SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name: Tumor Treatment Fields

Device Trade Name: NovoTTF™-100L System

Device Procode: QGZ

Applicant's Name and Address: Novocure, Ltd.
Topaz Building,
P.O.Box 15022,
MATAM Center
Haifa, 3190500, Israel

Date(s) of Panel Recommendation: None

Humanitarian Device Exemption (HDE) Number: H180002

Humanitarian Use Device (HUD) Designation Number: HUD # DEV-2017-0381

Date of HUD Designation: May 8, 2017

Date of Notice of Approval to Applicant: May 23, 2019

The NovoTTF™-100L System is a modified version of the Optune System (formerly the NovoTTF-100A System), approved on April 8, 2011 for a different indication, the treatment of newly diagnosed and recurrent glioblastoma multiforme (GBM) (P100034 and associated Premarket Approval (PMA) supplements). The Summary of Safety and Effectiveness (SSED) to support the indication is available on the Center of Devices and Radiological Health (CDRH) website
https://www.accessdata.fda.gov/cdrh_docs/pdf10/P100034B.pdf.
The NovoTTF-100L System and the Optune System have the same principles of operation, comprise essentially the same components, but differ in technological characteristics (frequency, output current, transducer array size and configuration) and area of application (chest vs. scalp).

II. INDICATIONS FOR USE

The NovoTTF™-100L System is indicated for the treatment of adult patients with unresectable, locally advanced or metastatic, malignant pleural mesothelioma (MPM) to be used concurrently with pemetrexed and platinum-based chemotherapy.

The indication for use statement has been modified from that granted for the HUD designation. The HUD designation was for "use, concomitant to pemetrexed and platinum-based chemotherapies, to treat patients with inoperable malignant pleural mesothelioma (MPM)." It was modified for the HDE approval because the revised indications for use (IFU) statement more clearly identifies the patient population that the NovoTTF-100L

System is intended to treat and in which the safety and probable benefit of the device is supported by the available clinical data. The modified IFU is within the patient population limit granted by the HUD designation.

III. CONTRAINDICATIONS

- Do not use the NovoTTF-100L System if you have implantable electronic medical devices including a pacemaker, implantable automatic defibrillatore, etc. Use of the NovoTTF-100L System together with implanted electronic devices has not been tested and may lead to malfunctioning of the implanted device.

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

IV. WARNINGS AND PRECAUTIONS

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

V. DEVICE DESCRIPTION

The NovoTTF-100L System (**Figure 1**) is a portable, battery or power supply operated device which produces alternating elelctrical fields within the body by means of non-invasive surface transucer arrays. The device delivers tumor treatment fields (TTFields) at 150 kHz to the applied area through sterile transducer arrays. These surface arrays are electrically insulated, such that resistively coupled (direct) electric currents are not delivered to the patient. The arrays, which have a layer of adhesive hydrogel and a layer of hypoallergenic medical tape, are placed on the patient’s shaved skin in the area surrounding the tumor. The device is used at home and operated by the patient to deliver continuous treatment to the chest.

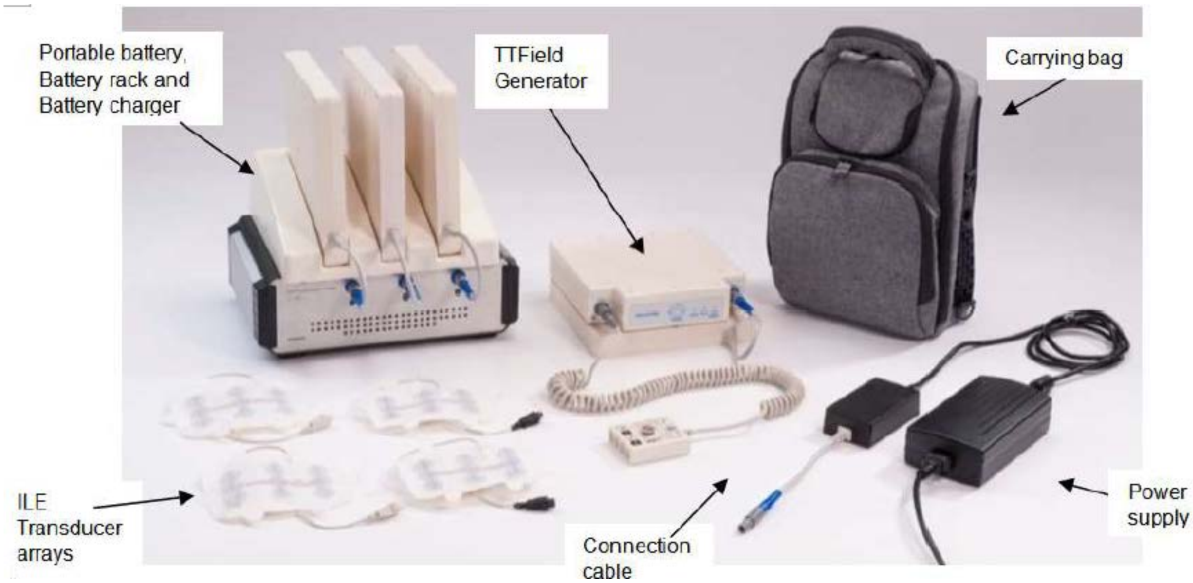


Figure 1: NovoTTF™-100L System

A. Technological Characteristics

The NovoTTF-100L is comprised of two (2) main components, an Electric Field Generator and ILE Insulated Transducer Arrays, and several additional components.

Electric Field Generator: The Electric Field Generator is a portable, battery or power supply operated device. The outputs are connected to two (2) pairs of insulated transducer array sets operated sequentially. The intensity of the field, the frequency of the waves, and the maximum allowable temperature of the transducer arrays are pre-set, and are controlled by two (2) microcontrollers which run Novocure's software.

The output parameters of the Electric Field Generator are either pre-programmed or set by the service technician through a "service only" USB-type connector. The device status and monitored parameters are continuously stored in an internal log memory and can be transferred by an isolated serial connection to a personal computer (PC). In addition, the front panel includes visual indicators for power ON, Treatment ON, alarms and low battery.

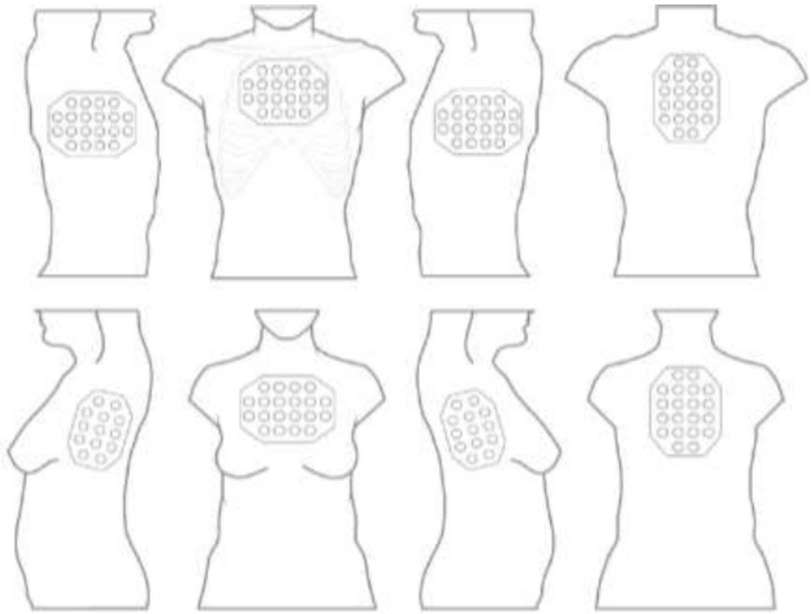


Figure 2: Possible transducer array placements in the thorax region

Transducer Arrays: Two (2) sets of ILE Insulated Transducer Arrays are connected to the Electric Field Generator and used to deliver two perpendicular field directions through the chest (**Figure 2**). Each set includes a pair of arrays. The arrays come in two (2) sizes to fit different patient body sizes. Small arrays consist of 13 ceramic discs each, and large arrays (**Figure 3**) consist of 20 ceramic discs each, with the ceramic discs serially interconnected in each array. The arrays are sterile, single use devices and incorporate the following parts:

