Protocol Signature Page

PROTOCOL TITLE: Multicenter Study of Cryoablation for Palliation of Painful Bone Metastases (MOTION)

PROTOCOL NUMBER: CGC15-BNE098

PROTOCOL VERSION: 03

PHASE: Pivotal

CT.GOV REGISTRATION: NCT02511678

DATE: 31JUL2017

Galil Medical Protocol Approval

We, the undersigned, have read and approve the protocol specified above and agree on its content.

[redacted]

[redacted]
Signature

[redacted]

[redacted]
Signature

Investigator Signature

I, the undersigned, have read and understand the protocol specified above and agree on its content. I agree to perform and conduct the study as described in the protocol.

Printed Name	*Signature*	*Date*

GALILMEDICAL

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SPONSOR:	Galil Medical 4364 Round Lake Rd W Arden Hills, MN 55112
PROTOCOL RESPONSIBILITY:	[redacted]
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CONFIDENTIAL

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1 INTRODUCTION

1.1. History of Cryoablation

Cryotherapy (or cryoablation) is an FDA-cleared technology for selective ablation and treatment of different kinds of benign and malignant conditions, such as: prostate and renal cancer, liver tumors, soft tissue tumors, fibroadenoma of breast, ear-nose and throat applications, thoracic applications (atrial fibrillation, pulmonary tumors), cryoanalgesia, dermatology, as well as precancerous tumors of the cervix. Galil Medical has developed a range of products based on its cryotherapy platform and incorporating updated freezing technology and needle design.

Applying cold energy to human tissues is a well-known technique for treating various tumors as an alternative to surgery.[1-11] The first modern physician to utilize this technique was James Arnott (England, 1865). Since Arnott's first experience, many trials have been conducted utilizing various techniques and devices.[8,10] These have included precooled metal blocks, precooled needles,[11,12] dry ice applications, spray/pour freezing with compressed or liquefied gasses,[12,13] refrigeration systems, thermoelectric methods and cryogenic heat pipes,[14] cryogenic needles,[15] Joule-Thomson-effect-based cryoprobes,[15,16] and boiling-effect-based cryoprobes.[13] To increase the effectiveness of the cryo-treatment, the freezing protocols used by these physicians were adjusted with the known maximal cryo-destruction criteria such as extremely fast cooling,[9] low cooling rate at the freezing front,[17] slow thawing,[18] and repeated freeze/thaw cycles.[14]

As tissue temperatures fall, extracellular water begins to crystallize and a hyperosmotic extracellular environment is created that draws water out of the cells. As the process continues, extracellular ice crystals grow, cells shrink, and membranes and cell constituents are severely damaged. Within a short time (minutes), the increased extracellular electrolyte concentration is sufficient to destroy the cells. This effect of cell dehydration and solution concentration, called solution-effect injury, is not always lethal to cells; on the other hand, intracellular ice formation is a more significant threat to cell viability and is almost always lethal.[8] Solution-effect injury is associated with low freezing rates, while intracellular ice formation is commonly associated with fast freezing rates. Although pure water begins to freeze at 0°C, extracellular ice formation occurs at approximately -7°C to -10°C, by -15°C intracellular ice begins to form (heterogeneous nucleation). Depending on the tissue characteristics (e.g., vascularity, density, etc.) at -20°C to -40°C all metabolic processes are expected to have ceased (homogenous nucleation). The most destructive effect on biological tissue is achieved by either an extremely low temperature or a very rapid freezing rate (on the order of hundreds of degrees Centigrade per minute).[8,9] More recent *in vitro and in vivo* work has identified apoptosis as the mechanism associated with direct cell injury. Cell death has been demonstrated in the central part of the ablation zone by evidence of coagulation, while apoptosis is evident generally 8-12 hours after cryoablation in the peripheral part of the tumor.[19]

Cryoablation is an advantageous therapy as it preserves collagenous and other cellular architecture in virtually any frozen tissue and offers the ability to see low attenuating ice as it covers soft tissue.[20]

