of patients			% of patients		
Preferred Term	**All AEs**	**Severe**	**Related**	**All AEs**	**Severe**	**Related**
Balance disorder	2	0	0	0	0	0
Brain edema	1	0	0	2	0	0
Cognitive deterioration	2	1	0	2	0	0
Cognitive disorder	2	0	0	2	0	0
Convulsion	9	3	0	4	2	0
Coordination abnormal	2	0	0	4	0	0
Cranial nerve disorder	3	0	0	1	0	0
Difficulty in walking	1	0	0	2	0	0
Dizziness	3	0	0	2	0	2
Dysaesthesia	2	0	0	1	0	0
Dysphasia	3	0	0	2	0	0
Headache	16	2	3	10	0	2
Hemianopia	2	0	0	4	1	0
Hemiparesis	9	0	0	4	1	0
Hyperreflexia	3	0	0	2	0	0
Hypoaesthesia	2	0	0	3	0	0
Hyporeflexia	0	0	0	2	0	0
Memory impairment	2	0	0	0	0	0
Nervous system disorder	3	1	0	3	0	0
Neuropathy peripheral	2	1	0	1	0	0
Tremor	2	0	0	2	0	0
Psychiatric disorders	10	0	0	8	0	0
Agitation	2	0	0	0	0	0
Depression	2	0	0	5	0	0
Insomnia	2	0	0	2	0	0
Mental status changes	5	0	0	1	0	0
Renal and urinary disorders	6	1	0	3	0	1
Pollakiuria	2	0	0	0	0	0
Urinary incontinence	3	1	0	2	0	0
Respiratory, thoracic and mediastinal disorders	6	0	0	11	1	0
Cough	3	0	0	4	0	0
Dyspnea	2	0	0	4	1	0
Nasopharyngitis	0	0	0	2	0	0
Skin and subcutaneous tissue disorders	8	0	1	10	0	5
Alopecia	0	0	0	3	0	3

Table 30 Percentage of Patients with AEs in the NovoTFF-100A versus BSC Groups (Including incidence of severe and of related AEs) ≥ 2%

	NovoTTF-100A			BSC Chemotherapy		
	(N=116)			(N=91)		
System Organ Class	% of patients			% of patients		
Preferred Term	**All AEs**	**Severe**	**Related**	**All AEs**	**Severe**	**Related**
Rash	4	0	0	0	0	0
Swelling face	2	0	0	1	0	0
Vascular disorders	4	2	0	7	2	2
Hypertension	1	0	0	3	0	0
Pulmonary embolism	1	1	0	2	2	1

Figure 25 Comparison of Treatment Related AE Incidence Between NovoTTF-100A and BSC Patients



8.8.1.1 Blood and Lymphatic System Disorders

Blood and lymphatic system disorders are a classic outcome of chemotherapy due to the systemic delivery of IV and PO chemotherapy to the bone marrow. NovoTTF-100A, on the other hand, delivers treatment localized to the brain. Since the amount of bone marrow in the skull is negligible, blood and lymphatic system disorders are not expected for device treatment.

In agreement with this expectation, these disorders were seen in a significantly higher proportion of BSC patients than in NovoTTF-100A patients (19% vs. 4%, respectively; p=0.0009).

None of the NovoTTF-100A events was related to treatment and only three cases were moderate to severe. These cases were most likely due to prior chemotherapy use which led to depletion of the bone marrow's potential to regenerate lymphocytes after infection in these patients.

On the contrary, in the BSC group, 17% of patients had 18 events that were moderate to severe, including febrile neutropenia, lymphopenia, leucopenia and thrombocytopenia. Almost all cases of blood and lymphatic disorders were related to treatment in the BSC group and the febrile neutropenia was an SAE since it led to hospitalization. Similarly, temozolomide has shown an incidence of 22% of patients with severe or life threatening myelosuppression [1].

In summary, NovoTTF-100A did not lead to blood and lymphatic disorders in the trial whereas BSC chemotherapy, as expected, led to a significant proportion of patients with related, moderate to severe disorders (mainly thrombocytopenia).

8.8.1.2 Cardiac Disorders

Cardiac disorders were seen in 7% of patients in both treatment arms. These included mainly peripheral edema, cyanosis and tachycardia. Only one case of peripheral edema was rated as severe, however this case was considered unrelated to device treatment. On the contrary 2% of patients in the BSC group reported peripheral edema which was related to chemotherapy. We conclude that the NovoTTF-100A did not cause any cardiac toxicity in the trial.

Overall, there were slightly more cases of peripheral edema in the NovoTTF-100A group than the BSC group (5% vs. 3%, respectively). However, the company has concluded that NovoTTF-100A treatment did not lead to peripheral edema in the pivotal study for the following reasons:

1. The mechanism of action of the device cannot explain the appearance of peripheral edema. In fact, the TTField intensity in the torso of animals treated with electrodes on the scalp is zero.
2. The difference between groups was negligible (5% vs. 3%) and was not statistically significant (p=0.5113).
3. None of the events was assessed by the investigators as related to the device.
4. Other underlying medical reasons were found for every case.

Thus, we conclude the difference of 5% vs. 3% in this specific adverse event is a random finding of no clinical significance.

8.8.1.3 Gastrointestinal Disorders

Gastrointestinal (GI) side effects are the hallmark of treatment with chemotherapy and a part of life all cancer patients must currently learn to live with. This is also one of the major causes of the decrease in quality of life in BSC treated recurrent GBM patients. In the pivotal trial, 30% of BSC patients suffered from GI AEs compared to only 8% of NovoTTF-100A patients. This difference was highly statistically significant (p<0.0001). The actual number of GI AEs was also much higher in the BSC group than in the NovoTTF-100A group (51 vs. 12 reported events). This was mainly due to a

very high frequency of diarrhea and nausea. These values are comparable to the expected rates of GI toxicities seen with chemotherapies. Temozolomide leads to nausea in 49% of patients, vomiting in 29%, diarrhea in 10% and abdominal pain in 5% of patients [1]. Bevacizumab (without irinotecan) is associated with diarrhea in 22% of patients [10].

In the BSC group, abdominal pain, diarrhea, nausea and vomiting were the most common GI AEs. Fifteen percent of BSC patients had moderate to severe GI AEs, and 30% of patients had AEs related to treatment. Only 7% had GI AEs unrelated to treatment, very similar to the percentage of NovoTTF-100A patients with GI AEs (8%). Due to the nature of these AEs, and the preference for outpatient management of GI toxicities in cancer in general, only one AE led to hospitalization and was captured as an SAE.

In the NovoTTF-100A group, 8% of patients had GI AEs. None were related to treatment with the device and only 4% of patients had moderate to severe AEs (compared to the 15% in BSC patients). None of the GI AEs was an SAE.

We conclude that treatment with the NovoTTF-100A device in this study did not cause GI toxicity and led to a significant decrease in one of the main causes of morbidity in this patient population.

8.8.1.4 General Disorders and Administration Site Conditions

General disorders were seen in the same proportion of NovoTTF-100A (13%) and BSC chemotherapy patients (15%). The majority of general disorders were malaise seen in 9% of NovoTTF-100A patients and 11% of BSC patients. General disorders were severe in 1% of NovoTTF-100A and 1% of BSC patients. In 2% of NovoTTF-100A patients, malaise was assessed as possibly related to device use, while in 8% of BSC patients, malaise was assessed as possibly and probably related to BSC treatment. One BSC patient had systemic inflammatory response syndrome which was definitely related to BSC chemotherapy. One NovoTTF-100A patient had general health decline which led to hospitalization and was captured as an SAE. This event was unrelated to treatment and was probably a case of disease progression without radiological evidence. Weakness and fatigue have been reported in the past in 61% and 7% of temozolomide patients during their maintenance phase [1]. Fatigue has been reported in 45% of patients receiving bevacizumab [10] and in 21.7% of patients implanted with Gliadel Wafers [6].

We conclude that general disorders including mainly malaise and general health decline are equal in incidence in both treatment groups and represent a part of the symptom array seen in recurrent GBM patients. In some cases, BSC chemotherapy increased the incidence of these AEs, whereas NovoTTF-100A did not.

8.8.1.5 Infections and Infestations

Infections are a known outcome of blood and lymphatic system disorders in chemotherapy treated patients. With proper management of these disorders, however, rarely should they lead to significant infections. Proper management usually includes chemotherapy dose modifications and bone marrow stimulation. As seen above, blood and lymphatic system disorders are almost non-existent in NovoTTF-100A patients, so infections should be limited to opportunistic infections.

As expected, more infections were seen in BSC chemotherapy patients (12%) than in NovoTTF-100A patients (4%). This difference was statistically significant ($p=0.0376$). None of the infections reported in the study were considered related to either treatment option. In the NovoTTF-100A patients, all 4 cases were local fungal infections whereas in the BSC patients, infections were seen in the skin, mouth, lungs, urinary tract, eyes and ears. Only one severe infection was seen in the

study – a case of severe pneumonia in a BSC patient. Three BSC patients had infections (cellulitis, pneumonia and UTI) that required hospitalization and were assessed as SAEs.

Infections associated with chemotherapies have been seen in the past at a higher incidence than were observed in the BSC group; for example, in approval studies for Gliadel Wafers [6] (infection 18.3%; UTI 8.3%; pneumonia 8.3%) and for bevacizumab [10] (55%).

We conclude that, although none of the infectious AEs in the study was considered treatment related, in the BSC patients infections were more common, more severe and of a more systemic nature (e.g., severe pneumonia leading to hospitalization). Fungal infections seen in a handful of NovoTTF-100A patients were most likely the outcome of steroid use.

8.8.1.6 Injury, Poisoning and Procedural Complications

This system captured mainly AEs related to skin damage beneath device electrodes. Therefore, it is not unexpected that these complications were seen in 18% of device patients (16% with skin irritation beneath the electrodes) and only one BSC patient (excoriation). All medical device site reactions were related to NovoTTF-100A treatment, however, none were severe and none led to hospitalization. All device site reactions resolved after stopping therapy with the NovoTTF-100A device.

In addition, 4% of NovoTTF-100A patients had an AE of “fall”. Only one of these events was considered by the investigator as possibly related to treatment and the rest unrelated. None were severe. These events were most likely related to neurological deficits of the underlying disease.

Finally, one NovoTTF-100A patient had a CSF leak from his surgical incision, which was unrelated to device treatment, mild in severity and resolved without sequelae. This patient had undergone tumor resection with Gliadel Wafer insertion prior to entering the trial. CSF leak is a known possible complication of neurosurgical procedures in general and it is known to be more common after Gliadel Wafer placement in recurrent GBM patients (5%; see Brem et al. 1995 [6]).

We conclude that the medical device site reaction seen in less than 20% of NovoTTF-100A patients is a mild to moderate, transient side effect which resolves completely after device removal.

8.8.1.7 Metabolism and Nutrition Disorders

Metabolic and nutritional disorders were seen in 8% of NovoTTF-100A patients and 13% of BSC patients. None of the disorders were related to NovoTTF-100A treatment, while 3 cases of anorexia were related to BSC treatment and one of these led to patient death. In the NovoTTF-100A group, one patient had a severe AE of dehydration unrelated to device treatment, which was resolved without sequelae. In the BSC group, 3 patients had severe anorexia, hyperglycemia and hypokalemia.

Temozolomide has been reported in the past to be associated with anorexia in 27% of patients in the maintenance therapy phase [1].

We conclude that NovoTTF-100A did not lead to metabolic or nutritional disorders in the trial, whereas BSC chemotherapy led to a single case of a possibly treatment related patient death.

8.8.1.8 Nervous System Disorders

Since recurrent GBM is a severe neurological disease, all patients in the trial are expected to have some sort of neurological disorder at some point in their disease. Accordingly, in the pivotal trial,

neurological AEs were very common in both arms. There was no significant difference in the incidence of neurological AEs between groups (36% and 43% in BSC and NovoTTF-100A, respectively). The AEs reported were seen in almost every assessable neurological function. The incidence of specific AEs was relatively low in both groups with most events appearing in individual patients.

Severe neurological AEs were seen in 7% of NovoTTF-100A patients and 5% of BSC patients. These included 3% and 2% severe convulsions (seizures) in the device and BSC groups, respectively. Almost none of the neurological AEs in the trial were related to the NovoTTF-100A device or to BSC chemotherapy. "Headache" was assessed as related to treatment in three percent of patients in the NovoTTF-100A arm and in two percent of patients in the BSC arm. "Dizziness" was related to treatment in two percent of patients in the BSC group and was not seen in NovoTTF-100A patients.

The only neurological and psychiatric AEs where the NovoTTF-100A patients appeared to have a higher incidence than BSC patients were headaches, convulsions, hemiparesis and mental status change (psychiatric). Based on a question from the agency, NovoCure further examined the frequency of these nervous system and psychiatric disorders in the NovoTTF-100A group compared to the BSC group.

To assess relatedness of AEs to the device, the investigators were instructed to use pre-defined WHO guidelines. In order to define an AE as possibly, probably or definitely related to device use, the event must "follow a known response pattern to the device"; i.e., in order to cause neurological or psychiatric AEs, it must lead to electrical excitation of neuronal activity in the brain in patients treated by the device.

However, given the operating characteristics of the NovoTTF-100A device, there should be no causal relationship with the cerebral events noted by FDA. The electric fields used by the NovoTTF-100A device alternate at a frequency of 200 kHz. Since the time constant of the plasma membrane of neurons is on the order of 1 ms [78, 79], any electric potential difference which alternates more rapidly than the membrane time constant (i.e., frequencies above 1 kHz), will lead to membrane hyperpolarization before full depolarization can occur, and an action potential will not be generated. The higher the frequency, the lower the excitatory potential of the voltage pulse across the membrane. At 200 kHz, it is scientifically impossible to stimulate nerves in the CNS. In addition, the peak intensity of the electric field waveform generated by the device is approximately 1 V/cm. Thus, the voltage "felt" by the plasma membrane of nerves (which are only about 100Å wide) is on the order of 0.001 mV. This amplitude is much lower than the pulse amplitude needed to stimulate nerves (several mV).

Based on the mechanism of action of NovoTTF-100A, if the device caused neuronal excitation, CNS adverse events would be expected to appear immediately, or within a few moments at most from turning on the device. In order to rule out AEs due to neuronal excitation, the trial design included an initial 24 hour hospitalization of all NovoTTF-100A patients. No serious adverse events and none of these four types of CNS events specified by the agency appeared during the first 24 hour hospitalization. In addition, none of these events resumed after re-challenge with the device.

As requested by FDA, the company performed an analysis of the time from treatment start to the appearance of headaches, hemiparesis, convulsions or mental status change in the NovoTTF-100A and BSC patients. The temporal distribution in both groups was similar with very few AEs seen during the first week of therapy and the maximal incidence appearing after 2 months, when most patients in the study (in both treatment arms) progressed. The first convulsion to appear in the NovoTTF-100A group started 3 days after treatment initiation in a patient with a rapidly progressive

GBM (progressed radiologically within 1 month). We conclude that neuronal excitation by the NovoTTF-100A device did not cause these events.

In addition, we compared the distribution of CNS AEs from event start to progression (per MRI). The majority of events in the NovoTTF-100A group (69%) occurred in the month prior to MRI determination of progression. In the BSC group, only 47% of events occurred in the month prior to progression. We conclude that the temporal distribution of headaches, hemiparesis, convulsions and mental status change was similar in NovoTTF-100A and BSC patients, except for a higher proportion of events in the NovoTTF-100A patients which occurred close to progression. This suggests that the higher incidence of these events seen in NovoTTF-100A patients than in BSC patients (not statistically significant), was a chance clustering of specific CNS symptoms as the clinical presentation of disease progression.

Furthermore, GBM is a neurological disease characterized by a plethora of neurological clinical symptoms at all stages of the disease. The exact symptoms experienced by each patient depend mainly on tumor location and size, although additional parameters such as extent of peri-tumoral edema also play a role in the neurological presentation of the disease. The four above-mentioned adverse events (convulsions, headaches, hemiparesis and mental status change) are probably the best characterized and well known symptoms of brain tumors in general. According to the definitions of causality of AEs, because these events are "most likely produced by other factors such as the subject's clinical condition," they are by definition no more related to the device than "unlikely". A specific discussion of the expected incidence of each of these symptoms in the recurrent GBM population follows:

a. Convulsions are expected in 20-50% of GBM patients at various stages of their disease [80]. In fact, in the Gliadel registration trial, patients with active Gliadel Wafers suffered from a 40% incidence of convulsions while the incidence was 32% in those receiving placebo wafers [6]. In the bevacizumab (Avastin) registration trial, patients receiving bevacizumab alone had an incidence of 15% for convulsions (19% in the bevacizumab combination arm) [10].
b. Headaches are also a hallmark symptom of GBM. In the bevacizumab registration trial, headaches were self-reported in 37% of patients. In the Gliadel Wafer registration trial, headaches were self-reported in 28% of patients in the treatment arm and 37% of patients in the placebo control arm.
c. Hemiparesis and/or hemiplegia are a clear symptom of brain tumors in general and are thus usually not reported in recurrent GBM trials. However, in the Gliadel Wafer registration trial, hemiplegia was seen in 41% and 44% of treatment arm and placebo control arm patients, respectively.
d. Mental status change was reported in the Gliadel Wafer registration trial in 6% and 8% of patients in the treatment arm and placebo control arm, respectively (termed – "thinking abnormal").

The incidence of all four AEs was lower in both the NovoTTF-100A group and BSC group than in prior trials reported in the literature. In fact, less than 10% of these AEs were severe in intensity and the majority of the events were resolved without any sequelae. In addition, for none of these adverse event terms was the incidence statistically significant between groups.

The company also reviewed each patient record and analyzed the reasons for each of the above-mentioned AEs in NovoTTF-100A patients. In the NovoTTF-100A patients, the underlying cause of the event is clearly tumor growth immediately before or after the event (within a week) in about half of the cases (24 of 51 events). In addition, there are several cases (6 of 51 events) where patients had enormous baseline tumors (6-8 cm in diameter) and were not optimally treated with systemic steroids and antiepileptics for prevention of neurological symptoms. In fact, in only 12 NovoTTF-

100A cases was no alternative underlying cause readily identifiable besides having a brain tumor. On the other hand, of the 19 AEs in BSC patients, only 7 occurred immediately before or after tumor growth and only 2 could be explained by other medical conditions. In fact, as seen in **Table 31** below, when comparing only the cases *where an underlying cause of the AE is unknown*, the same number of events is seen in both NovoTTF-100A and BSC patients (12 and 10 events in 10 (9%) and 9 (10%) patients, respectively). Since, according to the protocol and WHO guidelines referenced above, when an AE is known to be caused by the underlying disease condition and the treatment is not likely to cause the event based on its mechanism of action, the event is not considered related to the treatment. Thus, the correct comparison between AEs should only take into account those with no known medical explanation, as presented in **Table 31** below.

Table 31 Treatment Emergent AEs with No Known Medical Explanation by Treatment Group Safety Population

	NovoTTF-100A (n=116) # Patients (# Events)	**BSC (n=91) # Patients (# Events)**
Convulsions	2 (2)	2 (2)
Headaches	2 (3)	5 (5)
Hemiparesis	4 (4)	1 (1)
Mental status change	2 (3)	1 (2)
Total	10 (12)	9 (10)

The following is a summary discussion of each of the four adverse event terms based on the above analyses:

1. Convulsions: Convulsions were seen in 9% of NovoTTF-100A patients and in 4% of BSC patients (ns). Both rates are lower than previously reported in recurrent GBM patients and thus do not raise a safety concern regarding the device. Additionally, all but one event in the NovoTTF group were considered unrelated to device use by the trial investigators based on predefined criteria in the protocol. Only 3 cases in the NovoTTF-100A group and 2 cases in the BSC group were rated as severe by the investigators and all but one case were resolved without any sequelae. Finally, a case-by-case review of all convulsions in the trial showed that all but 2 events in the NovoTTF-100A group and 2 events in the BSC group could readily be attributed to other causes. These included mainly disease progression in close temporal proximity to the event and a case of a patient with Gliadel Wafer implantation (known to lead to an increase in convulsions). The remaining events are balanced between groups and are most likely symptoms of the underlying disease process.

2. Headaches: Headaches were seen in 16% vs. 10% of NovoTTF-100A and BSC patients, respectively (ns). Both rates are lower than previously reported for recurrent GBM patients and thus do not raise a safety concern regarding the device. It is theoretically possible that this difference is the result of minor discomfort due to the electrodes being interpreted by the patients as a headache. Only 2 headaches in the NovoTTF-100A group were severe and both resolved without sequelae. Finally, a case-by-case review of all headaches in the trial showed that all but 3 events in the NovoTTF-100A group and 5 events in the BSC group could readily be attributed to other causes. These included disease progression in close temporal proximity to the event, one case where the event started 5 days before treatment was initiated and a case where no steroids were given to control headaches due to recurrence at trial entry. The remaining events are most likely symptoms of the underlying disease process.

3. Hemiparesis: Hemiparesis is the hallmark of any tumor process in the brain, and is the first sign or symptom seen in over a third of patients presenting to emergency departments with a primary brain tumor [81]. As such, hemiparesis is not even reported in many trials. In the present study, hemiparesis was seen in 9% and 4% of NovoTTF-100A and BSC patients, respectively (ns). None of the cases were severe in the NovoTTF-100A group and only one case was severe in the BSC group. Additionally, none of the cases of hemiparesis was considered related to treatment (in either group) by the trial investigators based on predefined criteria in the protocol. Finally, a case-by-case review of all cases of hemiparesis in the trial showed that the majority could readily be attributed to other causes. These included disease progression in close temporal proximity to the event, a case where hemiparesis was known prior to entering the trial (in which case it should not have been reported as an AE since it is a pre-existing condition), and one case where hemiparesis started prior to treatment initiation. The remaining events are most likely symptoms of the underlying disease process.

4. Mental Status Change: Mental status change was seen in 5% and 1% of NovoTTF-100A and BSC patients, respectively (ns). None were severe (in either group) and none of the cases of mental status change was considered related to treatment (in either group) by the trial investigators based on predefined criteria in the protocol. All but 3 events in the NovoTTF-100A group and the 2 events in the BSC group were resolved without sequelae. Finally, a case-by-case review of all cases of mental status change in the trial showed that all but 3 events in the NovoTTF-100A group and 2 events in the BSC group could readily be attributed to other causes. These included disease progression in close temporal proximity to the event, a patient with a $32cm^2$ tumor at baseline who was not receiving steroids and one patient who had just failed bevacizumab (Avastin) and had his third resection of a rapidly growing tumor. The remaining events are balanced between the treatment groups and are most likely symptoms of the underlying disease process.

In summary, it is our assessment that the larger number of patients in the NovoTTF-100A group with these specific adverse event terms is a random finding and not related to the use of the device. This assessment is supported by the underlying mechanism of action of the device, with which there is no possibility of neuronal stimulation, as well as by historical reports of adverse event frequency in the literature. It is also supported by the investigators' opinions based on their understanding of each of the patients and knowledge of their medical histories, following the clear guidelines provided in the protocol for defining adverse event relatedness to treatment (including the fact that the events did not resume upon re-challenge with the device). Finally, this assessment is supported by a case-by-case review of all of these adverse events, including their temporal relationship to device initiation and progression, which showed that almost all cases could be attributed to other underlying causes.

We conclude that the incidence of neurological disorders is the same between treatment groups and that the NovoTTF-100A does not cause an increase in the incidence of the neurological symptoms of the underlying disease.

8.8.1.9 Psychiatric Disorders

Psychiatric disorders in GBM patients are usually the outcome of a subtle neurological disorder that manifests with psychiatric symptoms. As seen above for neurological disorders, psychiatric disorders were also seen in equal proportions of patients in the NovoTTF-100A (10%) and BSC (8%) groups. None of these events was severe and none related to either NovoTTF-100A or BSC treatment.

See **Section 8.8.1.8**, above, for a detailed discussion of the incidence of mental status changes in the NovoTTF-100A trial.

8.8.1.10 Vascular Disorders

Vascular disorders were seen in 4% of device patients and 7% of BSC patients. Two severe AEs (cerebral hemorrhage and DVT) were seen in device patients and three severe AEs (DVT, and two PE) in BSC patients. None of the vascular AEs were related to NovoTTF-100A treatment, whereas two cases were assessed as related to BSC chemotherapy (DVT and Epistaxis). Both DVT and cerebral hemorrhage are seen in almost all recurrent GBM clinical trials and are known symptoms of the underlying disease. Bevacizumab has been shown to be associated with 40% bleeding or hemorrhage, 26% epistaxis, 5% cerebral hemorrhage, 32% hypertension and 14% thromboembolic events (including pulmonary embolism) [10]**.**

8.8.2 Serious Adverse Events

As seen in **Table 32** below, the incidence of SAEs was the same in the NovoTTF-100A and BSC groups (13 vs. 11%). These events were considered SAEs mainly due to patient hospitalization and not because they were life threatening. SAEs are presented in **Table 32** only until disease progression since, after progression, patients were hospitalized often due to the very severe stage of their disease (2-7th progression). There were no SAEs seen at an incidence above 3%.

The low number of SAEs in this study reflects the preference for outpatient management of oncologic side effects and symptoms.

Table 32 Treatment Emergent SAEs by Body System and Preferred Term Safety Population

	NovoTTF-100A [N=116]		**BSC [N=91]**	
System Organ Class	**# of Events**	**# of Pts.**	**# of Events**	**# of Pts.**
Preferred Term	**(Frequency)**	**(Incidence)**	**(Frequency)**	**(Incidence)**
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)**
Peripheral edema	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)

Table 32 Treatment Emergent SAEs by Body System and Preferred Term Safety Population				
	NovoTTF-100A [N=116]		BSC [N=91]	
System Organ Class	**# of Events**	**# of Pts.**	**# of Events**	**# of Pts.**
Preferred Term	**(Frequency)**	**(Incidence)**	**(Frequency)**	**(Incidence)**
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)
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)**
Dyspnea	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)

8.8.3 Adverse Events Leading to Treatment Discontinuation

The same incidence of AEs leading to treatment discontinuation was seen in the BSC and NotoTTF-100A groups (4%). This number is comparable with other clinical trials [10] and is a reflection of good medical management of AEs in the trial.

8.8.4 Unanticipated Adverse Device Effects

There were no UADEs in the trial.

8.8.5 Safety Discussion and Conclusion

A similar number of NovoTTF-100A patients had AEs of any type as BSC chemotherapy patients (55% versus 59%, respectively).

Significantly more patients in the BSC group suffered from hematologic, gastrointestinal and infectious AEs than in the NovoTTF-100A group. Specifically, NovoTTF-100A did not cause any blood and lymphatic disorders (4% of patients, all unrelated to treatment) whereas BSC chemotherapy, as expected, caused a significant proportion of patients to suffer from moderate to severe blood and lymphatic disorders (27 AEs in 19% of the patients), mainly thrombocytopenia (12% of patients). The difference was statistically significant (p=0.0009). Gastrointestinal (GI) AEs are one of the main causes of morbidity in this recurrent GBM patient population. In this trial, there were 51 events of gastrointestinal toxicity in 30% of BSC patients. Forty of these events were related to BSC treatment. The small number of GI AEs seen in the NovoTTF-100A patients (12 events in 8% of patients) were all unrelated to treatment and were similar in incidence to the unrelated GI AEs in the BSC group. However, in the BSC group (only), there were many additional GI AEs which were related to chemotherapy, including numerous cases of moderate to severe nausea, vomiting, diarrhea, abdominal pain and constipation. The difference in incidence between groups was highly significant (p<0.0001). Finally, one of the main outcomes of hematological and lymphatic disorders in patients treated with chemotherapies is that these conditions can lead to serious infections. None of the infectious AEs in the study was considered treatment related. However, there were significantly more infectious events in the BSC group than the NovoTTF-100A group (p=0.0376). In the BSC patients, infections were more common, more severe and of a more systemic nature (e.g., severe pneumonia leading to hospitalization). Mild fungal infections were seen in a handful of NovoTTF-100A patients but these were most likely secondary to steroid use.

Based on a detailed, event-by-event analysis of neurological and psychiatric adverse events requested by the agency, the company found no difference in the incidence of CNS related AEs between NovoTTF-100A and BSC chemotherapy patients. The neurological and psychiatric AEs seen in both treatment groups were symptoms of the underlying disease process or symptomatic manifestations of disease progression. The company believes that the NovoTTF-100A device does not cause neurological adverse events (“AEs”) for the following reasons:

(1) these are typical, expected adverse events for GBM patients and their frequency is no greater than expected;
(2) the mechanism of action of the NovoTTF-100A device is such that it is inconsistent with causation of these cerebral events;
(3) the clinical trial investigators did not find that these events were related to use of the study device;
(4) a case-by case review shows that the majority of the cases have other medical causes;
(5) these events were more likely to take place closer to progression than initiation of treatment;
(6) none of the events occurred during the first 24 hour hospitalization required in the protocol;
(7) none of the events repeated itself upon re-challenge with the device; and
(8) the non-significant differences in the incidence of specific terms of neurological and psychiatric AEs appears to be a random finding when looking at multiple terms in each body system.