Table 1: Transducer Array Components

	Part Name	**Functions**
1	Cover tape	Provides adhesion of the array to patients' skin
2	ILE transducer array	The array delivers the treatment to the patient and measures the temperature
3	Conductive gel layers and Ceramic discs (beneath)	Gel: Ensures electric contact between the transducer array and the skin Ceramic disc: Used for the TTFields transmission
4	Mid-pads	Mechanically stabilizes the gel over the array
5	Overlapping liner	Covers the gel and the cover tape
6	Applied part cable with black or white connecotr	Connects the transducer array to the connectin box

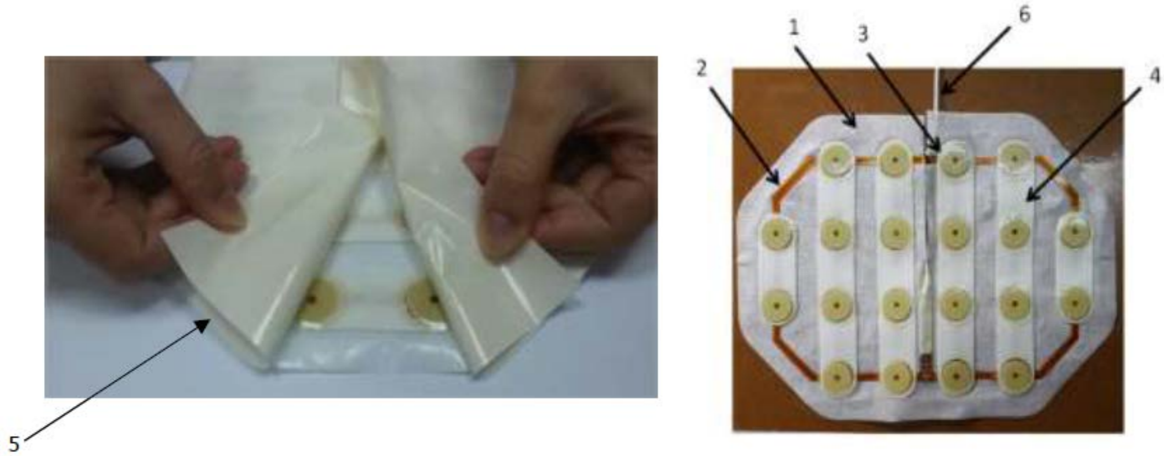


Figure 3: A large transducer array (arrows correspond to parts in Table 1)

Thermistors: Each transducer array includes eight (8) thermistors (accuracy ±1ºC) to measure skin temperature beneath the arrays every second. These thermistors are read by the NovoTTF-100L System while the fields are not being delivered in order to avoid any interference with the temperature measurements. If the temperature measured is below the pre-set maximum temperature (Tmax) of (38.5-40.0ºC) ± 0.3ºC between two (2) subsequent measures, the current will rise until it reaches the maximal treatment current (4 Amps peak-to-peak). If the temperature reaches Tmax + 0.3ºC and continues to rise, the device will automatically lower the treatment current. If the temperature rises to 41ºC, the device will shut off the TTFields therapy and the overheating alarm will be trigered.

Additional Components: In addition, the NovoTTF-100L System includes: power supply, portable battery, battery rack, battery charger, connection cable and carrying bag, as shown in **Figure 1**.

B. Principle of Operation

The NovoTTF-100L System is a home-use medical device operated by the patient with the help of a caregiver when needed. Patients will be trained in the use of the device by a designated health care provider or technician trained by Novocure. 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 or when the patient is stationary.

Treatment with the device is continuous with breaks allowed for personal needs (e.g., showering, array exchange). Patients carry the device in a specialized over-the-shoulder bag to receive continuous treatment. Patients are encouraged to use the device daily for at least 18 hours a day on average per cycle. Treatment is continued until radiological disease progression, death, or unacceptable side effects to patient. Patients should use the device for a minimum of 4 weeks from treatment initiation. In order to maintain optimal electrical contact with the skin, patients should replace the transducer arrays approximately every 3 to 4 days (2-3 times per week) with the help of a caregiver and the chest reshaved if necessary. The device log is downloaded by Novocure every month and compiled by Novocure personnel to assess patient compliance with the TTFields treatment plan. A compliance report for each participating patient is provided to the prescribing physician by Novocure on a routine basis.

C. Mechanism of Action

The NovoTTF-100L System produces alternating electrical fields within the human body that are believed to disrupt the rapid cell division exhibited by cancer cells with the alternating electrical fields applied through the surface of the chest.[1]

TTFields harness electric fields which were shown in non-clinical experiments 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 their 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., 150 kHz for MPM). 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 above mechanisms of action are consistent with the research regarding the effects of TTFields. These results demonstrate both disruption of cell division up to complete cessation of the process, as well as destruction of the dividing cells.

VI. <u>ALTERNATIVE PRACTICES AND PROCEDURES</u>

Conventional procedures used in the treatment of malignant pleural mesothelioma include surgery, chemotherapy, radiation, and different combinations of these modalities.

VII. <u>MARKETING HISTORY</u>

The NovoTTF-100L System for malignant pleural mesothelioma has not been marketed in the United States or any foreign country.

The NovoTTF-100L System is a modified version of the Optune System (formerly the NovoTTF-100A System), which has been marketed for a different indication - the treatment of recurrent and newly diagnosed GBM (P100034). The Optune System has been available commercially in the US and the European Union (EU) since October 2011 and in Japan since 2018.

The Optune System has not been withdrawn from marketing for any reason related to the safety or effectiveness of the device in any country.

VIII. <u>POTENTIAL ADVERSE EFFECTS OF THE DEVICE ON HEALTH</u>

Below is a list of the potential adverse effects (i.e., complications) associated with the use of the device.

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

For the specific adverse events that occurred in the clinical study, please see Section X below.

IX. SUMMARY OF NON-CLINICAL STUDIES

A. In Vitro Studies

Objectives. The objective of the in vitro studies was to validate the effect of 150 kHz TTFields on mesothelioma cells in vitro, which are the basis for setting the output frequency of the NovoTTF-100L System to 150 kHz.

Table 2: In Vitro Studies

Test/Setup	Purpose	Results	Conclusion
The inhibitory effect of TTFields was tested in various cultures at a range of frequencies between 50 - 500kHz.[2,3]	Investigate whether there is an optimal frequency for the antimitotic effect of TTFields and identify the main parameters that may affect treatment.	The effect of TTFields is frequency-dependent with frequency inversely related to cell size.	Optimal frequency for mesothelioma cells is 150 kHz.
Cancer cell cultures were exposed to TTFields of increasing intensities and a dose-response curve constructed for each cell type.[2,3]	Test whether the effect of TTFields is intensity dependent and the threshold for inhibition of mitosis.	The effects of TTFields are dose-dependent.	Effective inhibition of mesothelioma cell culture growth seen at an IC_{50} (inhibitor concentration where the response is reduced by half) intensity of 1.7 V/cm.
Kinetic modeling of compartmental tumor growth kinetics.[4]	Test the time needed to achieve tumor growth reversal using TTFields.	Tumor growth reversal is seen only if TTFields are applied continuously for several weeks.	Tumor growth reversal is not immediate.
Effects of combined TTFields with chemotherapeutic agents.	Assess effects of TTFields when combined with chemotherapy commonly used to treat mesothelioma.	Simultaneous application of TTFields with each one of several chemotherapeutic agents enhances probable benefit of treatment as compared to the chemotherapy alone.	TTFields have an additive effect to chemotherapy in mesothelioma cell lines in vitro.

B. Additional Studies

Numerical Simulations: Numerical simulations were performed to evaluate the safety and probable benefit of the NovoTTF-100L System when delivering Tumor Treating Fields to the torso. A virtual representation of the NovoTTF-100L System was used to deliver TTFields to the lungs of three (3) different human computational models – a female model, a male model, and an obese male model with a range of body mass index (BMI) values from normal to obese. The simulations showed that for all models, the NovoTTF-100L System delivers therapeutic intensities of over 0.7 V/cm RMS to over at least 76% of the lungs. Thermal safety threshold levels were determined by current density and specific absorption rate (SAR). Current density within the models was below the safety threshold of 100 mA/cm^2. SAR values within the internal organs were below the levels at which thermal damage occurs. In the superficial body layers, higher SAR values were observed. However, the NovoTTF-100L System incorporates temperature control that prevents the skin from heating to levels at which thermal damage can occur. Thus the numerical simulations support the observations that the NovoTTF-100L System delivers TTFields to the lungs at therapeutic levels and that the device is safe for use with adequate mitigation measures.