Modern cryoablation dates back to 1961, when automated cryosurgical units that pump liquid nitrogen through the tip of the cryoprobe were introduced.[1] This innovation led to the investigation of cryoablation for different diseases, but cumbersome cryoprobes and a lack of control over the freezing process made widespread use impractical. The resurgence in interest in cryoablation results from the introduction of modern cryoprobes, which exploit the Joule–Thomson (J–T) effect.[5] The J–T effect predicts changes in temperature as gases expand through narrow ports from high to low pressure. This is a constant enthalpy expansion that, in the case of argon gas, results in rapid cooling to the boiling point of argon (-186°C). To accomplish this, high-pressure (3,000 – 3,500 psi) ambient-temperature argon gas is circulated to the cryoablation needle tip where it expands rapidly as it drops to room pressure. Under the

J–T effect, some gases - such as helium - warm up rather than cool when expanded. Accordingly, helium can and has been incorporated into cryogenic systems to rapidly warm the cryoablation needle in order to arrest the freezing process or thaw the iceball. The flow of argon and helium is controlled by computer-modulated gas regulators. The temperatures of cryoablation needles controlled by gas systems are finely adjustable and respond within seconds to user input. (By comparison, liquid nitrogen systems have a lag time of up to 2 minutes.)[6,7] The expanded gases are circulated back to the cryogenic unit through the larger outer lumen of the cryoablation needle and the supply hose. The venting of used gas, usually into the room, occurs at the cryogenic machine. Both argon and helium are inert gases, making such venting harmless.

The cryoablation technology developed by Galil Medical, Ltd. (Yokneam, Israel) is based on Joule-Thomson effect, and utilizes argon gas for freezing. Passive thaw, helium gas thaw or electric thaw may be used.

This study will utilize Galil Medical's commercially available cryoablation system and needles. Each cryoablation needle forms a different shape and size of iceball. Multiple cryoablation needles may be inserted into the tumor, or even into 2 or 3 tumors concomitantly. This significantly shortens the length of treatment and provides flexibility in treating tumors of varying sizes by matching the cryoablation needle number and configuration for a specific tumor.

Tissue thermal sensors may be employed to enable the real-time tissue temperature monitoring, thus, contributing to the safety and effectiveness of the procedure.

Cryoablation procedures using Galil Medical's systems may be performed under the guidance of Ultrasound (US), Computed Tomography (CT) or Magnetic Resonance Imaging (MRI).

1.2. Historical Background of Bone Metastases and Standard Treatments

It is estimated that more than 1.6 million new cases of cancer will be diagnosed in 2015 in the United States. Prostate cancer is the most common cancer among men (26%), followed by lung (14%) and colon & rectum (8%) cancers. Up to 85% of patients with these primary cancers have evidence of metastasis to the bone at the time of death.[21,22] As the tumor invades the bone tissue, this creates holes that make the bone thin and weak, and nerve endings in and around the bone send pain signals to the brain. Bone metastases frequently result in pain, pathologic fractures, hypercalcemia, and spinal cord compression. Pain symptoms are typically intermittent, but can be sharp and severe. Pain may be partially eased by activity, and is commonly worse at night. Metastases to the bone are best identified with imaging, most commonly radiography (X-rays) and scintigraphy (bone scans), and occasionally MRI.[23]

The standard of care for patients with bone metastases is mainly palliative and consists of local therapy (radiation, also called radiotherapy, and surgery), systemic therapy (chemotherapy and hormone therapy), and analgesics. Unfortunately, metastatic bone disease often does not respond to chemotherapy or hormonal therapy and surgery may not be an option for those patients with advanced disease or poor overall health.22

