

**DE NOVO CLASSIFICATION REQUEST FOR
EDISON SYSTEM**

REGULATORY INFORMATION

FDA identifies this generic type of device as:

Focused ultrasound system for non-thermal, mechanical tissue ablation. This device uses focused ultrasound to mechanically ablate soft tissue. The device is not intended to thermally ablate tissue.

NEW REGULATION NUMBER: 21 CFR 878.4405

CLASSIFICATION: Class II

PRODUCT CODE: QGM

BACKGROUND

DEVICE NAME: Edison System

SUBMISSION NUMBER: DEN220087

DATE DE NOVO RECEIVED: December 2, 2022

SPONSOR INFORMATION:

HistoSonics, Inc.
16305 36th Avenue N
Plymouth, Minnesota 55446

INDICATIONS FOR USE

The Edison System is indicated as follows:

The Edison System is indicated for the non-invasive destruction of liver tumors, including unresectable liver tumors, using a non-thermal, mechanical process of focused ultrasound.

LIMITATIONS

The sale, distribution, and use of the Edison System are restricted to prescription use in accordance with 21 CFR 801.109.

Use of The Edison System must be administered under the direct supervision of a qualified and trained physician, after appropriate evaluation.

The Edison System has not been evaluated for the treatment of any specific disease or condition. The safety and effectiveness of the device for the treatment of cancer has not been established.

PLEASE REFER TO THE LABELING FOR A MORE COMPLETE LIST OF CONTRAINDICATIONS, WARNINGS AND PRECAUTIONS.

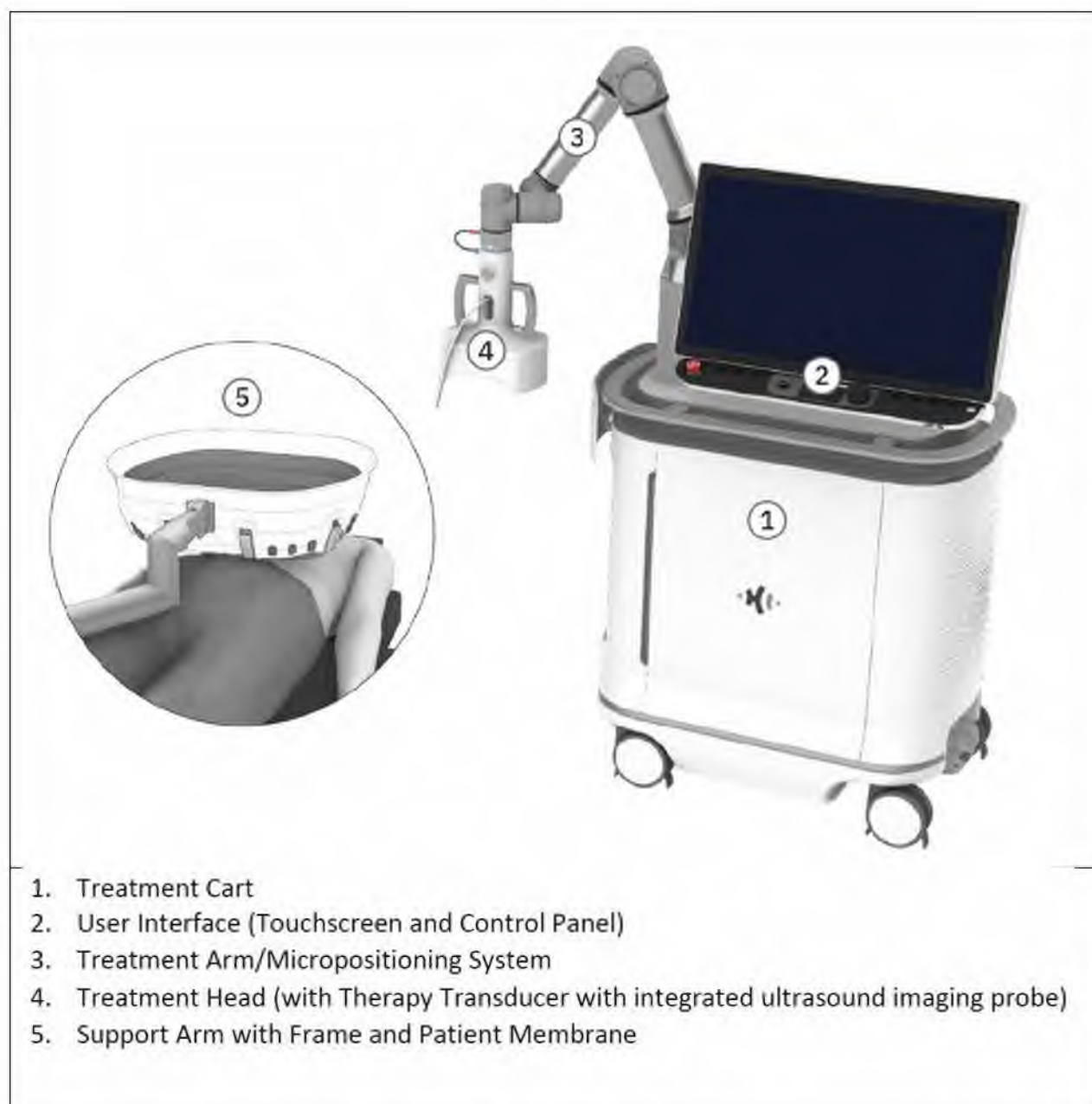
DEVICE DESCRIPTION

The HistoSonics Edison™ System (the “System”) provides users with a means to identify, target and destroy tissue non-invasively via non-ionizing, non-thermal, mechanical process of focused ultrasound.

By delivering high amplitude, very short (microsecond), focused ultrasound pulses the device can induce acoustic cavitation at a known focal location in the form of a "bubble cloud". The bubble cloud is a cluster of microbubbles that form, rapidly expand and rapidly collapse, imparting stress and strain on target soft tissue. After a number of pulses, soft tissue within the bubble cloud is mechanically destroyed, resulting in a homogenous acellular lysate with limited to no recognizable cellular structures. The bubble cloud appears hypoechoic (bright) when viewed on diagnostic (B-mode) ultrasound. Additionally, the bubble cloud is detectable audibly.

The System is comprised of reusable medical equipment and disposable, single-patient use components. Reusable portions of the System include the Treatment Cart and a Support Arm and Frame that is used to contain ultrasound medium (degassed water) that acoustically couples the System to the patient. Disposable aspects of the System include a clear, acoustically transparent and deformable membrane that holds the ultrasound medium as well as various non-active accessories used during patient setup.

The System is functionally integrated with a GE LOGIQ E10s ultrasound system (K211524), which is provided by HistoSonics with each Edison System. The LOGIQ E10s is provided with a preset configuration designed to optimize viewing of the bubble cloud. This configuration falls within the available performance parameters of the LOGIQ E10s covered by K211524.



The Treatment Cart is mobile and contains all hardware and software components necessary to localize, plan and deliver treatments. The Treatment Cart includes a large touchscreen user interface and control panel, a high voltage power supply, integrated amplifier circuitry, waveform generator boards, Control PC, and Treatment Arm/Micropositioning System with connected Treatment Head.

The System user interface guides the user step by step through the required workflow including Patient Preparation, Localize, Plan and Treat.

The treating physician uses the user interface to assess ultrasound images to localize the targeted tissue and define a Planned Treatment Volume (PTV) comprised of a target contour and margin

contour. During targeting, the diagnostic ultrasound probe can be extended up to 5 cm in the Z axis to reduce the offset of the ultrasound medium, thereby improving the targeting process versus a non-extended probe. An optional workflow enables the physician to view DICOM images (MRI, CT and PET) adjacent to the live ultrasound to aid the target identification process. Additionally, an image fusion function is an optional workflow that allows physician to fuse the live ultrasound image from the GE LOGIQ E10s onto the previously obtained DICOM images.