Electrical Safety and Electromagnetic Compatibility Tests: Novocure commissioned an independent laboratory to evaluate the electrical safety and electromagnetic compatibility of the NovoTTF-100L System. The laboratory tested the device according to Underwriters Laboratory Standard for Safety of Medical and Dental Equipment (UL 544) and found it to be free from safety hazards and in compliance with the requirements of that standard.

Table 3. Electrical Safety and EMC Testing

Test	Purpose	Standard	Results
Safety - general	Equipment when transported, stored, installed, operated in normal use, and maintained according to the instructions of the manufacturer, causes no safety hazard which could reasonably be foreseen and which is not connected with its intended application in normal condition (NC) and in single fault condition (SFC).	IEC 60601-1[a]	Pass
Safety - classification	Type of protection against electric shock. Internally powered equipment.	IEC 60601-1	Pass
Safety – degree of protection against electric shock	Type BF applied part.	IEC 60601-1	Pass
Safety – mode of operation	Continuous operation.	IEC 60601-1	Pass
Safety – use in the home environment	Home environment use.	IEC 60601-1-11[b]	Pass

Test	Purpose	Standard	Results
Emissions	Radiated RF emissions, Class B.	EN/IEC 60601-1-2[c]	Pass
Immunity	Immunity to electrostatic discharge (ESD). Radiated immunity to radio frequency electromagnetic field. Conducted immunity to electrical fast transients/bursts (EFT/ B). Conducted immunity to disturbances induced by radio frequency field. Radiated immunity to power frequency magnetic field, 50/60 1 Hz.	EN/IEC 60601-1-2	Pass

[a]IEC-60601-1 “Medical electrical equipment -- Part 1: General requirements for basic safety and essential performance

[b]IEC-60601-1-11 “Medical electrical equipment -- Part 1-11: General requirements for basic safety and essential performance -- Collateral standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment

[c]IEC-60601-1-2 “Medical electrical equipment - Part 1-2: General requirements for basic safety and essential performance - Collateral Standard: Electromagnetic disturbances - Requirements and tests

Software Verification and Validation Test: Novocure provided software information for the NovoTTF-100L System in accordance with the FDA guidance document “Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices” issued on May 11, 2005. In accordance with this guidance, the software used in the NovoTTF-100L System has a major level of concern and the applicant provided documentation of appropriate controls and testing including:

- Level of Concern
- Software Description
- Device Hazard Analysis
- Software Requirements Specifications
- Architecture Design Chart
- Software Design Specification
- Traceability
- Software Development Environment Description
- Verification and Validation Documentation
- Revision Level History
- Unresolved Anomalies
- Run-Time Error Detection

The NovoTTF-100L System includes three (3) software elements: Device software; a related connection cable (CAD) software; and a separate NovoTerminal software. The Device software controls the intensity of the field, the frequency of the waves, and the temperature of the transducer arrays by a micro-controller. The connection cable includes software and provides communication of the transducer arrays to the device. The NovoTerminal software allows access to the device from a PC to be able to extract or present data from the device and update device settings, if needed. The user is not permitted to make any changes to the software and has no means or access to do so.

Biocompatibility: The transducer arrays are the only patient-contacting components of the NovoTTF-100L System. Based on the indication for use, the arrays are in direct contact with intact skin for permanent duration. The biocompatibility testing of Optune System (P100034) was leveraged to support the biocompatibility of NovoTTF-100L System because the two (2) arrays are made of the same materials, are identical in formulation, processing, and sterilization and no other chemicals have been added (e.g., plasticizers, fillers, additives, cleaning agents, mold release agents).

Sterilization: Novocure will be using the same validated gamma irradiation sterilization cycle as approved in P100034, since the design and the material construction of the transducer arrays remain unchanged. The sterilization validated and established in P100034 for the Optune System were used to support the sterilization of NovoTTF-100L System.

The tolerability of the transducer arrays to high dose gamma irradiation limit was determined to be 40 kGY for one irradiation cycle and the compatibility of materials with this dose was validated. Package integrity was validated and found in full compliance with ISO 11607-1, "Packaging for terminally sterilized medical devices -- Part 1: Requirements for materials, sterile barrier systems and packaging systems" and ISO 11607-2, "Packaging for terminally sterilized medical devices -- Part 2: Validation requirements for forming, sealing and assembly processes."

Table 4. Biocompatibility, Sterilization, and Shelf Life Testing

Test	Standard/Method	Result	Conclusion
Biocompatibility testing, including cytotoxicity, skin irritation, intracutaneous reactivity, and sensitization.	FDA Guidance Document: Use of International Standard ISO 10993-1 and the FDA recognized consensus standard ISO 10993-1:2009/(R) 2013.[a]	Pass The test results showed that no leachable substances were released in cytotoxic concentrations from the transducer arrays. Furthermore, the tests show that the arrays have no sensitizing properties and do not cause skin irriatation.	The materials that may come in contact with the patient are safe and biocompatible considering the biocompatibility requirements, the nature of contact, and duration.
Gamma irradiation sterilization validation	The ILE Electrodes are sterilized per EN 556-1[b] and comply with EN/ISO-11137-1[c], EN/ISO 11137-2[d], EN/ISO 11137-3[e], EN/ISO 11737-1[f], and EN/ISO 11737-2[g].	Pass	Electrodes are sterile.
Shelf-Life validation (ILE Electrodes)	Test whether electrical and mechanical properties of the electrodes remain within their specifications at the end of their shelf life.	Pass	Shelf life for the ILE electrodes is 9 months

[a]ISO 10993-1 Biological Evaluation of Medical Devices – Part 1: Evaluation and Testing

Within a Risk Manangemnt Process
[b]EN 556-1 Sterilization of Medical Devices - Requirements for Medical Devices to Be Designated "Sterile" - Part 1: Requirements for Terminally Sterilized Medical Devices
[c]EN/ISO-11137-1 Sterilization of health care products -- Radiation -- Part 1: Requirements for development, validation and routine control of a sterilization process for medical devices
[d]EN/ISO 11137-2 Sterilization of health care products -- Radiation -- Part 2: Establishing the sterilization dose
[e]EN/ISO 11137-3 Sterilization of health care products -- Radiation -- Part 3: Guidance on dosimetric aspects of development, validation and routine control
[f]EN/ISO 11737-1 Sterilization of health care products -- Microbiological methods -- Part 1: Determination of a population of microorganisms on products
[g]EN/ISO 11737-2 Sterilization of medical devices -- Microbiological methods -- Part 2: Tests of sterility performed in the definition, validation and maintenance of a sterilization process

Table 5. Hardware, Functional and Usability Testing

Test	Methods	Acceptance Criteria	Results	Conclusion
Electrode temperature measurement accuracy across functional range	Temperatures were measured in all electrodes' thermistors in the range of 35°C – 41°C and compared to a concomitant measurement by standard calibrated reference thermometers.	Temperature accuracy of ± 1°C in all electrodes' thermistors.	Temperature accuracy of ± 1°C in all electrodes' thermistors in the range of 35°C – 41°C was confirmed.	Temperature measurements in the electrodes meet the accuracy requirement throughout the functional range.
Device temperature measurement accuracy across functional range	Temperatures were measured in all the device's thermistors at room temperature (22°C) and also in 65°C - 69°C. The results were compared to a concomitant measurement by standard calibrated reference thermometers.	Temperature accuracy of ± 2°C in all device's thermistors.	Temperature accuracy of ± 2°C in all device's thermistors in the range of 22°C – 69°C was confirmed.	Temperature measurements in the device meet the accuracy requirement throughout the functional range.