External beam radiation has been proven to provide good pain relief for some patients. In their Cochrane review, McQuay et al. concluded that radiation therapy is clearly effective at reducing pain from painful bone metastases. A review of twenty trials reported on 43 different radiation fractionation schedules and eight studies of radioisotopes in which radiation produced complete pain relief at one month in 395/1580 (25%) patients, and at least 50% relief in 788/1933 (41%) patients at some time during the trials.[24]

Radiopharmaceuticals may be beneficial for patients with diffuse bone metastases, but it is not a standard of care.[25] Bisphosphonates, drugs that bind to exposed bone mineral around resorbing osteoclasts and disrupt chemical processes with bone resorption, are frequently prescribed to patients to prevent bone breaking.[26] Examples of the bisphosphonates that are

marketed in the United States are Actonel, Actonel with Calcium, Aredia, Boniva, Didronel, Fosamax, Fosamax Plus D, Reclast, Skelid, and Zometa.

1.3. Other Treatment Options

Percutaneous image guided therapies are being explored for the treatment of palliation of painful bone metastases, including ethanol, interstitial laser, high intensity focused ultrasound (HIFU), microwave ablation (MWA), radiofrequency ablation (RFA), and cryoablation.

RFA has been evaluated in a multi-center study and demonstrated substantial pain reduction in patients with bone pain that had previously been unresponsive to standard treatments. Goetz et al. reported a series of 43 patients in which RFA was performed with the RITA medical system. The median follow-up was 16 weeks. Prior to ablation the mean score for worst pain in 24 hours was 7.9/10. Following treatment, the pain decreased to 4.5, 3.0, and 1.4 at 4, 12, and 24 weeks respectively. Clinical significant reduction in pain relief was achieved in 95% of the patients. This study concluded that RFA is effective, however there are limitations to the therapy, including the inability to see the ablation margin with CT monitoring, associated procedural pain, and increased pain for a period of weeks after the ablation.[28,27] Callstrom et al. reported a single arm, observational study of 12 patients treated with RFA for a single painful osteolytic metastasis. The tumor size ranged from 1-11 cm. Prior to RFA, the mean worst pain in 24 hours was 8/10. Four weeks after RFA, the mean worst pain in 24 hours had decreased to 3.1 ($P<0.001$).[28]

Belfiore et al. have studied long term (1 year) pain reduction in patients with painful bone metastases using RFA. Immediate pain relief after treatment was experienced by nine of 12 patients, but in two cases, pain recurred within the first week. Long-lasting palliation was obtained in seven of 12 patients. Brief Pain Index (BPI) mean scores for worst and average daily pain decreased from 7.7 and 5.0, respectively, at baseline, to 3.1 and 1.8, respectively, at one year.[29]

Hurwitz et al. reported on a multicenter, single-blind, placebo controlled pivotal trial of 147 subjects with metastatic bone pain randomized 3:1 (treatment versus control arm). One hundred twelve subjects were assigned to receive MR-guided focused ultrasound surgery (MRgFUS) and 35 to the placebo arm. The primary endpoint was evaluated in numerical rating score (NRS) score for worst pain with no increase in morphine equivalent dosing (MEDD) intake at 3 months compared to baseline, showing a clinically significant response rate of 64.3% and 20%, respectively. A secondary endpoint assessed the change in Brief Pain Index Quality of Life (BPI-QoL) (compared to baseline, showing statistically significance of 2.4 points greater in the treatment arm compared to placebo arm at 3 months. The study concluded that MRgFUS is an alternative treatment for patients that have had unsuccessful treatment, refused, or not candidates for radiation to alleviate pain and increase in quality of life.[30]

Research continues to explore the risks and benefits of ablative therapies for the palliation of painful bone metastases. Many articles support the statement that if ablative therapies are used, careful selection of tumors and probe placement are crucial to avoid inadvertent ablation of critical structures such as the spinal cord, major nerves, bowel, and bladder.