The Treatment Arm/Micropositioning System is comprised of a six degree of freedom (6 DOF) dual encoded robotic arm and is used to direct the movement of the Treatment Head. The Treatment Arm provides mechanical support to the Treatment Head (containing the Therapy Transducer and the coaxially aligned GE LOGIQ E10s Diagnostic Imaging Probe) and allows gross and fine positioning prior to initiating therapy. The Treatment Head is available in two configurations with different maximum treatment depths to provide physicians with options based on target anatomy. Both Treatment Heads are supplied with the System.

Electronic signals from the Treatment Cart are applied to the Therapy Transducer to create a bubble cloud at a known focal point. Note that the bubble cloud location is fixed relative to the position of the Treatment Head. The System uses the software-controlled Micropositioning System to move the Treatment Head, and the resulting bubble cloud, through a programmed treatment pathway to enable treatment delivery at all bubble cloud locations included as part of the PTV.

SUMMARY OF NONCLINICAL/BENCH STUDIES

The following non-clinical test were leveraged to demonstrate safety and effectiveness for the subject device's indication for use.

BIOCOMPATIBILITY/MATERIALS

The Edison System, per the patient contact classification and Table A.1 of the FDA Biocompatibility guidance entitled, “*Use of International Standard ISO 10993-1, “Biological evaluation of medical devices – Part 1: Evaluation and testing within a risk management process”*”, has two components categorized as Skin Contacting, surface device with limited (<24 hour) tissue contact and the following biocompatibility endpoints were assessed separately and as a unit:

Endpoint	Test Method
Cytotoxicity	MEM Elution Test ISO 10993-5:2009
Sensitization	Guinea Pig Maximization ISO 10993-10:2010
Irritation	Intracutaneous Irritation Test ISO 10993-10:2010
Acute Systemic Toxicity	Acute Systemic Injection Test ISO 10993-11:2017

SHELF LIFE/STERILITY

The Edison System does not have a shelf-life specification. The Edison System accessories (Coupling Kit) were tested after exposure to 45 degrees Celsius for 75 days per ASTM F1980-21, "Standard Guide for Accelerated Aging of Sterile Barrier Systems for Medical Devices", in order to establish 12 months shelf life.

There are no sterilization requirements for the Edison System or its accessories. Cleaning and maintenance instructions for the Edison System have been provided in the labeling.

ELECTROMAGNETIC CAPABILITY & ELECTROMAGNETIC SAFETY

The following Electrical/Mechanical/Thermal Safety and Electromagnetic Compatibility (EMC) testing has been performed and results support electrical safety and electromagnetic compatibility:

- IEC 60601-1-2:2014 "Medical Electrical Equipment - Part 1-2: General Requirements for Basic Safety and Essential Performance-Collateral Standard: Electromagnetic disturbances - Requirements and Tests."
- IEC 60601 -1 :2005, AMD1:2012 "Medical Electrical Equipment; Part I: General requirements for basic safety and essential performance."
- IEC 60601-2-62 Ed. 1.0 2013-07 "Medical electrical equipment Part 2-62: Particular requirements for basic safety and essential performance of High Intensity Therapeutic Ultrasound (HITU) equipment."

The device was evaluated in consideration of the following essential performance:

- Real-time ultrasound imaging is available throughout the procedure.
- Planned treatment volume overlay (e.g., contours) is correctly displayed on the real-time ultrasound images within tolerance.
- Therapy output is according to settings provided by the user during treatment planning and is limited to pre-programmed performance specifications and safety limits.
- Therapy output effect (bubble cloud) is limited to and consistent across the planned treatment volume boundaries (e.g., contours) within tolerance.

- Bubble cloud predicted location overlay (e.g., crosshair) is correctly displayed on real-time ultrasound images within tolerance.
- Therapy output status (i.e., whether therapy output is active) is correctly indicated and can be controlled (i.e., turned on/off) by the user at all times.

MAGNETIC RESONANCE (MR) COMPATIBILITY

This device is not MR compatible and should not be used in or near MR equipment.

SOFTWARE

A failure or latent flaw in the software of the Edison System could indirectly result in severe injury or death to the patient; therefore, the software of this device is considered to have a "Major" level of concern.

The submission contained all the elements of software documentation corresponding to a "Major" level of concern, as outlined in the FDA guidance document "Guidance for the Content of Premarket Submissions for Software Contained in Medical Devices", issued May 11, 2005 (<https://www.fda.gov/media/73065/download>). Adequate documentation describing the software, firmware, software specifications, architecture design, software development environment, traceability, revision level history, unresolved anomalies and cybersecurity provide the foundation that the software will operate in a manner as described in the specifications. A hazard analysis was performed to characterize software risks including device malfunction and measurement related errors. The submission included verification and validation (V&V) testing to address the potential hazards with satisfactory results.

PERFORMANCE TESTING - BENCH

The following additional bench testing was conducted to demonstrate the safety and effectiveness of the subject device:

- Thermal Characterization: characterization of on-site and off-site tissue heating potential
- Thermal Mapping: mapping of energy deposition in support of thermal safety for ablation protocols
- Micropositioner Testing: the force exerted on a patient by the Micropositioner was characterized via an integrated force transducer with:
 - A resolution of 4.0N or better in the range of 0 to 50N
 - A resolution of 3.5N or better in the range of 50 to 110N
- Acoustic Characterization: demonstrates the cavitation performance of the subject device, including the ability to generate the pressure necessary to induce cavitation both on-site and off-site. demonstrates the safety and effectiveness of mitigations intended to minimize unintended off-target cavitation. Additionally, the testing was used to demonstrate the acoustic transparency of the acoustic coupling medium and membrane.

- **Ultrasound Imaging Accuracy:** testing should demonstrate the ultrasound imaging system can perform the following functions:
 - **B-Mode Imaging:** the device must demonstrate it can provide brightness mode imaging and can provide a minimum of 10 frames per second at the largest field of view at a minimum depth of 20cm.
 - **Axial Resolution:** the device must demonstrate it can provide a minimum axial resolution of 2mm at a depth of 10.5mm
 - **Lateral Resolution:** the device must demonstrate it can provide a minimum lateral resolution of 4mm at a depth of 10.5mm
 - **Contrast Differentiation:** testing must demonstrate the device can differentiate low contrast objects from background scatter at a depth of 11.5cm. Low contrast is defined as +3dB and -3dB in scatter amplitude.
- **Usability Testing:** testing was conducted to demonstrate users can perform all critical tasks when using the User Manual.

The test results satisfactorily met acceptance criteria and demonstrate that the device has been appropriately evaluated for performance on the bench.

HUMAN FACTORS TESTING

Human Factors testing was performed on the device. Task analysis for the was performed through functional analysis, contextual inquiries, and user interview during device development. Subsequently, formative usability evaluations were conducted to capture all tasks which will be conducted by device users. The information gathered during formative evaluation if the device tasks were used to determine scenarios in which human error may lead to hazard situations for patients or users. The information gathered resulted in design modification to mitigate the potential hazard scenarios due to human error. Summative testing was conducted to demonstrate the design mitigations, identified in the formative evaluation, adequately mitigated the potential hazardous scenarios and limited the impact of human error.

This summative evaluation was performed by simulated use with a multi-modality abdominal phantom with liver targets. All components of the system were used for evaluation except for the coupling kit assembly as it was not required to complete critical tasks. No ancillary equipment was required to use the system in a simulated use environment and the user interface was identical for all users participating in the test. A total of fifteen (15) users participated in the summative evaluation, which included a broad demographic with different clinical backgrounds and backgrounds.