Test	Methods	Acceptance Criteria	Results	Conclusion
Over-temperature error testing	Device was exposed to increasing temperatures signals from the electrodes within the functional temperature range, until the temperature exceeded 41°C. Log-files of the device were reviewed to examine its response.	Device turns-off once the detected temperature exceeds 41°C, and an “over-temperature” notification is triggered.	Log files of the devices showed that once the device detects a signal from the electrodes of a temperature over 41°C, the device triggers an alarm signal (“over temperature” notification) and turns-off the treatment.	Over-temperature error testing meets the requirements: treatment is stopped and an error notification is triggered.
Alarm response time	Using a simulation of exposure to 42°C, and following the output signal of the treatment as well as the signal from the audible notification, measure the time of response to treatment stop and audible notifications.	Device identifies the error situation when at least one thermistor temperature is above 41°C for more than 4 seconds.	Output signal graphs demonstrate that the device is turned off within 2 seconds from the first detection of 42°C (i.e. > 41°C) by the thermistor. Treatment was not resumed.	Alarm response time meets the response to the “over temperature” requirement, and stops treatment within no more than 4 seconds.
Simulated lifetime use of ILE arrays	A simulation of one week of continuous use of the ILE arrays was performed by exposing electrodes to 1260 simulated torso bendings, and then testing the thermistor accuracy at the end of the use period.	Electrodes maintain the accuracy of thermistors’ temperature measurements at the end of the simulated lifetime use.	Temperature accuracy of ± 1°C in all electrodes’ thermistors in the range of 22°C – 41°C was confirmed.	Temperature measurements in the electrodes meet the accuracy requirement throughout the functional range, and throughout the longest recommended use period of one week.

Test	Methods	Acceptance Criteria	Results	Conclusion
Human factors assessment	Evaluation of Human Factors Engineering (HFE) and Usability Engineering (UE) of the intended users through accumulated clinical experience and analysis of the user-device interface.	The device is usable by the intended users, and for its indication for use and use environments.	Accumulated data and a detailed risk assessment confirm that usability/human factors have been addressed through engineering and instructions, and use error risks have been reduced to the extent possible.	The device is usable by the intended users, and for its uses and use environments.

Battery Testing: Performance of the battery was tested by establishment of its ability to supply power for at least 60 minutes with the NovoTTF-100L System set to output of 4000 mA peak-to-peak attached to a simulated equivalence of patient load of 40 Ω. Furthermore, the battery was tested for performance following at least 100 charging cycles. It has been demonstrated that the battery meets these requirements.

The battery with therapeutic output stimulation parameters was tested to demonstrate that under simulation of treatment conditions the temperature within the battery does not exceed the predetermined limit of 60°C. This test was done while powering a NovoTTF-100L System (150kHz, 4000 mA peak-to-peak) and battery temperature. The tests showed that the batteries maintain temperature levels within specifications even following 100 cycles of charging and discharging.

For further qualification of the battery, tests were performed to verify and demonstrate that the battery design and performance comply with Underwriters Laboratories (UL)-1642, namely the safety requirements for lithium batteries. Furthermore, tests verify and demonstrate that the battery passed the requirements of safety as per recognized standard EN 60601-1, "Medical electrical equipment - Part 1: General requirements for basic safety and essential performance" namely that the batteries meet the requirements concerning basic safety and essential performance of medical electrical equipment. Battery tests also include collateral testing as per 60601-1-11, "General requirements for basic safety and essential performance - Collateral Standard: Requirements for medical electrical equipment and medical electrical systems used in the home healthcare environment" in order to demonstrate that the battery meets the safety and essential performance required of a medical electrical system intended for use in the home healthcare environment.

X. SUMMARY OF CLINICAL INFORMATION

A. Study Design

The STELLAR Study (EF-23) was a prospective, single-arm study evaluating pemetrexed and cisplatin or carboplatin in combination with TTFields (delivered by the NovoTTF-100L System) in patients outside the U.S. (OUS) with inoperable, untreated MPM. This trial was designed to study the safety and assess outcomes in these patients. TTFields were administered until radiological disease progression according to the Modified Response Evaluation Criteria in Solid Tumors (RECIST) criteria for malignant pleural mesothelioma, or unacceptable toxicity based on investigator assessment was seen.

Patients were treated between February 2015 and March 2018. The database for this HDE reflected data collected through March 2018 and included 80 patients at 13 investigational sites.

1. <u>Clinical Inclusion and Exclusion Criteria</u>

Enrollment in the STELLAR Study was limited to patients who met the following inclusion criteria:

- Pathological or histological evidence of mesothelioma;
- ≥ 18 years of age;
- Tumor, node, and metastases (TNM) Stage IV, not candidate for curative treatment (surgery or radiotherapy);
- At least 4 weeks since major surgery;
- At least one measurable or evaluable lesion according to modified RECIST criteria for MPM;
- Eastern Cooperative Oncology Group (ECOG) Performance Status ("PS") of 0-1;
- Life expectancy of at least 3 months;
- Participants of childbearing age must use effective contraception as indicated by the investigator;
- All subjects must sign written informed consent;
- Able to operate the NovoTTF-100L System independently or with the help of a caregiver.

Patients were not permitted to enroll in the STELLAR Study if they met any of the following exclusion criteria:

- Previous chemotherapy or radiation;
- Prior malignancy requiring anti-tumor treatment or concurrent malignancy;
- Significant co-morbidities within 4 weeks prior to enrollment, resulting in the following laboratory findings:
  - Significant liver function impairment:
  - Aspartate aminotransferase (AST) or Alanine aminotransferase (ALT) >3 times the upper limit of normal
  - Total bilirubin $\geq$1.5 upper limit of normal
  - Significant renal impairment (serum creatinine >1.7 mg/dL);
  - Coagulopathy (as evidenced by prothrombin time (PT) or activated partial thromboplastin time (aPTT) >1.5 times control in subjects not receiving anticoagulants);
  - Thrombocytopenia (platelet count < 100 x 10^3/μL);
  - Neutropenia (absolute neutrophil count < 1.5 x 10^3/μL);
  - Anemia (Hb <10 g/dL);

  - Severe acute infection;
- Significant comorbidity expected to affect patient's prognosis or ability to receive the combined therapy:
  - History of significant cardiovascular disease unless the disease is well controlled. Significant cardiac disease includes second/third degree heart block; significant ischemic heart disease; poorly controlled hypertension; congestive heart failure of the New York Heart Association (NYHA) Class II or worse (slight limitation of physical activity; comfortable at rest, but ordinary activity results in fatigue, palpitation or dyspnea).
  - History of arrhythmia that is symptomatic or requires treatment. Patients with atrial fibrillation or flutter controlled by medication are not excluded from participation in the trial.
  - Active infection or any serious underlying medical condition that would impair the ability of the patient to receive protocol therapy.
  - History of any psychiatric condition that might impair the patient's ability to understand or comply with the requirements of the study or to provide consent.
- Untreated brain metastases. Asymptomatic, pretreated brain metastases not requiring steroids are allowed;
- Implanted pacemaker, defibrillator or other electrical medical devices;
- Known allergies to medical adhesives or hydrogel;
- Pregnant or breastfeeding (all patients of childbearing potential must use effective contraception method during the entire period of the study based on the recommendation of the investigator or a gynecologist);
- Admitted to an institution by administrative or court order.

2. Follow-up Schedule

Assessments during the study were conducted every 3 weeks, with additional testing performed every 6 weeks, and in cases of progression/treatment termination. A matrix of the study procedures is shown in **Table 6**. Assessment of local and distant disease progression was performed per the revised RECIST criteria version 1.1. Overall response rate was assessed by the investigator at each site. The protocol specified a minimum follow-up of at least 12 months.