2 DEVICE DESCRIPTION

Galil Medical's Visual-ICE® Cryoablation System and needles are FDA cleared via the 510K process. The Galil Medical cryoablation systems are intended for cryogenic destruction of tissue during surgical procedures; various Galil Medical ancillary products are required to perform these procedures. Galil Medical cryoablation systems are indicated for use as a cryosurgical tool in the fields of general surgery, dermatology, neurology (including cryoanalgesia), thoracic surgery, ENT, gynecology, oncology (ablation of cancerous or

malignant tissue and benign tumors, and palliative intervention), proctology and urology. These systems are designed to destroy tissue (including prostate and kidney tissue, liver metastases, tumors, and skin lesions) by the application of extremely cold temperatures.

3 CLINICAL BACKGROUND

3.1 Cryoablation for the Palliation of Painful Bone Metastases

Cryoablation for the palliation of painful bone metastases has previously been limited due to the large diameter of the probes and the use of liquid nitrogen. With prior technology, early applications of cryotherapy resulted in a high incidence of post-procedure bleeding, injury to adjacent bone and soft tissue, resulting in high rates of fractures and infections. With the advent of new cryoablation systems and needles, more recent applications of cryotherapy have demonstrated considerable success in disease control.[31,45]

Cryoablation is more advantageous than RFA because the ablation zone can easily be monitored real-time with CT or MRI imaging, allows the simultaneous use of multiple needles, and is compatible with the use of tissue displacement devices such as balloons, to allow for safe displacement of adjacent structures.[32]

In addition, cryoablation does not require the placement of grounding pads, thereby eliminating the problem of grounding pad injuries. A frequently mentioned benefit to cryoablation over other heat-based thermal ablative methods like RFA and MWA is the apparent ability to preserve collagenous and other structural cellular architecture in virtually any frozen tissue.[33,34,35] The reaction of large arteries and veins to freezing in situ is detailed in reports describing experimental cryogenic injury to a variety of major blood vessels.[36,37,38,39,40] The large blood vessels have been demonstrated to be remarkably resistant to structural change after freezing and their function as a conduit of blood is not impaired.[19]

3.2 Previous Clinical Studies Leading Up to and Supporting the Proposed Research

Ullrick et al. reported a series of 4 patients treated with cryoablation for palliation of metastatic bone pain. Three of the four patients reported significant improvement in pain immediately after treatment. The fourth patient experienced more pain due to an insufficiency fracture which resulted because the tumor was not amenable to post-procedure enforcement.[35]

Sewell et al. reported the use of MRI guided cryoablation for bone tumors in 2002. A series of 16 tumors were treated in patients using the Galil CryoHit System. Mild procedural pain associated with probe placement was reported. Immediate postoperative reduction in pain was documented. No immediate or long term complications were reported. Early results demonstrated continued pain relief and significant increase on the patient's quality of life.[41]

Callstrom et al. evaluated the safety and effectiveness of percutaneous cryoablation in series of 14 patients with metastatic bone tumors for the reduction of pain. Patients were included in the study if they presented with one or two painful metastatic tumors, had a score of 4 or greater out of 10 for worst pain in 24 hours, and did not respond to or refused radiation or chemotherapy. The CT guided percutaneous cryoablation was performed with one or more cryoprobes (Endocare; Perc-17, Perc-22, and Perc-24). A single probe was used for tumors < 3cm and 2-7 probes were used in larger tumors. A 10 minute freeze, 8 minute thaw, and a 10 minute freeze followed by a final thaw was intended, however treatment times ultimately varied due to coverage and proximity of adjacent structures. All tumors involved bone with osteolytic bone destruction or periosteal reaction and a soft tissue mass. Tumors ranged in size from 1-11 cm in diameter. The mean cryoablation procedure time was 139 minutes ± 53. The mean time required in the CT suite was 185 minutes ± 56. No major complications were reported with the