The NovoTTF-100A device also caused an expected mild to moderate skin reaction beneath the device electrodes in 16% of patients. None of these cases was assessed as severe by the investigator. The skin reaction resolved in all cases after discontinuing treatment and was easily

treated with topical steroids or antibiotic creams (if there were open sores). Treatment is not interrupted by this condition due to the ability to shift between alternative electrode locations.

Many other rare disorders are seen in any cohort of sick patients followed for many months. Thus, in both groups of patients there were individual cases of cardiac disorders, blood chemistry test abnormalities, metabolic disorders, ENT disorders, eye disorders and vascular disorders. No differences were seen between groups in the incidence, severity or relatedness of these AEs.

From the pivotal study results, it is clear that NovoTTF-100A treatment is not associated with gastrointestinal, hematological or infectious adverse events, which are the hallmark of chemotherapeutic treatments, and are seen in a significantly higher proportion of BSC chemotherapy patients and at a much higher frequency than NovoTTF-100A patients in the trial ($p<0.05$). These findings are supported by the analysis of quality of life data presented above (as a secondary efficacy endpoint), in which BSC patients complained of a higher incidence of nausea, vomiting, diarrhea, constipation and pain than NovoTTF-100A patients while on treatment.

In conclusion, the classic gastrointestinal, hematological and infectious adverse events of almost all chemotherapies are seen in a significantly higher proportion of BSC control patients than in NovoTTF-100A patients and at much higher frequencies. These differences appear in severe and related event categories as well. Thus, the difficult and debilitating side effects of chemotherapy are lowered significantly when using the NovoTTF-100A device. The NovoTTF-100A has a benign adverse event profile and is significantly less toxic than BSC chemotherapy. The only treatment related adverse event seen in a significant proportion of patients is the known and expected, mild to moderate, local skin reaction beneath the electrodes.

9.0 OTHER CLINICAL STUDIES

The NovoTTF device has also been studied (in combination with chemotherapy) in two pilot trials in newly diagnosed GBM, and non small cell lung cancer, as described in detail below.

9.1 Effect of NovoTTF-100A on Newly Diagnosed GBM Patients - A Pilot Study

The efficacy and safety of the NovoTTF-100A device in the treatment of GBM also have been evaluated in patients with newly diagnosed GBM in a pilot study (reported in the Proceedings of the National Academy of Science in 2007 [42]).

The study design is similar to that for the pilot study of NovoTTF-100A in the treatment of recurrent GBM (see **Section 6.0** above) and was conducted at the same center during the same years. Ten NovoTTF-100A patients were planned and enrolled in the study. All patients had histologically proven diagnosis of GBM. Patient characteristics at baseline were essentially identical between the NovoTTF-100A treated and retrospectively reviewed comparator group patients.

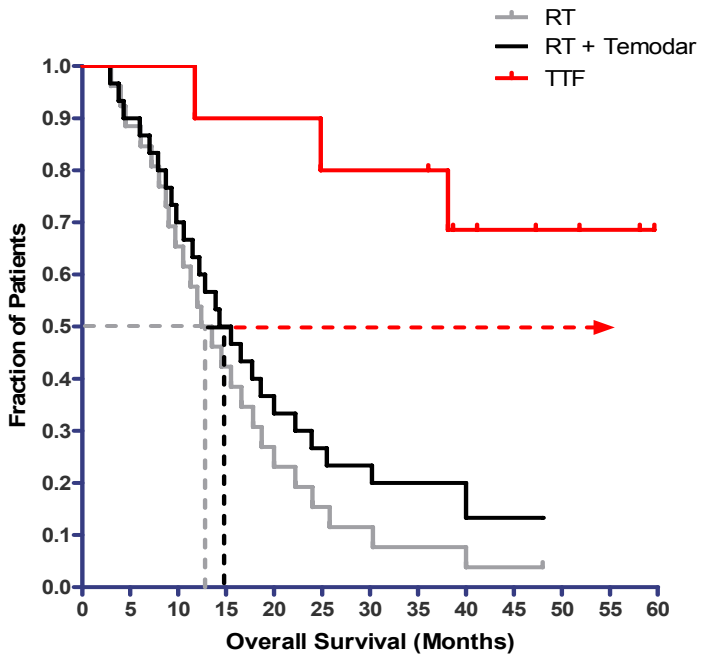
All patients underwent surgery and radiotherapy for the primary tumor prior to study entry. Only one patient had biopsy only. All NovoTTF-100A patients were treated with temozolomide in addition to NovoTTF-100A treatment as maintenance therapy. The NovoTTF-100A treatment consisted of multiple four-week treatment courses with continuous TTFields, 24-hour a day, 200 kHz, 0.7 V/cm.

The NovoTTF-100A patients completed between 1 and 16 treatment courses leading to maximal treatment duration of 15.2 months. Overall, 73 treatment courses were completed (7.3 courses per patient on average). The treatment was well tolerated with no treatment related serious adverse events seen in any of the patients. Compliance with treatment was very high with patients receiving treatment on average 76% of the scheduled time (>18 hours a day on average). Mild to moderate contact dermatitis appeared beneath the electrode gel in 9 of the 10 patients during treatment. The skin reaction improved with use of topical corticosteroids. Regular relocation of the electrode arrays was necessary in order to allow for continuous treatment. One patient discontinued treatment after 2 months of treatment due to the development of delayed hypersensitivity to the hydrogel used for maintaining electrode contact to the scalp. All patients received over 4 weeks of NovoTTF-100A treatment. At the time of progression, two patients presented with left sided Hemiparesis, one patient with a generalized seizure and one patient with headache. None were treatment related.

Progression free survival (PFS) of NovoTTF-100A treated patients was significantly longer than concurrent comparator patients. The median PFS of the patients in this study exceeded a concurrent control group considerably, 155 weeks versus 31 weeks, respectively. The median overall survival was greater than 40 months, compared to 14.7 months reported for temozolomide alone (**Figure 26**; historical comparator group from Stupp et al. NEJM 2005 [1]).

Although the number of patients in this pilot trial is small, the results demonstrated that NovoTTF-100A treatment is highly effective in the treatment of newly diagnosed GBM. The study also reaffirms the excellent safety profile of this treatment modality.

Figure 26 Newly Diagnosed GBM Pilot Study – Overall Survival



9.2 Effect of NovoTTF-100L on Patients with Advanced Non-Small Cell Lung Cancer - A Pilot Study

NovoCure also conducted a pilot study to evaluate the safety and effectiveness of the NovoTTF-100L device in the treatment of advanced non-small cell lung cancer (NSCLC). Results of this study were presented by Pless et al. at the Euorpean Society for Medical Oncology Conference in 2010. This device is very similar to the NovoTTF-100A in that it delivers TTFields regionally (lungs instead of head). The device output settings differ in frequency and intensity from the NovoTTF-100A based on preclinical studies in lung cancer. The NovoTTF-100L operates at 150 kHz and 4000mA p2p in order to allow the same field intensity achieved within the brain with the NovoTTF-100A to be achieved in the lungs (1 V/cm).

The study was a single arm, open label, historically controlled, multi-center trial. The primary endpoints of the trial are safety and progression free survival. Overall survival and response rates are secondary endpoints. Results of the Pemetrexed registration trial [82] were used as historical controls in this trial. The results described below are based on an interim analysis at 6 months after completing recruitment of all patients to the trial.

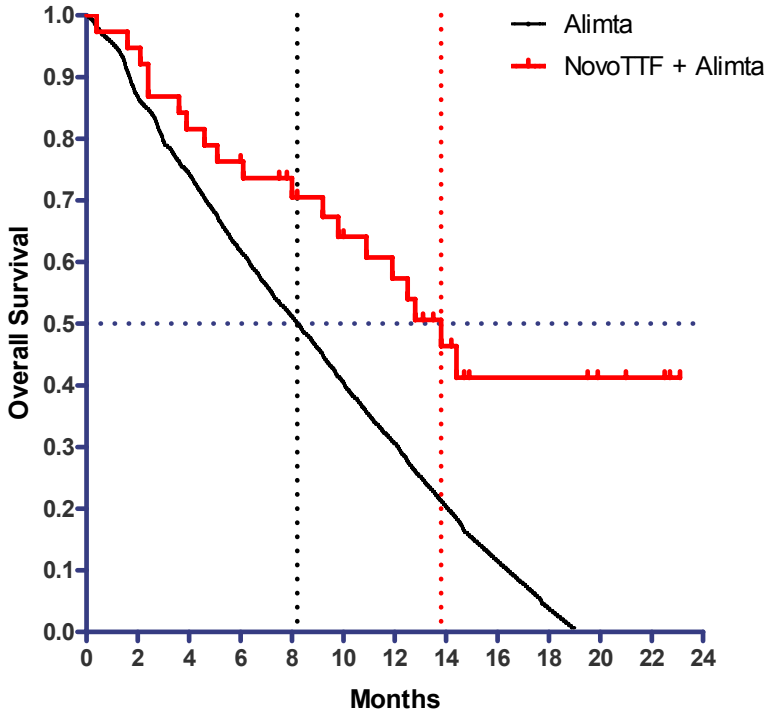
A total of 43 patients were recruited to the study in 4 centers in Switzerland with a minimal follow-up of 6 months. All patients had failed prior chemotherapy before entering the trial. Patients were 18 years of age or older (median 64) and ECOG (Eastern Cooperative Oncology Group) performance 0-2 (median 1). Patients with significant co-morbidities, pregnancy or pacemakers were excluded.

All patients were treated with the NovoTTF-100L device in addition to standard Pemetrexed chemotherapy. Patients received Pemetrexed according to its package labeling (every three weeks) and daily TTFields treatment with the NovoTTF-100L device for an average of 12 hours a day until disease progression.

No systemic adverse events related to the device were seen in any of the patients. The only device related toxicities were mild to moderate local skin damage beneath the ILE electrodes seen in most of the patients. This condition was managed by topical corticosteroids and electrode relocation. In persistent cases, either oral corticosteroids were used or transient treatment breaks were made for several days. No increase was seen in Pemetrexed related adverse events compared to the drug labeling.

Efficacy results based on 41 evaluable patients showed both time to disease progression and overall survival to be significantly increased compared to historical control data (hazard ratio of 0.34 and 0.48, respectively). Median progression free survival in the device group was 28 weeks (compared to 12 weeks in historical controls) and median overall survival was 13.8 months (compared to 8.2 months in historical controls; **Figure 27**).

Figure 27 NovoTTF-100L Pilot Study – Overall Survival*



*Overall survival of NovoTTF-100L treated patients (n=41) was much longer than reported for Alimta (reconstructed from the Alimta package insert). Median OS in NovoTTF-100L treated patients was 13.8 months versus 8.2 months in historical control patients. Dashed lines mark the median values for each curve.

10.0 RISK-BENEFIT ANALYSIS

Recurrent GBM is a fatal, end-stage disease with a 1-year survival of about 10%. 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. When optimally treated, the 4-year survival of GBM patients from initial diagnosis is only 12%, with a median survival of 14.7 months [1]. Overall survival of these patients is currently less than 7 months from first recurrence. Patients with recurrent GBM who have received maximal standard therapy and who have entered clinical trials for investigational therapies have a median survival of 25 weeks and a PFS6 of approximately 15% [2]. Quality of life of recurrent GBM patients is compromised due to the neurological deficits caused by the tumor itself together with the debilitating side effects of the various standard chemotherapies and extreme experimental treatments.

Treatment options for recurrent GBM are extremely limited. These include tumor resection in a minority of cases (with or without Gliadel Wafer implantation), additional radiotherapy boost in selected cases and chemotherapy (including bevacizumab). Surgery is principally a primary therapy; operative intervention for recurrence is possible only in selected cases and is never curative. In fact, in a recent review [3] reporting the re-operation rate of patients with recurrent GBM in a series of 13 studies carried out between 1995 and 2009, the average operation rate for recurrent GBM patients was 20.5±12.8 percent (median ± standard deviation). The effect of reoperation on disease progression and survival is controversial.

Only two treatment options for recurrent GBM have been approved by FDA in the past 15 years. The first, the Gliadel Wafer, which was approved in 1996, offers a reported 1.9 month survival benefit to patients compared to placebo control wafers (6.5 months versus 4.6 months, respectively). However, Gliadel Wafers are available only to about one-fifth of recurrent GBM patients, namely those who are surgical candidates. More recently, bevacizumab (Avastin) was approved for the treatment of recurrent GBM based on two single arm studies comparing radiological endpoints to historical control data [10]. Bevacizumab has been a significant addition to the treatment options for this extremely difficult patient population. However, common side effects of bevacizumab (>10%) include epistaxis, headache, hypertension, rhinitis, proteinuria, taste alteration, dry skin, rectal hemorrhage, lacrimation disorder, back pain and exfoliative dermatitis.

The NovoTTF-100A pivotal trial was a very well designed trial in that it was randomized at a 1:1 ratio versus an active best standard of care chemotherapy control group. The primary endpoint of the trial was the gold standard in oncology trials - overall survival. The trial included all types of recurrent GBM patients. Specifically, the trial enrolled surgical and non-surgical patients, patients with any number recurrence prior to enrollment, patients with any location and tumor size, and finally no specific tumor marker was necessary (e.g., MGMT methylation status, EGFR status, etc.). The control group consisted of the best standard of care chemotherapies available, including Avastin which was allowed in the trial due to its approval by FDA during the trial. The primary endpoint results were homogenously distributed between the different countries where the trial was performed and the different effective chemotherapies used in the trial were poolable.

The results of the pivotal trial clearly demonstrate that NovoTTF-100A is at least as effective as the best standard of care chemotherapy for recurrent GBM. The treatment effect of NovoTTF-100A on overall survival is superior to the effective best standard of care chemotherapy available in the US today when comparing NovoTTF-100A patients who completed at least one treatment course to BSC patients who received any chemotherapy on or off study (median OS 7.8 vs. 6.4 months; Wilcoxon p=0.013), or who received only protocol specified chemotherapies (median OS 7.8 vs. 6.5 months; Wilcoxon p=0.04). In the ITT population, NovoTTF-100A treatment is as effective ("non-inferior") as the BSC treatment; the effect of NovoTTF-100A on overall survival was almost identical

to BSC chemotherapies (median OS 6.3 vs. 6.4 months; HR=1.0; p=0.98). Furthermore, the OS data showed a slight trend in favor of NovoTTF-100A in the US.

In addition, secondary endpoints support the primary efficacy findings. One year survival was identical in both treatment groups in the ITT population (22%). In the PP population 1-year survival was higher in NovoTTF-100A patients (27.8%) than in BSC patients (21.6%). PFS6 was higher in NovoTTF-100A patients than in BSC chemotherapy patients in the ITT population (21.4% vs. 15.2%) and significantly so in the PP population (26.2% vs. 12.7%; chi-square p = 0.0181). Radiological response rate for NovoTTF-100A patients was higher than for BSC chemotherapy patients in the ITT population (14.0% vs. 9.6%) and significantly so in the PP population (15.9% vs. 6.7%; chi-square p=0.0456). Finally, quality of life based on QLQ C-30 and BN-20 questionnaires was improved in NovoTTF-100A patients compared to BSC chemotherapy patients.

The only risk clearly associated with the NovoTTF-100A device is a mild to moderate skin irritation beneath the device electrodes. The trial has also shown a highly significant reduction in the frequency of gastrointestinal, hematological and infectious toxicities with NovoTTF-100A use, which are the hallmark of daily morbidity of cancer patients receiving chemotherapies. Other adverse events seen in the trial were seen at a lower incidence than reported in previous recurrent GBM trials.

NovoCure concludes that the benefits of the NovoTTF-100A device for treatment of recurrent GBM, including comparable efficacy to best available chemotherapies without the severe associated side effects, outweigh the risks, particularly in this very sick population.

11.0 OVERALL CONCLUSIONS

Compared to previous chemotherapy approvals for recurrent GBM, the NovoTTF-100A pivotal trial was very well designed and conducted (randomized control, active control group, multi-center, half of the patients in the US, data poolable between countries, and minimal loss to follow-up). NovoTTF-100A treatment exhibits negligible toxicity, and comparable or better primary and secondary efficacy outcome measures compared to the best available chemotherapies today.

As a well-controlled investigation, the pivotal clinical study of the NovoTTF-100A device constitutes valid scientific evidence, as defined in 21 C.F.R. §860.7(c)(2), upon which the agency can make a determination of the safety and effectiveness of the device. NovoCure believes that the pivotal study results demonstrate a reasonable assurance that the NovoTTF-100A is safe (as defined in 21 C.F.R. §860.7(d)(1)), as the probable benefits to health from use of the device for its intended uses and conditions of use, when accompanied by adequate directions and warnings against unsafe use, outweigh any probable risks. In addition, the study results demonstrate the absence of unreasonable risk of illness or injury associated with the use of the device for its intended uses and conditions of use. NovoCure also believes that the pivotal study provides a reasonable assurance that the NovoTTF-100A is effective (as defined in 21 C.F.R. §860.7(e)(1)) because, in a significant portion of the target population, the use of the device for its intended uses and conditions of use, when accompanied by adequate directions for use and warnings against unsafe use, provides clinically significant results.

For these reasons, the company believes that the clinical data support approval of the NovoTTF-100A device as a treatment for adult patients (greater than 21 years of age) with histologically- or radiologically-confirmed GBM, following recurrence in the supra-tentorial region of the brain, as a monotherapy (after surgical and radiation options have been exhausted) in place of standard medical therapy for GBM. In granting expedited review status for the NovoTTF-100A PMA, the agency has recognized that the condition the NovoTTF-100A device is intended to address (recurrent GBM) is a potentially irreversibly debilitating condition, and that no legally marketed alternative device is currently available. Given the limitations and high toxicity of existing treatment options for recurrent GBM, the NovoTTF-100A will provide an important additional, non-pharmaceutical treatment option for this very sick patient population.

12.0 APPENDICES

The following appendices can be found in **Tab XI**:

Appendix A – Mechanism of Action Animation Video

Appendix B – *In Vitro* Evidence Video of Mechanism of Action

Appendix C – Representative Post Contrast T1 Weighted MRI Images

Appendix D – Recurrent GBM Patient Testimonials

13.0 REFERENCES

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A Prospective, Multi-center Trial of NovoTTF-100A Compared to Best Standard of Care in Patients with Progressive or Recurrent GBM

THERAPEUTIC PROTOCOL

Protocol EF-11

Version 5.1 (November 7th, 2007)

IDE G030181

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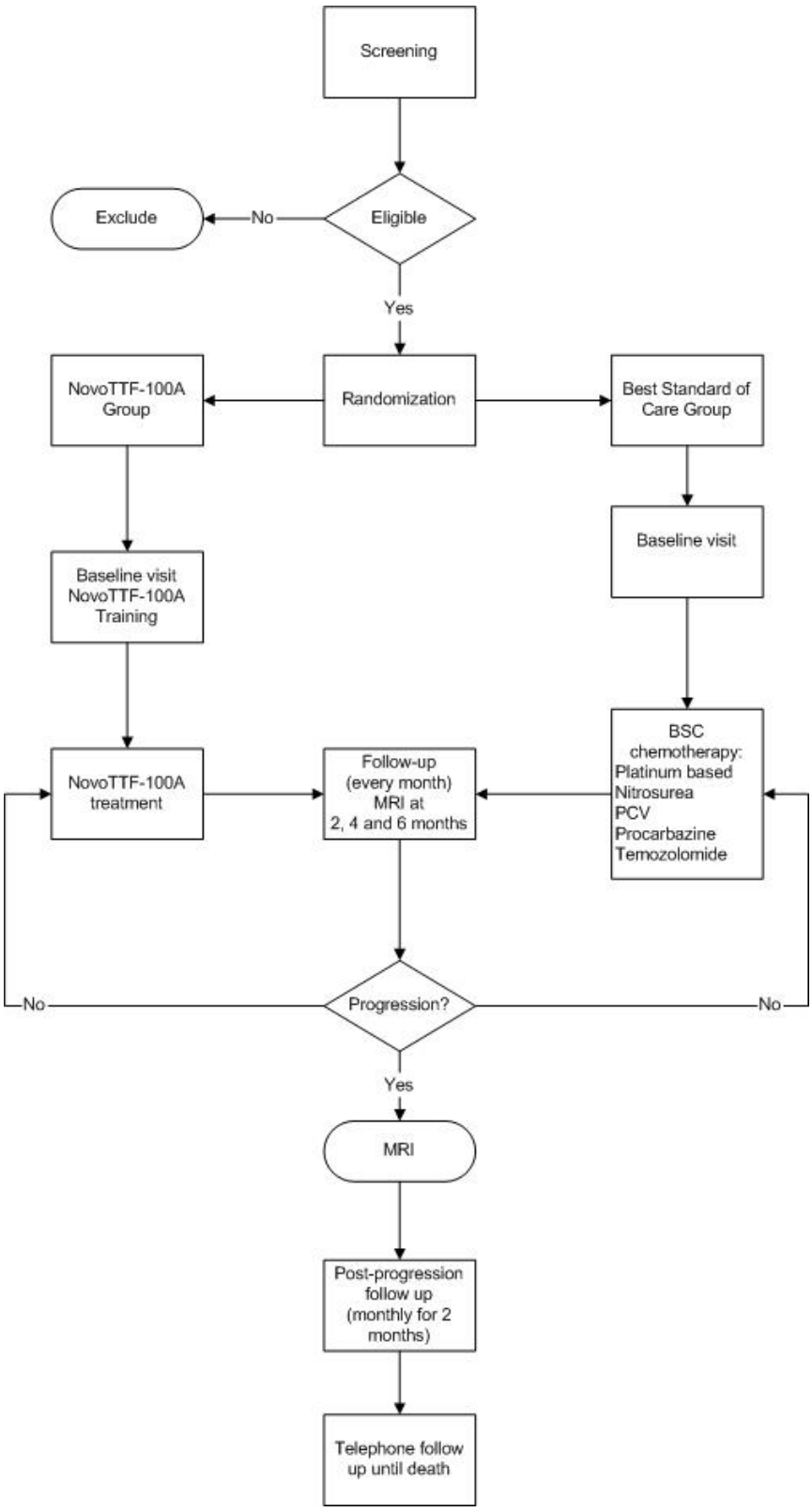
I. PROTOCOL SUMMARY AND SCHEMA

1. SUMMARY

Title:	A Prospective, Randomized, Multi-center Trial of NovoTTF-100A Compared to Best Standard of Care in Patients with Progressive or Recurrent GBM
Device:	NovoTTF-100A
Study Objectives:	To compare the efficacy and safety outcome of recurrent GBM patients treated with NovoTTF-100A to those treated with best standard of care (BSC)
Study Design:	Prospective, Randomized, Open Label, Best Standard of Care Control
Study Hypothesis:	The hypothesis of this study is that NovoTTF-100A will significantly increase median overall survival of recurrent GBM patients compared to patients treated with BSC
Sample Size:	236 patients with progressive or recurrent GBM
Study Population:	Patients with tissue based diagnosis of GBM, above 18 years of age, of both genders, who have recurred or progressed after surgery and radiation therapy
Primary endpoint:	Median overall survival
Secondary endpoints:	• Progression free survival at 6 months (PFS6) • Median Time to Disease Progression (TTP) • % 1-year survival • Radiological response (Macdonald criteria) • Quality of life assessment (EORTC QLQ-C30) • Adverse events severity and frequency
Sponsor:	NovoCure Ltd. POB 15022 MATAM Center Haifa, 31905, Israel

2. PROTOCOL SCHEMA



II. OBJECTIVES AND SCIENTIFIC AIMS

- To prospectively compare the median overall survival of recurrent GBM patients treated with NovoTTF-100A to those treated with best standard of care (BSC)
- To prospectively determine PFS6, TTP, %1-year survival and quality of life (TAB H) of patients treated with the NovoTTF-100A compared to BSC.
- To collect evidence of the safety of TTFields applied to patients with recurrent GBM using the NovoTTF-100A device.
- To compare the median overall survival of recurrent GBM patients treated with NovoTTF-100A to historical control data.

III. BACKGROUND AND RATIONALE

Glioblastoma multiforme (GBM), a malignant form of astrocytoma, is the most common primary intracranial neoplasm. The incidence of GBM increases steadily above 45 years of age with a prevalence of approximately 7500 cases in the USA. Despite numerous attempts to improve the outcome of patients with GBM, the 3-year survival of these patients is only 6% with median survival of 10 months[1].

Patients with recurrent GBM who have received maximal standard therapy and have entered clinical trials for investigational therapies have a median survival of 25 weeks and a median progression free survival of approximately 9 weeks[2]. Thus, there is a critical need for new therapeutic options for treatment of GBM. TTFields are a new experimental modality for the treatment of malignant tumors. Pre-clinical studies[12,22] have shown this treatment modality to effectively inhibit the growth of experimental tumors both in-vitro and in-vivo without any systemic side effects.

There are currently four principal treatment options for GBM: surgical resection, radiotherapy, chemotherapy and/or Gliadel Wafer implantation. Each of these options is briefly described below:

1. Surgical resection - Treatment of patients with GBM usually begins with resection (in conjunction with the biopsy or after it), with maximal debulking of the tumor as the main goal because curative resection is very rare. Surgery is principally a primary therapy; operative intervention for recurrence is possible only in selected cases. The effect of re-operation on disease progression and survival is controversial[27,28].

2. Radiation therapy - Post-surgical radiation therapy has been shown to improve survival, though even with maximal treatment, survival is still limited to several months. Since GBM is a relatively radio-resistant tumor, several approaches have been used to improve its sensitivity. These include sensitizing chemical agents and hyper-fractionated radiation treatments. Although these techniques may offer some benefit in anaplastic astrocytoma, the overall outcome of patients with GBM is not affected. The full standard dose of 60 Gy is given after primary diagnosis such that irradiation for recurrence is usually not possible.

3. Chemotherapy - Chemotherapy following surgery and radiation therapy has been shown to improve survival modestly. Nitrosourea based combination chemotherapy appears to

have a small advantage over monotherapy. Recently, adjuvant Temozolomide treatment has shown modest improvement in time to disease progression (from 5 to 6.9 months) and overall survival (from 12.1 to 14.6 months)[29]. In the past, Temozolomide was approved for recurrent anaplastic astrocytoma[30], but not for recurrent GBM. Since Temozolomide has recently been approved for GBM at primary diagnosis, and has no clinically significant effect on time to disease progression in recurrent GBM (9.1 to 12.4 weeks[23-25] versus 9 weeks in historical control data[2]), it will probably rarely be used for recurrence.

4. GLIADEL® Wafer in combination with surgical resection – Gliadel Wafer delivers carmustine (BCNU) directly to the site of the recurrent brain tumor. The package insert indicates that for recurrent GBM, Gliadel increased mean overall survival from 20 to 28 weeks compared to placebo. No data is presented regarding the effect of Gliadel wafers on progression free survival. This approach, however, necessitates the use of surgical resection for recurrent GBM, which is limited to selected cases, as discussed above.

In conclusion, despite the immense effort made over the years with different treatment modalities, the survival of patients with recurrent GBM is still very poor; no treatment is curative; and the quality of life of patients with this tumor is compromised significantly, not only by their disease but also by side effects of these rigorous treatment plans. A treatment modality is needed that will show similar or better results than standard treatments while allowing this population the benefit of improved quality of life for their limited life span.

Introduction to electric fields

In the laboratory setting and in clinical practice, alternating electric fields show a wide range of effects on living tissues. At very low frequencies (under 1 kHz), alternating electric fields stimulate excitable tissues through membrane depolarisation[3]. The transmission of such fields by radiation is insignificant and therefore they are usually applied directly by contact electrodes, though some applications have also used insulated electrodes. Some well known examples of such effects include nerve, muscle and heart stimulation by alternating electric fields[3,4]. In addition, low frequency pulsed electric fields have been claimed to stimulate bone growth and accelerate fracture healing[5]. However, as the frequency of the alternating electric field increases above 1 kHz, the stimulatory effect diminishes. Under these conditions although a greater fraction of the fields penetrates the cells, due to the parallel resistor-capacitor nature of all biological membranes, the stimulatory power greatly diminishes as the alternating cell membrane hyper –depolarization cycles are integrated such that the net effect is nulled.

At very high frequencies (i.e., above many MHz), while the integration becomes even more effective, a completely different biological effect is observed. At these frequencies tissue heating becomes dominant due to dielectric losses. This effect becomes more intense as field intensity or tissue dissipation factor increase[6]. This phenomenon serves as the basis for some commonly used medical treatment modalities including diathermy and radio frequency tumor ablation, which can be applied through insulated electrodes[7].

Intermediate frequency electric fields (i.e., tens of kHz to MHz), alternate too fast for causing nerve-muscle stimulation and involve only minute dielectric losses (heating). Such fields, of low to moderate intensities, are commonly considered to have no biological effect[6]. However, a number of non-thermal effects, of minor biological consequence, have been reported even at low field intensities. These include microscopic particle alignment (i.e., the pearl chain effect[8]) and cell rotation[9,10]. With pulsed relatively strong electric fields, > 10^3 V/cm and 100 ms pulse length, reversible pore formation appears in the cell membrane, a phenomenon usually called electroporation[11].