Table 6. Study Procedures

	Baseline (day –28 to 0)	Every 3 weeks ± 3 days	Every 6 weeks ± 3 days	Within 3 days of radiological progression	30 days post treatment termination	Post progression follow-up (every 2 months, ± 7 days)
Written informed consent	X					
History/Physical Examination	X	X		X		
Weight	X	X		X		
Performance Status	X	X				

	Baseline (day –28 to 0)	Every 3 weeks ± 3 days	Every 6 weeks ± 3 days	Within 3 days of radiological progression	30 days post treatment termination	Post progression follow-up (every 2 months, ± 7 days)
Blood sample*	X	X		X		
Thoracic CT-scan	X		X			
Abdominal CT-scan	X		X			
PET scan**	X		X			
Brain CT-scan/MRI**	X		X			
Bone Scan**	X		X			
Tumor Assessment per modified RECIST	X		X	X		
Pregnancy Test**	X					
Device compliance		X				
Adverse Event Evaluation		X		X	X	
Concomitant	X	X		X		
Pain evaluation (Visual Analog Scale)	X	X				
Survival Evaluation						X

*Complete blood count (CBC), creatinine, glucose, electrolytes, Lactate dehydrogenase (LDH), Serum Glutamic Oxaloacetic Transaminase (SGOT), serum glutamic-pyruvic transaminase (SGPT), Gamma-glutamyl-transpeptidase (gammaGT), alkaline phosphatase (ALP), bilirubin. Total protein, PT and aPTT will only be performed at baseline

**If clinically indicated

3. Clinical Endpoints and Analysis

Primary Endpoint

The primary endpoint of the trial was overall survival (OS) as measured from time of diagnosis until date of death. Patients lost to follow-up had their OS censored at the last date they were known to be alive. OS was calculated based on the Kaplan-Meier method.

Secondary Endpoints

- Progression free survival (PFS) was based on investigator assessment of CT scan imaging according to the modified RECIST criteria V1.1. PFS rates were estimated using the Kaplan- Meier method.

- Radiological response rate (“RR”) was presented as the real incidence of each response type (complete response, partial response, stable disease, progressive disease) in the trial population with the denominator being the number of patients in the trial evaluable for response assessment (i.e., patients with at least one CT scan after baseline).

- One and two year survival rates were analyzed based on the Kaplan-Meier estimated proportions with 95% confidence interval of patients who are alive at 12 and 24 months.

- Safety profile

Missing data were not imputed as the Kaplan-Meier methodology appropriately censors patients at their last follow-up.

B. Study Population Demographics

The demographic and clinical characteristics of the 80 patients enrolled in the study are shown in **Table 7**. The median age of the patients is 67 years (27-78 years) and 67% were male. The percentages of patients with performance status (ECOG) score of 0 and 1 were 45% and 35%, respectively (2 patients did not have ECOG scores at baseline). Most of the patients (84%) had locally advanced disease and 66% had epithelioid histology.

The median number of chemotherapy cycles was 6 (range 1-7), and the median number of 3 week TTFields cycles was eight (8) (range 2-41). The median compliance with TTFields in the first 3 months was 68% (i.e., 16.3 hours/day on average). Eight (8) patients (10%) were lost to follow up before completing the required minimum of 12 months follow up specified in the protocol.

The study was conducted at 13 sites in Europe (Belgium, France, Spain, Italy, Poland, and the Netherlands).

Table 7. Patient Baseline Characteristics and Treatment Details

Characteristics	NovoTTF-100L System/Chemotherapy (N=80)
Age (Years)	
n	80
Mean (SD)	64.8 (9.28)
Median (range)	67.0 (27-78)
Sex, No. (%)	
Female	13 (16%)
Male	67 (84%)
Ethnicity, No. (%)	
Caucasian	80 (100%)
Smoking, No. (%)	
Currently Smoke	8 (10%)
Formerly Smoked	37 (46%)
Never Smoked	35 (44%)
Tumor stage, No. (%)	
Locally Advanced	67 (84%)
Metastatic	13 (16%)

Characteristics	NovoTTF-100L System/Chemotherapy (N=80)
Tumor pathology, No. (%)	
Epithelioid	53 (66%)
Sarcomatoid/Biphasic	21 (26%)
Unknown	6 (8%)
Performance status (ECOG), No. (%)	
0	45 (56%)
1	35 (44%)
Visual Analog Pain Scale at Baseline	
Mean (SD)	15.1 (20.68)
Median (range)	5.0 (0-93)
Number of TTFields Cycles	
Mean (SD)	8.7 (6.08)
Median (range)	8.0 (2-41)
Number of Chemotherapy Cycles	
Mean (SD)	4.6 (1.81)
Median (range)	6.0 (1-7)

C. Safety and Probable Benefit Results

Safety Results

The safety results of the STELLAR Study are summarized in **Table 8 and 9**. Thirty-two (32) patients (40%) had severe (grade 3-4) adverse events (AEs) during the study period. Most severe AEs occurred only in one patient each. Twenty (20) patients (25%) had serious adverse events (SAEs) during the study (**Table 9**) requiring hospitalization. The most common severe AEs were: anemia (11%), neutropenia (9%), both unrelated to device use, and medical device site skin reaction in four (4) patients (5%) which resulted in interruption of treatment with the NovoTTF-100L System. The overall adverse event of treatment-related skin toxicity occurred in 53 (66%) of the treated patients. No patients exited the study due to a device related adverse event.

The nature and frequency of adverse events in the STELLAR Study are consistent with what would be expected from other clinical trials with MPM patients using pemetrexed.

Table 8. Adverse Events by Severity according to Common Terminoloy Criteria for Adverse Events (CTCAE) Version 4.0

System Organ Class	NovoTTF-100L System / Pemetrexed / Platinum (N=80)	
Preferred Term	Low-Medium	Severe
Number of Patients with >=1 AE	43 (54%)	32 (40%)
Blood and lymphatic system disorders	27 (34%)	18 (23%)
Anemia	25 (31%)	9 (11%)
Febrile neutropenia	0	1 (1%)
Leukocytosis	1 (1%)	0
Leukopenia	5 (6%)	3 (4%)
Neutropenia	7 (9%)	7 (9%)
Thrombocytopenia	2 (3%)	4 (5%)
Cardiac disorders	3 (4%)	3 (4%)
Angina pectoris	1 (1%)	0
Atrial fibrillation	3 (4%)	1 (1%)
Atrial flutter	1 (1%)	0
Cardiac tamponade	0	1 (1%)
Pericardial effusion	0	2 (3%)
Supraventricular tachycardia	1 (1%)	0
Ear and labyrinth disorders	1 (1%)	0
Tinnitus	1 (1%)	0
Eye disorders	5 (6%)	0
Cataract	1 (1%)	0
Conjunctival hemorrhage	1 (1%)	0
Lacrimation increased	2 (3%)	0
Periorbital edema	1 (1%)	0
Visual impairment	1 (1%)	0
Gastrointestinal disorders	30 (38%)	3 (4%)
Abdominal distension	1 (1%)	0
Abdominal pain	2 (3%)	0
Abdominal pain upper	1 (1%)	0
Abdominal rigidity	1 (1%)	0
Constipation	8 (10%)	0
Diarrhea	5 (6%)	0
Dyspepsia	2 (3%)	0
Dysphagia	1 (1%)	0
Gastric ulcer	1 (1%)	0
Gastric ulcer hemorrhage	0	1 (1%)
Gastritis	1 (1%)	0
Gastroesophageal reflux disease	1 (1%)	0
Hemorrhoidal hemorrhage	1 (1%)	0

Nausea	17 (21%)	0
Stomatitis	4 (5%)	0
Vomiting	4 (5%)	2 (3%)
General disorders and administration site	34 (43%)	6 (8%)
Administration site pain	1 (1%)	0
Administration site rash	1 (1%)	0
Asthenia	11 (14%)	1 (1%)
Chest discomfort	1 (1%)	0
Chest pain	10 (13%)	1 (1%)
Extravasation	1 (1%)	0
Fatigue	10 (13%)	3 (4%)
Hyperthermia	1 (1%)	0
Malaise	3 (4%)	0
Non-cardiac chest pain	2 (3%)	0
Edema peripheral	4 (5%)	0
Pain	0	1 (1%)
Pyrexia	7 (9%)	0
Thrombosis in device	1 (1%)	0
Hepatobiliary disorders	1 (1%)	1 (1%)
Biliary colic	1 (1%)	0
Cholelithiasis	0	1 (1%)
Infections and infestations	17 (21%)	2 (3%)
Bronchitis	1 (1%)	0
Bronchopneumonia	0	1 (1%)
Conjunctivitis	2 (3%)	0
Cystitis	2 (3%)	0
Folliculitis	1 (1%)	0
Gastroenteritis	1 (1%)	0
Genital infection fungal	1 (1%)	0
Gingival abscess	1 (1%)	0
Hepatitis B	1 (1%)	0
Lower respiratory tract infection	1 (1%)	0
Nasopharyngitis	3 (4%)	0
Oral candidiasis	0	1 (1%)
Penile infection	1 (1%)	0
Pharyngitis	1 (1%)	0
Rash pustular	1 (1%)	0
Upper respiratory tract infection	2 (3%)	0
Urinary tract infection	1 (1%)	0
Injury, poisoning and procedural complications	4 (5%)	0