Study participants were given a system overview at the start of each session. The system overview included a review of the technology, user interface, software workflow, and description of the phantom. After the system overview, the participants were introduced to the summative evaluation protocol and given the user guide to study prior to the testing portion of the session. The critical tasks included in this testing included Wheel Lock, System Check, Localize, Plan, Test Pulses, and Treatment. All other steps/use cases were determined to be non-critical because failure to perform or errors in performing could not

result in user or patient harm. The Human Factors testing demonstrated all device use risks have been mitigated via adequate device use training.

PERFORMANCE TESTING - ANIMAL

The sponsor provided 3 GLP animal studies, including one chronic multi-arm study comparing a microwave ablation (MWA) technique vs. the subject device, a chronic single-arm study involving only the subject device, and an acute animal study.

Comparative Chronic Multi-Arm Animal Study:

The multi-arm chronic animal study was designed to evaluate the safety profile of the subject device compared to a commonly used alternative ablation technique (MWA). Six healthy porcine subjects were administered MWA treatments within the liver and 8 healthy porcine subjects were treated with the subject device. CT scan examinations were obtained in both arms pre-ablation and at several designated times post-ablation (2, 7, 14, and 28 days). Endpoints included an evaluation and comparison of all adverse events, CT scan differences, clinical pathology, gross, and histopathologic assessments of each treatment arm. The study demonstrated that both treatment modalities resulted in low grade adverse events (42 and 19 for MWA and subject device respectively). In the MWA arm, there were greater incidences and severity of CT-scan observed perfusion defects and thromboemboli. Similar CT scan findings were observed in the subject device arm, but in lower frequency at all time points. Additionally, at later time points in the subject device treatment arm, the thrombus and perfusion defect findings decreased, compared to similar findings remaining consistent or increasing in the MWA arm. It is notable that in the subject device arm, CT scan changes showed a consistent decrease in discernable treatment size over time compared to the MWA arm.

Clinical pathology, gross, and histopathologic findings were consistent between the two groups. Of note, at 28-day necropsy, both ablation techniques induced well defined zones of permanent remodeling with an outer rim of fibrosis encapsulating an inner area of coagulative and liquefactive necrosis, respectively for the MWA and subject device treatment arms. There were gross and histopathologic changes demonstrating tissue damage at the skin insertion sites of the MWA arm, while no such findings were reported for the subject device.

Single-Arm Chronic Animal Study:

The single-arm chronic GLP animal study was designed to evaluate the safety and effectiveness of the subject device. Eight healthy pigs were selected to undergo liver ablation with the subject device. The objectives evaluated the procedural data, CT data, daily observations, clinical pathology, adverse events, gross necropsy, and histopathology.

Eight normal, healthy, female Yorkshire cross swine were enrolled in this study. System (ultrasound)- guided transcutaneous treatment procedures were performed successfully in all animals. All 8 treatment sessions were performed without incident and all animals successfully completed the treatment procedures and immediate follow-up CT procedures.

CT scan examinations were performed pre-treatment and at designated intervals post-treatment (Day 0, 2-, 7-, 14-, and 28-days post-procedure). The sponsor notes that due to the production of liquefactive necrosis (compared to coagulative necrosis induced by heating), rapid involution of the treatment lesion is often observed over time on follow up CT scan examinations.

Daily clinical observations noted only one minor event, which was unrelated to the test article. Overall, there were no adverse clinical observations following the treatment procedures that were directly related to the test article and the animals remained in suitable condition to assess the objectives of the study. Clinical pathology results demonstrated that the animals were healthy upon enrollment. Clinical pathology results included excursions from the normal ranges, but none were deemed clinically significant by the facility veterinarian. No evidence of thermal tissue effect was noted during the pathological examinations.

There were 11 adverse events in this study, all were not serious, and none were device related. Approximately 91% of all adverse events (10 of 11) were considered “expected adverse events”.

Twenty-eight-day post treatment necropsy and histopathology assessments concluded that no thromboembolism, ischemia, and infarction were identified downstream of the hepatic treatment sites within the liver or within the lungs. There were no gross or histological effects of the treatment to the skin at the contact site with the HistoSonics Platform (System) identified after treatment. There were no collateral lesions observed within adjacent tissues including the diaphragm, abdominal peritoneum, and abdominal. Any abnormal tissues underwent evaluation by a board-certified veterinary pathologist macroscopically and microscopically. Necropsy and histopathology assessments demonstrated that each treatment site had a well demarcated lesion with a surrounding thin zone of fibrosis encapsulating a central area of necrotic parenchyma and evidence of liquefactive necrosis.

Acute Animal Study:

For the acute GLP study, following the immediate post-treatment CT procedure, all animals were euthanized. Gross and microscopic pathology examinations were performed by a board-certified veterinary pathologist. The HistoSonics Platform (System) successfully created a hepatic lesion at each pre-determined and contoured treatment site. The gross and histological characteristics of the lesions were consistent with inducing necrosis which will result in permanent remodeling of the liver parenchyma consistent with successful therapy for volume reduction therapy of targeted treatment volumes. The pathology assessment did not identify any safety concerns related to the use of the HistoSonics Platform in the normal, porcine liver model immediately after treatment. Histological changes within the adjacent non-necrotic hepatic parenchyma were minimal and consisted only of small foci of hemorrhage and necrosis in centrilobular areas within a short distance of the main contiguous lesions, consistent with short venous extensions of the lesion, and occasional clots/thrombi within veins a short distance from the main treatment site lesion.

It is notable that both the CT scan dimensions and cross section necropsy dimensions closely resemble the planned treatment diameter, with some variations attributed to off-center cross sections and/or sectioning not aligned with the mid-transverse plane.

Histopathologic assessment of the ablated lesions demonstrated a consistent pattern of well demarcated zones of normal liver tissue next to a thin transition zone of coagulative necrosis, followed by a larger inner area of liquefactive necrosis. These findings are consistent with a non-thermal necrotizing lesion.

In summary, the 3 animal studies provide supporting evidence of the safety and efficacy of the device. Specifically, the combined data provides evidence to validate the selected efficacy endpoint, demonstrating that a preplanned treatment volume corresponds to acute CT scan changes which ultimately correlate to dimensionally similar gross and microscopic changes consistent with permanent tissue destruction. While the animal studies show that over time, the CT appearance of the lesions appear to decrease in size, which could be due to the rapid involution of liquefied parenchyma, the gross and histologic assessments in the acute animal study provide evidence that immediately after treatment with subject device, tissue destruction appears to occur in a volume with similar dimensions to both the pre-planned treatment diameter and corresponding CT scan findings.

SUMMARY OF CLINICAL INFORMATION

A clinical study was conducted by Histosonics to support the safety and effectiveness of the Edison System for the non-invasive destruction of unresectable liver tumors, using a non-thermal, mechanical process of focused ultrasound.

Study Design

A multicenter non-randomized, prospective single arm study involving 8 sites (U.S.) and 6 (OUS) sites with 44 subjects.

The trials were developed with an identical study design using the same device in both the US and EU, the data from both studies were pooled for a primary analysis that was conducted on the first 44 consecutive subjects. The pooled data contains 21 subjects treated in the US and 23 subjects treated in Europe. Co-primary endpoints of primary effectiveness and primary safety were defined with a pre-specified performance goal to indicate success. The primary effectiveness endpoint was achieving a complete tumor ablation rate of 70% or higher, as determined by CT/MRI imaging obtained 36 hours or less after the initial treatment. The rate of 70% is consistent with comparative success rates from other liver ablation modalities (47.7%-94.8%¹⁻⁷) reported in the literature. The primary safety endpoint was achieving a rate of 25% or less of index-procedure device-related major complications of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher at 30-days. The safety performance goal was likewise determined by comparing published major complication rates from other liver ablation methods (2.0%-11.2%⁸). Results for both endpoints needed to be positive and meet the performance goals within the bounds of a 95% Confidence Interval for the trial to be considered a success.