NovoCure's Tumor treating electric fields (*TTFields*)

NovoCure has shown[12] that when properly tuned, very low intensity, intermediate frequency electric fields (TTFields) stunt the growth of tumor cells. This inhibitory effect was demonstrated in all proliferating cell types tested, whereas, non-proliferating cells and tissues were unaffected. Interestingly, different cell types showed specific intensity and frequency dependences of TTField inhibition. It has been shown that two main processes occur at the cellular level during exposure to TTFields: arrest of proliferation and dividing cell destruction. The damage caused by TTFields to these replicating cells was dependent on the orientation of the division process in relation to the field vectors, indicating that this effect is non-thermal. Indeed, temperature measurements made within culture dishes during treatment and on the skin above treated tumors in-vivo, showed no significant elevation in temperature compared to control cultures/mice. Also, TTFields caused the dividing cells to orient in the direction of the applied field in a manner similar to that described in cultured human corneal epithelial cells exposed to constant electric fields[13]. At the sub-cellular level it was found that TTFields disrupt the normal polymerization-depolymerization process of microtubules during mitosis. Indeed, the described abnormal mitotic configurations seen after exposure to TTFields are similar to the morphological abnormalities seen in cells treated with agents that interfere directly[14,15] or indirectly[16-18] with microtubule polymerization (e.g., Taxol).

Modeling the mechanism of action of *TTFields*

In order to explain how TTFields cause orientation dependent damage to dividing cells and disrupt the proper formation of the mitotic spindle NovoCure modeled the forces exerted by TTFields on intracellular charges and polar particles using finite element simulations. Two main mechanisms by means of which the electric fields may affect dividing cells were recognized. The first relates to the field effect on polar macromolecule orientation. Within this framework, during the early phases of mitosis, i.e., in pre-telophase, when tubulin polymerization-depolymerization drives the proliferation process, the electric field forces any tubulin dimers, positioned further than 14nm away from the growing end of a microtubule, to orient in the direction of the field. This force moment, (10^{-5} pN) acting on the dimers, is sufficient to interfere with the proper process of assembly and disassembly of microtubules that is essential for chromosome alignment and separation[19]. This effect can explain the mitotic arrest of TTField treated cells[20].

The second mechanism, which interferes with cell division, and is most likely to play an important role in cell destruction, becomes dominant during cleavage. As seen in simulations, the electric field within quiescent cells is homogenous, whereas the field inside mitotic cells, during cytokinesis, is not homogenous. An increased field line concentration (indicating increased field

intensity) is seen at the furrow, a phenomenon that highly resembles the focusing of a light beam by a lens. This in-homogeneity in field intensity exerts a unidirectional electric force, on all intracellular charged and polar entities (including induced dipoles), pulling them towards the furrow (regardless of field polarity). For example, for a cleavage furrow that reached a diameter of 1μm in an external field of only 1 V/cm, the force exerted on the microtubules is in the order of 5pN. This magnitude is compatible with the reported forces necessary to stall microtubule polymerization which is 4.3 pN[21]. With regards to other particles, such as cytoplasmatic organelles, they are polarized by the field within dividing cells. Once polarized, the forces acting on such particles may reach values up to an order of 60 pN resulting in their movement towards the furrow at velocities that may approach 0.03 μm/sec. At such velocity, cytoplasmatic organelles would pile up at the cleavage furrow within a few minutes, interfering with cytokinesis and possibly leading to cell destruction. It has also been found that the electric forces acting on intracellular particles are maximal when the axis of division is aligned with the external field. This is consistent with the dependence of the destructive effect of TTFields on the angle between division axis and the field, as demonstrated experimentally. In addition, the calculated dependence of the magnitude of this force on frequency is consistent with the experimentally determined frequency dependence of the inhibitory effect of TTFields on melanoma and glioma cell proliferation (120 kHz vs. 200 kHz, respectively).

In Vivo effects of TTFields

NovoCure has shown[22] that TTFields can be applied effectively to animals through electrodes placed on the surface of the body. Using a special type of electrically insulated electrodes, 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. This growth inhibition was accompanied by a decrease in angiogenesis within the tumor, due to inhibition of endothelial cell proliferation.

Extensive safety studies in healthy rabbits and rats exposed to TTFields for protracted periods of time have shown no treatment related side effects. The reasons for the surprisingly low toxicity of TTField treatment can be explained in the light of the known passive electric properties of normal tissues within the body and the effects of electric fields applied via insulated electrodes. More specifically, two types of toxicities may be expected in an electric field based treatment modality. First, the fields could interfere with the normal function of excitable tissues within the body causing, in extreme cases, cardiac arrhythmias and seizures. However this is not truly a concern with TTFields since, as frequencies increase above 1 kHz, excitation by sinusoidal electric fields decreases dramatically due to the parallel resistor-capacitor nature of the cell membrane (with a time constant of about 1ms). Thus, as expected, in both acute and chronic application of TTFields to healthy animals, no evidence of abnormal cardiac rhythms or pathologic neurological activity was seen.

Secondly, the anti-mitotic effect of TTFields might be expected to damage the replication of rapidly dividing normal cells within the body (bone marrow, small intestine mucosa). Surprisingly, no treatment related toxicities were found in any of the animal safety trials performed by NovoCure, even when field intensities 3 fold higher than the effective anti-tumoral dose were used. The lack of damage to intestinal mucosa in TTField-treated animals is probably a reflection of the fact that the small intestine mucosal cells have a slower replication cycle than

neoplastic cells and that the intestine itself most likely changes its orientation in relation to the applied field quite often, lowering the efficacy of TTField mediated mitotic disruption. Bone marrow, on the other hand, is naturally protected from TTFields by the high electric resistance of both bone and bone marrow compared to most other tissues in the body. To test the later assumption, the TTField intensity within the bone marrow of a long bone was modeled using the finite element mesh (FEM) method. It was found that the intensity of TTFields was 100-fold lower within the bone marrow compared to the surrounding tissues (including within solid tumors). Thus, hematopoietic cell replication should not be affected even when TTField intensities 10-fold higher than necessary to inhibit tumor growth are applied.

The NovoTTF-100A Device

The NovoTTF-100A device is a portable battery operated device which produces TTFields within the human body by means of surface electrodes. The TTFields are applied to the patient by means of surface electrodes that are electrically insulated, so that resistively coupled electric currents are not delivered to the patient. The electrodes are placed on the patient's shaved head over a layer of adhesive hydrogel and held in place with hypoallergenic plasters. The gel beneath the electrodes must be replaced every three to four days and the scalp re-shaved in order to maintain optimal capacitative coupling between the electrodes and the patient head. All the treatment parameters are pre-set by NovoCure so there are no electrical output adjustments available to the patient. The patient must learn to change and recharge depleted device batteries and to connect to an external battery pack overnight.

Effect of NovoTTF-100A on recurrent GBM patients – clinical pilot study

A pilot study was performed so far on ten recurrent GBM patients treated with the NovoTTF-100A device. All patients underwent surgery and radiotherapy for the primary tumor. Only 1 patient was chemotherapy naïve, the rest having received either Temozolomide or other chemotherapeutic agents, as adjuvant treatment, prior to recurrence.

All patients were treated with multiple four-week treatment courses using continuous, 24-hour a day, 200 kHz, 0.7 V/cm TTFields. TTFields were applied through two sets of opposing insulated electrode arrays and alternated at a 1 second duty cycle between two perpendicular field directions through the tumor. Patients completed between 1 and 13 treatment courses leading to maximal treatment duration of 14.5 months. Overall, more than 65, 4 week treatment courses were completed to date (> 6.7 courses per patient on average).

The treatment was well tolerated with no treatment related serious adverse events seen in any of the patients. Patients received treatment on average about three quarters of the scheduled time. Considering the continuous nature of NovoTTF treatment (i.e., 24 hours a day for many months) this figure indicates that compliance with treatment was very high, with patients taking very few days off treatment and stopping only for short periods of time during treatment for personal needs.

Mild to moderate contact dermatitis appeared beneath the electrode gel in 8 of the 10 patients 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. Regular relocation of the electrode arrays was necessary in order to allow for continuous treatment.

The median progression free survival (PFS) of the patients in this study exceeded historical controls[2] dramatically (25 weeks versus 9 weeks, respectively). The PFS at 6 months (PFS6) is currently 50% compared to 15% in historical controls[2]. So far 4 of the 10 patients have died. The remaining 6 patients are still alive and 3 of them are progression free. Median overall survival is greater than 53 weeks. Response rate was 25% (1 CR + 1 PR) and only two patients had progressive disease despite treatment.

Although the number of patients in this pilot trial is small, the excellent safety profile of this treatment modality and the highly promising efficacy data gathered so far indicate the potential of NovoTTF-100A treatment as an effective therapy for recurrent GBM patients.

Effect of NovoTTF-100A on patients with locally advanced and/or metastatic solid tumors – a phase I study

Six patients with locally advanced or metastatic solid tumors were treated so far with the NovoTTF-100A device in this study. The first two patients, who suffered from metastatic skin lesions, were treated for two weeks using 100 kHz TTFields. The third patient, who suffered from an advanced pleural mesothelioma, was treated for four weeks using 120 kHz TTFields. The fourth patient, who also suffered from metastatic skin lesions, was treated continuously for 4 weeks using 100 kHz TTFields. The fifth patient having a rapidly progressive GBM was treated for four weeks using 200 kHz, 3 directional fields. Finally, the sixth patient who also had metastatic skin tumors was treated for six weeks using 100 kHz TTFields until systemic progression.

The treatment was well tolerated with no treatment related serious adverse events in any patient. Two patients developed mild skin reactions to the electrode hydrogel and the medical grade plasters used to fix the electrodes to the torso. All other adverse events were related either to concomitant medication or disease progression.

In the first two patients, previously progressive lesions were stabilized for two to three weeks and then resumed growth. In the third patient, local minimal regression of the mesothelioma was seen in the treated area (the abdomen) while in the chest and pelvis the disease was stable and progressive, respectively. The fourth patient showed a partial response to treatment with a 51% decrease in tumor area after 4 weeks of treatment. The fifth patient progressed during treatment. Finally, the sixth patient showed a 20% decrease in tumor size before systemic progression occurred.

These results indicate the complete lack of systemic toxicity of NovoTTF-100A treatment when applied to the head, chest, abdomen, and limbs of advanced cancer patients. In addition, promising initial efficacy results were observed in these patients.

IV. STUDY DESIGN

A prospective, randomly controlled pivotal study will be conducted on 236 patients with previously diagnosed GBM who have relapsed or progressed despite conventional therapy (surgery and radiation therapy). The control group will receive the best standard of care (BSC) practiced at each of the participating centers for recurrent GBM patients. Sample size was chosen assuming patients treated with the NovoTTF-100A will have a median overall survival time significantly greater than BSC controls (48 weeks compared to 30 weeks, respectively; with a significance level of 0.0475 and power of 0.80).

Progression free survival at 6 months will be compared between the two groups as a secondary endpoint. The following will be considered disease progression for determination of TTP (based on the Macdonald criteria; Tab D):

1. Tumor growth > 25% compared to the smallest tumor area measured in this patient during the trial.
2. Appearance of 1 or more new tumors in the brain (diagnosed radiologically as GBM).
3. New neurological symptoms which are correlated with radiological findings on contrast MRI of the head.

Final determination of progression will be made by CORE radiology review, in cases where an MRI is available (which should be the great majority of cases). In cases where an MRI is not available, clinical progression will be diagnosed according to the following criteria:

1. Decline in functional status as indicated by a decrease in KPS of > 10, and
2. Decline in neurological function as indicated by a decrease of 2 points or more in MRC scale (TAB I), and
3. ≥50% increase in steroid dose.

Since CORE MRI review will not be immediately available, the determination of whether to stop treatment due to progression will be based on the investigator's evaluation. Guidance given to investigators includes continuing treatment until known clinical progression based on the MacDonald criteria, as set forth above, even if there is a suspicion of progression according to the local MRI reading. In all cases, prior to stopping treatment, the investigator will confer with the trial PIs (Dr. Gutin for US centers; Dr. Stupp for European centers). This will avoid stopping treatment too early in the case of an error in local interpretation of the MRI.

Patients will be recruited to the study by the principal investigator (PI) or one of the co-investigators (CI) in twenty three centers (at least 14 centers will be in the USA and the remainder in Europe). Immediately following screening, patients will be randomized at a 1:1 ratio to receive either NovoTTF-100A treatment or the BSC practiced at the participating centers.

Patient accrual is expected to continue for 18 months based on an estimated recruitment rate of GBM patients at approximately 1 patient every 2 months per center. Patient follow up will continue until 6 months from accrual of the last patient in each center. Analyses will be performed at two time points. The first analysis will be conducted after about 15 months from initiation of accrual based on approximately 132 patients. The final analysis (after about 2 years

from initiation of accrual) will compare the median overall survival among all study patients. In order to allow for two analyses in the trial the alpha level used at each time point will be calculated based on the O'Brien-Fleming method[31,36] (i.e., approximately 0.0105, depending on the sample size, at the interim analysis and 0.0475 at the final analysis).

Treatment arm

At treatment initiation patients will be hospitalized for 24 hours. During this period baseline examinations will be performed and NovoTTF-100A treatment will be initiated under continuous medical supervision. The patients will also be instructed on the operation of the NovoTTF-100A and battery replacement. Once the patients are trained in operating the device they will be released to continue treatment at home. The patients will receive multiple four-week courses of continuous NovoTTF-100A treatment. Treatment will be stopped in the case of treatment related serious adverse events or clinical disease progression.

Control arm

All patients will have baseline examinations performed prior to treatment initiation. Patients will receive the best standard of care practiced at each of the participating centers. The BSC will be comprised of one of the following chemotherapies:

1. Platinum based chemotherapy (Carboplatin)
2. Nitrosureas (BCNU)
3. Procarbazine
4. Procarbazine, lomustine and vincristine (PCV)
5. Temozolomide

Treatment protocol will be according to standard procedures at each of the participating centers.

Follow-up Evaluations

During treatment, and until progression for patients who stopped treatment before progression, all patients will be seen once every month at an outpatient clinic where they will undergo medical follow-up and routine laboratory exams. An MRI will be performed after 2, 4 and 6 months from initiation of treatment. In the case of clinical progression an additional MRI will be obtained within 1 week of the investigator becoming aware of the clinical progression. In patients where clinical progression occurs before 6 months from treatment initiation, no additional MRIs will be required after clinical progression. Central MRI review will be performed by a neuro-radiologist blinded to the treatment group of each patient. Medical follow-up will continue for 2 months after disease progression. Since all patients will have progressed already at this stage, patient mortality will be assessed based on monthly telephone interviews with the patients' caregivers.

Core MRI review

All MRI's will be sent to an independent radiologist, blinded to the treatment groups of the patients. Either digital (DICOM) images or analog films can be used for this purpose. Contrast agent and dose per body weight must be kept constant between scans for each patient.

V. CRITERIA FOR PATIENT ELIGIBILITY

Any patient with a histological diagnosis of GBM who has suffered a recurrence despite standard therapy (surgery/biopsy, 45-60Gy radiation therapy), and meets all of the specific eligibility criteria listed below may by enrolled on this study. Operable patients must undergo surgery for recurrence prior to randomization. Patients receiving steroids to control edema may be included in the trial, however, any change in steroid dose must be documented during the follow-up visits. An increase in steroid dose will preclude a diagnosis of partial or complete response (as suggested by Macdonald et al; TAB D)

1) PATIENT 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. Patients 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 patients must sign written informed consent.

2) PATIENT 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)

VI. RECRUITMENT PLAN

Patients will be recruited to this study from either the outpatient clinic or inpatient hospital setting at each center. All patients will be seen by the corresponding investigator. Every effort will be made to encourage eligible women and minorities to participate. All patients will be required to sign a written informed consent prior to being registered on this protocol. Every effort will be made to answer questions raised by the patient and their family or advocate regarding the protocol and alternative therapies prior to asking the patient to sign the consent form.

VII. RANDOMIZATION

Patients who meet the above inclusion/exclusion criteria will be randomized by a computer program either to the treatment group who will receive NovoTTF-100A treatment, or to the BSC group who will receive the best standard of care as practiced at each of the participating centers. Randomization will be performed after stratification into patients who did or did not undergo re-operation for their recurrence. This will avoid unequal distribution of operated patients in both groups.

VIII. PRE-TREATMENT EVALUATION (TAB A)

Prior to beginning treatment all patients will undergo the following studies:

- Baseline contrast enhanced MRI of the brain.
- ECG
- Complete physical examination
- Neurological status and KPS (Karnofsky performance scale).
- Complete blood count (CBC) and differential
- Biochemistry panel (Electrolytes, BUN, creatinine, bilirubin, liver enzymes, albumin, total protein, glucose, cholesterol)
- Coagulation study (PTT, INR)
- Quality of life questionnaire (EORTC QLQ-C30)

IX. TREATMENT PLAN – NOVOTTF-100A GROUP

All patients will be hospitalized within 1 week from baseline evaluation for 24 hours during which NovoTTF-100A treatment will be initiated as described in the Investigator's Brochure, as follows:

"Treatment will be initiated in the hospital by the investigator at each center. In addition to clinical evaluation (as elaborated in section VIII), the investigator will perform the following actions for the treatment arm patients:

- Train the patient in using the device:
    - Battery replacement and recharging
    - Turning the device on and off
    - Disconnecting and reconnecting the electrodes from the device for personal needs
    - How to handle device error messages (see trouble shooting section in User manual)
    - What adverse events can be expected during treatment.
    - How to handle irritated skin
    - What to do in case of new or worsening clinical signs (call investigator)
- Review the baseline MRI and decide where to place the electrodes (according to the guidelines elaborated in section X below).
- Shave the patients scalp (can be performed by other medical staff in the hospital)
- Place the electrodes
- Connect the electrodes to the device (through the connection cable)
- Turn on the device."

The device will be set in advance by a device technician with the following treatment parameters:

- Frequency – 200 kHz
- Output current – 707 mA RMS
- Number of field directions – 2
- Duty cycle – 1 sec in each direction

The patients will continue treatment at home after their initial 24 hour hospitalization, provided that there are no serious adverse events within the first 24 hours.

The treatment group patients will receive multiple four-week courses of continuous NovoTTF-100A treatment. The decision to add each additional treatment course will depend on the lack of treatment related serious adverse events which reappear upon re-challenge and lack of clinical disease progression. As described in the Investigator's Brochure: "After initiation of treatment by

the physician during the first 24 hour hospitalization, maintenance of NovoTTF-100A treatment is performed by technicians trained by the sponsor. All technical aspects of the treatment are handled by these technicians at technical clinics. Technical clinics are situated in close proximity to each center. Patients in the treatment arm report to these clinics twice per week for treatment maintenance and immediately following a monthly follow up visit (to replace the electrodes). The following actions are performed by the technician:

- Periodic electrode replacement (twice per week) – patients will come to technical clinics for this purpose. Electrodes will be placed in the same locations every time, according to the locations originally decided upon by the investigator during treatment initiation.
- Periodic download of device log (once every 2 weeks)
- Replacement of faulty equipment
- Device, electrode and accessory accountability tracking, and requests for replacements from NovoCure
- Problem solving – by phone between visits to the technical clinic or directly during these visits. "
- "For technical support the patient will contact the local technical clinic. A list of clinics and their contact information will be supplied to the patients separately. If the patient is unable to get a hold of the local device technician or if the patient has a technical problems with the device beyond working hours he/she should call the following Toll free number for NovoCure's international support center: 800 - NOVOCURE."

During treatment the patient will be permitted to interrupt treatment for periods of up to an hour twice a day for personal needs. Any pause in treatment beyond this must be coordinated in advance with the principal investigator or one of the co-investigators. Patients will be allowed an additional 1-3 days off treatment between courses according to personal needs.

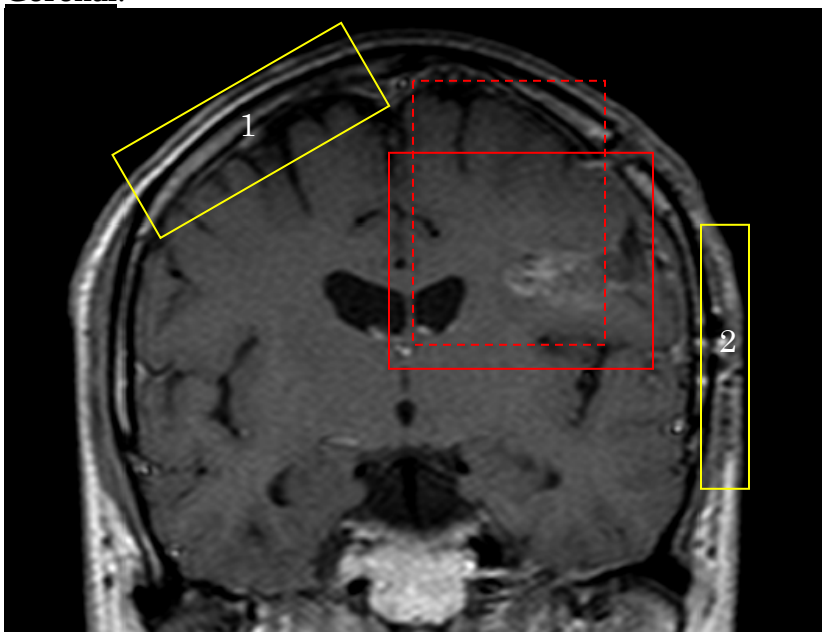
Once per month, until disease progression, all patients will report to an outpatient clinic where they will be assessed clinically and undergo routine laboratory examinations. The follow-up window for these visits is +/- 7 days if the visit occurs prior to the 6 month follow-up window and +/- 14 days on or after the 6 month visit window. During these visits the investigator will remove the electrodes and examine the skin beneath them. Electrode replacement will be performed at the local technical clinic after the follow-up visit. Medical follow-up and routine laboratory exams for all patients will continue once per month for 2 months following progression. After this post-progression follow up period, patients will be followed by telephone interview until death.

X. ELECTRODE PLACEMENT PROTOCOL:

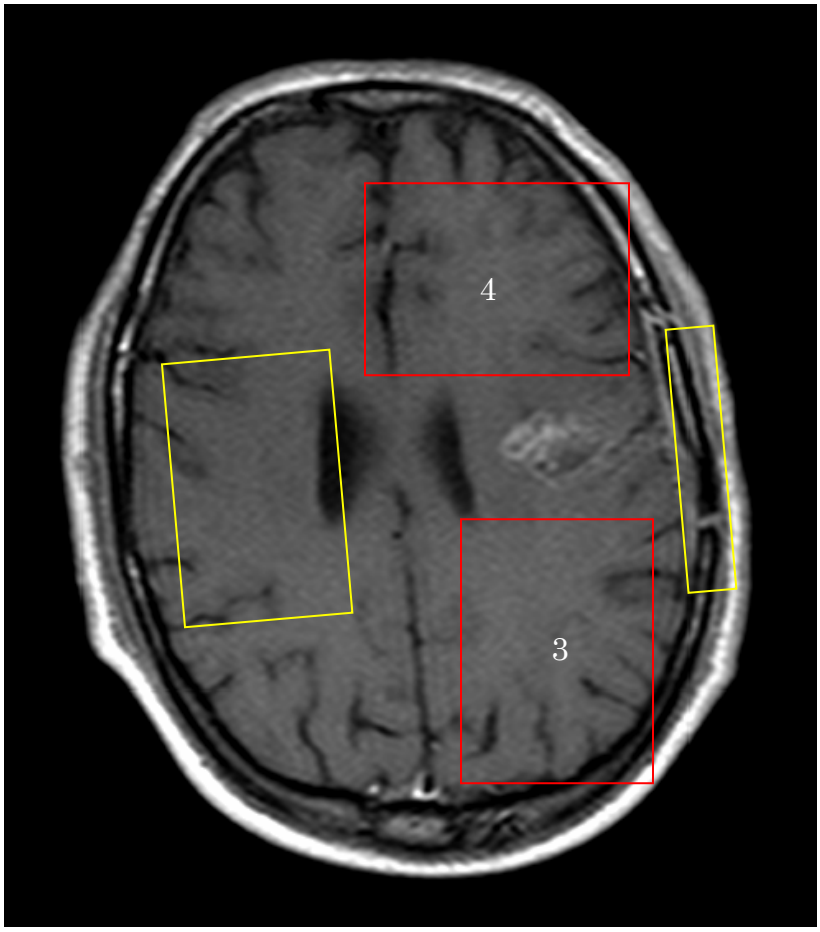
The specific locations of each electrode set will be determined by the treating investigator according to tumor location as follows: the electrode locations will be determined so as to minimize the distance between each electrode set and the center of the tumor, while maintaining a distance of at least one tumor diameter between the electrode sets. This means that the closer the tumor is to the calvarium, the closer the electrode sets will be to each other, and the closer the tumor is to the center of the brain, the further the electrode sets will be from each other. At all times a right angle will be maintained between the imaginary lines connecting each pair of electrode sets.

{Example: Direction 1 = set 1 versus set 2; Direction 2 = set 3 versus set 4**}**

Coronal:



Horizontal:



XI. EVALUATION DURING NOVOTTF-100A TREATMENT

During electrode gel replacement, the skin below the electrode will be inspected by the physician (during follow up visits) and by the patient himself or herself (at home or technical center). In the event of significant skin breakdown (leading to pain or bleeding) or evidence of infection, the electrode will be moved to an alternate site. Skin breakdown and/or infection will be treated according to the treating physician's clinical judgment based on a dermatologist's recommendation. Skin breakdown or evidence of infection, either of which requires a break in NovoTTF-100A treatment greater than 3 days, will be captured as an Adverse Event. Mild to moderate contact dermatitis is expected to appear beneath the electrode gel during the first or second treatment course. This condition will be treated as follows:

1. Electrode location will be shifted between two alternate sites at every electrode gel change.
2. Topical corticosteroids (0.1% Hydrocortisone cream) will be applied to the inflamed area.
3. Oral antihistamines and analgesics will be prescribed at the treating physician's discretion to control pruritus and pain.

XII. TREATMENT PLAN – BEST STANDARD OF CARE GROUP

Patients randomized to the BSC group will be treated with one of the following chemotherapies according to the BSC practiced at each center. The following are representative agents and dosing regimens for this group:

- Platinum based chemotherapy:
  - Carboplatin – 300 mg/m^2 IV on day 1 every 4 weeks for six cycles.
- Nitrosureas:
  - BCNU – 150-200 mg/m^2 IV every 8 weeks, for a maximum of 6 cycles..
- Procarbazine
  - Dose – 150 mg/m^2/day PO or 125 mg/m^2/day PO (prior chemotherapy) for 28 days, repeated every 56 days, until tumor progression.
- Procarbazine, lomustine and vincristine
  - Dose – CCNU (110 mg/m^2) on Day 1, procarbazine (60 mg/m^2) daily for 14 days beginning on Day 8, and vincristine (1.4 mg/m^2) on Days 8 and 29 of each 6-week cycle of therapy. Repeat until tumor progression
- Temozolomide
  - Dose – 150 – 200mg/m^2 daily for 5 days, repeated every 28 days

Patients who have already failed on one of the above treatments will not be offered the same treatment again with either the same agent or an agent from the same group (e.g., patients who have had Gliadel wafers implanted at primary diagnosis will not receive Nitrosureas; patients who received Temozolomide for their primary GBM will not be offered Temozolomide again). Patients may be moved from one BSC treatment to another due to adverse events. The exact treatment protocol and treatment specific follow-up will be performed according to the

standard procedures carried out at each center. All the patients will also adhere to the study specific follow-up protocol as detailed below. All attempts will be made to combine trial follow up examinations with standard follow up visits indicated by the specific treatment regimen chosen.

XIII. PERIODIC EVALUATION UNTIL DISEASE PROGRESSION

Patients in both groups will undergo the following studies or review every month until disease progression:

- Physical examination
- Neurological status
- Quality of life questionnaire (EORTC QLQ-C30) – every three months until progression
- ECG
- Blood exams (CBC, Chemistry, Coagulation)
- Steroid dose
- Record of Adverse Events

The patients will have a contrast MRI of the head performed after 2, 4 and 6 months of treatment. In case of clinical progression an MRI will be performed as soon as possible. Contrast agent type and dose will be kept constant for each patient between scans. Central MRI review will be performed by a neuroradiologist blinded to the treatment group of each patient.
Treatment will be continued until disease progression. In the event of treatment termination due to treatment related SAE which precludes further treatment, the same follow-up examinations will be performed every month until disease progression. Disease progression, tumor size, mortality and adverse events will be documented on the case report forms.