procedures. Patients were evaluated with the Brief Pain Inventory (BPI) - Short Form prior to treatment, at 4 days post-procedure, weekly for the following 4 weeks, and every 2 weeks for total of 6 months. CT or MRI was performed at 4-6 weeks after the cryoablation procedure. Prior to treatment, the mean score for worst pain in 24 hours was 6.7/10. Four weeks after treatment the score had decreased to 3.8/10 (P=.003), at 6 weeks 2.5/10 (P=.001), and 8 weeks 3.4/10 (P=.007). Eighty-six percent (12) of patients reported at least a 3 point drop in their worst pain score in 24 hours during the 24 week follow-up. Durable pain relief was reported in 80% (4/5) patients followed for 24 weeks after cryoablation. A reduction in the use of narcotics was reported by 100% of patients.[28]

Following the initial report of safety and efficacy, Callstrom et al. later reported outcomes following a multicenter, prospective study of cryoablation for palliative treatment of metastatic lesions involving bone. Patients were included with 1 or 2 painful bone metastases with a score of 4 or greater on a scale of 0 to 10 related to worst pain in the last 24 hours, and who refused or failed conventional treatment (e.g. radiation). The BPI was used to evaluate response at each interval following treatment. A total of 69 tumors ranging in size from 1 to 11 cm (mean diameter 4.8 cm) were treated in 61 patients. Prior to cryoablation, the mean worst pain in a 24-hour period was 7.1/10. Following treatment at 1, 4, 8, and 24 weeks, the mean score for worst pain in a 24-hour period decreased to 5.1/10, 4.0/10, 3.6/10, and 1.4/10, respectively. A 2-point drop in average pain was reported in 69% of patients over the course of the 24 week follow up period. Of the 77% of patients reporting the use of opioid analgesics prior the procedure, 83% reported a reduction in the use of opioid analgesics after cryoablation. One major complication, osteomyelitis at the site of ablation, was reported. There was no significant difference in pain scores throughout follow up for those patients who had or had not received radiation prior to cryoablation. The authors concluded that percutaneous cryoablation demonstrated an effective and durable method for the palliation of pain caused from metastatic bone tumors.[42]

Galil Medical has conducted an international study of cryoablation for the palliation of painful bone metastases. The objective of this study was to assess the feasibility of cryoablation in the palliation of painful bone metastases using the Galil Medical device. Study subjects received cryoablation of 1 or 2 painful metastatic lesions and had follow up assessment through 6 months post ablation. The Brief Pain Inventory (BPI) - Short Form was utilized to assess the subjects' pain response to cryoablation. A total of 29 subjects were consented for the study, however, one subject died prior to the cryoablation procedure day and was omitted from the study analysis. A total of 28 patients were treated in the study. Sixteen subjects completed the study through the 24 week visit. The remaining 11 subjects were withdrawn early (n=1) or expired due to their overall cancer burden (n=10) prior to study completion. One subject had an additional cryoablation at week 20 due to tumor growth and associated pain. The rate of attrition during follow up is consistent with the Callstrom et al. study, owing to the stage of disease and anticipated life expectancy for this population.

Tumors ranged in size from 1.3-9.5 cm in diameter with an average diameter of 6.0 cm. The average cryoablation procedure time was 97.5 minutes (38-204). One (3.7%) CTCAE Grade 3 complication, vasovagal reaction, was reported as possibly related to the procedure among the 28 subjects. Two additional CTCAE Grade 3 complications were not associated with the device or procedure. There was one report of death, unrelated to the disease under study, occurring 32 days after the cryoablation procedure related to respiratory distress due to staphylococcus aureus pneumonia. This event was determined by the investigator to have no causality to the procedure or study device. No reports of moderate to severe complications due to injury of major motor nerves, bowel or bladder were recorded.

