HISTOSONICS®	**CAIN Protocol Synopsis** **NCT05432232**

Official Title: The HistoSonics Investigational System for treatment of primary solid renal tumors using histotripsy (CAIN)

NCT Number: NCT05432232

Protocol Date: November 22, 2023 (CSP2276 Revision E)

Title	The HistoSonics Investigational System for treatment of primary solid renal tumors using histotripsy (CAIN)
Clinical Investigation Protocol Identification Code	CAIN Sponsor Clinical Study Number: CSP2276 Revision E (22Nov2023) ClinicalTrials.gov Identifier: NCT05432232
Trial Purpose	The purpose of this trial is to evaluate the technical success and safety profile of the HistoSonics Investigational System for the treatment of primary solid renal tumors.
Trial Design	This trial is a prospective, multi-center, single-arm pilot trial designed to evaluate the effectiveness and safety profile of the HistoSonics Investigational System in treating primary solid renal tumors. Following histotripsy treatment of the solid renal tumor, subjects will undergo imaging ≤36 hours post-index procedure to determine technical success. Additionally, subjects will be followed 180 days (6 months) post-index procedure, with evaluations at the 14-day, 30-day, 90-day, and 180-day time points to establish the efficacy and safety profile of the HistoSonics Investigational System.
Trial Population	Subjects who are 18 years of age or older with a diagnosis of a solid renal tumor.
Objective	The objective of this trial is to generate data to support a pivotal trial for the HistoSonics Investigational System for use in the kidney.
Device Name	HistoSonics Investigational System (System)
Indication Under Investigation	The indication under investigation is use of the HistoSonics Investigational System for the non-invasive destruction of kidney tissue using histotripsy, a non-thermal mechanical process of focused ultrasound.
Enrollment	Up to twenty (20) combined male and female subjects treated at up to four (4) clinical sites located in Europe and/or United Kingdom.
Duration of Trial	The duration of this trial is expected to be approximately eighteen (18) months.
Primary Endpoints	<u>Primary Effectiveness Endpoint:</u> Technical success defined as complete coverage of the tumor as determined ≤36 hours post-index procedure by magnetic resonance imaging (MRI) or computerized tomography (CT). [Core Lab Adjudicated] <u>Primary Safety Endpoint</u>: Freedom from index procedure related major complications, defined by Clavien-Dindo Classification Grade 3 or higher up to 30 days after the last histotripsy procedure. [Clinical Events Committee Adjudicated]
Secondary Endpoints	1. Technique efficacy (primary) defined as the percentage of targeted tumors successfully eradicated post-index procedure assessed via MRI or CT at 90-days post-index procedure without repeat Histotripsy [Core Lab Adjudicated] 2. Technique efficacy (secondary) defined as the percentage of targeted tumors successfully eradicated post-index procedure assessed via MRI or CT at 90-days post-index procedure after repeat Histotripsy [Core Lab Adjudicated]
Follow-Up Visits	All treated subjects will have a 14-day, 30-day, 90-day, and 180-day follow up assessment 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) 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 a non-metastatic solid renal mass ≤3cm confirmed via CT or MRI ≤ 30 days prior to the index procedure date. 4. Subject can tolerate general anesthesia. 5. Subject has an Eastern Cooperative Oncology Group Performance Status (ECOG PS) grade 0-2 at baseline screening. 6. Subject meets all the following functional criteria at ≤14 days prior to the planned index procedure date: • White Blood Cell (WBC) ≥3,000/mm^3 • Absolute Neutrophil Count (ANC) ≥1,200/mm^3 • Hemoglobin (Hgb) ≥9 g/dL • Platelet count ≥100,000/mm^3 (≥100 10*9/L) • White Blood Count (WBC) ≤40 cells/µL via urinalysis • Albumin ≤300,000 mg/L via urinalysis 7. Subject has an eGFR ≥45mL/min, ≤14 days prior to the planned index procedure date. 8. International Normalized Ratio (INR) score of <1.5: • If on anticoagulants, other than aspirin or non-steroidal anti-inflammatory drugs, assessment must be performed on the day of the procedure; **OR** • If only on aspirin or non-steroidal anti-inflammatory drugs, assessment must be performed ≤14 days prior to the planned index procedure date; **OR** • If not on anticoagulants, assessment must be performed ≤14 days prior to the planned index procedure date 9. Biopsy is required to determine the type of tumor and must be performed ≥14 days prior to the planned index procedure date.
Imaging Inclusion	10. The tumor selected for histotripsy treatment must be ≤3cm in longest diameter. 11. Subject has an adequate acoustic window to visualize targeted tumor using the HistoSonics Investigational System. 12. Subject will undergo histotripsy treatment of only one (1) tumor during the index procedure, regardless of how many tumors the subject has.
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 and being actively treated in another investigational pharmaceutical or device trial ≤30 days prior to planned index procedure date.