XIV. POST-PROGRESSION EVALUATION

After disease progression the patient will be seen at an outpatient clinic once per month for two additional months. Physical and neurological examination, blood tests (CBC and Chemistry panel) and ECG will be performed during these visits. Patient mortality and adverse events will be documented on the case report forms. After the two post progression monthly follow up visits, patients will not be required to return to the clinic for follow-up but will be followed monthly until death by telephone to monitor their status.

XV. POTENTIAL ADVERSE EFFECTS

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

- Local warmth and tingling sensation beneath the electrodes
- Allergic reaction to the plaster or to the gel
- Skin breakdown
- Infection at the sites of electrode contact with the skin
- Electrode overheating leading to pain and/or local skin burns
- Headache

- Fatigue
- Seizure

Treatment with platinum based chemotherapy commonly (>30%) causes the following adverse events:

- Leukopenia
- Anemia
- Thrombocytopenia
- Nausea and vomiting
- Electrolyte disturbances
- Renal toxicity

Treatment with nitrosurea based chemotherapy commonly (>30%) causes the following adverse events:

- Leukopenia
- Thrombocytopenia
- Nausea and vomiting
- Pain or burning at administration site, usually associated with rapid infusion rate
- Redness of face, skin flushing, usually associated with rapid infusion rate

Treatment with procarbazine commonly (>30%) causes the following adverse events:

- Leukopenia
- Anemia
- Thrombocytopenia
- Nausea and vomiting
- Loss of appetite

Treatment with PCV can cause the side effects seen with each of the individual components.

Treatment with temozolomide commonly (>30%) causes the following adverse events:

- Leukopenia
- Headache
- Fatigue
- Nausea
- Vomiting or Constipation

Adverse events and complications associated with the underlying GBM disease process, which are unlikely but unknown if related to treatment with the NovoTTF-100A include the following adverse events:

- Seizure, including status epilepticus
- Neurological and functional decline
- Headaches, nausea and/or vomiting
- Death

The above provides the principal adverse events associated with the various BSC therapies. A complete listing of adverse events for these therapies are available in their respective package inserts.

XVI. ADVERSE EVENT REPORTING

Definition of Adverse Events

As defined by the ICH Guidelines for Good Clinical Practice E2A (CPMP/ICH/377/95), an adverse event (AE) is any untoward medical occurrence in a patient administered a medicinal product and which does not necessarily have to have a causal relationship with this treatment. An adverse event can therefore be any unfavorable and unintended sign (for example, an abnormal laboratory finding), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to this medicinal product. Adverse events include the following:

- All suspected medication adverse reactions
- All reactions from medication overdose, abuse, withdrawal, sensitivity, or toxicity.
- Apparently unrelated illnesses, including the worsening of a preexisting illness
- Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (a fall secondary to dizziness), the medical condition (dizziness) and the accident (fall) should be reported as 2 separate adverse events.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test).
- Laboratory abnormalities that require clinical intervention or further investigation (beyond ordering a repeat [confirmatory] test) unless they are associated with an already reported clinical event. Laboratory abnormalities associated with a clinical event (elevated liver enzymes in a patient with jaundice) should be captured in the source documents.

Each adverse event is to be classified by the investigator as serious or non-serious. This classification of the gravity of the event determines the reporting procedures to be followed.

Grading of an Adverse Event:

The descriptions and grading scales found in the revised NCI Common Toxicity Criteria (CTC) version 3.0 will be utilized for assessing severity of adverse events. If the toxicity is not characterized adequately by the NCI toxicity scale, the investigator will use the adjectives MILD, MODERATE, SEVERE to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

MILD	Grade 1	Transient or minimal symptoms, no change in activity or need for medication
MODERATE	Grade 2	Symptomatic change, interferes to some extent with patient's usual function
SEVERE	Grade 3	Incapacitating, significantly interferes with patient's usual function

Determination of Causality of Adverse Events

The relationship of the adverse event to the study treatment must be specified using the following definitions:

None:	The event is clearly related to an event that may be due to environmental or accidental occurrence or other factors such as the subject's clinical state, therapeutic interventions, or concomitant drugs administered to the subject.
Unlikely	The event is most likely produced by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject, **and** does not follow a known response pattern to the study drug or device.
Possible	The event follows a reasonable temporal sequence from the time of drug administration or use of device, **and/or** follows a known response pattern to the study drug or device, **but** could have been produced by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject.
Probable	The event follows a reasonable temporal sequence from the time of drug administration or use of device, **and** follows a known response pattern to the study drug or device, **and** cannot be reasonably explained by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject.
Definite	The event follows a reasonable temporal sequence from the time of drug administration or use of device, **and** follows a known response pattern to the study drug or device, **and** cannot be reasonably explained by other factors such as the subject's clinical condition, therapeutic interventions, or concomitant drugs administered to the subject, **and either** occurs immediately following study drug administration or use of device **or** improves on stopping the study drug or device, **or** reappears on repeat exposure

Serious Adverse Events

An adverse event that meets one or more of the following criteria/outcomes is classified as serious:

Death
Life-threatening (i.e., at immediate risk of death)
Inpatient hospitalization or prolongation of existing hospitalization
Persistent or significant disability/incapacity
Congenital anomaly/birth defect

Important adverse events that may not result in death, may not be life-threatening, or do not require hospitalization may be considered serious when, based upon appropriate medical judgment, they may acutely jeopardize the patient without immediate medical intervention to prevent one of the outcomes listed above. Serious may also includes any other event that the investigator or company judges to be serious. In addition, sites are responsible for reporting

serious adverse events to their local IRB according to their institutional requirements. Death due to disease progression need not be reported to the study monitor. These SAEs will be captured in the CRFs as described for regular AEs.

Routine Adverse Event Reporting

All adverse events must be reported in the source documentation and CRFs with appropriate information, including severity and rating of causality to the study drug/treatment. Adequate source documentation must be available to characterize the severity, duration and causality of each reported adverse event.

Unanticipated Adverse Device Effect Event (UADE) Reporting

Any potential unanticipated adverse device effect (UADE) will be reported to the Sponsor, study monitor and local IRB as soon as possible, but not later than 10 working days of the investigator learning of the event. The Sponsor will investigate whether the adverse event is a UADE and, if so, report the UADE to FDA and all other reviewing IRBs as soon as possible but no later than 10 working days after first learning of the event.

The report will contain the following:

- The initials of the subject, patient MRN #, protocol # and title
- The date the event occurred
- A description of the UADE
- An explanation of how the UADE was handled
- A description of the subject's condition
- Indication if the subject remains on the study
- Indication if the event is considered related to the NovoTTF-100A
- Indication if an amendment to the protocol and/or consent form is recommended as a result

Eliciting Adverse Event Information

The investigator is to report all directly observed adverse events and all adverse events spontaneously reported by the trial patient using concise medical terminology. In addition, each trial patient will be questioned about adverse events at each clinic visit following initiation of treatment. The question asked will be, “Since your last clinic visit have you had any health problems?”

Adverse Event Reporting Period

The adverse event reporting period will begin immediately following initiation of treatment with the NovoTTF-100A device or BSC chemotherapy. Adverse events will be collected for two months following treatment termination. All adverse events that occur in trial patients during the adverse event reporting period specified in the protocol must be reported on the CRFs, whether or not the event is considered study treatment-related. In addition, any known untoward event

that occurs beyond the adverse event reporting period that the investigator assesses as possibly related to the investigational medication/product should also be reported as an adverse event.

Follow-up of Unresolved Adverse Events

All adverse events should be followed until they are resolved or the investigator assesses them as chronic or stable or the patient's participation in the trial ends.

In addition, all serious adverse events and those non-serious events assessed by the investigator as probably related to the investigational medication/product should continue to be followed even after the patient's participation in the trial is over. Such events should be followed until they resolve or until the investigator assesses them as "chronic" or "stable." Resolution of such events is to be documented on the appropriate CRF.

XVII. STUDY OUTCOME MEASURES

1. Efficacy analysis:

a. Primary Endpoint

- The primary outcome of the study will be the median overall survival time (OS)

b. Secondary Outcome Measures

- Rate of progression free survival at 6 months (PFS6) (subject of formal hypothesis test)
- Time to progression (TTP)
- One year survival rate (%1 year survival)
- Quality of life (EORTC QLQ-C30 questionnaire; TAB H)
- The radiological response of the tumor will be assessed by the MRI studies according to Macdonald criteria for progressive disease, stable disease, partial response or complete response (see TAB D). All patients will have their tumor measurements recorded at baseline and at the time of each MRI scan. Lesions must be measured in two dimensions. The dose and type of contrast agent must be held constant from scan to scan for each patient.

2. Safety analysis:

- Safety and tolerability of NovoTTF-100A treatment based on the incidence and severity of adverse events and toxicities. Toxicities will be assessed according to the "Common toxicity criteria (CTC), version 3.0" (see TAB B).

XVIII. CRITERIA FOR REMOVAL FROM STUDY

- Any serious adverse event deemed life threatening by the treating physician that is definitely related to the study treatment or the best standard of care control will be cause for immediate cessation of treatment for the patient.
- The investigator may remove a patient from the study in case of not complying with study protocol.
- Patients will be able to withdraw from the trial at their own request (these patients will be censored during the final comparison between the treatment and BSC groups).

XIX. STATISTICAL CONSIDERATIONS

A. Anticipated control group results based on the literature

In order to predict the median overall survival and the rate of progression free survival at 6 months (PFS6) of the control group patients in our trial we performed a review of the literature on this patient population. The predicted OS is used in conjunction with the results of the pilot trial of the effect of TTFields on recurrent GBM patients, in order to calculate the needed sample size for this trial.

- A PubMed search was performed using the following term: "Recurrent high grade glioma clinical trial". The search resulted in 100 articles. We narrowed this list to 54 phase II-III therapeutic clinical trials by reviewing the abstracts of articles published after 1999 (when the last large meta-analysis was published – Wong et al.[2])
- The 54 manuscripts were obtained and the references they cite were cross checked with the search results to verify that our search was complete.
- The list was then narrowed to 37 trials by taking only those trials with efficacy data relating to a homogenous recurrent GBM population (not mixed with grade III gliomas and thus have a much better outcome than "pure" GBM).
- The efficacy measures of these trials were analyzed. The overall survival ranged from 12-57 weeks and PFS6 ranged from 0-48%. Most of this variability appeared to be due to the small sample sizes used in most of these trials.
- Based on this, the search was narrowed to prospective trials with more than 50 GBM patients. This led to a set of 4 large trials with very similar efficacy data despite the variability in the precise patient populations included in each study.
- Comparison tables were generated which summarize these trials together with the large 1999 meta-analysis by Wong et al. (see Tab G).
- The average historical OS based on the above studies is 30±6 weeks.
- The average historical PFS6 based on the above studies is 15.3±3.8 %.

B. Sample Size Calculation

Based on the insignificant side effects of NovoTTF-100A treatment observed in the pilot studies performed so far in Europe, we assume that any significant increase in overall survival compared to the BSC group would justify use of the NovoTTF-100A device in recurrent GBM patients. While the experience from the NovoTTF-100A pilot trial performed in recurrent GBM patients in Europe suggest that the median time to overall survival is 25 weeks for the BSC group and 53 weeks for the treatment group, we anticipate that a smaller difference in the median overall survival may be observed in the current study. Therefore, conservative estimates of median time to overall survival of 30 weeks for the BSC group and 48 weeks for the treatment group will be used for purposes of sample size calculations.

The sample size required to evaluate a primary efficacy endpoint of an increase in median overall survival of 18 weeks, in NovoTTF-100A treated patients compared to BSC control patients (i.e., 48 weeks versus 30 weeks, respectively), is 218 total patients (109 per group). This sample size was calculated based on a log-rank test, assumes an accrual time of 78 weeks, a minimum follow-up time of 26 weeks, a two-sided alpha level of 0.0475 and a power of 80%. To allow for losses to follow-up, a total of 236 patients will be enrolled in the trial. However, the loss to follow-up is expected to be minimal.

The above alpha level of 0.0475 was chosen based on the alpha spending function (DeMets & Lan, 1994) based on an O'Brien-Fleming type boundary to allow for a single interim analysis which will be performed at approximately 15 months after initiation of study accrual. The alpha level used for the interim analysis will be determined using the alpha spending function based on an O'Brien-Fleming type boundary which varies according to the number of patients with data available at the time of the analysis. It is anticipated that data will be available on approximately 132 patients for the interim analysis which would result in testing at an alpha level of 0.0105. However, this alpha level of 0.0105 will be adjusted, as necessary, based on the sample size at the time of the interim analysis.

The sample size of 220 evaluable patients is sufficient to evaluate the secondary endpoint of PFS6. Based on experience from the NovoTTF-100A pilot trial performed in recurrent GBM patients in Europe, we predict that in the present trial an increase of 17% or more in PFS6 may be expected in the treatment group compared to BSC control group. The sample size required to evaluate a secondary efficacy endpoint of an increase in PFS6 of 17%, in NovoTTF-100A treated patients compared to BSC control patients (i.e., 32% versus 15%, respectively), is 220 total patients (110 per group). This sample size was calculated based on Pearson's chi-square test with a continuity correction, a two sided alpha level of 0.05 and a power of 80%.

C. Statistical analysis

1. Analysis will be performed at two time points during the study:
    a. Interim analysis – based on approximately 132 patients at 15 months after the initiation of the study: If overall survival is significantly greater in the NovoTTF-100A group than in the BSC group (using a log-rank test with an alpha of approximately 0.0105), then the trial will be terminated early due to achievement of the primary endpoint. In this case all patients recruited to the treatment arm will continue to receive treatment according to protocol and will be followed for 6 months, however no new patients will be accrued.
    b. Final analysis – at the end of the completed trial, based on approximately 220 patients: The primary endpoint will be achieved if the median overall survival is significantly greater in the NovoTTF-100A group than in the BSC group (using a log-rank test with an alpha of 0.0475).

2. The statistical hypothesis that will be tested for the primary endpoint of overall survival is:

$$H_0: \beta=0 \qquad \text{versus} \qquad H_A: \beta=0$$

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 will be tested using the log-rank test at an alpha of 0.0475.

3. PFS6 will be compared between groups. The statistical hypothesis that will be tested is:

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

where, P_t and Pc are the proportions of patients with progression free survival at 6 months in the treatment and control groups, respectively. Since PFS6 is the only secondary endpoint with a formal hypothesis test, the endpoint will be tested at significance level of 0.05.

4. An analysis will be performed to assess the similarity between the two stages of the study (i.e., before and after the interim analysis) with regard to patient baseline characteristics and treatment differences in outcomes.

5. An intent-to-treat (ITT) analysis including all randomized patients will be performed using a multiple imputation method based on a logistic regression. Additionally, a sensitivity analysis will be performed that will include various imputation methods such as last observation carried forward, treating all missing data as failures, treating all missing data as successes, treating all missing data in the device group as failures but all successes in the control group ("Worst Case") and treating all missing data in the control group as failures but all successes in the device group ("Best Case").

D. Covariates

The effect of the following covariates will be compared and adjusted for between the NovoTTF-100A and BSC groups:

1. Age
2. Operation for recurrence prior to treatment initiation
3. Baseline Karnofsky performance scale score
4. Tumor size
5. Tumor location
6. Number of prior recurrences
7. Percent of the total treatment time in which the NovoTTF-100A treated patients actually received treatment (will be calculated by analyzing the internal computerized log file of each NovoTTF-100A device and dividing the total device ON time by the prescribed number of four week treatment courses).

E. Additional variables

The following parameters will be also recorded and compared between the treatment and control groups:

- OS
- TTP
- % 1-year survival
- Quality of life (EORTC QLQ-C30 questionnaire)
- Radiological response rates
- Incidence and severity of adverse events
- Each MacDonald criteria used in determining disease progression

In addition, the correlation will be measured between the percent of time patients received NovoTTF-100A treatment and their TTP. Finally, steroid dose will be controlled for in the results by assessing the correlation between steroid dosage and TTP.

F. Supplementary analysis

As a supplementary analysis, the median overall survival of the NovoTTF-100A treated group will be compared to that of an historical control (objective performance criteria). The historical control OS will be assessed using the literature review elaborated in section XVII.1 and Tab G, based on the following rationale:

1. In all of these trials, OS was reported.
2. Temozolomide (Temodar/Temodal) showed an OS of 23.5- 32 week (three studies), whereas the other chemotherapies had an OS of 25-39 weeks (two studies).
3. Since Temozolomide is now indicated for primary GBM, it will not be available to most recurrent GBM patients as they have progressed on Temozolomide.
4. From this comparison, we conclude that there has been very little progress made since 1999 in increasing overall survival (range 23.5-39 weeks compared to 25 weeks reported by Wong et al.).
5. However, since a small increase in OS (5 weeks) was seen on average between trials performed after 1999 and the Meta-analysis performed by Wong et al in 1999, we plan to use the average OS of these trials (30 weeks) as the historical OS in this trial.

OS in the NovoTTF-100A treated group will be compared to the historical control OS.

G. Justification for pooling of data

The study results will be presented by site and by BSC chemotherapy. However, while the number of centers participating in this study is smaller than many recurrent GBM trials (e.g., Xenova's TransMID™ Convection Enhanced Delivery of Tf-CRM107 Trial)[35], the low expected

recruitment rate (about 0.3-0.5 patient/center/month) makes it impractical to enrolled a large number of subjects per site and BSC chemotherapies.

The BSC control was chosen based on the following rationale: First, this is the reality of treatment for recurrent GBM patients – since no FDA approved treatment exists for this patient population after surgery, they are offered one of several off label chemotherapies according to the treating physician's discretion. None of these agents has shown statistically significant superiority over no-treatment at all, and most of the data collected was in small clinical trials in the past. Thus, if not for the study device or other experimental treatments, this would be what these patients are offered. Second, FDA has already approved such a control group design in the above mentioned TransMID^{TM} trial, despite the larger number of centers in that study (323 patients in 36 centers).

Please note that while variability is expected, the table below shows that the reported variability is relatively small and the range of median survival times is considerably less than the anticipated median overall survival benefit for the NovoTTF-100A group.

Agent	**Median OS (weeks)**	**Number of patients**	**Reference**
BCNU	32	40	Brandes et al, 2004[32]
Carboplatin	23	45	Robins et al, 2002[33]
PCV	33	63	Kappelle et al, 2001[34]
Procarbazine	25	113	Yung et al, 1999[23]
Temozolomide	32	142	Chang et al, 2003[25]
Temozolomide	31	112	Yung et al, 1999[23]

XX. RISK/BENEFIT ANALYSIS

The risks associated with use of the NovoTTF-100A are principally the risk of electrical or mechanical failure leading to electrical shock, electromagnetic interference, etc., as well as the risk that the treatment will not be effective in delaying tumor progression or causing regression. Additional risks include skin irritation, and skin breakdown or infection at electrode sites. Technical failure is extremely unlikely due to stringent compliance with all standard design and manufacturing safety protocols. In addition, appropriate measures have been taken to minimize the risk to study subjects, including preclinical *in vitro* and *in vivo* testing to ensure safe operation of the device. The 16 patients treated to date as part of pilot studies suffered no treatment related serious adverse events after > 70 months of treatment (cumulatively). In fact the only complication seen was a mild to moderate skin irritation beneath the electrode gel.

In the pilot trial performed on 10 recurrent GBM patients, median TTP in NovoTTF-100A treated patients was 24 weeks and overall survival greater than 42 weeks. Although these results are not statistically significant due to the small number of patients in the trial, they raise the possibility that the NovoTTF-100A device will benefit patients in the current study with regards to both TTP and OS. Up to 100 patients will be exposed to NovoTTF-100A treatment during the current trial. Considering the minimal toxicity and promising efficacy seen in the pilot trials, the small number of patients exposed to this treatment in the current study and the complete lack of treatment alternatives for these patients – we conclude that the possible benefits of NovoTTF-100A treatment drastically exceed its potential risks.

XXI. STUDY MONITORING AND QUALITY ASSESSMENT

Study monitoring will be performed by a CRO assigned this responsibility by the sponsor. Study monitoring functions will be in compliance with recognized Good Clinical Practices, FDA's IDE guidance documents, and as outlined in 21 C.F.R. § 812.43(d) and 21 C.F.R. § 812.46. The principal function of the clinical monitor is to observe and assess the quality of the clinical study. The monitor's duties include: on-site visits and review of study documents and results. The CRO will operate under written procedures to ensure compliance with the protocol.

On-site monitoring visits will take place at each center prior to study initiation and at least once during the course of the study, and a final visit at the close of the study. The pre-study visit is intended to provide an opportunity for the monitor to review the Investigational Plan with the Investigators and to ensure that the Investigators:

- have appropriate training, facilities, patient load, time, and willingness to comply with study requirements;
- have the approval of the supervising Institutional Review Board (IRB) for the Investigational Plan;
- have all study documentation and required records on site; and
- assume responsibility for the investigation at their center.

Visits during the study are intended to assess Investigators' adherence to the Investigational Plan, maintenance of records, reports and investigational devices, and review of source documents for accuracy, completeness, and legibility. During these in-study visits, the monitor is required to assess the progress of the study toward meeting study objectives, and to identify any concerns that stem from observations of device performance and/or review of the Investigator's patient records, study management documents, and informed consent documents, and to ensure accountability of all patients that have been treated under the study.

The monitor's final on-site visit at completion of the study is intended to assure that all the data have been properly completed and to have a closing meeting with the Investigators and their staff members. Reports of the on-site visits will be made by the monitor and should include resolution of concerns, completion of appropriate follow-up activities, completion of assigned

tasks, and any necessary corrective actions. At the close of the study, the monitor will prepare a final report.

An independent Data and Safety Monitoring Board (DSMB), comprised of a neurosurgeon, neuro-oncologist and statistician will be formed to monitor the safety data from the study. Although there are no anticipated significant safety issues with the device, the adverse event data will be reviewed by the DSMB to determine if there are any unexpected safety concerns with the device that warrant study termination or if the study should be stopped for futility purposes. Specifically, DSMB review will be performed after 70 and 140 patients have completed the study procedures to determine if:

- there is clear evidence of unacceptably harmful side-effects of NovoTTF-100A treatment; or
- there is no likelihood of demonstrating treatment benefit or equivalence.

The DSMB will base their recommendation to the Sponsor on an evaluation of data such as:

- All adverse events, including serious adverse events and device or drug related AEs
- PFS6 and overall survival

XXII. PROTECTION OF HUMAN SUBJECTS

A. Privacy

It is the responsibility of the Research Staff to ensure that protocol patients have received the Center's Notice of Privacy Practices. If the subject has not already done so, personnel of the relevant participating Center must try to obtain acknowledgment before the patient participates in this study.

The Center's Privacy Office may allow the use and disclosure of protected health information pursuant to a completed and signed Research Authorization form. The use and disclosure of protected health information will be limited to the individuals described in the Research Authorization form. A Research Authorization form must be completed by the Principal Investigator and approved by the IRB and Privacy Board.

XXIII. INFORMED CONSENT PROCEDURES

RESEARCH AUTHORIZATION

Procedures for obtaining Research Authorization: Prior to carrying out any protocol-specific procedures, investigators or designated staff will explain fully the details of the protocol, study procedures, and the aspects of patient privacy concerning research specific information. In addition to signing the IRB Informed Consent, all patients must sign the Research Authorization

component of the informed consent form. The Research Authorization requires a separate signature from the patient. The original signed documents will become part of the patient's medical record, and each patient will receive a copy of the signed documents. All patients must provide written informed consent prior to registration and treatment.

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XXV. PROTOCOL SIGNATURE PAGE

Investigator:

Center - _____

Investigator Name - _____

Signature - _____

Date - _____/_____/_____

Sponsor:

NovoCure Ltd.

Name - Eilon Kirson

Signature - _____

Date - _____/_____/_____

SUMMARY OF SAFETY AND EFFECTIVENESS DATA

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: [To be inserted by FDA]

Premarket Approval Application (PMA) No.:	[To be inserted by FDA]
Date of Notice of Approval To Applicant:	[To be inserted by FDA]

II. INDICATIONS FOR USE

The NovoTTF-100A System is intended as a treatment for adult patients (greater than 21 years of age) with histologically- or radiologically-confirmed glioblastoma multiforme (GBM), following recurrence in the supra-tentorial region of the brain. The device is intended to be used as a monotherapy, after surgical and radiation options have been exhausted, in place of standard medical therapy for GBM.

III. 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. The TTFields are inferred to 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. The patient must simply 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 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^{o}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 inferred 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 little 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. It is noted that, because TTFields are only applied to the brain, they have no 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 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. It is important to note that all the described effects can be obtained by fields of low intensity such that they are not accompanied by any significant elevation of temperature.

IV. CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS

Contraindications

- Do not use the NovoTTF-100A if you have an implanted electronic device (e.g. deep brain stimulator, spinal cord stimulators, vagus nerve stimulator, pacemaker, defibrillator). Use of the device together with implanted electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device.
- Do not use the NovoTTF-100A if you have a skull defect (missing bone with no replacement) in areas intended for electrode placement. Placement of electrodes in these locations has not been tested and may cause skin breakdown and infections in the skin
- Do not use the NovoTTF-100A if you have a known hypersensitivity to conductive hydrogels like the gel used on EKG stickers or TENS electrodes. In this case, skin contact with the INE electrode gel may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings

- The NovoTTF-100A should be on and active for at least 18 hours a day in order to achieve the best response to treatment. Using the NovoTTF-100A for less than 18 hours a day lowers the chances that you will respond to treatment.
- Do not stop using the NovoTTF-100A before completing at least four weeks of contiguous therapy from treatment start. Stopping treatment before completing the first four weeks of therapy lowers the chances that you will respond to treatment.
- Continue use of the NovoTTF-100A even if you have used it less than the recommended 18 hours per day, unless instructed otherwise by your physician
- If you plan to be away from home for more than 2 hours, a back-up battery, and/or the power supply should be carried with you in the event the battery life is exhausted. Failure to take a spare battery and/or the power supply may result in treatment interruption. Interruptions in treatment may lower your chance to respond to treatment.
- Make sure you have at least 12 extra electrodes at all times to last you until the next electrode shipment arrives.
- Batteries may weaken over time and need to be replaced. You will know this has happened when the device running time on a fully charged battery begins to shorten (for example, when then low battery indicator light flashes within only 1.5 hours from the start of treatment). Failure to seek replacement batteries may result in delays in treatment. Interruptions in treatment may lower your chance to respond to treatment.
- The Troubleshooting guide should be carried with the user at all times. This guide is necessary to ensure proper operation of the NovoTTF-100A System.

Precautions

- Do not use the NovoTTF-100A if you are 21 years old or younger or if you are pregnant. The NovoTTF-100A has not been tested in children or pregnant women. It is unknown what side effects it may cause in these cases.
- Do not use the NovoTTF-100A if your tumor is located in the lower parts of the brain close to the spinal cord. The NovoTTF-100A has not been tested in patients with tumors in these locations and it is unknown whether these tumors will respond to treatment.
- In case of skin irritation such as redness beneath the electrodes, use of over the counter topical corticosteroids (0.1% hydrocortisone cream) when replacing electrodes can alleviate symptoms. If you do not use this cream, the skin irritation is likely to become more serious and may even lead to skin break down, infections, pain and blisters.
- In case of skin break down, infection, pain or blisters, contact your physician. You will be prescribed an antibacterial cream which should be applied when replacing electrodes. If you do not use this cream, your symptoms may continue and you may have to take a break from treatment, which may lower your chance to respond to treatment.
- Do not wet the electric filed generator or electrodes. Getting the electric filed generator wet may cause the generator to fail preventing you from receiving treatment for the recommended duration. Getting the electrodes wet is likely to cause the electrodes to come loose from your head. This will lead to shutdown of the generator and will require you to change the electrodes.

- Do not use any component not originally supplied with the NovoTTF-100A Treatment Kit. Use of other components can result in damage to the device, less than adequate therapy or increase in risk to the patient.
- The NovoTTF-100A is to be operated only after receiving training from qualified personnel. This training will include a detailed walk through of this manual and assisted practice in the use of the system. In addition you will be trained through simulated fault conditions, in what to do in the case of problems with treatment. Use of the NovoTTF-100A without receiving this training can result in damage to the device, less than adequate therapy or increase in risk to the patient.
- Do not operate the NovoTTF-100A if the generator, the INE Electrodes or any additional parts are obviously damaged (torn wires, loose connectors, loose sockets, cracks or breaks of the plastic enclosures). Use of damaged components can result in damage to the device, less than adequate therapy or increase in risk to the patient.
- Before connecting or disconnecting the electrodes, ensure that the NovoTTF-100A power switch is in the OFF position. Disconnecting electrodes with the device power switch in the ON position may cause a device alarm to sound.
- Do not block the device vents (located on the sides of the NovoTTF-100A device). Blocking the vents may cause the device to overheat internally, leading to device shutdown and a break in treatment. If this occurs, unblock the vents, wait 5 minutes and restart therapy.
- Do not block the battery charger vents (located at the front of the battery chargers). Blocking the vents may cause the charger to overheat internally, leading to a charger malfunction. This could prevent your batteries from charging.
- Before using an INE Electrode, make sure its package is sealed by gently rubbing the package on all four sides. If the package is not sealed, the electrode may be damaged. A damaged electrode will not operate properly and will lead to device shutdown.
- Do not use an INE Electrode which has been opened previously. If the package is not sealed, the electrode may be damaged. A damaged electrode will not operate properly and will lead to device shutdown.
- The INE Electrodes are for single use and should not be re-used. Re-use will lead to poor adherence of the electrode to your skin and to device shutdown.
- Keep the NovoTTF-100A out of the reach of children.
- The suitability of the NovoTTF-100A System and INE Electrodes for full body scanners used in airports has not been tested. It is unknown what effects such scanners may have on the device.
- The NovoTTF-100A System and INE Electrodes will activate metal detectors.
- All servicing procedures must be performed by qualified and trained personnel.