Clinical Inclusion and Exclusion Criteria

Inclusion Criteria

Subjects are eligible for the trial if all the following criteria are met:

1. Subject is ≥ 18 years of age
2. Subject has signed the Ethics Committee (EC) or Institutional Review Board (IRB) approved trial Informed Consent Form (ICF) prior to any trial related tests/procedures and is willing to comply with trial procedures and required follow-up evaluations.
3. Subject is diagnosed with hepatocellular carcinoma (HCC) or liver metastases (mets) from other primary cancers
 - Subject that is an HCC patient must have a targetable lesion(s) which meets the United Network for Organ Sharing and Organ Procurement and Transplantation Network (UNOS-OPTN) class 5 diagnostic criteria for HCC
 - Subject that is diagnosed with liver metastases must have prior diagnosis of primary tumor or metastatic tumor to identify the primary cancer type. Subjects must have untreated new or growing liver tumor(s) radiologically consistent with metastases. Note: A biopsy is required to confirm metastatic disease and the pathological results must be obtained prior to the index procedure (does not need to be a targeted tumor(s))
4. Subject is able to undergo general anesthesia
5. Subject has a Child-Pugh Score of A or B (up to B8)
6. Subject has an Eastern Cooperative Oncology Group Performance Status (ECOG PS) grade 0-2 at baseline screening
7. Subject meets the following functional criteria, ≤ 7 days prior to the planned index-procedure date:
 - Liver function: Alanine transaminase (ALT) and Aspartate transaminase (AST) $< 2.5 \times$ upper limit of normal (ULN) and/or bilirubin $< 2.5 \times$ ULN, and
 - Renal function: serum creatinine $< 2 \times$ ULN, and
 - Hematologic function: neutrophil count $> 1.0 \times 10^9/L$ and platelet $> 50 \times 10^9/L$
8. Subject has an International Normalized Ratio (INR) score of < 2.0 , ≤ 7 days prior to the planned index procedure date

9. Subject has not responded to and/or has relapsed and/or is intolerant of other available therapies including, surgery, chemotherapy, immunotherapy and targeted and/or locoregional therapies

Imaging Inclusion

10. The tumor(s) selected for ablation treatment must be ≤ 3 cm in longest diameter
11. Subject has an adequate acoustic window to visualize targeted tumor(s) using ultrasound imaging
12. A maximum of three (3) tumors are allowed to be treated with ablation during the index procedure, regardless of how many tumors the subject has.
 - Note: If the subject is treated with surgical resection prior to the index procedure, the resection must be performed ≥ 2 weeks prior to the planned index-procedure date

Exclusion Criteria

Subjects are not eligible for participation in the trial if any of the following criteria are met:

1. Subject is pregnant or planning to become pregnant or nursing (lactating) during the trial period
2. Subject is enrolled in another investigational trial and/or is taking investigational medication and/or has been treated with an investigational device ≤ 30 -days prior to planned index procedure date
3. In the Investigator's opinion, the subject has co-morbid disease(s) or condition(s) that would cause undue risk and preclude safe use of the HistoSonics System
4. Subject has a serum creatinine > 2.0 mg/dL or estimated glomerular filtration rate (EGFR) < 30 , unless on dialysis
5. Subject has major surgical procedure or significant traumatic injury ≤ 2 weeks prior to the planned index procedure date or not fully recovered (CTCAE grade 1 or better) from side effects/complications of such procedure or trauma
6. Subject has not recovered to Common Terminology Criteria for Adverse Events (CTCAE) grade 1 or better from any adverse effects (except alopecia, fatigue, nausea, vomiting and peripheral neuropathy) related to previous anti-cancer therapy
7. Subject has a history of, or suspected to have, bleeding disorders that is uncorrectable
8. Subject has a coagulopathy that is uncorrectable

9. Subject has a planned cancer treatment (e.g., resection, chemotherapy, etc.) after the planned index-procedure date and prior to completion of the 30-day follow-up visit
10. Subject has previous treatment with bevacizumab that has not been discontinued >40 days prior to the planned index-procedure date
11. Subject has planned bevacizumab treatment prior to completion of the 30-day follow-up visit
12. Subject has previous treatments with chemotherapy and/or radiotherapy that has not been discontinued ≥ 2 weeks prior to the planned index-procedure date and has not recovered (CTCAE grade 1 or better) from related toxicity (except alopecia and peripheral neuropathy)
13. Subject has previous treatment with immunotherapies that has not been discontinued ≥ 4 weeks prior to the planned index-procedure date and has not recovered from related toxicity (CTCAE grade 1 or better)
14. Subject has a life expectancy less than six (<6) months
15. In the opinion of the Investigator, ablation is not a treatment option for the subject
16. Subject has a concurrent condition that, in the Investigator's opinion, could jeopardize the safety of the subject or compliance with the protocol
17. Subjects' tumor(s) is not treatable by the System's working ranges (refer to User Manual)
18. Subject has a known sensitivity to contrast media and cannot be adequately pre-medicated
19. Subjects' targeted tumor(s) has/have had prior locoregional therapy (e.g., ablation, embolization, radiation)
20. Subject is eligible for surgical resection

Imaging Exclusion

21. Targeted tumor(s) treatment volume overlaps a non-targeted tumor visible via imaging
22. The targeted tumor(s) is not clearly visible with diagnostic ultrasound and computed tomography (CT) or magnetic resonance (MR) imaging
23. The targeted tumor(s) is located in liver segment 1

24. The Planned Treatment Volume intended to cover the targeted tumor includes or encompasses any portion of the main portal vein, common hepatic duct, common bile duct, gallbladder, or stomach/bowel.

Follow up Schedule

All patients were schedule for study follow up 7, 14, and 30 days post ablation procedure for the primary safety and effectiveness endpoints with continuing follow up out to 5 years. Adverse events and complications were recorded at all visits. Key time points are shown in the table below:

Table 1: Patient Follow Up Schedule and Testing

Procedure / Test / Data Collection	Baseline ¹¹	Pre-Procedure	Index Procedure\Treatment Procedure	Post-Procedure / Discharge	7-Day Follow-up Assessment ¹²	14-Day Follow-up Phone Assessment	30-Day Follow-up Visit ¹¹	6-Month Follow-up Visit ¹¹	1-Year Follow-up Visit ¹¹	2, 3, 4, 5-Year Follow-up Visit ¹¹
Visit Window	≤30 Days prior to Index Procedure	≤7 Days	Procedure	≤36 hours	±3 Days	±3 Days	±3 Days	±30 Days	±60 Days	±60 Days
Informed Consent ¹	X									
Inclusion / Exclusion Criteria	X ¹⁸		X ²							
Child Pugh Score	X						X	X	X	X
ECOG PS Grade	X						X	X	X	X
Medical History with Demographics	X									
Physical Exam	X									
Imaging (CT/MR) ⁴	X ⁵			X ³			X	X	X	X
Trial Enrollment			X ²							
Index Procedure Details			X ¹⁴							
FACT-G	X					X	X	X	X	X
Survey ¹⁹							X			
VAS			X ⁶	X						
Technical Success				X						
Technique Efficacy							X			
End of Trial										X
Clinical Laboratory Test										
Blood Tests (CBC/basic metabolic panel/Liver panel/tumor biomarkers)		X					X	X	X	X
Blood Repository (optional) ¹²		X		X ¹³	X		X	X	X	
Pregnancy Test ⁷ (urine or blood)		X ⁸								
Other										
Adverse Events ⁹			X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰	X ¹⁰
Complaints/Device Deficiencies			X							

Protocol Deviations	X	X	X	X		X	X	X	X	X
Notes: 1 Must be collected prior to trial-required testing or procedures that are not standard of care (SOC) 2 Imaging I/E criteria, trial enrollment if all eligibility criteria met 3 Complete a Target Tumor Imaging Form per treated tumor 4 CT/MRI baseline through trial completion must be same imaging modality (refer to Core Lab Imaging Guidelines) and must be completed using contrast 5 CT/MRI must be completed ≤ 30 days prior to Index Procedure – (Additional CT/MRI may be completed as clinically indicated) 6 VAS must be completed prior to anesthesia 7 Subjects who become pregnant during the trial will be followed for the duration of the trial 8 For female subjects of childbearing potential (urine or blood) 9 The reporting of adverse events will begin once enrollment is confirmed 10 Submit appropriate source documents for review of Adverse Events 11 The use of health-related services via telecommunication (Telehealth) can be completed for Test/Data Collection that do not require subject to be physically present with Physician or Hospital/Clinic Staff 12 Subject must provide informed consent for this purpose. 13 Obtained between 5-8 hours post index-procedure AND 22-27 hours post index-procedure 14 If a subject undergoes a second treatment, the follow-up assessments will be calculated based on the second treatment procedure date.										