	3. Subject is undergoing active chemotherapy for any cancer ≤14 days prior to planned index procedure date. 4. Subject is undergoing active immunotherapy ≤40 days prior to planned index procedure date. 5. 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 Investigational System. 6. Subject is on dialysis or being considered for dialysis. 7. Subject has not recovered to Common Terminology Criteria for Adverse Events (CTCAE) grade 2 or better from any adverse effects (except alopecia and neuropathy) related to previous anti-cancer therapy. 8. Subject has an uncorrectable coagulopathy other than that induced by aspirin or non-steroidal anti-inflammatory drugs. 9. Subject has a planned cancer treatment (e.g., nephrectomy, chemotherapy, immunotherapy etc.) prior to completion of the 30-day follow-up visit. 10. Subject has had previous treatments with chemotherapy, radiotherapy, or both that have not been discontinued ≥14 days prior to the planned index procedure date and have not recovered (CTCAE grade 2 or better) from related toxicity (exclusive of alopecia and neuropathy). 11. Subject has previous treatment with immunotherapies that has not been discontinued ≥40-days prior to the planned index procedure date and has not recovered from related toxicity (CTCAE grade 2 or better). 12. Subject has a life expectancy less than one (< 1) year. 13. In the investigator's opinion, histotripsy is not a treatment option for the subject. 14. Subject has a concurrent condition that could jeopardize the safety of the subject or compliance with the protocol. 15. Subjects' targeted tumor has had prior locoregional therapy (e.g., ablation, embolization, radiation). 16. Subjects' tumor is not treatable by the HistoSonics Investigational System's working ranges (refer to User Guide). 17. In the physician's opinion, the anticipated risk of intervention outweighs the potential benefits of the intervention. 18. Subject has acute renal failure. 19. Subject has a genetic predisposition to kidney cancer such as: • Von Hippel Lindau (VHL) • Hereditary Papillary Renal Carcinoma (HPRC) • Birt-Hogg-Dubé Syndrome (BHD) • Tuberous Sclerosis Complex (TSC) • Hereditary Leiomyomata's Renal Cell Carcinoma (HLRCC) • Reed's Syndrome

	• Succinate Dehydrogenase B Deficiency (SDHB) • BRCA 1 associated protein -1 (BAP1) Renal Cell Carcinoma • MITF predisposed Renal Cell Carcinoma 20. Tumor is an angiomyolipoma. 21. Subject has a known sensitivity to contrast media and cannot be adequately pre-medicated.
Imaging Exclusion	22. The targeted tumor is not clearly visible with diagnostic ultrasound and either magnetic resonance imaging (MRI) or computerized tomography (CT). 23. Targeted tumor with adequate margin overlaps the renal pelvis, main renal vessel, ureter, or other vital structure. 24. Targeted tumor with adequate margin overlaps a non-targeted tumor visible via imaging. 25. The treatment of the tumor will not allow for an adequate margin as determined by the investigator.
Statistical Methods	All endpoints will be summarized descriptively with 95% (Wilson) confidence intervals. As a pilot trial, no formal hypotheses will be defined; the endpoints are designed to provide additional information for the development of a pivotal trial.
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