V. ALTERNATIVE PRACTICES AND PROCEDURES

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

VI. 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 device in any country. In addition, there have been no reportable adverse events in any country.

VII. 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 will 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 IX.B.5** below.

VIII. 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].

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

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

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 inhibition.

1. Mechanism of Action Studies

Studies assessing the mechanism of action of TTFields 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 that the axis of division of the dividing cells in relation to the electric fields is important in effecting cell death.

2. Proof of Concept Studies

NovoCure performed *in vitro* studies to assess the relationship between dose and frequency response using 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 and human pilot clinical studies.

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 Efficacy 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 patients was set at 28 days.

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 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.

C. Biocompatibility, 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 EMC standards at a certified laboratory. The electrodes that contact the patient 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

[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.

demonstrates that the NovoTTF-100A System operates per its specifications and in accordance with its intended use.

IX. SUMMARY OF 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 1. Summary of Clinical Studies

Study Type	Study Design	Objective	Number of Sites	Number of Subjects	Accountability
Pilot	Prospective single arm trial	To assess the safety and efficacy of NovoTTF-100A treatment compared to recurrent GBM historical controls	1	10	All patients were followed until death. The 2 patients still alive today were followed formally until June 2009
Pivotal	Prospective, open label, best standard of care randomized control trial	To compare the overall survival of patients treated with the NovoTTF-100A alone to patients treated with the best standard of care chemotherapy available for recurrent GBM	28	237	207 patients received treatment. Vital status is known for 221 (93%) of patients. Last follow up date – June 29, 2010

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

The efficacy and safety of the NovoTTF-100A device in the treatment of GBM were first evaluated in a pilot study in 10 patients with recurrent GBM. The study was an open-label prospective single arm study to evaluate the safety and efficacy of TTFields for the treatment of recurrent GBM.

The efficacy endpoints of the study included the overall survival and time to disease progression, based on radiological assessment of disease progression by monthly 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 efficacy results were compared to two different populations: a concurrent best standard of care comparator group that was assembled retrospectively and an active historical comparator group that was reconstructed from the Gliadel package insert.[4]

All patients underwent surgery and radiotherapy for the primary tumor, and all had their first or second GBM recurrence at study entry. All patients had histologically proven diagnosis of GBM. The two study groups were comparable in baseline characteristics. All NovoTTF-100A patients were treated with TTFields as monotherapy, with continuous,

[4] Gliadel Wafer Package Insert, available at http://www.gliadel.com/docs/pdf/Gliadel_PI.pdf.

24-hour a day, 200 kHz, 0.7 V/cm TTFields. Patients 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 patient on average). All patients 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 patients. Compliance with treatment was high with patients 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 patients 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 TTP in the NovoTTF-100A patients was 26 weeks compared to 9 weeks in historical control data (Wong et al., 1999[5]). The PFS6 was 50% compared to 15% in historical control data (Wong et al., 1999[6]). Since most of the patients in the trial were re-operated, the overall survival in NovoTTF-100A patients was compared to that reported for Gliadel Wafers. The median overall survival was 14.7 months in NovoTTF-100A patients compared to the 6 months reported for Gliadel Wafers. The one-year survival in NovoTTF-100A patients was 60%. Response rate in the NovoTTF-100A treated patients was 25% (1 CR + 1 PR) and only two patients had progressive disease despite treatment. The study demonstrated the excellent safety profile of this treatment modality. Based on these pilot study results the decision was made to test the NovoTTF-100A device in a randomized pivotal study in recurrent GBM patients.

B. Pivotal Study for Recurrent GBM

1. Protocol Summary

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.

Patients were randomized to receive either NovoTTF-100A monotherapy or the best standard of care effective chemotherapies (BSC) for recurrent GBM patients as practiced at each of the participating clinical centers. The hypothesis of this study is that NovoTTF-100A will significantly increase the overall survival of recurrent GBM patients compared to patients treated with BSC. The specific aims of the study were:

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

[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.

Patients 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) US and OUS clinical centers.

Immediately following screening, patients were randomized at a 1:1 ratio to receive either NovoTTF-100A treatment or BSC effective chemotherapy. The nature of the treatment precluded blinding of patients and their treating clinicians to the actual treatment received by the patients. However, a central MRI review was performed by an independent neuro-radiologist blinded to the treatment group assignment of each patient. 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 efficacy results of the trial.

Patient accrual lasted 30 months and patient follow up continued for at least 6 months from accrual of the last patient in each center. The final study analysis compared the OS among 120 NovoTTF-100A patients and 117 best standard of care effective chemotherapy patients.

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. Patients 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 patients 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/μL)
    6) Neutropenia (absolute neutrophil count < 1 x 10^3/μL)
    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, patients 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 patients were also instructed by the investigator on the operation of the NovoTTF-100A System and battery replacement. Once the patients were trained in operating the device, they were released to continue treatment at home. The patients received continuous NovoTTF-100A treatment. Treatment was discontinued in the case of non-compliance or clinical disease progression.

Control Arm

All patients had baseline examinations performed prior to treatment initiation. Patients received the best effective standard of care chemotherapy practiced at each of the participating centers. The effective 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

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

Follow Up

During treatment, and until progression for patients who stopped treatment before progression, all patients 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 patient. Medical follow-up continued for 2 months following disease progression. Patient survival was assessed based on monthly follow up visits, monthly telephone interviews with the patients' caregivers, by review of hospital records, and by review of publically-available databases. Table 2 below provides the full schedule of evaluations in the study.

Table 2. Schedule of Evaluations to be Performed for Each Patient

	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*			
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

The primary outcome of the study was overall survival (OS).

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

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

2. Statistical Analysis Plan and Analysis Populations

Sample Size

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

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 and a Wilcoxon 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 patients 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.

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 patient was randomized.

- **Per Protocol (PP)**

The PP population includes:

- All subjects who do not have any major protocol violations that would affect the endpoints being assessed, and:
  - All subjects randomized to BSC treatment who received at least one protocol-specified best standard of care chemotherapy or Avastin (bevacizumab) alone or in combination with cytotoxic chemotherapy.
  - All subjects randomized to NovoTTF treatment who similarly received at least one full treatment course as defined in the protocol (28 days of treatment).

The PP population is based on patients in both treatment arms receiving the protocol specified treatment to which they were randomized and without any major protocol violations.

- **Safety Population**

The Safety Population includes all subjects who received at least one dose of best standard of care therapy or at least one treatment with the NovoTTF device. The safety analysis was performed by treatment group according to the treatment that the patient actually received. Only 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.

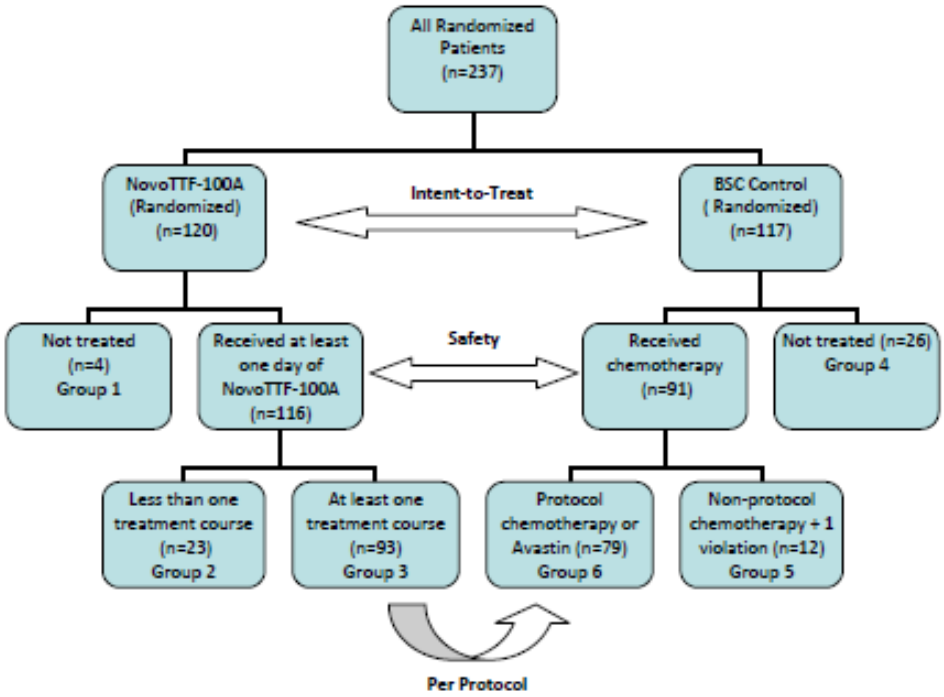

Figure 1. Analysis Populations

3. Patient Accountability

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

Patient disposition and follow up is shown in the table below.

Table 3. Patient Disposition
All Randomized Patients

	NovoTTF-100A	BSC	All Patients
	(N=120)	**(N=117)**	**(N=237)**
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 patients who never started treatment)	84 (70)	55 (47)	139 (59)
Reason for Discontinuation (for patients who started therapy)	n=116	n=91	n=207
Death	31 (27)	16 (18)	47 (23)
Adverse Event (Incl. SAE)	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, patients who moved to hospice care and could not return for visits, patients 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 patient off trial without specifying a reason beyond clinical judgment, etc.

4. Demographics and Baseline Characteristics

Baseline characteristics of the 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 failure: 19%. Baseline characteristics were similar between treatment groups 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 4. Demographics and Baseline Characteristics by Treatment Group Intent-to-Treat Population			
	NovoTTF-100A	**BSC**	
Characteristics	**(N=120)**	**(N=117)**	**P-Value**
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
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	

5. Study Results

Effectiveness Results

Primary Endpoint – Overall Survival

The prospectively defined primary endpoint in the trial was overall survival. In the ITT population, which included all randomized patients, NovoTTF-100A treatment was shown to be comparable in overall survival to the best available chemotherapy today for recurrent GBM (including the recently approved Avastin). In the PP population, which excluded patients who received less than one course of treatment in both arms and excluded patients who received non-protocol specified treatments, the overall survival was superior in patients treated with NovoTTF-100A device compared to patients treated with BSC chemotherapies.

In the ITT population, the median OS was comparable in NovoTTF-100A and in BSC chemotherapy patients (6.3 vs. 6.4 months; HR 1.0). In the PP population, the median OS in the NovoTTF-100A group is 20% longer compared to the effective BSC chemotherapy group, which is statistically significant using the Wilcoxon test (7.8 vs. 6.5 months; HR 0.84; Wilcoxon p=0.04).

The between group difference in the overall survival results is consistently observed in specific subgroups, including US vs. OUS sites, re-operated and non-re-operated patients, and across different countries in which the trial was conducted. In the US, the OS data in the ITT population showed a slight trend towards better survival in the NovoTTF-100A patients compared to BSC patients (median OS 6.1 vs. 5.3 months for US NovoTTF-100A and BSC patients, respectively).

Although the prospectively defined statistical test for the primary endpoint was the logrank test, the Wilcoxon test is a more appropriate method with which to analyze the data for overall survival. Since the logrank test weighs all time points equally when comparing survival curves, this test will exaggerate the effect of later parts of the survival curves (between 12 and 36 months). Using the Wilcoxon test[7], the NovoTTF-100A device is shown to be superior in overall survival when compared to BSC control in the PP population (p=0.04).

Table 5. Overall Survival Summary

		Treatment Group	
	Population	**NovoTTF**	**BSC**
N	ITT PP	120 93	117 79
Median OS (months)	ITT PP	6.3 **7.8**	6.4 **6.5**
Logrank p	ITT PP	0.98 0.28	
Wilcoxon p	ITT PP	0.72 **0.04**	
HR (95% CI)	ITT PP	1.00 (0.76 – 1.32) 0.84 (0.60 – 1.16)	

[7] Edmond A. Gehan. Biometnka 1966, 52, 1 and 2, p. 203 1974

Effect of Treatment Compliance on Overall Survival

Most of the patients in the trial (>80%) received treatment ≥75% of the time. Overall survival was found to be correlated with compliance with treatment. Patients with maximal compliance greater than or equal to 75% (18 hours a day on average) had an OS of 7.7 months compared to patients with compliance below 75% who had an OS of 4.5 moths (logrank p=0.0415).

Secondary Endpoints

The secondary endpoints for the NovoTTF-100A trial support the primary endpoint results, in that they show the NovoTTF-100A device comparable to or better than the BSC control. One-year-survival in the NovoTTF-100A group was very similar to that in the BSC chemotherapy group in the ITT population (21.9% vs. 22.1%, respectively) and was higher in the PP population (27.8% vs. 21.6%, respectively). PFS6 was higher in NovoTTF-100A patients than in BSC chemotherapy patients in the ITT population (21.4% vs. 15.2%) and significantly so in the PP population (26.2% vs. 12.7%; chi-square p = 0.018). Radiological response rate for NovoTTF-100A patients was higher than for BSC chemotherapy patients in the ITT population (14.0% vs. 9.6%) and significantly so in the PP population (15.9% vs. 6.7%; chi-square p=0.046). Median TTP for both groups was essentially the same in both analysis populations.

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

Table 6. Summary of Secondary Endpoints

Secondary Endpoints		**Treatment Group**	
	Population	**NovoTTF**	**BSC**
Number of patients	ITT PP	120 93	117 79
One-Year Survival (%)	ITT PP	21.9 27.8	22.1 21.6
PFS6 (%)	ITT PP	21.4 **26.2**	15.2 **12.7**
Chi-square p-value	ITT PP	0.13 **0.02**	
Radiological Response Rate (%)	ITT PP	14.0 **15.9**	9.6 **6.7**
Median TTP (weeks)	ITT PP	9.3 10.1	9.6 9.7

Safety Results

The analysis of safety was based on the safety population including 116 NovoTTF-100A patients and 91 BSC chemotherapy patients followed for 6 months since the inclusion of

the last patient in the trial. The key safety outcomes for this study are presented below in Tables 7 to 9.

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 patients treated with the device in the pivotal study, or in >2% of patients treated with BSC chemotherapy:

Table 7. Percentage of Patients with AEs in the NovoTTF-100A versus BSC groups (Including incidence of severe and related AEs) ≥ 2%

	NovoTTF-100A			BSC Chemotherapy		
	(N=116)			(N=91)		
System Organ Class	% of patients			% of patients		
Preferred Term	**All AEs**	**Severe**	**Related**	**All AEs**	**Severe**	**Related**
Percentage of Patients with >=1 AE	55	16	22	59	19	48
Blood and lymphatic system disorders	4	1	0	19	4	16
Anaemia	2	0	0	2	0	2
Leukopenia	1	0	0	7	1	4
Lymphopenia	2	1	0	3	1	2
Neutropenia	1	0	0	2	0	2
Thrombocytopenia	3	0	0	12	2	10
Cardiac disorders	7	1	0	7	0	2
Oedema peripheral	5	1	0	3	0	2
Tachycardia	1	0	0	3	0	0
Ear and labyrinth disorders	1	0	0	3	0	2
Ear pain	0	0	0	2	0	2
Endocrine disorders	2	0	0	2	0	0
Cushingoid	2	0	0	1	0	0
Eye disorders	3	0	0	5	0	1
Dry eye	2	0	0	0	0	0
Vision blurred	1	0	0	2	0	1
Gastrointestinal disorders	8	1	0	30	3	30
Abdominal pain	0	0	0	7	0	3
Aphthous stomatitis	0	0	0	2	0	2
Constipation	2	0	0	4	0	2
Diarrhoea	0	0	0	12	2	11
Nausea	3	0	0	16	0	14
Vomiting	3	0	0	7	0	7
General disorders and administration site conditions	13	1	2	15	1	9
General physical health deterioration	2	0	0	1	0	0

Table 7. Percentage of Patients with AEs in the NovoTTF-100A versus BSC groups (Including incidence of severe and related AEs) ≥ 2%						
	NovoTTF-100A			BSC Chemotherapy		
	(N=116)			(N=91)		
System Organ Class	% of patients			% of patients		
Preferred Term	**All AEs**	**Severe**	**Related**	**All AEs**	**Severe**	**Related**
Malaise	9	1	2	11	0	8
Pyrexia	2	0	0	1	0	0
Infections and infestations	4	0	0	12	1	0
Candidiasis	3	0	0	3	0	0
Ear infection	0	0	0	2	0	0
Urinary tract infection	0	0	0	3	1	0
Injury, poisoning and procedural complications	18	15	16	1	0	0
Fall	4	0	1	0	0	0
Medical device site reaction (rash under electrodes)	16	0	16	0	0	0
Investigations	7	2	0	5	1	2
Blood lactate dehydrogenase increased	2	0	0	1	0	1
Hepatic enzyme abnormal	1	0	0	2	1	2
Weight increased	1	0	0	2	0	0
Metabolism and nutrition disorders	8	1	0	13	3	3
Anorexia	0	0	0	4	1	3
Diabetes mellitus	2	0	0	0	0	0
Hyperglycaemia	2	0	0	2	1	0
Hypokalaemia	2	0	0	4	1	1
Musculoskeletal and connective tissue disorders	5	0	1	9	0	0
Back pain	2	0	0	3	0	0
Muscular weakness	0	0	0	3	0	0
Pain in extremity	0	0	0	2	0	0
Neoplasms benign, malignant and unspecified	2	2	0	2	1	0
Neoplasm progression	2	2	0	2	1	0
Nervous system disorders	43	7	3	36	5	3
Amnesia	3	0	0	0	0	0
Balance disorder	2	0	0	0	0	0
Brain oedema	1	0	0	2	0	0
Cognitive deterioration	2	1	0	2	0	0
Cognitive disorder	2	0	0	2	0	0
Convulsion	9	3	0	4	2	0
Coordination abnormal	2	0	0	4	0	0

Table 7. Percentage of Patients with AEs in the NovoTTF-100A versus BSC groups (Including incidence of severe and related AEs) ≥ 2%						
	NovoTTF-100A			BSC Chemotherapy		
	(N=116)			(N=91)		
System Organ Class	% of patients			% of patients		
Preferred Term	**All AEs**	**Severe**	**Related**	**All AEs**	**Severe**	**Related**
Cranial nerve disorder	3	0	0	1	0	0
Difficulty in walking	1	0	0	2	0	0
Dizziness	3	0	0	2	0	2
Dysaesthesia	2	0	0	1	0	0
Dysphasia	3	0	0	2	0	0
Headache	16	2	3	10	0	2
Hemianopia	2	0	0	4	1	0
Hemiparesis	9	0	0	4	1	0
Hyperreflexia	3	0	0	2	0	0
Hypoaesthesia	2	0	0	3	0	0
Hyporeflexia	0	0	0	2	0	0
Memory impairment	2	0	0	0	0	0
Nervous system disorder	3	1	0	3	0	0
Neuropathy peripheral	2	1	0	1	0	0
Tremor	2	0	0	2	0	0
Psychiatric disorders	10	0	0	8	0	0
Agitation	2	0	0	0	0	0
Depression	2	0	0	5	0	0
Insomnia	2	0	0	2	0	0
Mental status changes	5	0	0	1	0	0
Renal and urinary disorders	6	1	0	3	0	1
Pollakiuria	2	0	0	0	0	0
Urinary incontinence	3	1	0	2	0	0
Respiratory, thoracic and mediastinal disorders	6	0	0	11	1	0
Cough	3	0	0	4	0	0
Dyspnea	2	0	0	4	1	0
Nasopharyngitis	0	0	0	2	0	0
Skin and subcutaneous tissue disorders	8	0	1	10	0	5
Alopecia	0	0	0	3	0	3
Rash	4	0	0	0	0	0
Swelling face	2	0	0	1	0	0
Vascular disorders	4	2	0	7	2	2
Hypertension	1	0	0	3	0	0
Pulmonary embolism	1	1	0	2	2	1

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

Table 8. Treatment Emergent SAEs by Body System and Preferred Term				
	NovoTTF-100A [N=116]		BSC Chemotherapy [N=91]	
System Organ Class	**# of Events**	**# of Pts.**	**# of Events**	**# of Pts.**
Preferred Term	**(Frequency)**	**(Incidence)**	**(Frequency)**	**(Incidence)**
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)
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)

Table 8. Treatment Emergent SAEs by Body System and Preferred Term				
	NovoTTF-100A [N=116]		BSC Chemotherapy [N=91]	
System Organ Class	**# of Events**	**# of Pts.**	**# of Events**	**# of Pts.**
Preferred Term	**(Frequency)**	**(Incidence)**	**(Frequency)**	**(Incidence)**
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)

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

Table 9. 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)

Safety Discussion and Conclusions

NovoTTF-100A did not cause any blood and lymphatic disorders (4% of patients, all unrelated to treatment) whereas BSC chemotherapy, as expected, caused a significant proportion of patients to suffer from moderate to severe blood and lymphatic disorders (27 AEs in 19% of the patients), mainly thrombocytopenia (12% of patients). The difference was statistically significant (p=0.0009). In this trial there were 51 events of gastrointestinal toxicity in 30% of BSC patients. Forty of these events were related to BSC treatments. None of the GI AEs seen in the NovoTTF-100A patients (12 events in 8% of patients) were related to treatment. In the BSC group (only), there were many GI AEs which were related to chemotherapy, including moderate to severe nausea, vomiting, diarrhea, abdominal pain and constipation. The difference in incidence between groups was highly significant (p<0.0001). None of the infectious AEs in the study was considered treatment related. There were significantly more events in the BSC group than the NovoTTF-100A group (p=0.0376). In the BSC patients, infections were more common, more severe and of a more systemic nature (e.g., severe pneumonia leading to hospitalization). Mild fungal infections were seen in a handful of NovoTTF-100A patients but these were most likely secondary to steroid use.

Most of the symptoms related to the recurrent GBM disease itself are neurological and psychiatric in nature. Some common neurological symptoms of the disease are headaches, seizures, focal neurologic signs (e.g., hemiparesis, visual disturbances,

cognitive disturbances, speech disturbances, etc.) and general neurologic and or functional deterioration. Similar proportions of patients reported neurological AEs in both treatment groups: 36% of BSC patients and 43% of NovoTTF-100A patients (p=0.32). Each patient had almost two AEs on average in both groups. The two AEs that should be discussed in greater detail are headaches and convulsions.

Convulsions were seen in 9% of NovoTTF-100A patients and 4% of BSC chemotherapy patients. Only 3 cases in the NovoTTF-100A group and 2 in the BSC group were considered severe. One episode of Status Epilepticus in a NovoTTF-100A treated patient was assessed by the investigator as possibly related to the study device. Additional investigation revealed that the patient had progression of disease at the time of the event. It was concluded that this event was not related to the study device. None of the other convulsions was assessed by the investigators in the trial as treatment related. Since convulsions are expected in 20-50% of GBM patients at various stages of their disease[8], the differences in incidence of convulsions between groups are not statistically or clinically significant. In both treatment groups, the incidence of convulsions in this trial was low compared to other trials[9].

Headaches are an expected AE when using the NovoTTF-100A device. In addition, this is one of the basic symptoms of having a brain tumor in general and in recurrent GBM specifically. There was no significant difference in the incidence of headaches between treatment groups (16% vs. 10% in NovoTTF-100A and BSC patients, respectively). Only two cases of headache were considered severe and 4 cases were assessed as possibly related to the NovoTTF-100A device and 2 to the BSC chemotherapy.

In conclusion, the incidence of neurological adverse events seen in NovoTTF-100A treated patients in the trial is the same as in BSC chemotherapy patients, and represents the natural symptoms of this disease. This is supported by the fact that the neurological AEs in both arms are spread over multiple symptoms and signs and almost none were assessed as treatment related by the treating physicians. Finally, there were no device related convulsions seen in the trial and the incidence of convulsions in both treatment groups was relatively low.

The NovoTTF-100A device also caused an expected mild to moderate skin reaction beneath the device electrodes in 16% of patients. None of these cases was assessed as severe by the investigator. The skin reaction resolved in all cases after discontinuing treatment and was easily treated with topical steroids or antibiotic creams (in case there are open sores). Treatment is not interrupted by this condition due to the ability to shift between alternative electrode locations.

These findings are supported by the analysis of quality of life data presented above (as a secondary efficacy endpoint), in which BSC patients complained of a higher incidence of

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[8] Brem, H., S. Piantadosi, et al. (1995). "Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group." Lancet **345**(8956): 1008-12, Hildebrand, J., C. Lecaille, et al. (2005). "Epileptic seizures during follow-up of patients treated for primary brain tumors." Neurology **65**(2): 212-5, Friedman, H. S., M. D. Prados, et al. (2009). "Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma." J Clin Oncol **27**(28): 4733-40.

[9] Friedman, H. S., M. D. Prados, et al. (2009). "Bevacizumab alone and in combination with irinotecan in recurrent glioblastoma." J Clin Oncol **27**(28): 4733-40.
Brem, H., S. Piantadosi, et al. (1995). "Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group." Lancet **345**(8956): 1008-12.

nausea, vomiting, diarrhea, constipation and pain than NovoTTF-100A patients while on treatment

In conclusion, the classic gastrointestinal, hematological and infectious adverse events of almost all chemotherapies are seen in a significantly higher proportion of BSC control patients than in NovoTTF-100A patients and at much higher frequencies. These differences appear in severe and related events as well. Thus, the difficult and debilitating side effects of chemotherapy are lowered significantly when using the NovoTTF-100A System. The only treatment related adverse events seen in a significant proportion of patients is the known and expected, mild to moderate, local skin reaction beneath the electrodes.

X. CONCLUSIONS DRAWN FROM STUDIES

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. Recurrent GBM is an end-stage condition and it is uniformly fatal with a negligible 5-year survival. Quality of life of recurrent GBM patients is compromised due to the neurological deficits caused by the tumor itself together with the overwhelming side effects of the various standard chemotherapies and extreme experimental treatments. Treatment options for recurrent GBM are extremely limited, and all have limitations, including severe side effects. These 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 very well designed and conducted (randomized control, active control group, multi-center, half of the patients in the US, data poolable between countries, and minimal loss to follow-up). NovoTTF-100A treatment exhibits negligible toxicity, comparable or better primary and secondary efficacy outcome measures, and superior quality of life compared to the best available chemotherapies today and is highly reliable.

XI. PANEL RECOMMENDATION [To be completed by FDA]

The clinical data provided by the company to support the indications for use being requested was reviewed by the Neurological Devices Advisory Panel on _____. The panel recommended approval of the NovoTTF-100A System for use in the treatment of adult patients (greater than 21 years of age) with histologically- or radiologically-confirmed glioblastoma multiforme (“GBM”), following recurrence in the supra-tentorial region of the brain.

XII. CDRH DECISION [To be completed by FDA]

CDRH concurred with the Neurological Devices Advisory Panel recommendation of _____ and issued an approval order on _____. The device manufacturing facilities were inspected and found to be in compliance with the Quality System Regulation (21 C.F.R. Part 820).

XIII. APPROVAL SPECIFICATIONS

[To be completed by FDA]

XIV. REFERENCES

Brem, H., S. Piantadosi, et al. (1995). "Placebo-controlled trial of safety and efficacy of intraoperative controlled delivery by biodegradable polymers of chemotherapy for recurrent gliomas. The Polymer-brain Tumor Treatment Group." Lancet **345**(8956): 1008-12.

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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.

INSTRUCTIONS FOR USE
REVISION 1.0

NOVOTTF-100A System

This manual is intended for physicians prescribing the use of the NovoTTF-100A System.

Additional information is found in the following materials

1. Patient Information and Operation Manual
2. Portable Battery Leaflet – QSD-QR-309
3. Power Supply Leaflet – QSD-QR-326
4. Portable Battery Charger Leaflet– QSD-QR-307
5. Connection Cable Leaflet– QSD-QR-311
6. Battery Rack Leaflet– QSD-QR-312

Caution: Federal law restricts this device to sale by or on the order of a physician

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Indications for Use

The NovoTTF-100A System is intended as a treatment for adult patients (greater than 21 years of age) with histologically- or radiologically-confirmed glioblastoma multiforme, following recurrence in the supra-tentorial region of the brain. The device is intended to be used as a monotherapy, after surgical and radiation options have been exhausted, in place of standard medical therapy for GBM.