The primary endpoint evaluated the effectiveness of cryoablation based on measuring the pre-treatment and post-treatment "worst pain in 24 hours" average pain scores using the BPI. Subjects were evaluated with the BPI Form prior to treatment, at 1 week post procedure, at 4, 7,

12, 16, 20, and 24 weeks after treatment. Prior to treatment, the mean score for worst pain in 24 hours was 7.2/10. One week after treatment, the mean score was reduced to 5.5/10. Four weeks after treatment the score had decreased to 4.6/10, at 7 weeks 4.1/10, at 12 weeks 3.7/10, at 16 weeks 4.5/10, at 20 weeks 3.7/10, and 24 weeks 3.6/10. *(Data on file with Galil Medical)*

3.3 Rationale Behind the Proposed Research

In many patients, despite the availability of drugs and other pain treatments, effective pain relief is unable to be attained. The articles referenced previously have demonstrated that many patients have received pain relief from cryoablation therapy, but further data is needed with the Galil Medical cryotherapy technology in order to support a 510K labelling expansion application with the Food and Drug Administration (FDA) in a controlled clinical protocol.

4 STUDY OBJECTIVES

The objective of this study is to assess the efficacy of cryoablation for palliation of painful metastases in patients with metastatic lesions involving bone who have failed, are not candidates for, or are not experiencing adequate pain relief from current pain therapies (e.g. radiation, analgesics).

5 STUDY DESIGN

This is a multicenter, prospective, single arm study with subjects serving as their own control. This study is to enroll and treat approximately 60 subjects at approximately 10 centers in the US and internationally to reach at least 42 evaluable subjects at 8 weeks.

Patients with painful metastatic lesions involving bone who meet the eligibility criteria and who have been determined to be an appropriate candidate for cryoablation therapy will be offered enrollment into the study. Patients agreeing to participate will read and sign an informed consent form and thus become subjects in the study. Treatment will be performed using a Galil Medical cryoablation system and Galil Medical cryoablation needles. Subjects will have one cryoablation procedure and will be followed for up to 6 months for palliation of pain, quality of life and analgesic usage. Baseline and follow-up data will be collected for each subject via a web-based electronic data collection tool.

Study visits include a screening visit, a cryoablation procedure visit and follow-up visits at 1, 4, 8, 12, 16, 20, and 24 weeks post cryoablation procedure. See section 8 for specific requirements at each of these visits.

5.1 Primary Effectiveness Endpoint

The primary endpoint for this study will be measured as follows: improvement in self-reported pain scores defined by ≥ 2 point reduction in worst pain in the last 24 hours using the Brief Pain Inventory (BPI) from baseline to 8 weeks. A mean difference of 2 points reduction is considered clinically significant.

5.2 Safety Endpoints

The safety endpoint for this study is to assess the incidence and severity of procedure or device-related adverse events.

5.3 Other Assessments

Other assessments for this study will include:

- A responder analysis will be conducted. A responder is defined as a subject having ≥ 2 point reduction in the worst pain score in the last 24 hours using the BPI and no more than 25% increase in medication use (morphine equivalent) from baseline to 8 weeks
- Quality of Life (QoL) as measured by the overall BPI pain interference average score from baseline to 1, 4, 8, 12, 16, 20, and 24 weeks after cryoablation
- Change in physical function as measured by Karnofsky Performance Status (KPS) from baseline to 1, 4, 8, 12, 16, 20, and 24 weeks after cryoablation
- Additional therapies for persistent/recurrent pain associated with the index tumor under study or new bone metastases through 24 weeks
- Change in analgesic medications (morphine equivalent daily dosing and NSAID use) from baseline to 1, 4, 8, 12, 16, 20, and 24 weeks after cryoablation
- Difference in worst pain scores from baseline to 1, 4, 12, 16, 20, and 24 weeks after cryoablation as measured on the numeric 0 to 10 BPI scale
- Difference in average pain scores from baseline to 1, 4, 8, 12, 16, 20, and 24 weeks after cryoablation as measured on the BPI numeric rating scale
- Self-assessed Overall Treatment Effect (OTE) at 1, 4, 8, 12, 16, 20, and 24 weeks after cryoablation

5.4 Tumor Characteristics

Tumor characteristics will include, but are not limited to:

- Histology of primary cancer
- Proof of metastases
- Location of the index tumor
- Size of the index tumor

6 STUDY TREATMENTS

6.1 Cryoablation Treatment

For cryoablation in the palliation of painful bone metastases, subject preparation, anesthesia, intra-operative monitoring, and postoperative management are identical to those of standard cryoablation routinely performed at all clinical centers participating in this study.

