Official Title: The HistoSonics System for treatment of primary and metastatic liver tumors using histotripsy (#HOPE4LIVER US)

NCT Number: NCT04572633

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Title	The HistoSonics System for treatment of primary and metastatic liver tumors using histotripsy (#HOPE4LIVER US)
Clinical Investigation Protocol Identification Code	#HOPE4LIVER US Sponsor Clinical Study Number: CSP1427 Revision F (15Feb2022) ClinicalTrials.gov Identifier: NCT04572633
Trial Purpose	The #HOPE4LIVER US clinical trial data will be utilized to gain approval in commercializing the HistoSonics System.
Trial Design	This trial is a single arm, non-randomized prospective trial. Following histotripsy treatment of liver tumor(s), subjects will undergo imaging ≤36 hours post-index procedure to determine technical success. Subjects will then be followed for 30 days. Additionally, subjects will be evaluated at 6 months and followed annually for up to five (5) years post-index procedure.
Trial Population	Subjects who are 18 years of age or older with a diagnosis of primary or metastatic (from other primary cancers) liver cancer.
Objective	The objective of this trial is to evaluate the efficacy and safety of the HistoSonics System for the treatment of primary or metastatic tumors located in the liver.
Device Name	HistoSonics System (System)
IDE Indications for Use	The HistoSonics System is intended for the destruction of liver tissue using histotripsy, a non-thermal, mechanical process using focused ultrasound.
Enrollment	Up to forty-five (45) subjects enrolled targeting forty (40) evaluable subjects at up to eight (8) US clinical sites
Duration of Trial	The duration of this trial is expected to be approximately six and a half (6.5) years.
Primary Endpoints	Co-primary endpoints: 1. Efficacy: Technical success as determined, at ≤36 hours post-index procedure, by evaluating the histotripsy treatment size and coverage. Technical success is defined as the treatment volume/treatment dimensions being greater than or equal to the targeted tumor with complete tumor coverage, via CT or MR imaging. [Core Lab Adjudicated] [≤36 hours post-index procedure] 2. Safety: Index procedure related major complications, including device-related events, defined as Common Terminology Criteria for Adverse Events (CTCAE) grade 3 or higher toxicities, up to 30 days post index-procedure [Clinical Events Committee Adjudicated] [30-Day post-index procedure] Results must be positive for both co-primary endpoints for the trial to be considered successful.
Secondary Endpoints	<u>Efficacy:</u> 1. 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 MR or CT imaging at 30-days post index-procedure [Core Lab Adjudicated] <u>Safety:</u> 1. All adverse events reported within 30 days of index-procedure [Clinical Events Committee Adjudicated]

Follow-Up Visits	All enrolled subjects will have a 14-day, 30-day, 6-month, and annual post-index procedure (1, 2, 3, 4, 5 year) follow up assessment/visit or until the trial is closed, whichever comes first.
General Inclusion	*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 assessments 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) <2.5x upper limit of normal (ULN) and Aspartate transaminase (AST) <2.5x ULN and bilirubin <2.5 ULN, and • Renal function: serum creatinine <2x ULN, and • Hematologic function: neutrophil count >1.0 x 10^9/L and platelet >50 x 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 locoregional therapies, chemotherapy, immunotherapy and targeted therapies.
Imaging Inclusion	10. The tumor(s) selected for histotripsy treatment must be ≤3 cm in longest diameter 11. Subject has an adequate acoustic window to visualize targeted tumor(s) using ultrasound imaging 12. Subject has a maximum of three (3) tumors to be treated with histotripsy 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
General Exclusion	*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 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 are 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, histotripsy 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.
Statistical Methods	The primary efficacy and safety endpoints are based on a comparison to pre-specified performance goals established from relevant literature. <u>Primary Efficacy</u> A lesion success performance goal of 70% was established and the hypothesis was as follows: Null hypothesis: HistoSonics technical success rate ≤70% Alternative hypothesis: HistoSonics technical success rate >70% The proportion of observed Technical Success by lesion on those with evaluable imaging will be reported. As up to 3 treated lesions are allowed per subject, the 95% confidence interval for the observed Technical Success rate will be estimated by the bootstrap sampling with replacement method to account for potential within-subject lesion correlations. A subject will be the bootstrap sampling unit. A > 70% lower limit for the 95% confidence interval will indicate the HistoSonics Technical Success rate as statistically significantly higher than the performance goal of 70% at a 1-sided $p < 0.025$ level. <u>Primary Safety</u> A safety performance goal of 25% was established and the hypothesis was as follows: Null hypothesis: HistoSonics major complications patient incidence rate ≥25% Alternative hypothesis: HistoSonics major complications patient incidence rate <25% The patient incidence rate of index-procedure related major complications and its two-sided 95% Wilson Score CI will be calculated based on all subjects enrolled. The upper limit of the 95% CI must be <25% in order to regard the index procedure's safety as acceptable.

Secondary endpoints will be presented descriptively with no hypothesis test.

Determination of Sample Size

A literature review was conducted to identify rates of technical success in published studies on microwave and radiofrequency ablation of primary and metastatic liver tumors from 2010 to 2020. Eight studies reporting on 2,876 total tumors were assessed with a mean, weighted mean, and median rate of 81.5%, 86.6%, and 92.0%, respectively[1–8]. Sample size was determined from primary efficacy of technical success assuming one treated lesion per subject for simplicity. Forty evaluable subjects were targeted for enrollment. Using a technical success acceptance level of 85% (34/40 lesions), which is consistent with the literature review results, the Wilson Score 95% confidence interval is 70.9% to 92.9%. Using the lower limit of the 95% confidence interval, a null hypothesis of ≤70% success rate can be rejected at a 1-sided $p<0.025$ significance level. By binomial probability calculation, the false positive (alpha) error for this design is 0.024. Assuming a true histotripsy technical success rate of 90%, the power for observing ≥34/40=85% in the trial is approximately 0.90. Due to the allowance of up to three (3) treated lesions per subject, the actual 95% confidence interval for the lesion based technical success rate would be estimated by the bootstrap sampling with replacement method and subject would be the sampling unit. The confidence interval would be narrower, and the power would be higher than the above estimates.

A similar review of major complications (CTCAE grade 3 or higher equivalent) when treating liver lesions with radiofrequency ablation identified 5 independent studies reporting on 1,935 patients and one review article encompassing 32 studies[1–5,9]. Major complication rates ranged from 2.0% to 11.2%. For a new technology such as histotripsy, a conservative assumption for major complications was assumed to be close to the upper end of the literature results of 11.2%. Accordingly, with the sample size of 40 participants and a histotripsy major complication rate of 10% (4/40 participants), the Wilson Score 95% confidence interval is 4.0% to 23.1%. Assuming a true histotripsy event rate of 7%, the power of observing <4/40=10% in the trial is approximately 0.85.

A 5% - 10% attrition rate was anticipated; reasons for attrition included: both anticipated and unanticipated drop-out (e.g., subject withdrawal, loss-to-follow-up, and death) as well as the inability for the Core Laboratory to assess the primary efficacy endpoint due to missing or non-evaluable imaging. Therefore, up to forty-five (45) subjects were targeted for enrollment; subject replacement was not applicable in these cases.

Primary Analysis

The primary analyses of all primary and secondary endpoints will be performed after forty (40) evaluable subjects have been enrolled between the #HOPE4LIVER US (NCT04572633) and #HOPE4LIVER EU/UK (NCT04573881) trials and after those subjects have finished the 30-day assessment. This analysis will include at a minimum 10 subjects (25%) enrolled in the US. Data will be pooled between the two studies for the purposes of assessing the primary endpoints.

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