Contraindications, Warnings and Precautions

Contraindications

- Do not use the NovoTTF-100A if you have an implanted electronic device (e.g. deep brain stimulator, spinal cord stimulators, vagus nerve stimulator, pacemaker, defibrillator). Use of the device together with implanted electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device.
- Do not use the NovoTTF-100A if you have a skull defect (missing bone with no replacement) in areas intended for electrode placement. Placement of electrodes in these locations has not been tested and may cause skin breakdown and infections in the skin
- Do not use the NovoTTF-100A if you have a known hypersensitivity to conductive hydrogels like the gel used on EKG stickers or TENS electrodes. In this case, skin contact with the INE electrode gel may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings

- The NovoTTF-100A should be on and active for at least 18 hours a day in order to achieve the best response to treatment. Using the NovoTTF-100A for less than 18 hours a day lowers the chances that you will respond to treatment.
- Do not stop using the NovoTTF-100A before completing at least four weeks of contiguous therapy from treatment start. Stopping treatment before completing the first four weeks of therapy lowers the chances that you will respond to treatment.
- Continue use of the NovoTTF-100A even if you have used it less than the recommended 18 hours per day, unless instructed otherwise by your physician

- If you plan to be away from home for more than 2 hours, a back-up battery, and/or the power supply should be carried with you in the event the battery life is exhausted. Failure to take a spare battery and/or the power supply may result in treatment interruption. Interruptions in treatment may lower your chance to respond to treatment.
- Make sure you have at least 12 extra electrodes at all times to last you until the next electrode shipment arrives.
- Batteries may weaken over time and need to be replaced. You will know this has happened when the device running time on a fully charged battery begins to shorten (for example, when then low battery indicator light flashes within only 1.5 hours from the start of treatment). Failure to seek replacement batteries may result in delays in treatment. Interruptions in treatment may lower your chance to respond to treatment.
- The Troubleshooting guide should be carried with the user at all times. This guide is necessary to ensure proper operation of the NovoTTF-100A System.

Precautions

- Do not use the NovoTTF-100A if you are 21 years old or younger or if you are pregnant. The NovoTTF-100A has not been tested in children or pregnant women. It is unknown what side effects it may cause in these cases.
- Do not use the NovoTTF-100A if your tumor is located in the lower parts of the brain close to the spinal cord. The NovoTTF-100A has not been tested in patients with tumors in these locations and it is unknown whether these tumors will respond to treatment.
- In case of skin irritation such as redness beneath the electrodes, use of over the counter topical corticosteroids (0.1% hydrocortisone cream) when replacing electrodes can alleviate symptoms. If you do not use this cream, the skin irritation is likely to become more serious and may even lead to skin break down, infections, pain and blisters.
- In case of skin break down, infection, pain or blisters, contact your physician. You will be prescribed an antibacterial cream which should be applied when replacing electrodes. If you do not use this cream, your symptoms may continue and you may have to take a break from treatment, which may lower your chance to respond to treatment.
- Do not wet the electric filed generator or electrodes. Getting the electric filed generator wet may cause the generator to fail preventing you from receiving treatment for the recommended duration. Getting the electrodes wet is likely to cause the electrodes to come loose from your head. This will lead to shutdown of the generator and will require you to change the electrodes.
- Do not use any component not originally supplied with the NovoTTF-100A Treatment Kit. Use of other components can result in damage to the device, less than adequate therapy or increase in risk to the patient.

- The NovoTTF-100A is to be operated only after receiving training from qualified personnel. This training will include a detailed walk through of this manual and assisted practice in the use of the system. In addition you will be trained through simulated fault conditions, in what to do in the case of problems with treatment. Use of the NovoTTF-100A without receiving this training can result in damage to the device, less than adequate therapy or increase in risk to the patient.
- Do not operate the NovoTTF-100A if the generator, the INE Electrodes or any additional parts are obviously damaged (torn wires, loose connectors, loose sockets, cracks or breaks of the plastic enclosures). Use of damaged components can result in damage to the device, less than adequate therapy or increase in risk to the patient.
- Before connecting or disconnecting the electrodes, ensure that the NovoTTF power switch is in the OFF position. Disconnecting electrodes with the device power switch in the ON position may cause a device alarm to sound.
- Do not block the device vents (located on the sides of the NovoTTF-100A device). Blocking the vents may cause the device to overheat internally, leading to device shutdown and a break in treatment. If this occurs, unblock the vents, wait 5 minutes and restart therapy.
- Do not block the battery charger vents (located at the front of the battery chargers). Blocking the vents may cause the charger to overheat internally, leading to a charger malfunction. This could prevent your batteries from charging.
- Before using an INE Electrode, make sure its package is sealed by gently rubbing the package on all four sides. If the package is not sealed, the electrode may be damaged. A damaged electrode will not operate properly and will lead to device shutdown.
- Do not use an INE Electrode which has been opened previously. If the package is not sealed, the electrode may be damaged. A damaged electrode will not operate properly and will lead to device shutdown.
- The INE Electrodes are for single use and should not be re-used. Re-use will lead to poor adherence of the electrode to your skin and to device shutdown.
- Keep the NovoTTF-100A out of the reach of children.
- The suitability of the NovoTTF-100A System and INE Electrodes for full body scanners used in airports has not been tested. It is unknown what effects such scanners may have on the device.
- The NovoTTF-100A System and INE Electrodes will activate metal detectors.
- All servicing procedures must be performed by qualified and trained personnel.

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. The TTFields are inferred to disrupt the rapid cell division exhibited by cancer cells.[1]

The NovoTTF-100A System is comprised of two main components: (1) a Electric Field Generator (the NovoTTF-100A device); and (2) INE Insulated Electrodes (the electrodes). In addition, the following components are also included in the NovoTTF-100A Treatment Kit: power supply, portable battery, battery rack, battery charger, connection cable and carrying case.

Treatment parameters are preset by NovoCure such that there are no electrical output adjustments available to the patient. The patient must 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.

Principles of Operation

The NovoTTF-100A produces alternating electrical fields within the human body that are inferred 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 and geometrical shape of dividing 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).

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[1] 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.

In contrast, the TTFields have not been shown to have an effect on cells that are not undergoing division. Since most normal adult brain cells proliferate very slowly, if at all, they are hypothesized to be little 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. It is noted that, because TTFields are only applied to the brain, they have no 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 meaningful increase in tissue temperature Thus, TTField application has the advantage of being highly selective and is not expected to be associated with significant toxicity.

The above mechanisms of action are consistent with the extensive research regarding the effects of TTFields. These results demonstrate both disruption of cell division up to complete cessation of the process, as well as complete destruction of the dividing cells. It is important to note that all the described effects can be obtained by fields of low intensity such that they are not accompanied by any significant elevation of temperature.

Preclinical Data

TTFields have been shown both *in vitro* and *in vivo* to effectively inhibit cancer cell replication during mitosis without any 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[2].

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

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

frequencies (100-200 kHz), different intensities and for different periods of time[3].

Using a model developed to simulate the growth kinetics of a malignant tumor, the minimal treatment course duration for the NovoTTF-100A System has been determined to be approximately 4 weeks to reach tumor stabilization. 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.

[3] Kirson, E. D., V. Dbaly, et al. (2007).

Clinical Data

Pilot Clinical Study in Recurrent GBM[4]

The NovoTTF-100A has been tested in 10 recurrent GBM patients in a single center, pilot trial in Europe. In this trial, NovoTTF-100A monotherapy led to a significant increase in time to progression (from 13 to 26 weeks; p=0.013), PFS6 (from 15 to 50%) and overall survival (OS) (from 6.0 to 14.7 months; p=0.002) compared to matched concomitant and historical comparator groups. The only device related adverse event (AE) seen in this trial was a mild to moderate skin irritation beneath the device electrodes.

Other Clinical Experience in Recurrent GBM

In late 2009, NovoCure began limited marketing of the device in Europe under its CE mark approval. Fourteen (14) recurrent GBM patients have been treated so far with a median OS of 6.4 months, as of August 2010. No device events have been reported as of August 2010.

Pivotal Clinical Study in Recurrent GBM

Study Design: The study was a prospective, randomized, open label, active parallel control trial to compare the efficacy and safety outcomes of recurrent GBM patients treated with NovoTTF-100A to those treated with an effective best standard of care (BSC) chemotherapy (including bevacizumab).

The following were the objectives of the study:

- To prospectively compare the median overall survival of recurrent GBM patients treated with NovoTTF-100A to those treated with best standard of care (BSC)
- To prospectively determine PFS6, TTP, %1-year survival and quality of life of patients treated with NovoTTF-100A compared to BSC.
- To collect evidence of the safety of TTFields applied to patients with recurrent GBM using the NovoTTF-100A System.

[4] Ibid.

Eligibility Criteria: The inclusion and exclusion criteria for the trial were as follows:

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. Patients 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 patients 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/μL)
    6) Neutropenia (absolute neutrophil count < 1 x 10^3/μL)
    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)

Study Procedures:

Treatment Arm

At treatment initiation patients 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 patients were also instructed by the investigator on the operation of the NovoTTF-100A System and battery replacement. Once the patients were trained in operating the device they were released to continue treatment at home. The patients received continuous NovoTTF-100A treatment. Treatment was discontinued in the case of non-compliance or clinical disease progression.

Control Arm

All patients had baseline examinations performed prior to treatment initiation. Patients received the best effective standard of care chemotherapy practiced at each of the participating centers. The effective BSC treatments used in the study 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

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

Follow Up

During treatment, and until progression for patients who stopped treatment before progression, all patients 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 patient. Medical follow-up continued for 2 months following disease progression. Patient survival was assessed based on monthly telephone interviews with the patients' caregivers.

Subject Characteristics: 237 patients (120 NovoTTF-100A; 117 BSC) with progressive or recurrent GBM were enrolled in the study. Baseline characteristics 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 failure: 19%. Baseline characteristics were similar between treatment groups 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.

Demographics and Baseline Characteristics by Treatment Group		
Intent-to-Treat Population		
	NovoTTF-100A	**BSC**
Characteristics	**(N=120)**	**(N=117)**
	n (%)	**n (%)**
Race		
Caucasian	111 (93)	106 (91)
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)
Frontal Tumor Position	38 (32)	58 (50)
Bilateral or Midline Tumor Location	23 (19)	17 (15)
Prior Avastin Use	24 (20)	21 (18)
Re-operation for Recurrence	33 (28)	29 (25)
Prior Low-grade Glioma	12 (10)	11 (9)
Median Age (years) (min, max)	54 (24, 80)	54 (29,74)
Median Weight (kg)	80	80.5
Mean # of Prior GBM Recurrences	1.5	1.3
Median Karnofsky Performance Score (min, max)	80 (50, 100)	80 (50, 100)
Median Tumor Area (mm^2)	1440	1391
Median Time from GBM Diagnosis to Randomization (days)	334.5	340
Mean Time from last Radiotherapy Dose to Randomization (Months)	13.71	13.93

Efficacy Results:

Primary Efficacy Endpoint: Overall survival (OS)

The Per Protocol (PP) population excludes NovoTTF-100A and BSC patients who did not complete a full treatment course. The PP analysis showed a higher OS in the treated patients than in the BSC controls that was both clinically and statistically significant (median OS=7.8 vs. 6.5 months; p=0.04). Overall survival in patients treated with NovoTTF-100A compared with patients treated with BSC in the Intent-to-Treat (ITT) population was comparable (median OS=6.3 vs. 6.4 months; p=0.98). In the US, the median overall survival was 6.1 vs. 5.3 months in the ITT population and 7.3 vs. 5.9 months in the PP population. Considering both the ITT and PP results, the pivotal study data establish that NovoTTF-100A therapy is at least as effective as BSC therapy in extending OS.

Overall Survival Summary			
		Treatment Group	
	Population	**NovoTTF**	**BSC**
N	ITT PP	120 93	117 79
Median OS (months)	ITT PP	6.3 **7.8**	6.4 **6.5**
p- Value	ITT PP	0.72 **0.04**	
HR (95% CI)	ITT PP	1.00 (0.76 – 1.32) 0.84 (0.60 – 1.16)	

Correlation between Treatment Compliance and Overall Survival: The NovoTTF-100A device has an internal log file which allows the calculation of patient compliance with treatment. Significantly higher overall survival (p=0.0415) was observed in patients who were treated 75% or more of the time on average (OS=7.7 months) compared to patients treated less than 75% of the time on average (OS=4.5 months).

Secondary Efficacy Endpoints: Secondary endpoint results support the positive findings in the primary endpoint. The one-year survival is higher in the NovoTTF-100A group than in the BSC group in the PP population (27.8% vs. 21.6%) and is similar in the NovoTTF-100A and BSC groups in the ITT population (21.9% vs. 22.1%). Progression free survival at 6 months (PFS6) is higher in the PP population in NovoTTF-100A patients than in controls (26.2% vs. 12.7%; p=0.02) and is the same in the ITT population (21.4% vs. 15.2%; p=0.13). Radiological response rate is higher in the NovoTTF-100A group than in the BSC group in both the PP (15.9% vs. 6.7%) and ITT (14% vs. 9.6%) populations. Time to progression (TTP) was the same in both groups.

Summary of Secondary Endpoints			
Secondary Endpoints		**Treatment Group**	
	Population	**NovoTTF**	**BSC**
N	ITT PP	120 93	117 79
1-year survival %	ITT PP	21.9 27.8	22.1 21.6
PFS6 (%)	ITT PP	21.4 **26.2**	15.2 **12.7**
Chi-square p-value	ITT PP	0.13 **0.02**	
Radiological Response Rate (%)	ITT PP	14.0 **15.9**	9.6 **6.7**
Median TTP (weeks)	ITT PP	9.3 10.1	9.6 9.7

Quality of Life: Quality of life in patients using the NovoTTF-100A System was improved over that of those on BSC chemotherapy in most subscale domains, including vomiting, nausea, pain, diarrhea, constipation, cognitive and emotional functioning.

Safety Results: The characteristic adverse events of almost all chemotherapies are seen in a significantly higher proportion of BSC control patients than in NovoTTF-100A patients: gastrointestinal (30% vs. 8%; p=0.0009), hematological (19% vs. 4%; p<0.0001) and infectious (12% vs. 4%; p=0.0376). Mild to moderate skin reaction beneath the device electrodes was observed in 16% of NovoTTF-100A patients; none of these cases was assessed as severe by the investigator, all resolved after discontinuing treatment, and all were easily treated with topical steroids and periodic shifting of electrode positions.

Adverse Events by Body Systems			
	NovoTTF-100A	**BSC**	**P-value**
System Organ Class	**(n=116)**	**(n=91)**	
Gastrointestinal disorders	*9 (7.8%)*	*27 (29.7%)*	***<.0001***
Blood and lymphatic system disorders	*5 (4.3%)*	*17 (18.7%)*	***0.0009***
Infections and infestations	*5 (4.3%)*	*11 (12.1%)*	***0.0376***
Respiratory, thoracic and mediastinal disorders	7 (6.0%)	10 (11.0%)	0.1975
Metabolism and nutrition disorders	9 (7.8%)	12 (13.2%)	0.1992
Ear and labyrinth disorders	1 (0.9%)	3 (3.3%)	0.2066
Eye disorders	3 (2.6%)	5 (5.5%)	0.2813
Musculoskeletal and connective tissue disorders	6 (5.2%)	8 (8.8%)	0.3034
Nervous system disorders	50 (43.1%)	33 (36.3%)	0.319
Renal and urinary disorders	7 (6.0%)	3 (3.3%)	0.3619
Vascular disorders	5 (4.3%)	6 (6.6%)	0.4673
Psychiatric disorders	12 (10.3%)	7 (7.7%)	0.5118
Skin and subcutaneous tissue disorders	9 (7.8%)	9 (9.9%)	0.5891
General disorders and administration site conditions	15 (12.9%)	14 (15.4%)	0.6137
Investigations	8 (6.9%)	5 (5.5%)	0.6798
Endocrine disorders	2 (1.7%)	2 (2.2%)	0.8059
Neoplasms benign, malignant and unspecified (including cysts and polyps)	2 (1.7%)	2 (2.2%)	0.8059
Cardiac disorders	8 (6.9%)	6 (6.6%)	0.9313
Injury, poisoning and procedural complications	*21 (18.1%)*	*1 (1.1%)*	*<.0001*

Conclusions: The NovoTTF-100A is a portable, battery operated device which delivers TTFields to patients with recurrent GBM. The results of the pivotal trial showed that NovoTTF-100A patients had equivalent or better overall survival than did patients receiving the best available chemotherapy in the US today (OS 6.3 vs. 6.4 months; HR 1.0; p=0.98). When comparing device patients who completed at least one treatment course (minimum 4 weeks) to effective chemotherapy control patients receiving at least one treatment course, the device extends overall survival (median OS = 7.8 vs. 6.5 months; p=0.04). Similar results showing equivalence of NovoTTF-100A compared to BSC chemotherapy in the ITT population were seen in all secondary endpoints. Of note, in the PP population, a significant increase was seen in PFS6 when using the device, as well as a higher radiological response rate (RR), over effective chemotherapy controls. The NovoTTF-100A patients experienced fewer adverse events in general, significantly fewer treatment related adverse events, and significantly lower gastrointestinal, hematological and infectious adverse events compared to BSC controls. The only device-related adverse events seen were a mild to moderate skin irritation beneath the device electrodes, which was easily treated with topical ointments. Finally, quality of life was superior in NovoTTF-100A patients when compared to effective BSC chemotherapy.

Directions for Use

Detailed directions for use for the NovoTTF-100A System can be found in:

- The NovoTTF-100A Patient Information and Operation Manual

Abbreviations

AE – Adverse event

BSC – Best standard of care (effective chemotherapies)

GBM – Glioblastoma Multiforme (Glioblastoma, Astrocytoma grade IV), the most common and anaplastic primary brain tumor.

ITT – Intent-to-Treat

kHz – kilo hertz; number of cycles per second

NovoTTF-100A (also called **TTField Generator** or **NovoTTF-100A device)** – A portable battery, or power supply, operated device for delivering 200 kHz TTFields to the brain of patients with recurrent GBM.

OS – Overall survival

PFS6 – Proportion of patients alive and progression free at 6 months from randomization

PP – Per Protocol

Radiological Response Rate - sum of complete and partial radiological response rates

TTFields – Tumor Treating Fields: Low intensity (1-3 V/cm), intermediate frequency (100-300 kHz), alternating electric fields, delivered using insulated electrodes to the region of the body inflicted with a solid tumor. The fields have been shown *in vitro* to arrest the replication of tumor cells by disrupting the proper formation of the microtubule spindle and by dielectrophoretic disruption of cell integrity during late telophase.

TTP – Time to progression

V/cm – Volts per centimeter; the unit of intensity measurement of electric fields

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NovoTTF-100A

Patient Information

and

Operation Manual

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Issue Date: [To be inserted]

Draft

1 Table of Contents

This manual is intended for both physicians prescribing the use of the NovoTTF-100A Treatment Kit and INE Electrodes (Sterile), and for patients receiving TTField treatment using this device.

Additional information is found in the following materials accompanying each of the system parts and accessories:

1. Portable Battery Leaflet – QSD-QR-309
2. Power Supply Leaflet – QSD-QR-326
3. Portable Battery Charger Leaflet– QSD-QR-307
4. Connection Cable Leaflet– QSD-QR-311
5. Battery Rack Leaflet– QSD-QR-312

2 Glossary of Medical Terms

Adverse events – problems that may occur when undergoing treatment
Best standard of care (BSC) – the best treatment available in the U.S.
Cancer – abnormal cell division that spreads without control
Chemotherapy – medication used to destroy cancer cells
Clinical trial – a research study that involves people
Contraindications – situations when a treatment should not be used
EN 60601-1 and 2 - Standards for safety of medical devices and their interactions with other electric appliances
Glioblastoma Multiforme (GBM) – a type of brain cancer; other medical names for GBM are "glioblastoma", "grade IV glioma" or "grade IV astrocytoma"
INE Electrodes – Insulated Electrodes
Local – in one part of the body
MRI scan - a procedure that uses a magnet to create pictures of areas inside the body
NovoTTF-100A – (also called **TTField generator** or **NovoTTF-100A device)** – A portable battery, or power supply, operated device for delivering 200 kHz TTFields to the brain of patients with recurrent GBM
NovoTTF-100A Treatment Kit – The TTField generator together with all associated components (batteries, charger, connection cable, power supply and carrying case)
NovoTTF-100A System – The NovoTTF-100A Treatment Kit together with the INE electrodes
Radiation – a treatment involving high-intensity x-rays used to kill tumor cells
Recurrence – when cancer comes back after removal
Steroids – a medication used to lower swelling around a brain tumor and help with symptoms related to the brain
Systemic – throughout the body
Topical – on the surface of the skin
TTFields – Tumor Treating Fields: Low intensity (1-3 V/cm), intermediate frequency (100-300 kHz), alternating electric fields, delivered using insulated electrodes to the region of the body inflicted with a solid tumor. The fields have been shown *in vitro* to arrest the

replication of tumor cells by disrupting the proper formation of the microtubule spindle and by dielectrophoretic disruption of cell integrity during late telophase.

Tumor – an abnormal growth of tissue

3 What is NovoTTF-100A Therapy and How Does It Work?

The NovoTTF-100A System is intended as a treatment for adult patients (greater than 21 years of age) with histologically- or radiologically-confirmed brain cancer (called glioblastoma multiforme, or "GBM"), following recurrence in the supra-tentorial region of the brain. The NovoTTF-100A is intended to be used alone, after surgical and radiation treatment options have been exhausted, in place of standard medical therapy for GBM. A discussion of brain cancer, treatment options and options for when brain cancer comes back can be found at the end of this Patient Manual in Sections 31.

The NovoTTF-100A System is a portable battery or power supply operated device which produces electrical fields, called tumor treatment fields ("TTFields"). TTFields are applied to your head through electrodes connected to an electric field generator. The TTFields are intended to destroy brain cancer cells. The TTField generator and battery are carried in a shoulder bag, and should be used all the time.

Throughout this manual, the term "NovoTTF-100A Treatment Kit" refers to the NovoTTF-100A electric field generator ("the device"), connection cable, power supply, battery, battery charger and battery rack. The term "NovoTTF-100A System" ("NovoTTF-100A") refers to the Treatment Kit plus the INE Electrodes.

4 Contraindications, Warnings and Precautions

Contraindications

- Do not use the NovoTTF-100A if you have an implanted electronic device (e.g. deep brain stimulator, spinal cord stimulators, , vagus nerve stimulator, pacemaker, defibrillator). Use of the device together with implanted electronic devices has not been tested and may theoretically lead to malfunctioning of the implanted device.
- Do not use the NovoTTF-100A if you have a skull defect (missing bone with no replacement) in areas intended for electrode placement. Placement of electrodes in these locations has not been tested and may cause skin breakdown and infections in the skin and rarely even in the brain.
- Do not use the NovoTTF-100A if you have a known hypersensitivity to conductive hydrogels like the gel used on EKG stickers or TENS electrodes. In this case, skin contact with the INE electrode gel may commonly cause increased redness and itching, and rarely may even lead to severe allergic reactions such as shock and respiratory failure.

Warnings

- The NovoTTF-100A should be on and active for at least 18 hours a day in order to achieve the best response to treatment. Using the NovoTTF-100A for less than 18 hours a day lowers the chances that you will respond to treatment.
- Do not stop using the NovoTTF-100A before completing at least four weeks of contiguous therapy from treatment start. Stopping treatment before completing the first four weeks of therapy lowers the chances that you will respond to treatment.
- Continue use of the NovoTTF-100A even if you have used it less than the recommended 18 hours per day, unless instructed otherwise by your physician
- If you plan to be away from home for more than 2 hours, a back-up battery, and/or the power supply should be carried with you in the event the battery life is exhausted. Failure to take a spare battery and/or the power supply may result in

treatment interruption. Interruptions in treatment may lower your chance to respond to treatment.

- Make sure you have at least 12 extra electrodes at all times to last you until the next electrode shipment arrives.
- Batteries may weaken over time and need to be replaced. You will know this has happened when the device running time on a fully charged battery begins to shorten (for example, when then low battery indicator light flashes within only 1.5 hours from the start of treatment). Failure to seek replacement batteries may result in delays in treatment. Interruptions in treatment may lower your chance to respond to treatment.
- The Troubleshooting guide should be carried with the user at all times. This guide is necessary to ensure proper operation of the NovoTTF-100A System.

Precautions

- Do not use the NovoTTF-100A if you are 21 years old or younger or if you are pregnant. The NovoTTF-100A has not been tested in children or pregnant women. It is unknown what side effects it may cause in these cases.
- Do not use the NovoTTF-100A if your tumor is located in the lower parts of the brain close to the spinal cord. The NovoTTF-100A has not been tested in patients with tumors in these locations and it is unknown whether these tumors will respond to treatment.
- In case of skin irritation such as redness beneath the electrodes, use of over the counter topical corticosteroids (0.1% hydrocortisone cream) when replacing electrodes can alleviate symptoms. If you do not use this cream, the skin irritation is likely to become more serious and may even lead to skin break down, infections, pain and blisters.
- In case of skin break down, infection, pain or blisters, contact your physician. You will be prescribed an antibacterial cream which should be applied when replacing electrodes. If you do not use this cream, your symptoms may continue and you may have to take a break from treatment, which may lower your chance to respond to treatment.

- Do not wet the electric filed generator or electrodes. Getting the electric filed generator wet may cause the generator to fail preventing you from receiving treatment for the recommended duration. Getting the electrodes wet is likely to cause the electrodes to come loose from your head. This will lead to shutdown of the generator and will require you to change the electrodes.
- Do not use any component not originally supplied with the NovoTTF-100A Treatment Kit. Use of other components can result in damage to the device, less than adequate therapy or increase in risk to the patient.
- The NovoTTF-100A is to be operated only after receiving training from qualified personnel. This training will include a detailed walk through of this manual and assisted practice in the use of the system. In addition you will be trained through simulated fault conditions, in what to do in the case of problems with treatment. Use of the NovoTTF-100A without receiving this training can result in damage to the device, less than adequate therapy or increase in risk to the patient.
- Do not operate the NovoTTF-100A if the generator, the INE Electrodes or any additional parts are obviously damaged (torn wires, loose connectors, loose sockets, cracks or breaks of the plastic enclosures). Use of damaged components can result in damage to the device, less than adequate therapy or increase in risk to the patient.
- Before connecting or disconnecting the electrodes, ensure that the NovoTTF power switch is in the OFF position. Disconnecting electrodes with the device power switch in the ON position may cause a device alarm to sound.
- Do not block the device vents (located on the sides of the NovoTTF-100A device). Blocking the vents may cause the device to overheat internally, leading to device shutdown and a break in treatment. If this occurs, unblock the vents, wait 5 minutes and restart therapy.
- Do not block the battery charger vents (located at the front of the battery chargers). Blocking the vents may cause the charger to overheat internally, leading to a charger malfunction. This could prevent your batteries from charging.
- Before using an INE Electrode, make sure its package is sealed by gently rubbing the package on all four sides. If the package is not sealed, the electrode may be damaged. A damaged electrode will not operate properly and will lead to device shutdown.

- Do not use an INE Electrode which has been opened previously. If the package is not sealed, the electrode may be damaged. A damaged electrode will not operate properly and will lead to device shutdown.
- The INE Electrodes are for single use and should not be re-used. Re-use will lead to poor adherence of the electrode to your skin and to device shutdown.
- Keep the NovoTTF-100A out of the reach of children.
- The suitability of the NovoTTF-100A System and INE Electrodes for full body scanners used in airports has not been tested. It is unknown what effects such scanners may have on the device.
- The NovoTTF-100A System and INE Electrodes will activate metal detectors.
- All servicing procedures must be performed by qualified and trained personnel.

5 What are the Risks of Treatment with NovoTTF-100A?

Mild to moderate skin irritation is commonly seen beneath the electrodes when using the NovoTTF-100A System. In general, these cases are not severe, can be treated with topical ointments (steroids, etc.) or by moving the electrodes, and are not permanent. Headaches, general weakness, convulsions and falls were seen in the clinical study. These events are often seen in patients with recurrent GBM who are not undergoing NovoTTF-100A treatment. There was not a significant increase in the number of these events compared to patients receiving chemotherapies. Only skin redness and open sores are clearly related to the NovoTTF-100A treatment itself.