Limb injury	1 (1%)	0
Skeletal injury	1 (1%)	0
Thermal burn	1 (1%)	0
Wound dehiscence	1 (1%)	0
Investigations	15 (19%)	2 (3%)
Alanine aminotransferase increased	3 (4%)	0
Aspartate aminotransferase increased	1 (1%)	0
Blood alkaline phosphatase increased	1 (1%)	0
Blood creatinine increased	5 (6%)	0
Blood lactate dehydrogenase increased	1 (1%)	0
Blood pressure increased	1 (1%)	0
Blood uric acid increased	2 (3%)	0
C-reactive protein increased	1 (1%)	0
Cardiac murmur	1 (1%)	0
Gamma-glutamyltransferase increased	6 (8%)	0
Hepatic enzyme abnormal	1 (1%)	0
Neutrophil count decreased	2 (3%)	1 (1%)
Platelet count decreased	0	1 (1%)
White blood cell count decreased	2 (3%)	1 (1%)
White blood cell count increased	1 (1%)	0
Metabolism and nutrition disorders	8 (10%)	0
Decreased appetite	1 (1%)	0
Hypercholesterolemia	1 (1%)	0
Hyperuricemia	2 (3%)	0
Hypoglycemia	1 (1%)	0
Hypokalemia	2 (3%)	0
Overweight	1 (1%)	0
Musculoskeletal and connective tissue disorders	6 (8%)	1 (1%)
Back pain	1 (1%)	0
Chest wall cyst	1 (1%)	0
Hypercreatinemia	1 (1%)	0
Joint swelling	1 (1%)	0
Musculoskeletal chest pain	1 (1%)	0
Musculoskeletal pain	1 (1%)	0
Neck pain	0	1 (1%)
Pain in extremity	1 (1%)	0
Neoplasms benign, malignant and unspecified	2 (3%)	0
Cancer pain	1 (1%)	0
Tumor pain	1 (1%)	0
Nervous system disorders	13 (16%)	0

Disturbance in attention	1 (1%)	0
Dysgeusia	3 (4%)	0
Epilepsy	1 (1%)	0
Loss of consciousness	1 (1%)	0
Neuropathy peripheral	1 (1%)	0
Paraesthesia	5 (6%)	0
Polyneuropathy	1 (1%)	0
Vocal cord paralysis	1 (1%)	0
Psychiatric disorders	4 (5%)	0
Anxiety	2 (3%)	0
Delirium	1 (1%)	0
Sleep disorder	2 (3%)	0
Renal and urinary disorders	4 (5%)	1 (1%)
Acute kidney injury	1 (1%)	0
Chronic kidney disease	1 (1%)	0
Dysuria	1 (1%)	0
Hematuria	1 (1%)	0
Oliguria	0	1 (1%)
Urinary incontinence	1 (1%)	0
Reproductive system and breast disorders	1 (1%)	0
Breast cyst	1 (1%)	0
Respiratory, thoracic and mediastinal disorders	17 (21%)	4 (5%)
Cough	8 (10%)	0
Dysphonia	1 (1%)	0
Dyspnea	5 (6%)	2 (3%)
Dyspnea exertional	3 (4%)	0
Hemothorax	1 (1%)	0
Hiccups	1 (1%)	0
Hypercapnia	1 (1%)	0
Middle lobe syndrome	1 (1%)	0
Pneumonitis	1 (1%)	0
Pulmonary embolism	0	1 (1%)
Respiratory failure	0	1 (1%)
Skin and subcutaneous tissue disorders	54 (68%)	4 (5%)
Erythema multiforme	1 (1%)	0
Hyperhidrosis	1 (1%)	0
Medical Device Site Reaction	53 (66%)	4 (5%)
Night sweats	1 (1%)	0
Pruritus	11 (14%)	0
Skin exfoliation	1 (1%)	0
Skin hyperpigmentation	1 (1%)	0

Vascular disorders	8 (10%)	0
Deep vein thrombosis	1 (1%)	0
Hot flush	1 (1%)	0
Hypertension	3 (4%)	0
Hypertensive crisis	1 (1%)	0
Hypotension	1 (1%)	0
Thrombosis	1 (1%)	0

Table 9. Serious Adverse Events

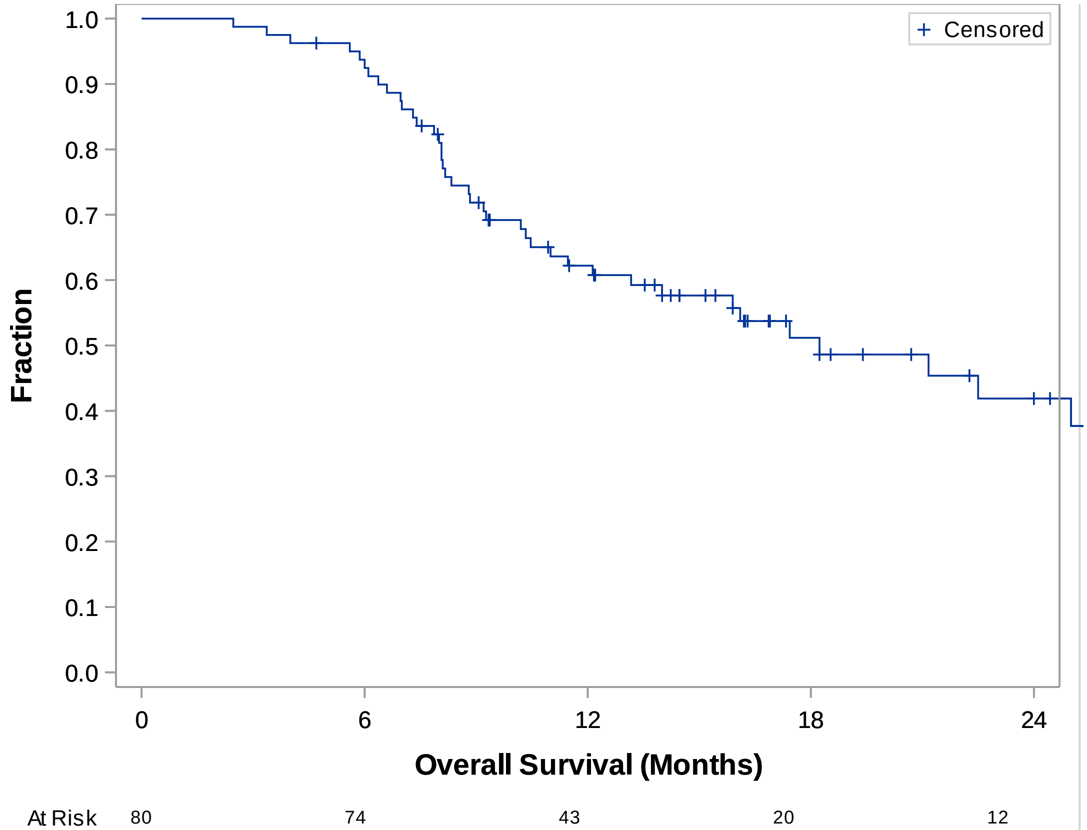
System Organ Class **Preferred Term**	**NovoTTF-100L System / Pemetrexed Platinum (N=80)**
Number of Patients with ≥ 1 AE	20 (25%)
Blood and lymphatic system disorders	4 (5%)
Anemia	3 (4%)
Neutropenia	1 (1%)
Cardiac disorders	4 (5%)
Atrial fibrillation	2 (3%)
Atrial flutter	1 (1%)
Cardiac tamponade	1 (1%)
Pericardial effusion	2 (3%)
Gastrointestinal disorders	4 (5%)
Gastric ulcer hemorrhage	1 (1%)
Gastritis	1 (1%)
Vomiting	2 (3%)
General disorders and administration site	1 (1%)
Asthenia	1 (1%)
Infections and infestations	4 (5%)
Bronchopneumonia	1 (1%)
Candida sepsis	1 (1%)
Lower respiratory tract infection	1 (1%)
Pneumonia	1 (1%)
Nervous system disorders	1 (1%)
Epilepsy	1 (1%)
Renal and urinary disorders	1 (1%)
Acute kidney injury	1 (1%)
Respiratory, thoracic and mediastinal disorders	4 (5%)
Dyspnea	1 (1%)
Dyspnea exertional	1 (1%)
Pulmonary embolism	1 (1%)
Respiratory failure	1 (1%)
Vascular disorders	1 (1%)
Deep vein thrombosis	1 (1%)

Probable Benefit Results

All analyses were performed in the Intent-to-Treat ("ITT") population.