Table 2: Study Endpoints

Primary effectiveness endpoint	Technical success was determined at ≤ 36 hours post-index-procedure by evaluating the ablation treatment size and coverage. Technical success was defined as the treatment volume/treatment dimensions being greater than or equal to the targeted tumor, and with complete tumor coverage, via computed tomography (CT) or magnetic resonance (MR) imaging. [Core Laboratory Adjudicated] [≤ 36 hours post-index procedure] A lesion success performance goal of 70% was established and the study hypothesis was as follows: Null hypothesis: technical success rate $\leq 70\%$ Alternative hypothesis: technical success rate $> 70\%$ For subjects with two treatments, technical success was to be evaluated at ≤ 36 hours post the second procedure.
Secondary effectiveness endpoint	Technique efficacy defined as the lack of a nodular or mass-like area of enhancement within or along the edge of the treatment volume assessed via CT or MR imaging at 30-days post-procedure (second procedure if applies). [Core Laboratory Adjudicated] [30-Day post-index procedure]
Primary safety endpoint	Safety success was determined using index procedure related major complications, including device-related events defined as Common Terminology Criteria for Adverse Events (CTCAE) (v 5.0) grade 3 or higher toxicities observed up to 30-days post

	index-procedure (if second procedure applies). [Clinical Events Committee Adjudicated] [30-Day post-index procedure]. A safety performance goal of 25% was established and the study hypothesis was as follows: Null hypothesis: major complications patient incidence rate $\geq 25\%$ Alternative hypothesis: major complications patient incidence rate $< 25\%$
Secondary safety endpoint	All adverse events reported within 30 days post-index procedure. [Clinical Events Committee Adjudicated] [30-Day post-index procedure]

Table 3: Subject Accountability

	US Sites	OUS Sites	Total
Enrolled subjects	21 (47.7%)	23 (52.3%)	44
Treated subjects	21 (47.7%)	23 (52.3%)	44
Evaluable for efficacy analysis	19 (47.5%)	21 (52.5%)	40
Reason for Discontinuation			
Non-evaluable	2	2	4
Evaluable for Safety analysis	19 (46.3%)	22 (53.7%)	41
Reason for Discontinuation			
Missed Visit	2	1	3

Patient population

Eligible subjects were 18 years or older with a diagnosis of primary or metastatic (from other primary cancers) liver cancer, who have not responded to and/or has relapsed and/or is intolerant of other available therapies including locoregional therapies, chemotherapy, immunotherapy, and targeted therapies.

In addition, all participants were deemed unresectable by a third-party tumor board consisting of a multi-disciplinary panel of specialty physicians. The designation of unresectable also precluded the possibility of liver transplant as a viable treatment option.

The tumor characteristics of the study population is presented in Table 4. Most subjects (26) presented with liver metastasis and 18 subjects had been diagnosed with primary hepatocellular cancer. For subjects with metastatic disease the most common demographic included patients for which their metastatic disease was from primary colorectal cancer, followed by pancreatic

and lastly from breast cancer. Table 4 contains additional information on the location of the primary tumor stratified by country.

Table 4: Summary of Tumor Characteristics

Type of Tumor			US, N (%)	EU/UK, N (%)	Total, N (%)
	Hepatocellular Carcinoma	N (%)	11 (52.4)	7 (30.4)	18 (40.9)
	Liver metastasis	N (%)	10 (47.6)	16 (69.6)	26 (59.1)

Table 5: Summary of Primary Tumor Origin for Metastatic

Primary tumor, location		US, N (%)	EU/UK, N (%)	Total, N (%)
	Colon: right	2 (20.0)	2 (12.5)	4 (15.4)
	Colon: left	0	1 (6.3)	1 (3.8)
	Rectum	3 (30.0)	2 (12.5)	5 (19.2)
	Breast	1 (10.0)	3 (18.8)	4 (15.4)
	Pancreas	2 (20.0)	3 (18.8)	5 (19.2)
	Other	2 (20.0)	5 (31.3)	7 (26.9)

Table 6: Summary of Demographic Information

Demographic Variable	US Sites	OUS Sites	Total
Enrolled Subjects	21	23	44
Age (mean, range)	64, 36-89	62, 43-81	65, 36-89
Gender			
Male	13 (61.9%)	9 (39.1%)	22 (50%)
Female	8 (38.1%)	14 (60.9%)	22 (50%)
Ethnicity			
Hispanic/Latino	1 (4.8%)	4 (17.4%)	5 (11.4%)
Not Hispanic/Latino	20 (95.2%)	19 (82.6%)	39 (88.6%)
Race			
African American	1 (4.8%)	0	1 (2.3%)
White	20 (95.2%)	22 (95.7%)	42 (95.5%)
Other		1 (4.3%)	1 (2.3%)
BMI			
<18.5	0	4 (17.4%)	4 (9.1%)
18.5 to <25	9 (42.9%)	4 (17.4%)	13 (29.5%)
25 to <30	8 (38.1%)	9 (39.1%)	17 (38.6%)

30 and over	4 (19%)	5 (21.7%)	9 (20.5%)
Missing	0	1 (4.3%)	1 (2.3%)
Childs-Pugh Class			
A	17 (81%)	14 (60.9%)	28 (63.6%)
B	6 (28.6%)	8 (34.8%)	14 (31.8%)
C	0	0	0
Missing	0	1 (4.3%)	1 (2.3%)
Number of tumors treated during the procedure			
1	18 (85.7%)	21 (91.3%)	39 (88.6%)
2	3 (14.3%)	2 (8.7%)	5 (11.4%)
3	0	0	0
Number of Lesions treated	23	21	44
Tumor Location (liver segment)			
1	0	0	0
2	1 (4.3%)	5 (23.8%)	6 (13.6%)
3	12 (52.2%)	12 (57.1%)	24 (54.5%)
4a	0	1 (4.8%)	1 (2.3%)
4b	6 (26.1%)	1 (4.8%)	7 (15.9%)
5	2 (8.7%)	1 (4.8%)	3 (6.8%)
6	2 (8.7%)	1 (4.8%)	3 (6.8%)
7	0	0	0
8	0	0	0
Pre-Treatment Tumor Volume (cc)			
Number	23	21	44
Mean (SD)	1.7835, (1.95063)	1.3176, (2.00798)	1.5611, (1.96913)
Median	1.0000	0.5620	0.6587
Min, Max	0.020, 6.200	0.098, 8.502	0.020, 8.502
Post-Ablation Treatment Zone Volume (cc)			
Number	23	21	44
Mean (SD)	19.1124, (19.73090)	15.6617, (14.79914)	17.4655, (17.43812)
Median	11.6476	11.8376	11.7426
Min, Max	0.137, 75.873	0.533, 62.978	0.137, 75.873

Table 7 contains additional demographic information regarding patients with hepatocellular carcinoma (HCC). Information includes prior treatments attempted before enrollment in the study.