The following is a list of the risks of medical problems in patients receiving NovoTTF-100A therapy compared to patients receiving chemotherapy:

Risk of medical problems in patients receiving NovoTTF-100A therapy compared to patients receiving chemotherapy (BSC)

Medical problems	NovoTTF-100A	BSC
Decreased white and red blood cell counts	5 out of 116 subjects	17 out of 91 subjects
Vomiting, nausea and diarrhea	9 out of 116 subjects	27 out of 91 subjects
General disorders	15 out of 116 subjects	14 out of 91 subjects
Infections	5 out of 116 subjects	11 out of 91 subjects
Rash under device electrodes and other injuries	21 out of 116 subjects	1 out of 91 subjects
Nutrition disorders	9 out of 116 subjects	12 out of 91 subjects
Brain disorders*	50 out of 116 subjects	33 out of 91 subjects
Behavioral disorders*	12 out of 116 subjects	7 out of 91 subjects
Breathing disorders	7 out of 116 subjects	10 out of 91 subjects

* Brain and behavioral disorders are normal symptoms of recurrent GBM

Below is a table of risks that certain events might happen if the NovoTTF-100A System is used correctly and incorrectly:

Risks of correct and incorrect use of the NovoTTF-100A System

Event	Likelihood of Event	Outcome/harm	Likelihood of outcome
Correct use			
Use of the device for at least 4 weeks	91 out of 120 subjects	Survival extended compared to chemotherapy	96 out of 100 ($p=0.04$)
Use of the device for at least 18 hours a day	85 out of 98 subjects	Survival 3 months longer compared to subjects treated less than 18 hours a day	95 out of 100 ($p<0.05$)
Skin reaction	18 out of 116 subjects	Mild scalp redness	17 out of 18 subjects
Skin reaction	18 out of 116 subjects	Moderate scalp redness	6 out of 18 subjects
Incorrect use			
Use of the device for any duration	116 out of 120 subjects	Survival equal to that of subjects receiving chemotherapy	95 out of 100 ($p<0.05$)
Use of the device for less than 18 hours a day	13 out of 98 subjects	Survival 3 months shorter compared to subjects treated at least 18 hours a day	95 out of 100 ($p<0.05$)
Skin reaction	1 out of 116 subjects	Open sore on scalp	1 out of 1 subjects
Use in a patient with a pacemaker	1 out of 121 subjects	Heart problems	0 out of 1 subject
Incorrect uses we did not predict	Unknown	Unknown	Unknown

6 What are the Benefits of Treatment with NovoTTF-100A?

By using the NovoTTF-100A System instead of chemotherapy drugs, patients are able to reduce the chances of experiencing the side effects of chemotherapy, such as infections, nausea, vomiting, loss of appetite, and fatigue. In addition, patients treated with the NovoTTF-100A System lived at least as long as patients treated with chemotherapy and had a better quality of life.

7 What Studies Have Been Conducted with NovoTTF-100A?

The NovoTTF-100A System was tested in a clinical study against the best standard of care (BSC) chemotherapy available today. 237 patients (120 NovoTTF-100A and 117 BSC) with progressive or recurrent GBM were enrolled in the study.

Patients who used the NovoTTF-100A System as recommended (for at least 4 weeks) showed improved survival over patients who were taking standard of care chemotherapies. That is, NovoTTF-100A patients lived for an average of 7.8 months after treatment was started, while chemotherapy patients lived for an average of 6.5 months. In addition, more patients who used the NovoTTF-100A as recommended were alive a year after starting treatment. That is, 28% of NovoTTF-100A patients were alive at one year compared to 22% of patients who received chemotherapy. Finally, when patients used the NovoTTF-100A as recommended (for at least 4 weeks), the tumor shrank (according to an MRI scan) in 16% of NovoTTF-100A patients compared to only 7% of patients who received chemotherapy. The NovoTTF-100A was at least as good as BSC chemotherapy in other measures of effectiveness of treating GBM. Quality of life was significantly improved in NovoTTF-100A patients over chemotherapy patients.

The percent of patients with adverse events classified as relating to the gastrointestinal system, blood, or infections were much lower in the NovoTTF-100A group than in the BSC chemotherapy group. Mild to moderate skin reaction beneath the electrodes was observed in 16% of NovoTTF-100A patients, which was expected. None of these cases of skin

irritation were severe, they were easily treated with topical steroids and periodic shifting of electrode positions, and they all resolved after stopping treatment. One patient developed an open sore beneath his electrodes, which healed after moving the electrodes to another location.

The clinical study found that the NovoTTF-100A was at least as effective as the BSC chemotherapy in treating GBM, with a better quality of life for patients and without the side effects of chemotherapy.

Quality of life with the NovoTTF-100A compared to chemotherapy

Overall quality of life	Better
Functional scales	
Thought functioning	Better
Emotional functioning	Better
Role functioning	Better
Social functioning	Better
Physical functioning	Worse
Symptoms	
Pain	Better
Appetite Loss	Better
Constipation	Better
Diarrhea	Better
Fatigue	Better
Sleep difficulties	Better
Nausea and Vomiting	Better
Financial difficulties	Worse
Breathing difficulties	Worse

Ask your doctor for more details about the clinical studies of the NovoTTF-100A System and the results of those studies. For more information, visit our website: *www.novocure.com*

8 About the NovoTTF-100A System

The NovoTTF-100A System is intended as a treatment for adult patients (greater than 21 years of age) with histologically- or radiologically-confirmed glioblastoma multiforme, following recurrence in the supra-tentorial region of the brain. The NovoTTF-100A is intended to be used as a monotherapy, after surgical and radiation options have been exhausted, in place of standard medical therapy for GBM.

The NovoTTF-100A System is a portable, battery operated medical device which delivers electric fields called "TTFields" to the brain by means of electrodes. TTFields are electric fields that are intended to destroy cancer cells.

The NovoTTF-100A is intended as a physician-prescribed, home use device. You are expected to use the NovoTTF-100A as many hours per day as possible with short breaks for personal needs. The minimal recommended treatment duration is four weeks. When starting treatment at your doctor's clinic, you will be instructed in how to use the system (put on your head, turn on and off, etc.), replace electrodes with the assistance of a caregiver, recharge and replace portable batteries, and connect to the power supply. You will also be taught what to do in the case of system alarms and will be given a telephone number to call for technical support. After this short initial training period at the physician's office, you, with the assistance of a family member or care provider, should be able to properly operate the NovoTTF-100A System, replace rechargeable batteries, charge the rechargeable batteries and replace electrodes as needed.

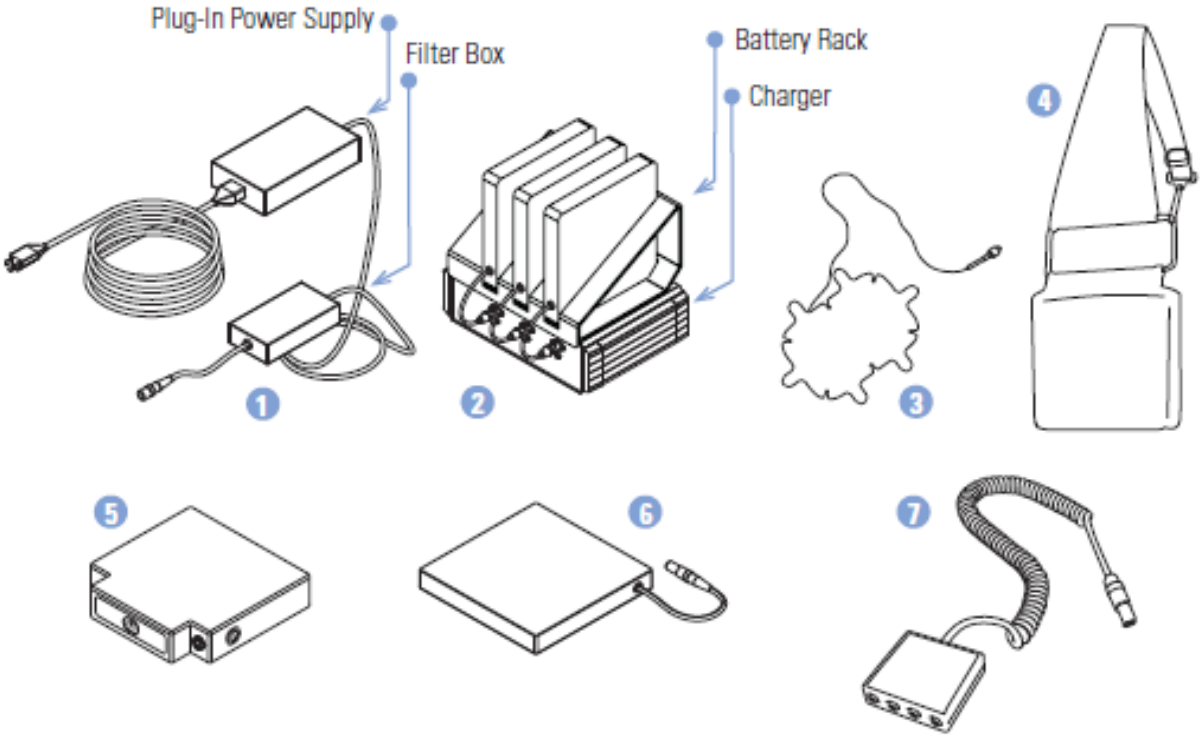
The NovoTTF-100A is intended to be portable when operated from a battery, which will allow you to continue your normal daily activities while carrying the generator and battery in a shoulder bag or backpack. The Treatment Kit includes four rechargeable batteries, each of which will operate the system for approximately two to three hours. For sleeping or other times when you plan to stay in the same place for a period of time, the device can be operated on a power supply plugged into a standard wall outlet without the need to change batteries.

The NovoTTF-100A does not require any periodic maintenance nor does it have any adjustments or settings that need to be manipulated. You only need to make sure the device has a power supply (a charged battery, or is plugged into the wall) and turn it on and off. If the device is not operating properly, either due to a problem with the set up or an internal error, an alarm will sound to notify you. A simple troubleshooting guide is provided in this manual and round-the-clock technical support is available through NovoCure.

The disposable, insulated electrode arrays will need to be replaced periodically, typically every 4-7 days (once or twice a week; up to 6 times a month), in order to re-shave the scalp to provide good contact between the electrode array and the scalp.

Treatment breaks should be kept to a minimum. Treatment may be interrupted for personal needs such as bathing, exercise, or any situation where the device may be a distraction. Treatment is also stopped for replacement of the electrodes. In order to take a shower, you will need to disconnect from the device (leaving the electrodes on your head), put on a shower cap and be cautious not to get your head wet. You can take a full shower and wet your head when you are not wearing the electrodes (for example, when you have taken them off, before replacing them with a new pair of electrodes). When leaving the house, you can put a wig or hat on your head over the electrodes, if you wish.

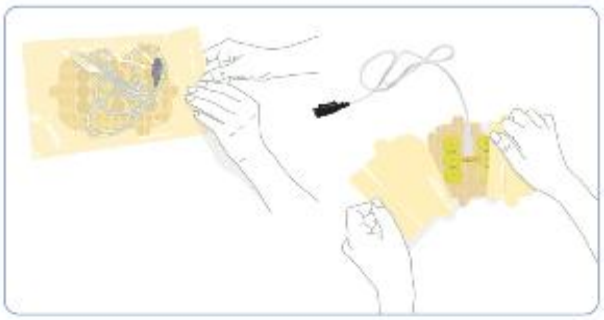
9 Overview of the NovoTTF-100A System



1 Plug in power supply **2** Charger for portable batteries **3** Insulated electrode
4 Device & battery carrying bag **5** NovoTTF-100A electric field generator (the Device)
6 Portable battery **7** Connection cable & box

10 Treatment Setup

1. Prepare Scalp
Shave and clean

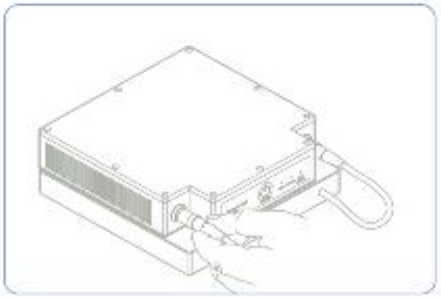


2. Remove 4 Electrodes From Package

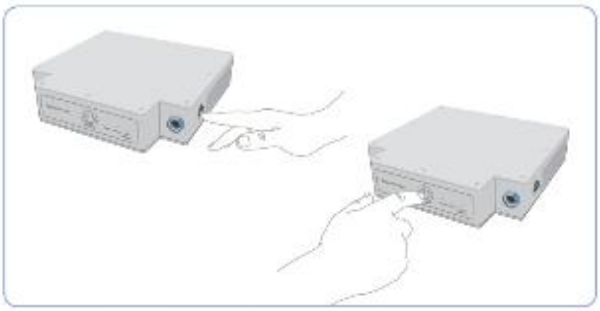
3. Place Electrodes on Scalp
Add color coded rings to indicate position; Apply based on electrode position diagram from physician

4. Connect Electrodes to Connection Cable & Box
Match colored rings to color coded sockets

5. Place Device and Battery in Bag (if applicable) and Connect Battery or Power Supply



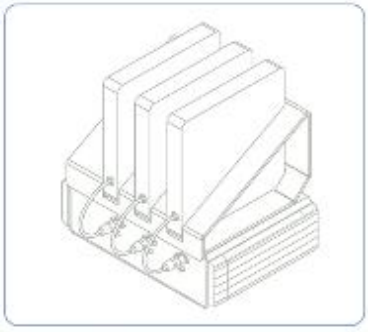
6. Connect Connection Cable to Device



7. Start Treatment
Turn on power switch and push TTFields button

8. Place Bag Over Shoulder and Clip
If applicable

9. Replace Electrodes as Needed

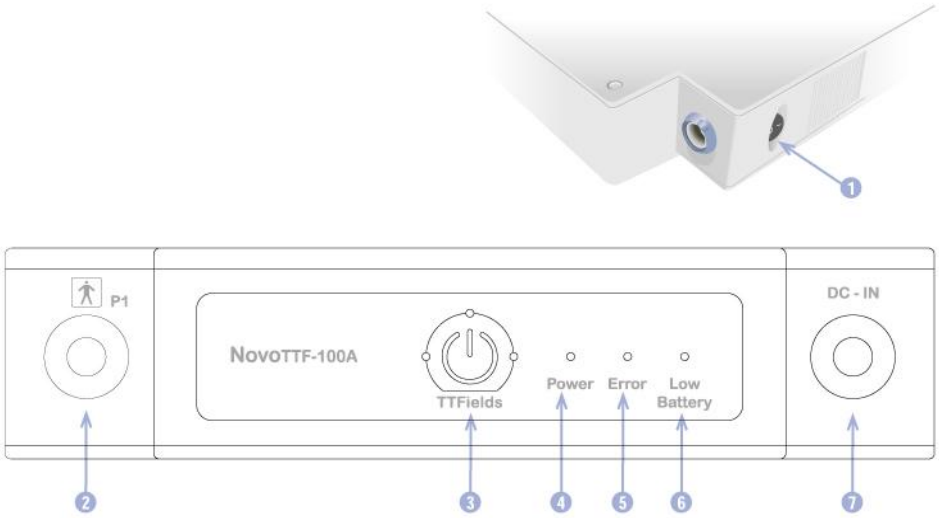


10. Recharge Batteries When Not in Use

11 The Electric Field Generator (the Device)

The NovoTTF-100A is an automatic system. The TTField treatment should be kept on continuously, to the extent possible, when awake and when sleeping. Breaks from treatment should be kept as short as possible.

The electric field generator has the following controls that will allow you to operate the system:



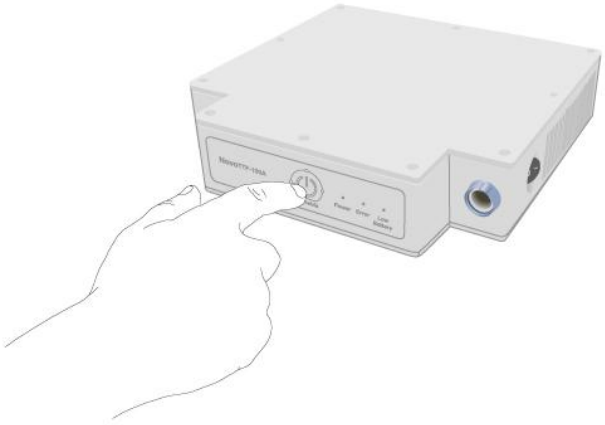
1 NovoTTF-100A power button **2** Connection cable socket (P1) **3** TTField therapy ON/OFF button **4** Power ON indicator **5** Error indicator **6** Low Battery indicator **7** Battery connector socket

12 Starting & Stopping the Electric Field Generator

To start treatment,

1. Apply electrodes to the scalp (with the assistance of a caregiver) and connect them to the connection cable as described in the INE Electrode User Manual.
2. Connect the connection cable to the device as described in section 16 keeping the arrows on the connector up, facing the "P1" label.
3. Connect a charged battery to the device (see section 13 for detailed instructions).
4. Turn the power button on the side panel of the device to the ON position.

5. Wait approximately 3 seconds for the blue lights surrounding the TTFields button to stop blinking.
6. Press the TTFields therapy button once – this will start treatment.

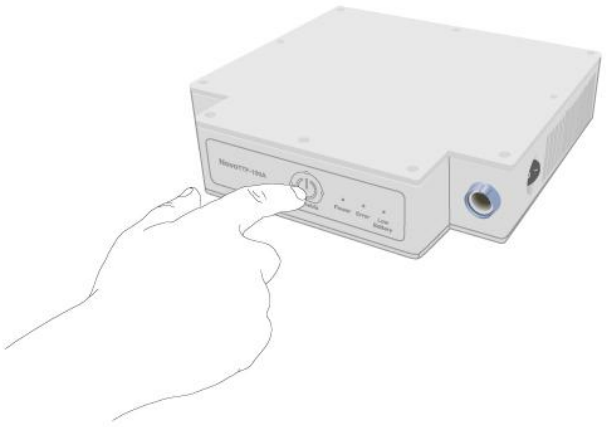


The three blue indicators surrounding the TTFields therapy button will light up and remain on for as long as treatment continues. The illumination of the three blue indicators around the TTFields button tells you that the treatment is operating. If these indicators are not illuminated, then the treatment is not running and you should re-check the setup and re-start the procedure. If, after re-checking the setup and re-starting the procedure, the indicators are still not illuminated, then consult the troubleshooting guide in this manual. If you still have problems operating the device, call the NovoCure technical support center at 1-800-978-0265.

Stopping treatment may be performed in each of the following situations:

A. When the Device is Running Properly, But You Need to Stop Treatment to Take a Break:

Press the TTFields button – The three blue lights surrounding the button will turn off. This turns the TTField therapy off, but the device power is still on.



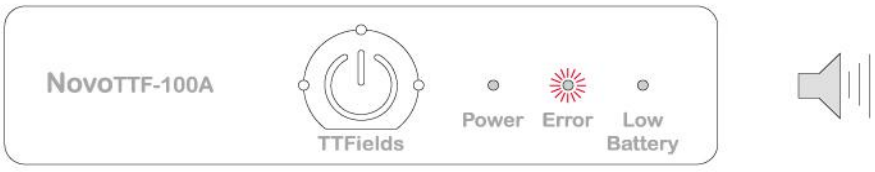
Then, turn off the device by turning the power button on the side panel of the device to the OFF position.

B. When an Error Condition Occurs:

If an error occurs, the device automatically shuts off the TTField output to the patient, the device makes a loud intermittent beeping noise, and the red Error indicator lights up (as shown below).

To turn off the device:

1. Press the TTFields button on the front panel in order to stop the alarm sound. The red Error indicator light will turn off.
2. Turn off the device by turning the power button on the side panel of the device to the OFF position.
3. Refer to the troubleshooting section of this guide for instructions on diagnosing and fixing problems. If no problem is found, the device can be re-started and treatment resumed. If the alarm continues and no problem can be found, then contact NovoCure technical support (see section 28).

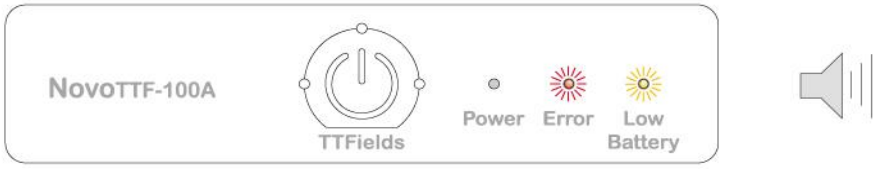


C. When the Low Battery Indicator Lights Up:

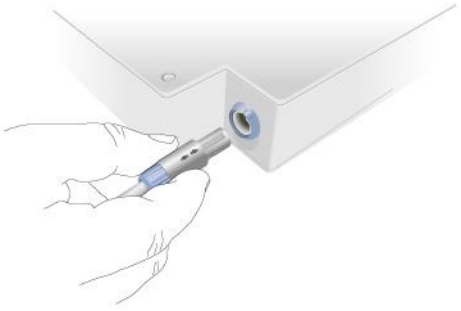
When your battery runs out (after about 2-3 hours), an alarm will sound, the TTFields therapy will shut down and both the yellow Low Battery indicator and red Error indicator will light up. This alarm sound is the same alarm sound the device makes for an error, but in this case *both the yellow and red indicators* will be illuminated instead of just the red indicator associated with an error.

To turn off the device:

1. Press the TTFields button on the front panel in order to stop the alarm sound. The red Error and the yellow Low Battery indicators will turn off.
2. You should now replace the battery according to the procedure in the next section (section 13).



13 Connecting & Disconnecting the Portable Battery



The NovoTTF-100A Treatment Kit comes with 4 rechargeable batteries, each with a cord to connect it to the device. The NovoTTF-100A uses one (1) battery at a time, and the other three (3) batteries should be kept in the battery charger. Each battery lasts 2-3 hours, and must be replaced each time it runs out (when the yellow Low Battery indicator lights up, as described in the previous section (section 12)). If you plan to be away from home for more than 2 hours, care should be taken to carry back-up batteries or a power supply.

The batteries will recharge in their charger (see section 14 of this manual) in about four to five hours. The batteries will generally hold their charge (not deplete) when they are off the charger for short periods of time (hours, but not days). For this reason, it is best to keep the batteries you are not using in the charger at all times, if possible. The batteries will be able to be charged and depleted (used up) repeatedly for a period of approximately six to nine months. Over time, the batteries will lose their capacity, so that the length of time they will be able to run the device (before getting a low battery alarm) gets shorter. You may contact NovoCure technical support (see section 28 of this manual) to get replacement batteries if you feel your batteries do not run the device for long enough.

When the yellow Low Battery indicator lights up, the battery should be replaced according to the following procedure:

1. Press the TTFields button once to turn off the alarm sound.
2. Turn OFF the device using the power button.
3. Disconnect the battery connector from the blue socket on the front panel.
4. Make sure to hold the connector as shown, holding the connector by its sleeve and not pulling on the cord.
5. Remove the battery from the device bag (do not lift or pull the battery by its cable).
6. Insert a fully charged battery into the device bag.
7. Connect the battery connector from the new, fully charged battery to the blue socket on the front panel holding the arrows on the connector up toward the "DC IN" label on the device.
8. Turn ON the device and initiate treatment per the instructions in Section 6.
9. Connect the used portable battery to its charger for charging (as described in section 14).

14 Charging the Portable Battery

The battery charger recharges depleted (no longer able to power a device) batteries using power from a standard wall socket. Each battery has a cord that connects it to the device and will also connect it to the charger.

The battery charger must be powered from a standard wall socket. Before charging your portable batteries, plug the charger power cord into a standard electric wall socket and turn on the power button located at the back.

To recharge a used battery:

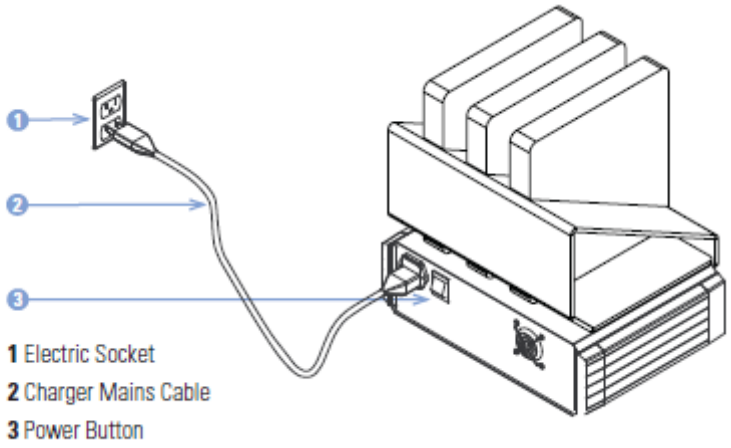
1. Place the depleted battery in the charger and connect its connector to an available charger socket, as shown in the diagram on the next page.
2. If connected correctly, the Charge indicator on the front face of the charger should light up in red, showing that the battery is charging.
3. Once a battery is fully charged, after about 4-5 hours, the Charge indicator light will turn from red to green.

All 3 portable batteries which are not in use should be placed in the charger and their cables connected to the charging sockets at all times. The batteries will not be hurt by keeping them plugged into the charger even after they are fully charged.

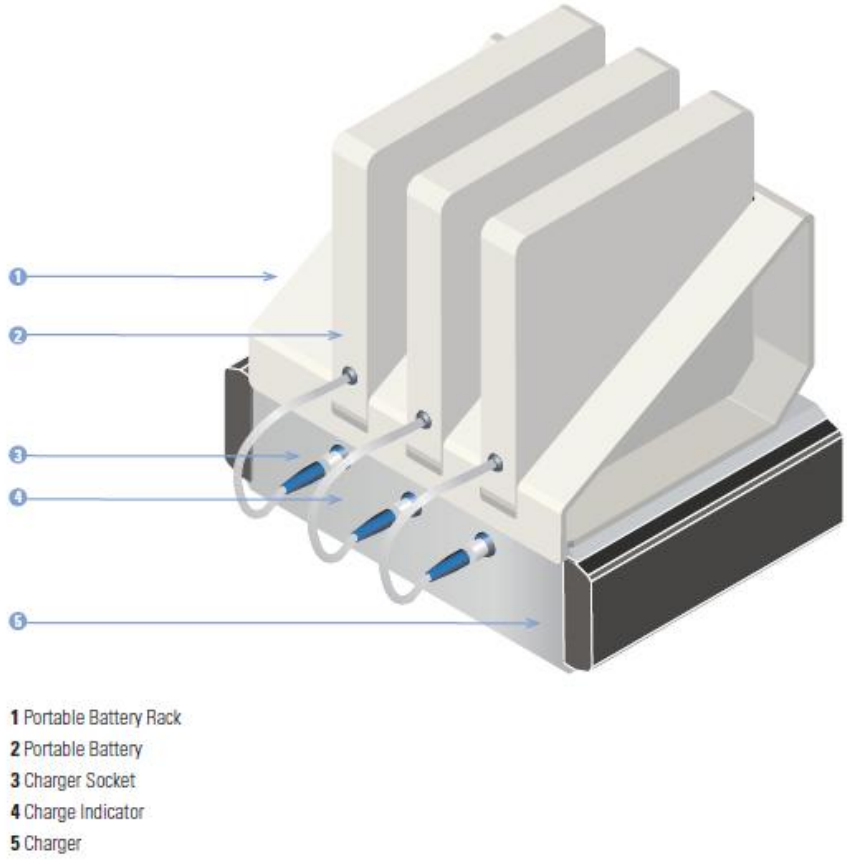
Always select a fully-charged battery when replacing a battery in the NovoTTF-100A device. A fully-charged battery will have a bright green Charge indicator light.

To remove a battery from the charger:

1. Disconnect the battery cable from the charger by pulling its connector out of the socket on the charger.
2. Make sure to hold the connector by its sleeve and not pull on the cord.



Back view of the battery charger and rack showing where to turn the charger on and off and where to connect the charger mains cable



Front view of the battery charger and rack showing where the portable battery cables connect to the charger sockets

15 Using the Plug-In Power Supply

When you plan to stay in one place for a period of time, for instance when you are sleeping, the device can be powered from the plug-in power supply, instead of using the rechargeable batteries. Unlike the batteries, there is no limit to how long the device can operate when using the plug-in power supply. The plug-in power supply input is designed to operate using either U.S. (120V AC) or European (230V AC) outlets.

Note: It is normal for the power supply to become warm when in use. If the power supply becomes too hot to touch, unplugged it and contact NovoCure technical support (section 28).

Note: The filter is intended to prevent the introduction of harmonic distortions to the power grid. The filter is molded to the power cord as a standard component. The filter cannot be removed or disconnected.

Connecting the Plug-In Power Supply

1. Plug in the power supply to a standard wall socket using the power cord that comes with the supply.
2. Stop the device as described in Section 12 by pressing the TTFields button and switching off the power switch.
3. Unplug the battery cable from the device by removing the battery connector from the blue socket on the front panel of the device.
4. Connect the blue connector on the plug-in power supply line to the blue socket on the front panel of the device where the battery was plugged in.
5. Start the device by turning on the power switch and pushing the TTFields button (as described in Section 12).
6. Make sure to support the filter box so the weight of the box is not hanging from the line to the blue connector.

Disconnecting the Plug-In Power Supply and Going Back to Battery Power

1. Stop the device as described in Section 12 by stopping the TTFields and switching off the power switch.
2. Remove the blue connector of the plug-in power supply from the blue socket on the front panel of the device.
3. Place a charged portable battery in the device bag.
4. Plug in the portable battery connector to the blue socket on the front panel of the device.
5. Start the device by turning on the power switch and pushing the TTFields button (as described in Section 12).
6. Store the plug-in power supply for future use.

16 The Connection Cable & Connection Box

The connection cable is the coiled, stretchable cord that goes from the device to the connection box which receives the four color coded-electrode connectors. The color coding corresponds to the electrode position on the head..