Primary Endpoint

The median OS in the trial was 18.2 months (95% CI 12.1-25.8) (**Figure 4**).



Subjects	Event	Censored	Median Survival	95% CL	
80	43	37	18.23	12.13	25.80

Figure 4: Median OS in STELLAR Study

Secondary Endpoints

As shown in **Figure 5**, the median PFS in the trial was 7.6 months (95% CI 6.7-8.6).

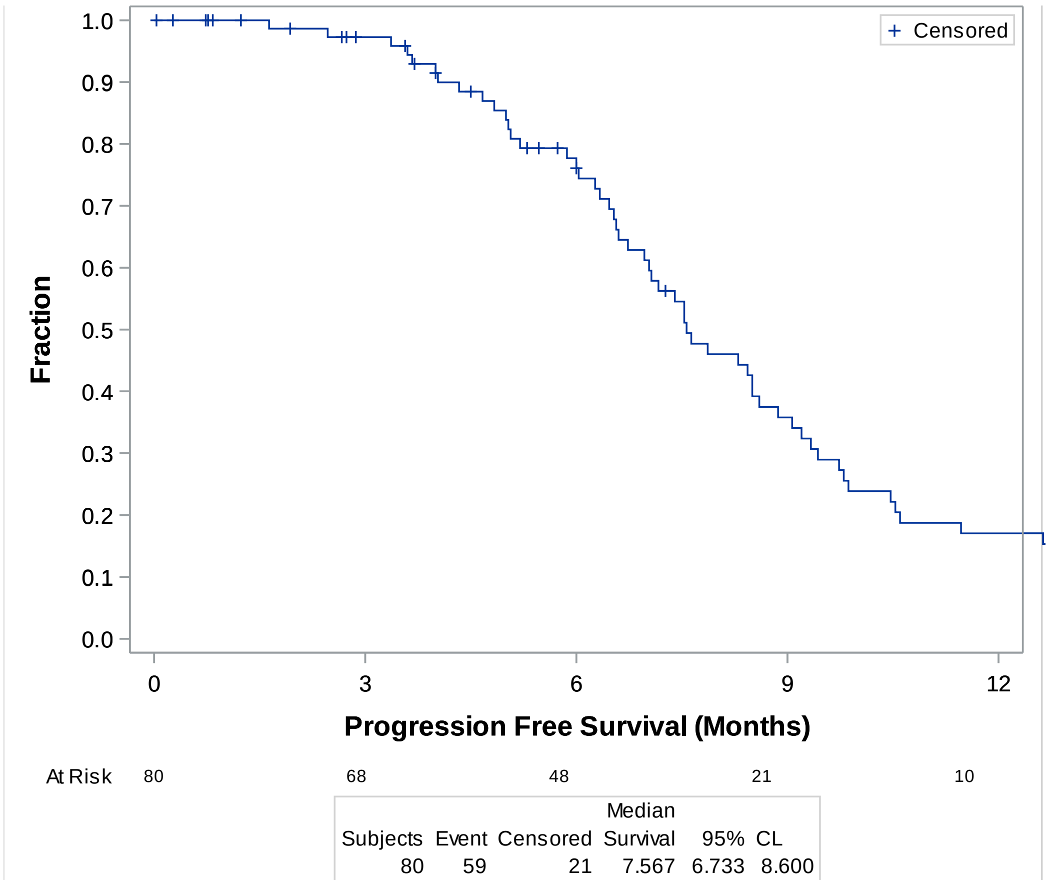


Figure 5: Median PFS in STELLAR Study

One-year survival in the study was 62% (95% CI 50%-72%) and 2-year survival in the study was 42%.

Seventy two (72) patients in the trial had at least one follow-up CT scan performed. Of these patients, 29 (40%) experienced a partial response, 41 stable disease (57%), and 2 (3%) patients progressed at their first follow-up scan.

Table 10. Summary of Results

Endpoint	NovoTTF-100L System / Pemetrexed / Platinum (n=80)
Overall Survival	
Median OS, months (95% CI)	18.2 (12.1-25.8)
Survival rate % (95% CI)	
1-year	62.2% (50.3- 72.0)
2-year	41.9% (28.0 ; 55.2)
Progression Free Survival	
Median PFS, months (95% CI)	7.6 (6.7-8.6)
Available Best Response, No. (%)	72 (90)

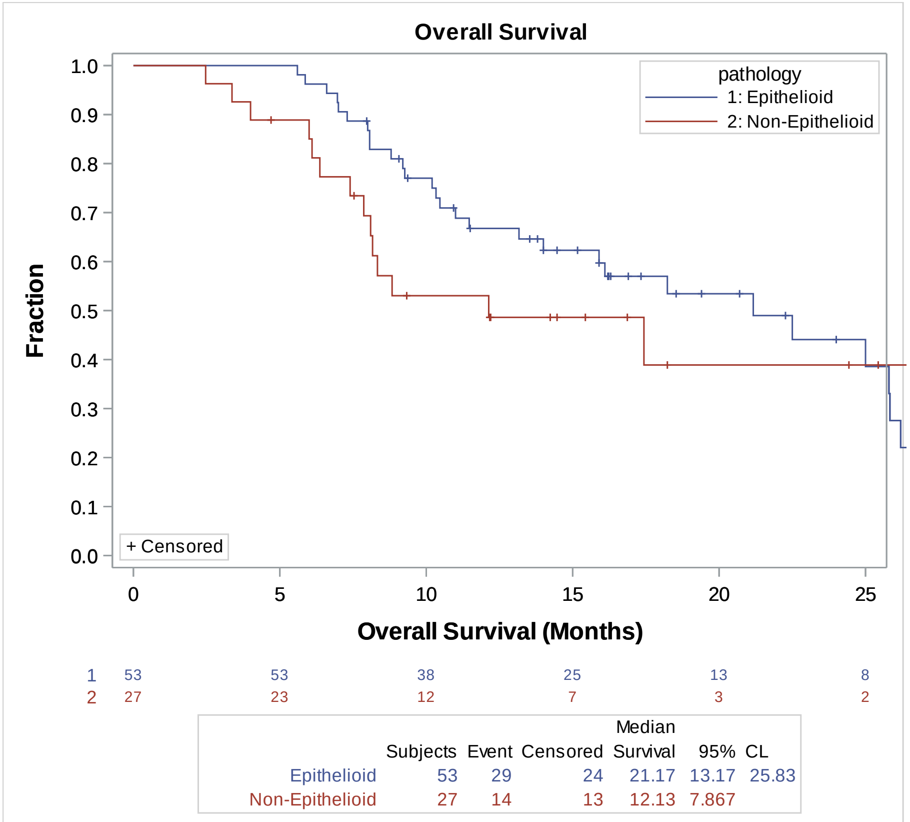
Endpoint	NovoTTF-100L System / Pemetrexed / Platinum (n=80)
Complete Response	0 (0)
Partial Response	29 (40)
Stable Disease	41 (57)
Progressive Disease	2 (3)
Disease Control Rate (CR+PR+SD)	70 (97)

D. Subgroup Analyses

The patient population enrolled in this study were mostly male (84%), older adults (mean age 64.8), and an OUS Caucasian population. A separate subanalyses was not performed for these subgroups as mesothelioma occurs mostly in older men. Race, ethnicity, gender, and location of study (which was OUS) is not expected to affect treatment decisions or the safety and probable benefit of the device in patients with mesothelioma.

OS and PFS by Histological Subtype

MPM patients with epithelioid histology have previously been shown to have significantly better outcomes than those with non-epithelioid histology.[5] Therefore, the company separately analyzed OS and PFS in the current EF-23 study in patients with epithelioid versus non-epithelioid histology. As shown below (**Figure 6**), OS and PFS were better in patients with epithelioid histology.