Table 7: Baseline Hepatocellular Carcinoma Tumor Information

Category	Sub-category	US, n (%)	EU/UK, n (%)	Total, n (%)
Subjects with HCC		11	7	18
Prior Surgery	Yes	2 (18.2)	2 (28.6)	4 (22.2)
	No	9 (81.8)	5 (71.4)	14 (77.8)
Prior Liver Ablation	Yes	3 (27.3)	1 (14.3)	4 (22.2)
	No	8 (72.7)	6 (85.7)	14 (77.8)
Prior intra-arterial treatment	Yes	6 (54.5)	3 (42.9)	9 (50.0)
	No	5 (45.5)	4 (57.1)	9 (50.0)
Prior chemotherapy	Yes	3 (27.3)	0	3 (16.7)
	No	8 (72.7)	7 (100)	15 (83.3)

Tables 8 and 9 contain information on total liver tumor burden for both the Hepatocellular carcinoma (HCC) subjects and metastatic disease cohorts respectively. Please note, while some subjects presented with extensive liver tumor burden, at most 2 lesions were targeted for treatment with the device per subject.

Table 8: HCC subject liver tumor burden

Category	Sub-category	US, n (%)	EU/UK, n (%)	Total, n (%)
Number of liver tumors	1-5	11 (100)	6 (85.7)	17 (94.4)
	6-10	0	0	0
	11-15	0	1 (14.3)	1 (5.6)
	16-20	0	0	0
	>20	0	0	0

Table 9: Metastatic subject liver tumor burden

Category	Sub-category	US, n (%)	EU/UK, n (%)	Total, n (%)
Number of liver tumors	1-5	7 (70.0)	10 (62.5)	17 (65.4)
	6-10	2 (20.0)	1 (6.3)	3 (11.5)
	11-15	0	0	0
	16-20	0	1 (6.3)	1 (3.8)
	>20	1 (10.0)	3 (18.8)	4 (15.4)

Safety definitions and reporting requirements

Safety analysis included description of all Adverse Events (AEs) which were followed through the 1-year follow up visit with 30 day reporting for the primary safety endpoint. AEs were further subdivided as Serious Adverse Events (SAEs) if they met the following criteria:

1. Death,

2. serious deterioration in the health of the subject, users, or other persons as defined by one or more of the following:
 - A life-threatening illness or injury, or
 - A permanent impairment of a body structure or a body function, or
 - Hospitalization or prolongation of patient hospitalization, or
 - Medical or surgical intervention to prevent life threatening illness or injury or permanent impairment to a body structure or a body function, or
 - Chronic disease,
3. fetal distress, fetal death or a congenital physical or mental impairment or birth defect

Note: Planned hospitalization for a pre-existing condition, or a procedure required by the protocol, without serious deterioration in health, is not considered a serious adverse event.

Additional definitions include the following descriptions. An Adverse Device Effect (ADE) is an adverse event-related to the use of an investigational medical device. A Serious Adverse Device Effect (SADE) is an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event. An Unanticipated Adverse Device Effect (UADE) is an adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report. An Unanticipated Serious Adverse Device Effect (USADE) is a serious adverse device effect which by its nature, incidence, severity, or outcome has not been identified in the current version of the risk analysis report.

Safety and Effectiveness Results

Effectiveness Endpoints:

The primary effectiveness endpoint was technical success, defined as the treatment volume/treatment dimensions being greater than or equal to the targeted tumor with complete tumor coverage as assessed by a CT or MRI imaging obtained ≤ 36 hours post-index procedure. Images were reviewed by a third-party laboratory, and the performance goal of 70% was consistent with the technical success rates of other liver ablation methods reported in literature (47.7%-94.8%¹⁻⁷). Effectiveness results could be assessed on 40 evaluable patients that included treatment of 44 total tumors. The $>70\%$ performance goal for the primary effectiveness endpoint was met with 95.5% [95% CI 83.72 – 100%] of the lesions having achieved technical success within 36 hours of the procedure.

Post-procedure CT findings were corroborated with the histopathology results from the pre-clinical acute animal study. The clinical study leveraged this information to support effectiveness, in lieu of collecting post-treatment liver biopsy samples to demonstrate adequate ablation.

Safety Endpoints:

The primary safety endpoint of the clinical studies was defined as index-procedure device-related major complications of Common Terminology Criteria for Adverse Events (CTCAE) Grade 3 or higher at 30-days as adjudicated by an independent Clinical Events Committee (CEC) with a

performance goal set at 25%. A performance goal of 25% was selected to encompass the reported literature range of major complications (2.0%-11.2%⁸) for other liver ablation techniques, within the bounds of a 95% Confidence Interval (CI). All 44 subjects enrolled were included in the analysis of the primary safety endpoint. The <25% performance goal for the primary safety endpoint was met with a reported procedure-related major complication rate (CTCAE ≥ 3) of 3/44 6.8% [95% CI 2.35 – 18.23%] of the subjects having a reported event within 30 days post-procedure. The safety conclusion is further supported by the secondary safety analysis which provides evidence that all adverse events reported within 30 days of the procedure are consistent with the established risk-analysis of the System.

Device Serious Adverse Events Through 30 Days:

System Organ Class	Preferred Term	Total Subjects (N=44) n (%)	Total Events (N=5) n (%)
Hepatobiliary disorders	Hepatic failure	1 (2.3)	1 (40.0)
		1 (2.3)	1 (20.0)
Infections and infestations	Sepsis	1 (2.3)	1 (20.0)
Injury, poisoning and procedural complications	Procedural pain	1 (2.3)	1 (20.0)
Respiratory, thoracic and mediastinal disorders	Pleuritic pain	1 (2.3)	1 (20.0)
Total		4 (9.1%)	4 (100)

Four subjects (4/44) 9.1% experienced device related SAEs within the 30 day safety reporting period. SAEs included: sepsis, pleuritic pain, procedural pain requiring admission, and hepatic failure. It was reported that the subject with liver failure died 37 days after the index procedure. This subject was enrolled due to metastatic breast cancer, originally having undergone surgery for the primary tumor, which subsequently recurred and progressed to metastatic disease, with over 20 identified liver tumors, despite two separate rounds of chemotherapy. The patient met all the laboratory-related liver function inclusion/exclusion criteria and underwent a single ablation treatment of one tumor, maximal diameter of 1.6 cm. Eleven days after treatment, the subject was admitted to the hospital with abdominal distension and was found to have CT scan findings consistent with ascites. Despite aggressive therapy, the patient expired 37 days after the index procedure from liver failure. The sponsor notes that multiple rounds of chemotherapy can place patients at risk of developing unrecognized liver disease^{9,10}. Despite having normal laboratory values, the sponsor attests that the subject likely had unrecognized underlying liver disease or poor hepatic reserve as the assessed treatment volume of 62.98cc should have left sufficient liver reserve to avoid hepatic failure.

A single subject was identified with having experienced sepsis which resolved 26 days after ablative procedure with inpatient intravenous antibiotic treatment. Two subjects experience pain resolving with non-narcotic pain medication. One subject experienced post procedure pain resolving 1 day post index ablation, and the other with left pleuritic pain resolving 3 days after the index procedure.