The connection cable connector plugs into the device in the P1 socket that has picture of a person next to it. This is the socket with the grey ring around it (the battery socket has a blue ring around it). The connection cable connector plugs into the socket with the arrows on the connector face up toward the P1 label. Push the connector in until a snap is heard, which indicates the connector is in the right place.

There are two ways to disconnect from the device in order to take a break from treatment:

1. Disconnecting the connection cable from the device
2. Disconnecting the electrodes from the connection cable

Disconnecting the connection cable from the device:

1. Stop TTField therapy by pressing the TTFields button.
2. Turn off the NovoTTF device using the power button.
3. Remove the connection cable connector from the socket by grasping the connector sleeve and pulling. Do not pull on the cord.

You may now move around without the device but still be connected to the connection cable and box. Once the break is over and you want to start treatment again:

1. Insert the connection cable connector into the P1 (grey) socket keeping the arrows pointing toward the P1 label.
2. Turn on the NovoTTF device using the power button.
3. Turn on the TTFields using the TTFields button.

Disconnecting the electrodes from the connection cable:

In order to take a break from treatment and completely disconnect from the device, you will need to disconnect the electrodes from the connection cable box. The four electrodes are plugged into the connection cable box as described in the INE Electrode User Manual. The connection cable plugs into the device at the P1 (patient) connector socket.

1. Stop TTField therapy by pressing the TTFields button.
2. Turn off the NovoTTF device using the power button.
3. Disconnect the electrode connectors from the connection box by pulling as shown. You may have to wiggle the electrode cables in order to remove them.

   To continue treatment, reconnect the electrodes to the connection box. Make sure to connect each electrode to its corresponding color indicating the electrode's position on the head as described in the INE Electrode User Manual.

4. When all 4 electrodes are connected, restart treatment as described in section 12 by turning on the power switch and pushing the TTFields button.

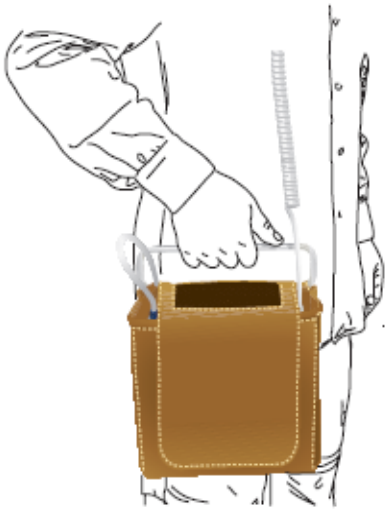
17 Carrying the Electric Field Generator

Both the electric field generator and the portable battery fit in a carrying bag equipped with a carrying handle and a detachable shoulder strap.

In order to wear the bag:

1. Place the strap over your shoulder.
2. Grab the snap hook at the end of the strap with your opposite hand.
3. Connect the snap hook to the handle as shown.

Note: Do not place the device in a bag not intended for use with the NovoTTF-100A device. The device has an internal fan that requires air flow. The device bag is ventilated to allow proper flow. If the device is placed in a bag without proper air flow, it could stop the treatment due to high internal temperature, in which case you would hear an alarm.

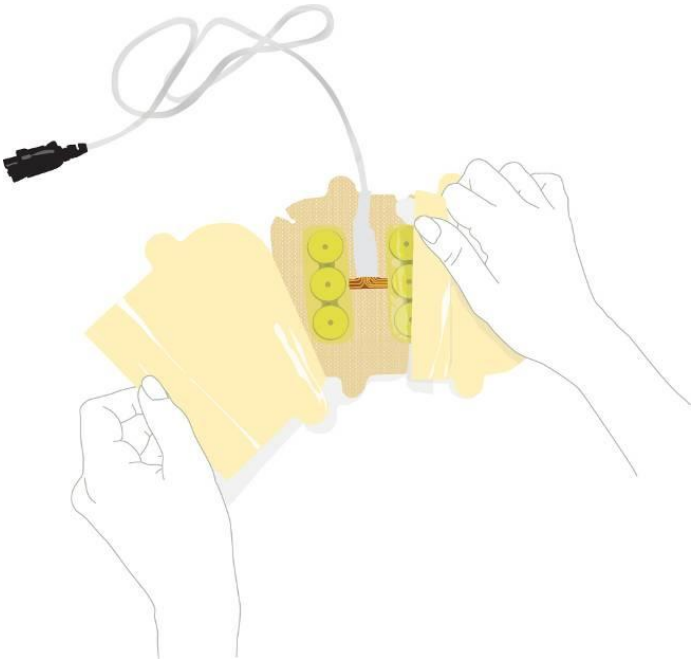


18 INE Electrodes Overview

INE Electrodes are electrodes that are to be used with the NovoTTF-100A Treatment Kit for treatment of patients with recurrent brain cancer (called "glioblastoma multiforme" or "GBM"). The INE Electrodes are supplied sterile and are to be used with the NovoTTF-100A Treatment Kit only.

The electrodes are applied to your clean shaven scalp. Four electrodes are used at one time. You place them in a location on your scalp as directed by your physician based on the location of your tumor. When you put the electrodes on your head, you will apply colored rings on the connectors that correspond to each electrode location – front (blue), rear (red), right (yellow), left (white).

The electrodes are disposable and will need to be replaced one to two times per week (every 4-7 days) due to hair growth, which prevents good contact between the electrodes and your scalp. At the time of replacement of the electrodes, you will need to re-shave the scalp and apply a new set of electrodes. Please contact NovoCure technical support at 1-800-978-0265 to arrange for used electrodes to be collected and properly disposed of.

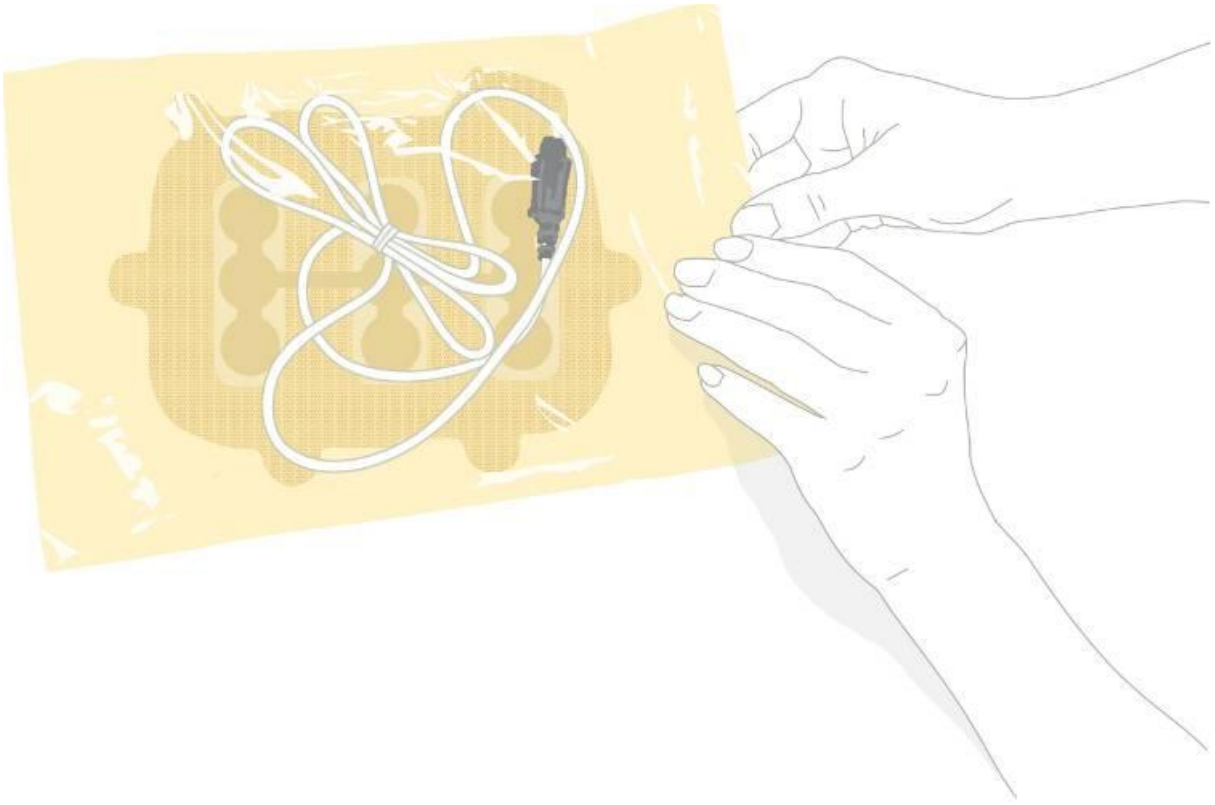


19 Before You Begin Placing Electrodes

You will need four (4) INE Electrodes for each treatment session. These 4 electrodes will need to be changed one to two times per week (every 4-7 days) with the assistance of a physician or caregiver in order to maintain treatment with the NovoTTF-100A System.

20 Removing the INE Electrode from Its Package

Open the see-through envelope of four (4) INE Electrodes by gently pulling apart the edges of the envelope as shown in the illustration.



21 Preparing Your Head for Electrode Placement

1. Wash your head using a gentle shampoo.
2. If this is the first time you have used the electrodes, ignore this step and go to step #3. If you are replacing electrodes, your physician or caregiver should ensure that any left over adhesive from your skin from prior electrodes has been removed by wiping the skin with baby oil. Baby oil is only intended to assist in the removal of left over adhesive from the scalp; it has no impact on device function.
3. Your entire scalp should be shaved using an electric shaver. No stubble should be left.
4. Your scalp should be wiped with 70% Alcohol (available over the counter at your local pharmacy).

If your scalp is red, an over-the-counter 0.1% hydrocortisone cream may be used. If you have any open sores on your scalp, they should be treated as instructed by your treating physician. If hydrocortisone cream is used, wait at least 15 minutes and repeat step #4 (gently wipe your scalp again with 70% Alcohol) to make sure that the electrodes stick to your skin. Electrodes should be applied after your scalp has completely dried.

22 Placing the Electrodes on Your Head

After the scalp is prepared (as described in the previous section), the electrodes can be placed on your head with the assistance of a physician or caregiver. Every 4 to 7 days, with assistance, the electrodes will need to be removed, the scalp re-shaved and prepared (as outlined in Section 4) and a new set of electrodes applied. You will know it is time to replace electrodes when the device alarm starts going off more frequently. This indicates that the device is not able to operate as intended because of hair growth that is preventing the electrodes from making good contact with your scalp.

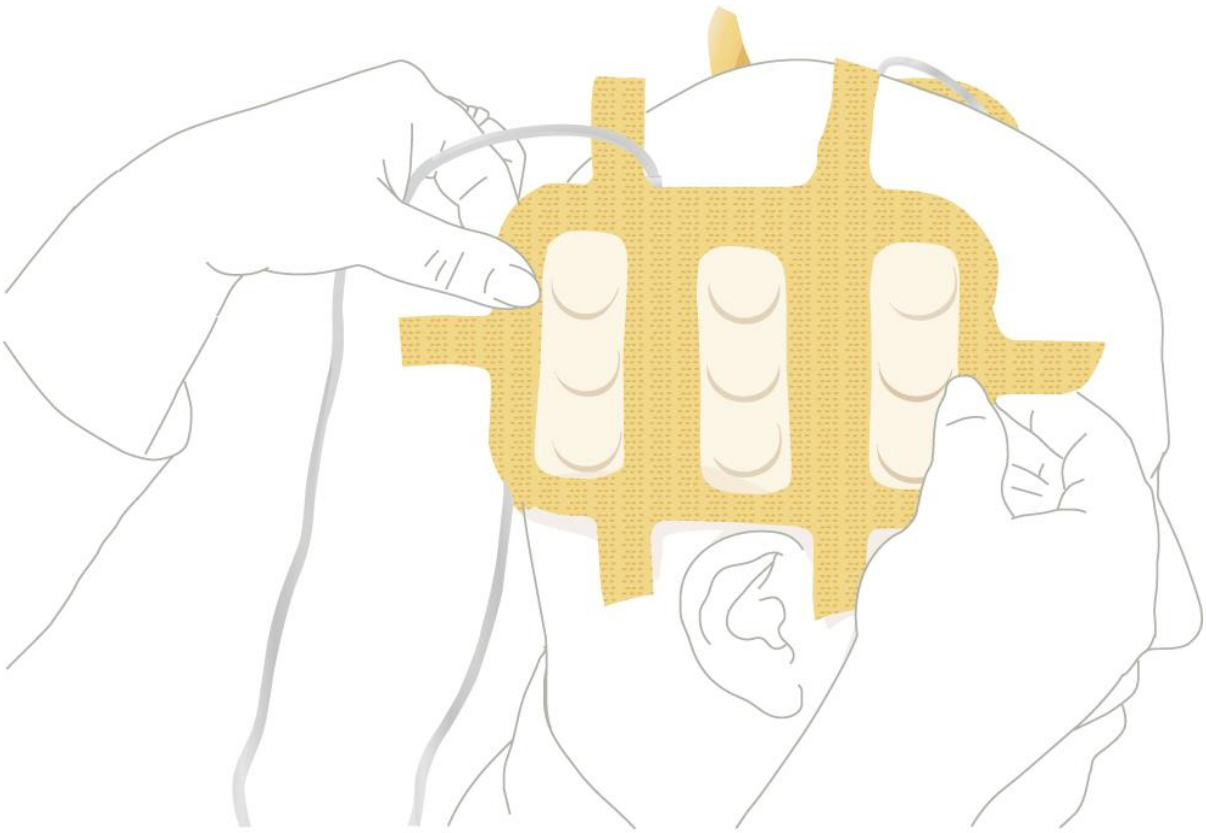
To place the electrodes on your head with the assistance of a caregiver or physician, follow the steps outlined below:

Note, if this is the first time you have used the electrodes, ignore step #1 and go to step #2.

1. Remove electrodes from your head by peeling the medical tape away from your scalp, with the assistance of your physician or caregiver .
2. Note the color coding of the electrodes (which color electrode goes where on your head). The electrode locations are: front (blue), rear (red), right (yellow), left (white).
3. Place the color coding rings on the electrode connectors of the four electrodes you have opened with the assistance of your caregiver. In the Treatment Kit, there are small, plastic rings of the four different colors corresponding to the color coding of the electrode placement diagram that you received from your physician. The rings snap over a groove on the body of the connector.
4. With the assistance of a caregiver or physician, prepare your skin for the electrodes, as described in the previous section (section 21).
5. Remove the electrode liner from the first electrode.
6. With the assistance of a caregiver or physician , position the electrodes on your head according to the electrode placement diagram that you received from your physician if this is the first time you use the electrodes. Positioning is based on the location of your tumor. When replacing the electrodes, placed the electrodes on your head in the same

location as before, but shifting the electrodes three quarters of an inch in the direction of the arrow in your electrode placement diagram. Moving the electrodes a small amount will help reduce skin irritation under the electrodes. Shifting the electrodes is not required for proper operation of the device.

7. With the assistance of a caregiver or physician, place the other three electrodes in the same way.
8. With the assistance of a caregiver or physician, pull the opposing tabs of each electrode (the small ears extending from the electrode body) and have them pressed firmly to your scalp.
9. Press the entire rim of the electrode tape to your scalp.



23 Connecting the Electrodes to the Device

1. Connect each of the four electrode connectors with its color-coded ring (that indicates electrode position) to the corresponding color coded socket on the NovoTTF-100A connection cable. For example, plug the electrode connector with the red ring (for the electrode that goes on the back of your head) into the red socket (labeled "N1"; see diagram below).
2. Connect the other three electrode connectors in the same way.
3. Press firmly to verify the connectors are inserted all the way.
4. Collect the electrode wires together and bind them with a small piece of tape, if convenient.

24 Disposal

Please contact NovoCure to arrange for proper disposal of used electrodes. Do not discard them in the trash.

25 Glossary of Graphic Symbols

Attention – consult accompanying documents

Date of Manufacturing

Fragile – handle with care

Do not enter rooms with high humidity or danger of direct exposure to water while wearing the device.
Do not carry the device outdoors if not within its carrying bag.
Do not expose the device to direct rain.

The charger is for indoor use only

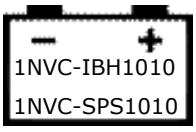
Batteries are Lithium Ion. NovoCure technical support should be contacted to arrange for proper disposal of batteries that are depleted or no longer in use.

The NovoTTF-100A device and Treatment Kit parts should be kept away from extreme heat and sources of radiation

BF type applied part – symbolizes the part which comes in contact with the patient

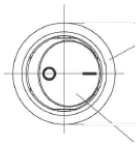
1NVC-CAD1010

Specifies the P/N of the applied part to be used with this device

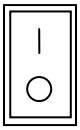


Battery socket – connect only 1NVC-IBH1010 Lithium Ion batteries or 1NVC-SPS1010 power supply manufactured by NovoCure Ltd.

Expiration date – do not use beyond this date



Power ON / OFF switch for the NovoTTF-100A device:
When the switch is in the — position the device is ON
When the switch is in the O position the device is OFF



Power ON / OFF switch for the portable battery and overnight battery chargers:
When the switch is in the | position the device is ON and will light up green. When the switch is in the O position the device is OFF.

Do not use the INE electrodes if their packaging is breached.

The INE Electrodes are for single use and should not be re-used.

The INE Electrodes are sterilized by Gamma irradiation

26 Storage and Transportation by the Distributer

Conditions for storage

Temperature range: 23°F to 104°F for the device and additional parts

Temperature range: 41°F to 81°F for the electrodes

Relative Humidity range: 15-75% for the device and additional parts

Relative Humidity range: 35-50% for the electrodes

Conditions for transport

Transportation of the device and additional parts shall be possible using air/ground transportation in weather protected conditions as specified below:

- Temperature range: -13°F to 104°F
- Maximal relative humidity 15-75%
- No direct exposure to water

Transportation of the electrodes shall be possible using air/ground transportation in weather protected conditions as specified below:

- Temperature range: 32°F to 104°F
- Maximal relative humidity 15-75%
- No direct exposure to water

27 Troubleshooting

Device power indicator does not light up after turning ON the device	1. Battery dead 2. Battery malfunction 3. Charger malfunction 4. Device malfunction	1. Replace battery. If problem persists: 1. Turn OFF power switch 2. Call technician
Any cable detached from electrode/connection cable/device	1. Excess physical force to cables 2. Device malfunction	1. Replace electrode. If problem persists: 1. Press TTFields button to stop therapy. 2. Turn OFF power switch 3. Call technician
Device dropped or wet	Incorrect use	1. Press TTFields button to stop therapy. 2. Turn OFF power switch 3. Call technician
Device alarm on	1. Low battery 2. Cable becoming loose or disconnected 3. Vents on the sides of the device and the front of the charger being blocked 4. Local hot spot on electrode from laying on a pillow or other insulator 5. Poor electrode contact due to hair growth or other reason 6. Device malfunction	**If Low Battery indicator is on:** 1. Replace battery as described above 2. Turn on treatment **If the Error indicator lights up but the Low Battery indicator is not lit:** 1. Press the TTFields button to stop the alarm 2. Turn off power switch 3. Check all connections to ensure nothing is loose 4. Check vents on device and charger to make sure they are not blocked 5. If lying down, reposition your head

		6. Make sure electrodes are well adhered to the head, add tape if necessary 7. Restart treatment 8. If alarm persists, turn off and call technician
Low Battery indicator remains on after battery replaced	1. Charger malfunction 2. Battery malfunction 3. Device malfunction	1. Replace battery with an additional charged battery. 2. If problem persists – call technician.
Redness of the skin beneath the electrodes	Common side effect	1. Use over the counter 0.1% hydrocortisone cream when replacing electrodes. 2. Place electrodes in a location shifted by 3/4 of an inch from the last location (so the adhesive gel is between the red marks). **If the redness gets worse:** 1. See your treating doctor
Blisters beneath the electrodes	Rare side effect	See your treating doctor for a prescription antibacterial cream and use as prescribed by your doctor.
Itching beneath the electrodes	Rare side effect	1. Use over the counter 0.1% hydrocortisone cream when replacing electrodes. 2. Place electrodes in a location shifted by 3/4 of an inch from the last location (so the adhesive gel is between the red marks).

		If the itching gets worse: 1. See your treating doctor.
Pain beneath the electrodes		Stop treatment
	Rare side effect	See your treating doctor

28 Assistance & Information

Technical support:

For technical support please contact NovoCure directly at 1-800-978-0265. This includes help with operation of the equipment, troubleshooting alarms, or getting replacement equipment or electrodes.

Clinical support:

If you feel any change in your health or any side effects from the treatment call your physician immediately.

29 Traveling with the NovoTTF-100A

NovoCure, Ltd. is not aware of any limitations regarding air, ground or sea travel when using the NovoTTF-100A. The system has been tested to meet all applicable electrical safety requirements for medical devices per EN 60601-1-1, 60601-1-2, 60601-1-4, and 60601-1-6, which demonstrates that the device can be safely operated in non-clinical settings.

Precaution: The suitability of the NovoTTF-100A System and INE Electrodes for full body scanners used in airports has not been tested. It is unknown what effects such scanners may have on the device.

Precaution: The NovoTTF-100A System and INE Electrodes will activate metal detectors.

30 Applicable Standards

The NovoTTF-100A system as a whole complies with the EN 60601-1 and 2 series latest editions.

31 Glioblastoma Multiforme (Brain Cancer)

What is Brain Cancer?

In simple terms, brain cancer is an uncontrolled growth of cells forming a tumor within the brain. Just like any other form of cancer, brain tumors can spread to any other part of the brain, though rarely do they spread outside of the brain. Even before the brain cancer grows and spreads, the tumor could cause problems inside the brain. Our brain controls the functions of the rest of the body. Any disturbance in the brain will affect our normal functioning. Therefore, symptoms of brain cancer depend on where and how big the tumor is.

GBM is a type of brain cancer which arises from a certain type of cell in the brain (called a glial cell). Other medical names for GBM are "glioblastoma", "glioblastoma multiforme", "grade IV glioma" or "grade IV astrocytoma". Close to 10,000 patients in the U.S. are diagnosed with this type of cancer every year, but it is still unknown what causes it. GBM is a very serious disease with a poor outcome. Less than 10% of patients with GBM are alive after 5 years despite the best available treatments.

Can Brain Cancer Be Treated?

There are currently four main options for the treatment of GBM:

- *Operation* – Treatment of patients with GBM usually begins with removal of all or some of the tumor.
- *Radiation* – Following operation, many patients receive radiation therapy.
- *Local Chemotherapy* – during the operation, the surgeon can place a wafer that delivers chemotherapy drugs in the site where the tumor was removed.
- *Systemic Chemotherapy* – Many GBM patients receive cancer drugs (chemotherapy); there are several approved drugs to treat GBM.

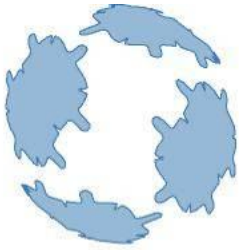
While both radiation therapy and chemotherapy can potentially modestly improve survival, they have serious side effects such as hair loss, skin irritation, possible hearing problems, nausea, vomiting, loss of appetite, effects related to the brain, and fatigue.

When Brain Cancer Returns (Recurrence of Brain Cancer)

Despite operations and the treatments described above, GBM can return. In these cases, some of the above treatments (operation, radiation, chemotherapy) may be available to treat the recurrent cancer. However, in most cases, operation and radiation are no longer an option for a patient. In those cases, systemic chemotherapies may be used, or, alternatively, the NovoTTF-100A System may be used.

The use of systemic chemotherapy leads to high incidence (>30%) of side effects like vomiting, nausea, diarrhea, low blood cell counts and infections, together with an increase of about 3 to 4 months in survival. Other therapies such as bevacizumab (Avastin) have not been tested in randomized clinical trials and have not shown a survival benefit or even equivalence to chemotherapies in extending survival, while both bleeding and clotting disorders are frequent.

The NovoTTF-100A is equivalent to chemotherapies in extending survival compared to no treatment at all, but with a much lower incidence of side effects like vomiting, nausea, diarrhea, low blood cell counts and infections. In addition NovoTTF-100A leads to a higher quality of life compared to the best available chemotherapies in the US today.



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CE0197

NovoTTF-100A System (P100034)
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Post-Approval Study Proposal

As outlined in the NovoTTF-100A PMA (P100034), the principal objective of post-approval studies (PAS) for PMA-approved medical devices is to evaluate device performance and potential device-related problems in a broader population over an extended period of time after a premarket determination of reasonable device safety and effectiveness. Essential postmarket information may include:[1]

- Longer-term performance including effect of re-treatment and product changes
- Real world device performance (patients and clinicians)
- Effectiveness of training program
- Subgroup performance
- Outcomes of concern (safety and effectiveness)

Outcomes of concern that are evaluated in a PAS often involve safety issues, such as evaluating potential device-related adverse events identified in the pivotal study, or characterizing the safety profile of the device in a U.S. population if the premarket approval is based largely on OUS data.

After careful consideration of various possible PAS options as outlined above, NovoCure is unable to identify any important postmarket questions that should be addressed in a PAS for the NovoTTF-100A device for the treatment of recurrent GBM patients according to the currently proposed indications for use. The company respectfully believes that none of the "typical" scenarios for a PAS apply to the NovoTTF-100A device or trial, specifically:

- Due to the end stage nature of recurrent GBM patients and the small number of patients alive after 1 year (about 20%), it is not feasible to seek long-term safety and efficacy data. It is noted that the company plans to follow the patients enrolled in the pivotal trial until death in any case.
- The device is easy to use, unlike, for example, a surgical implant for which surgeon skill and training may have a significant impact on device safety and effectiveness in the real world setting.
- The pivotal study did not identify any subgroup of patients that appeared to receive more or less of a benefit from the device.
- The only adverse event associated with the NovoTTF-100A device is a mild to moderate skin irritation which is easily treated. There were no adverse event "signals" associated with the device identified that would warrant additional study.
- The trial was not principally a foreign study (about half of the patients in the NovoTTF-100A study were recruited from U.S. sites); therefore, a PAS to assess use in the U.S. would not provide additional information.

In addition, there are no other relevant scientific questions or limitations of the pivotal study that NovoCure has identified that would reasonably require answers that are sufficient to be the subject of a PAS.

[1] CDRH Post-Approval Study Program Update, presented by Danica Marinac-Dabic, MD, PhD, Director, Division of Epidemiology, OSB, FDA, to the Ophthalmic Device Panel Meeting, March 27, 2009.

The company has also considered whether a repeat of the pivotal study to confirm the study results would be reasonable. First, the company does not believe such a study is necessary, as the pivotal study clearly demonstrated the safety and effectiveness of the NovoTTF-100A device. In addition, NovoCure believes that it would be difficult from a practical standpoint after the device is approved to recruit physicians or to enroll patients to participate in a randomized trial, where patients would have to limit their treatment options to the assigned treatment.

Accordingly, the company respectfully believes that in the absence of a good PAS option for recurrent GBM patients, a PAS may not be necessary.

Nevertheless, as suggested by FDA, the company has approached the Office of Surveillance and Biometrics ("OSB") to discuss what questions of interest the agency believes might need to be addressed by a post-approval study of the NovoTTF-100A.

NovoTTF-100A System (P100034)
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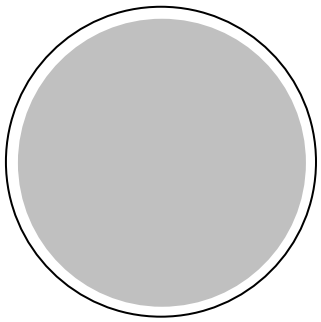
Tab XI. Appendices



March 17, 2011

NovoTTF-100A System (P100034)
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Key References

1. Kirson, E; Dbalý, V; Tovaryš, F; Vymazal, J; Soustiel, J; Itzhaki, A; Mordecovich, D; Steinberg-Shapira, S; Gurvich, Z; Schneidermann, R; Wasserman, Y; Salzberg, M; Ryffel, B; Goldsher, D; Dekel, E; Palti, Y. 2007. Alternating electric fields arrest cell proliferation in animal tumor models and human brain tumors. PNAS 104(24):10152-10157.

2. Kirson, E; Giladi, M; Gurvich, Z; Itahaki, A; Mordechovich, D; Schneiderman, R; Wasserman, Y; Ryffel, B; Goldsher, D; Palti, Y. 2009. Alternating electric fields (TTFields) inhibit metastatic spread of solid tumors to the lungs. Clin Exp Metastasis 26(7):633-640.

3. Kirson, E; Gurvich, Z; Schneiderman, R; Dekel, E; Itzhaki, A; Wasserman, Y; Schatzberger, R; Palti, Y. 2004. Disruption of cancer cell replication by alternating electric fields. Cancer Research 64:3288-3295.

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5. Schneiderman RS, Shmueli E, Kirson ED, Palti Y. 2010. TTFields alone and in combination with chemotherapeutic agents effectively reduce the viability of MDR cell sub-lines that over-express ABC transporters. BMC Cancer 10:229.

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