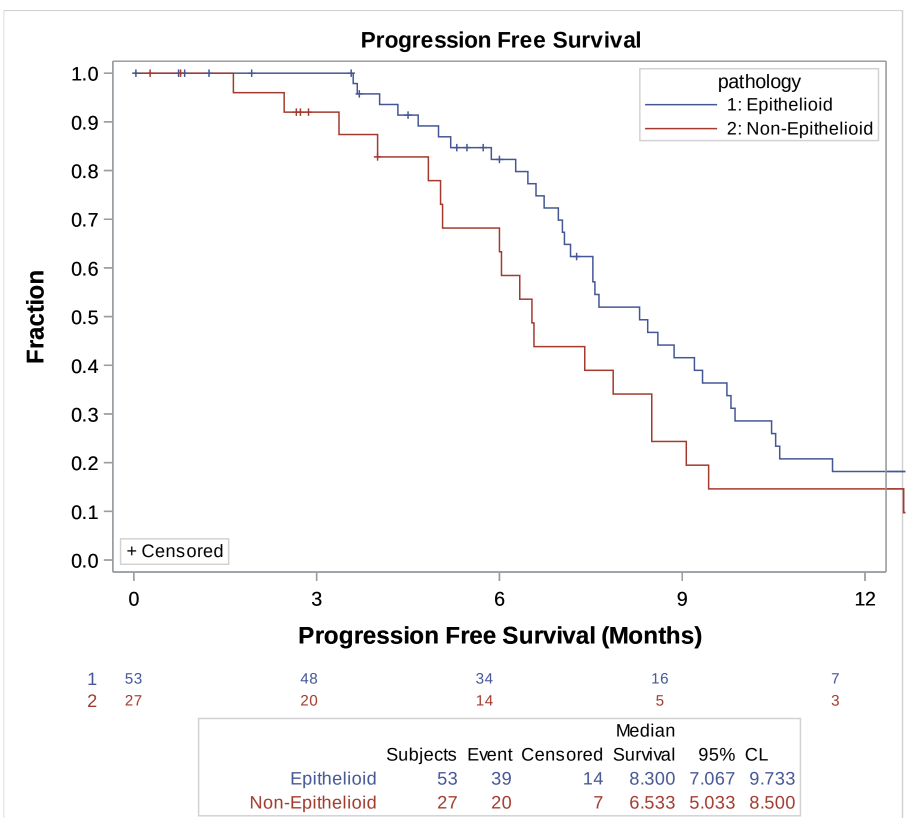


Figure 6: OS and PFS by Histology

E. Pediatric Extrapolation

In this premarket application, existing clinical data was not leveraged to support approval of a pediatric patient population.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The pivotal clinical study included 13 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. SAFETY AND PROBABLE BENEFIT ANALYSIS

A. Probable Benefit Conclusions

Malignant pleural mesothelioma (MPM) is an aggressive tumor that is associated with significant morbidity and mortality. It is associated with asbestos exposure and has a latency period of about 40 years after asbestos exposure.[6] In 2008, it was estimated that there would be 14,200 cases worldwide each year.[5] In the United States, there are about 3,000 new cases diagnosed each year. Recommendations for treatment are mainly chemotherapy as first line with pemetrexed plus platinum. It has been found that the addition of bevacizumab to pemetrexed-based chemotherapy improves survival in select patients. Surgical cytoreduction is also recommended in selected patients with early-stage disease. Adjuvant radiation can be offered for patients who have resection of intervention tracts found to be histologically positive or for palliation of symptomatic patients.[7]

The NovoTTF-100L System produces electrical fields (TTF-tumor treating fields) that is hypothesized to disrupt rapid cell division. The STELLAR Study evaluated the use of the device in 80 patients with inoperable MPM when used concurrent with pemetrexed and platinum-based chemotherapies. Study results showed a median overall survival (OS) of 18.2 months and median PFS of 7.6 months. Although the survival numbers reported in literature in the last 15 years for the Standard of care chemotherapy have varied (Median OS range = 8.5 to 16.1 months, Median PSF range = 4.6 to 8 months), the results obtained in STELLAR Study are within the range and show improvement (statistical significance not evaluated) over some reported survival rates.[8,9,10] The reported results and limited treatment options in this population supports the probable benefit with the use of the current device in patients with inoperable MPM. It should also be noted that there is currently no comparable device to treat MPM in this humanitarian use patient population. Limitations with regard to the STELLAR Study should be recognized, particularly the study's lack of a concurrent control.

B. **Safety Conclusions**

The risks of the device are based on nonclinical laboratory evaluations, clinical use of the Optune System in glioblastoma, and data collected in the OUS clinical study to support HDE approval as described above. In the STELLAR Study, the device related toxicities were mainly related to skin reactions under the transducer array in 66% of patients. Four (4) patients (5%) had severe skin reactions that led to interruption of treatment with the device. Although 25% of the patients had SAEs that resulted in hospitalization, these were related to complications of chemotherapy or disease progression. Deaths in the study were also related to disease progression. There was no evidence of augmentation of chemotherapy related SAEs or deaths related to the device. This study and prior experience with Optune supports a reasonable assurance of safety in this vulnerable population with limited options.

C. **Probable Benefit-Risk Conclusions**

The probable benefits of the device are based on data collected in the STELLAR Study that was conducted to support HDE approval as described above. The NovoTTF-100L System can be used concurrent to chemotherapy in patients with unresectable malignant mesothelioma. In a study of 80 patients, there was a median overall survival of 18.2 months and median PFS of 7.6 months. There are limited options for treatment in this vulnerable population. The NovoTTF-100L System has a humanitarian use designation. At this time, there are no other devices approved for concurrent use in this patient population. Since this was a single arm study, the probable benefit is extrapolated from publications with reported patient outcomes and analysis showed that the results of the STELLAR Study are within range of these publications and show improvement over some reported survival rates.

The probable risks of the device are also based on data collected in the clinical study conducted to support HDE approval as described above. The device related toxicities were mainly related to localized skin reactions. There was a 5% incidence of severe skin reactions that resulted in treatment interruption. There were no device related deaths or evidence of augmented chemotherapy toxicities. Overall the device was well tolerated with a reasonable safety profile.

Additional factors to be considered in determining probable risks and benefits for the NovoTTF-100L System included the following: MPM is a fatal disease with limited treatment options. Although the STELLAR Study was a single arm study, there are very few randomized trials for this patient group. The results of the median overall survival and median PFS are within the range reported in published literature. The safety profile is acceptable and no systemic toxicities were seen. At this time, there are also no devices approved for this indication.

1. Patient Perspectives
   This submission did not include specific information on patient perspectives for this device.

In conclusion, given the available information above, the data support that in adult patients with unresectable, locally advanced or metastaic, malignant pleural mesothelioma, the concurrent use of NovoTTF-100L System with chemotherapy, the probable benefits outweigh the probable risks.

D. **Overall Conclusions**

The data in this application support the reasonable assurance of safety and probable benefit of this device when used in accordance with the indications for use. Patients with unresectable MPM have limited treatment options and this device may potentially disrupt the rapid proliferation of cancer cells. The clinical data from the STELLAR Study demonstrated that the NovoTTF-100L System when used concurrently with pemetrexed and platinum-based chemotherapies for the treatment of MPM resulted in a median overall survival and median PFSl that was within the range reported in published literature. Most of the adverse events with the device were related to skin irritation and therefore, the device has an acceptable safety profile. Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk of illness or injury, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XIII. PANEL RECOMMENDATION

This HDE was not reviewed by an FDA Advisory Panel. The panel has previously reviewed the safety of a technically similar device under P100034 indicated for the treatment of glioblastoma multiforme. This HDE does not raise any unanticipated safety issues. Therefore, it was determined that this application need not be submitted to the advisory panel.

XIV. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, the NovoTTF-100L System will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risks of illness or injury. CDRH issued an approval order on May 23, 2019.

The applicant’s manufacturing facilities have been inspected and found to be in compliance with the device Quality System (QS) regulation (21 CFR 820).

XV. APPROVAL SPECIFICATIONS

Directions for use: See the device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

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