Device Related Adverse Events:

System Organ Class	Preferred Term	Total Subjects (N=44) n (%)	Total Events (N=47) n (%)
Gastrointestinal disorders		12 (27.3)	13 (27.7)
	Abdominal pain	10 (22.7)	10 (21.3)
	Abdominal distension	1 (2.3)	1 (2.1)
	Abdominal pain upper	1 (2.3)	1 (2.1)
	Vomiting	1 (2.3)	1 (2.1)
Injury, poisoning, and procedural complications		12 (27.3)	12 (25.5)
	Procedural pain	10 (22.7)	10 (21.3)
	Post procedural discomfort	1 (2.3)	1 (2.1)
	Post procedural edema	1 (2.3)	1 (2.1)
General disorders and administration site complications		10 (22.7)	11 (23.4)
	Pyrexia	7 (15.9)	7 (14.9)
	Pain	2 (4.5)	2 (4.3)
	Chest pain	1 (2.3)	1 (2.1)
	Fatigue	1 (2.3)	1 (2.1)
Hepatobiliary disorders		5 (11.4)	5 (10.6)
	Hepatic hypoperfusion	2 (4.5)	2 (4.3)
	Biloma	1 (2.3)	1 (2.1)
	Hepatic failure	1 (2.3)	1 (2.1)
	Hepatic lesion	1 (2.3)	1 (2.1)
Infections and infestations		1 (2.3)	1 (2.1)
	Sepsis	1 (2.3)	1 (2.1)
Investigations		1 (2.3)	1 (2.1)

	Gamma-glutamyltransferase increased	1 (2.3)	1 (2.1)
Musculoskeletal and connective tissue disorders		1 (2.3)	1 (2.1)
	Musculoskeletal chest pain	1 (2.3)	1 (2.1)
Psychiatric disorders		1 (2.3)	1 (2.1)
	Apathy	1 (2.3)	1 (2.1)
Respiratory, thoracic and mediastinal disorders		1 (2.3)	1 (2.1)
	Pleuritic pain	1 (2.3)	1 (2.1)
Skin and subcutaneous tissue disorders		1 (2.3)	1 (2.1)
	Rash	1 (2.3)	1 (2.1)
Total		32 (72.7)	47 (100)

Serious Adverse Events occurring in the population included pleuritic pain (1 patient, 2%), procedural pain (1 patient, 2%), sepsis (1 patient, 2%) and liver failure (1 patient, 2%), all of which are well documented risks of focal liver treatments in subjects with liver tumors and are not unique to mechanical ablation of tissue. The most common non-serious Adverse Device Effects (ADE) include abdominal pain (22.7%), procedural pain (22.7%), and pyrexia (15.9%).

Subjects underwent repeat liver function lab testing and follow up CT/MRI imaging at 30 days. Outside of the 1 patient with sepsis and 1 patient with liver failure, repeat imaging and lab tests demonstrated no further 30-day hepatic-related adverse events.

All reported ADEs are consistent with the known risks of the investigational device and were included in the risk analysis.

Secondary Endpoints:

The secondary efficacy endpoint was the rate of technique efficacy, as measured by evaluating the absence of nodular or mass-like areas of enhancement within or along the edge of the treatment volume at 30-days. These images were adjudicated by a 3rd party laboratory. The analysis demonstrated a technique efficacy rate of 83.3% (95% CI 67.65-92.11%). No performance goal was designated for this endpoint.

Pediatric Extrapolation

In this De Novo request, existing clinical data were not leveraged to support the use of the device in a pediatric patient population.

LABELING

The device user manual and instructions for use include a description of the device technical parameters and instructions for use for the device. The user manual also contains relevant findings from the clinical study with the detection performance characteristics of the device when used as intended. The document also states the shelf life for any sterile components as well as the necessary measures to properly dispose of any single use items and clean the reusable components of the device.

Labeling also includes the following:

- (i) A warning that focal therapy that focused ultrasound should only be considered in patients with sufficient hepatic functional reserve to withstand the destruction of the planned volume of tissue.
- (ii) A statement that the device has not been evaluated for the treatment of cancer or any specific disease or condition.
- (iii) A detailed summary of the clinical evaluations pertinent to use of the device and accessories; and
- (iv) A statement that the device shall only be used by personnel that have been trained in its operation.

RISKS TO HEALTH

The table below identifies the probable risks to health that are associated with use of a focused ultrasound system for non-thermal, mechanical tissue ablation:

Risks to Health	Mitigation Measures
Impaired tissue or organ function, abscess, pain, or other adverse events downstream of tissue ablation	Clinical performance testing Labeling Human factors testing
Acoustic path, non-targeted tissue injury	Clinical performance testing Human factors testing Animal performance testing Non-clinical performance testing
Tissue injury due to device malfunction or misuse	Clinical performance testing Software verification, validation and hazard analysis Non-clinical performance testing Labeling Human factors testing
Adverse tissue reaction	Biocompatibility evaluation
Electrical shock or electromagnetic interference	Electrical safety testing Electromagnetic compatibility testing Labeling

SPECIAL CONTROLS

In combination with the general controls of the FD&C Act, the focused ultrasound system for non-thermal, mechanical tissue ablation is subject to the following special controls:

- (1) Clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. Testing must document the adverse event profile and characterize tissue destruction.
- (2) Animal performance testing must demonstrate that the device mechanically destroys targeted tissue while characterizing the chronic safety profile, including thermal and mechanical injury to adjacent, non-target tissue.
- (3) Non-clinical performance testing must demonstrate that the device performs as intended under anticipated conditions of use. The following performance characteristics must be tested:
 - (i) Acoustic characterization at clinically relevant settings;
 - (ii) Determination of the minimum drive voltages necessary to sustain a bubble cloud in the target tissue;
 - (iii) Validation of mechanisms to prevent energy delivery that would result in adverse thermal effects;
 - (iv) Availability of real-time monitoring during the procedure;
 - (v) Validation that the treatment zone is limited to the defined target tissue; and
 - (vi) Validation of mechanisms to prevent, pause and terminate ablation in the event of device failure.
- (4) Performance data must support the electrical safety and electromagnetic compatibility of the device.
- (5) All patient-contacting components of the device must be demonstrated to be biocompatible.
- (6) Software validation, verification, and hazard analysis must be performed.
- (7) Human factors testing must demonstrate that the user can safely and correctly use the device.
- (8) Labeling must include the following:
 - (i) A warning that focused ultrasound ablation should only be considered in patients with sufficient functional reserve to withstand the destruction of the planned volume of tissue;
 - (ii) A statement that the device has not been evaluated for the treatment of any specific disease or condition; and
 - (iii) A detailed summary of the clinical testing with the device.

BENEFIT-RISK DETERMINATION

The clinical studies in the US and UK were non-curative and limited in that they were not designed for the purposes of assessing any clinical outcomes related to the treatment of any disease or condition including that of cancers of the liver. The Edison System was evaluated using a short-term (30 day) safety performance goal of <25% reported procedure-related major complication rate (CTCAE ≥ 3) and an effectiveness performance goal of >70% technical success defined as treatment volume/treatment dimensions being greater than or equal to the targeted tumor with complete tumor coverage as assessed by a CT or MRI imaging obtained ≤ 36 hours post-index procedure. Subjects enrolled in the study are being followed out to 5 years for subject welfare/protection but not to characterize or evaluate the Edison System's safety or effectiveness of long term cancer outcomes such as overall survival, recurrence, and disease free survival. The purpose of this study was to demonstrate that the device may safely and effectively destroy unresectable liver tumors, non-invasively, with real-time verification via ultrasonography. No conclusions regarding benefit-risk for the Edison System's ability to treat liver cancer or any disease/condition can be made given the study design limitations.

Risks:

The risks of the device are based on nonclinical laboratory studies as well as data collected in a clinical study described above.

The clinical data to support the primary safety endpoint demonstrated that adverse events equal or greater to common terminology criteria for adverse event reporting (CTCAE) grade 3 occurred at rate of 6.8%, or 3/44 of the subjects reported an event within 30 days post procedure. This rate is consistent with major complication rates reported in the literature for other liver ablation techniques (2.0%-11.2%⁸).

Thirty Day SAEs occurred at a rate of 9.1% (4/44 subjects) including pleuritic pain, sepsis, procedure pain, and liver failure. Ablating liver tissue carries the risk of liver failure and/or exacerbating underlying chronic liver conditions. The subject experiencing liver failure died 37 days post index procedure outside the 30-day reporting period. The rate of liver failure in the clinical study was 2.3% which is consistent with liver failure rates reported for other liver ablative techniques (0.2%-4.3%¹¹). Follow up liver function testing and imaging at 30 days (excluding two subjects who experienced SAEs, one experiencing liver failure and one with sepsis) provide evidence of acceptable short-term safety, which showed no deleterious effects related to the use of the device.

One-hundred and one (101) AEs were reported during the 30-day follow up period with 43.6% of AEs reported as device-related AEs. The most common adverse events were abdominal pain (22.7%), procedural pain (20.5%), and fever (13.6%), which in most cases of AEs were reported as mild. These events are expected and are consistent with those observed for other focal therapies.

The degree to which these risks will be experienced by patients using the Edison System is uncertain given the moderate degree of risk uncertainty due to sample size of the study. The

clinical study enrolled 44 subjects, therefore the study may not have observed all clinical scenarios, adverse event rates and severity. However, the AEs that occurred in the study were consistent with known AEs from other liver ablation devices. No new device-related AEs were identified, and rates of AEs were consistent with rates reported in the literature (major liver ablation complications ranging from 2.0-11.2%⁸). When the factors related to risk uncertainty are considered against the known risk profile of liver ablation devices and the well-published AE rates, it can be concluded that the risks of the Edison system are comparable to other liver ablation devices. Additionally, patients received up to 2 treatments in two separate liver lesions. There is no information on patients receiving greater than 2 treatments for more than 2 lesions 3cm or less in diameter or for patients receiving more than one treatment session. As such, there is uncertainty regarding the safety and effectiveness of the device for the treatment of more than two lesions of greater than 3cm diameter or repeat use in multiple ablation procedures. Finally, there is uncertainty in the potential long-term impacts to patient health. Cavitated animal liver tissue treated with the device underwent histopathologic evaluation, which demonstrated that treated areas developed an "acellular lysate" that appeared to be non-viable. It is unknown what long-term clinical effect similar acellular lysates may have in humans.

Benefits:

The probable benefits of the device are based on nonclinical laboratory studies as well as data collected in a clinical study described above.

The clinical benefit was demonstrated by the clinical study data which exceeded the primary effectiveness endpoint of >70% technical ablation success with 95.5% [95% CI 83.72 – 100%] or 42/44 of the liver lesions having achieved technical ablation success within 36 hours of the procedure. Limitations of the clinical study enrollment size (N=44), short term ablation-centric technical success endpoints, and use in patients with unresectable liver tumors leads to uncertainty with regards to the magnitude and duration of clinical benefit. However, the 95.5% technical ablation success rate is consistent with the technical success rates of other liver ablation methods reported in literature (47.7%-94.8%¹⁻⁷). In comparison to available ablative alternatives, the device is able to destroy liver tumors without the need for percutaneous access. This provides significant patient benefit from the perspectives of reduced infection risk at the insertion site or along the insertion route, preclusion of insertion pain, and an alternative option for patients who do not wish or cannot undergo invasive surgical procedures. As an additional benefit to patients the device's intended function requires real-time imaging of the ablation zone and the procedure would not require alternative imaging modalities such as CT or MRI to evaluate the results of ablation.

It is probable that the device provides ancillary benefits to both the patient and the operator. Active cavitation of tissue can be seen and monitored on ultrasound, which allows real-time visualization of target ablation tissues. If abnormalities are identified during use, visualization of the target allows users to halt or modify energy delivery in response. If particular target areas are difficult to visualize on ultrasound, the software contained within the subject device allows users to review CT or MRI images as an additional reference during ultrasound ablation. Finally, it is

probable that human error and could be reduced due the automation feature provided by the subject device, as the device provides precise, incremental movement throughout a pre-planned treatment volume as demonstrated by the adequate verification, validation, and pre-clinical testing.

The risks of the Edison System's technology and clinical study limitations are mitigated by the special controls and labeling. Specifically, labeling include warnings for the risk of liver failure due to destruction of liver tissue and use limitations based on the clinical data of ablation area of no more than 2 lesions ablated, 3cm or less in diameter. Additionally, labeling includes language that the Edison System has not been evaluated for the treatment of cancer and is not intended for the treatment of cancer or any other specific disease or condition.

Patient Perspectives

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

Benefit/Risk Conclusion

In conclusion, given the available information above, for the following indication statement:

The Edison System is indicated for the non-invasive destruction of liver tumors, including unresectable liver tumors, using a non-thermal, mechanical process of focused ultrasound.

The probable benefits outweigh the probable risks for the Edison System. The device provides benefits, and the risks can be mitigated by the use of general controls and the identified special controls.

CONCLUSION

The De Novo request for the Edison System is granted and the device is classified as follows:

Product Code: QGM

Device Type: Focused ultrasound system for non-thermal, mechanical tissue ablation

Regulation Number: 21 CFR 878.4405

Class: II

References:

1. Shady W, Petre EN, Gonen M, et al. Percutaneous Radiofrequency Ablation of Colorectal Cancer Liver Metastases: Factors Affecting Outcomes--A 10-year Experience at a Single Center. Radiology. 2016;278(2):601-611. doi:10.1148/radiol.2015142489

2. Solbiati L, Ahmed M, Cova L, Ierace T, Brioschi M, Goldberg SN. Small liver colorectal metastases treated with percutaneous radiofrequency ablation: local response rate and long-term survival with up to 10-year follow-up. *Radiology*. 2012;265(3):958-968. doi:10.1148/radiol.12111851
3. Wahl DR, Stenmark MH, Tao Y, et al. Outcomes After Stereotactic Body Radiotherapy or Radiofrequency Ablation for Hepatocellular Carcinoma. *J Clin Oncol*. 2016;34(5):452-459. doi:10.1200/JCO.2015.61.4925
4. Zhang L, Wang N, Shen Q, Cheng W, Qian GJ. Therapeutic efficacy of percutaneous radiofrequency ablation versus microwave ablation for hepatocellular carcinoma. *PloS One*. 2013;8(10):e76119. doi:10.1371/journal.pone.0076119
5. Pompili M, Saviano A, de Matthaeis N, et al. Long-term effectiveness of resection and radiofrequency ablation for single hepatocellular carcinoma ≤ 3 cm. Results of a multicenter Italian survey. *J Hepatol*. 2013;59(1):89-97. doi:10.1016/j.jhep.2013.03.009
6. Kim Y sun, Lim HK, Rhim H, et al. Ten-year outcomes of percutaneous radiofrequency ablation as first-line therapy of early hepatocellular carcinoma: analysis of prognostic factors. *J Hepatol*. 2013;58(1):89-97. doi:10.1016/j.jhep.2012.09.020
7. Hamada A, Yamakado K, Nakatsuka A, et al. Radiofrequency ablation for colorectal liver metastases: prognostic factors in non-surgical candidates. *Jpn J Radiol*. 2012;30(7):567-574. doi:10.1007/s11604-012-0089-0
8. Lahat E, Eshkenazy R, Zendel A, et al. Complications after percutaneous ablation of liver tumors: a systematic review. *Hepatobiliary Surg Nutr*. 2014;3(5):317-323. doi:10.3978/j.issn.2304-3881.2014.09.07
9. Fonseca AZ, Saad WA, Ribeiro MA. Complications after Radiofrequency Ablation of 233 Hepatic Tumors. *Oncology*. 2015;89(6):332-336. doi:10.1159/000439089
10. Kong WT, Zhang WW, Qiu YD, et al. Major complications after radiofrequency ablation for liver tumors: analysis of 255 patients. *World J Gastroenterol*. 2009;15(21):2651-2656. doi:10.3748/wjg.15.2651
11. Odisio BC, Richter M, Aloia TA, et al. Use of Prophylactic Antibiotics to Prevent Abscess Formation Following Hepatic Ablation in Patients with Prior Enterobiliary Manipulation. *J Gastrointest Surg*. 2016;20(8):1428-1434. doi:10.1007/s11605-016-3117-z