6.2 Subject Enrollment

To minimize selection bias within the enrolled subject population, participation in the study is to be offered to all eligible patients on a consecutive basis as they present to the physician at the site. Each study site will maintain a screening log to include minimal health information regarding each non-enrolling patient (e.g., sex, age, reason for not enrolling, etc.). As the non-enrolled patients will not sign an informed consent form the data collected will not include personally identifiable information (as defined in 45 CFR 164.514).

Patients who wish to participate in this study and sign a written informed consent form will be considered to be enrolled in the study and will be assigned a unique subject identifier number to be used throughout the study.

6.3 Subject Withdrawal

Subjects may withdraw from this study at any time, with or without a reason, without prejudice to further treatment. Investigators should make every effort within the bounds of safety and subject choice to have each subject complete the study. If a subject does not return for a scheduled visit, every effort should be made to contact the subject. In any circumstance, every effort should be made to document the subject's outcome, if possible. The investigator should inquire about the reason for withdrawal; request the subject return for a final visit, if applicable and follow-up with the subject regarding any unresolved adverse events. As possible, the reason(s) for withdrawal (if given) will be recorded.

If the subject withdraws from the study and also withdraws consent for disclosure of future information, no further evaluations should be performed for the study and no additional data should be collected. The sponsor may retain and continue to use any data collected before such withdrawal of consent.

6.4 Risks

Potential risks of bone tumor cryoablation in the intraoperative/early postoperative period include bleeding, infection, fracture, nerve injury, skin injury (burn/frostbite) and injury to adjacent tissues or organs.

Potential delayed risks of cryoablation include complications that may lead to death. A list of anticipated adverse events may be found under Appendix B. There may be unforeseen complications, and other complications may occur in the location of the tumor treated by cryoablation.

6.5 Potential Benefits

Cryoablation is an FDA-cleared treatment modality for the ablation of cancerous or malignant tissue and benign tumors, and palliative intervention. Potential benefits of cryoablation for the palliation of painful bone metastasis include the reduction of pain and the reduction of pain medication. Other benefits may include a reduction in other treatment methods for pain control.

6.6 Study Supplies

Study sites will use Galil Medical's commercially available Visual-ICE Cryoablation System and needles labeled for use for this study. A Regulatory Documents binder will be provided to each site. Questionnaires, subject instructions and applicable worksheets will also be provided to each site, if applicable. The study monitor should be contacted for any issues related to these study supplies. Cryoablation needles are supplied in single use, sterilized packages. Once opened, they should be used immediately for the current procedure or discarded. Store cryoablation needles according to the recommendations on the commercial packaging.

6.7 Pain Medications and Non-drug Therapies

Pain medication use, specifically opioid medications and non-steroidal anti-inflammatory drugs (NSAID), both prescription and over the counter (OTC) shall be documented. Detailed specifics with regards to medication name, dose, frequency, and reason will be collected regarding pain medication usage at the time of screening and throughout the study. The total medication used

in the immediate 24 hours prior to the visit will be recorded. In the event of death or the subject is lost to follow up, the last known 24 hour period intake of opioid or NSAID medication will be collected if known. Opioid medications will be converted to morphine equivalent doses for comparison and evaluation purposes.[43] See Appendix E for Instructions for Morphine Equivalent Daily Dose (MEDD) conversion.

Supplemental treatment which, in the investigator's opinion, becomes necessary during the course of the study must not be denied to the subject. If this supplemental treatment is described as a therapy expressly not permitted, the subject's participation in the study may need to be discontinued due to non-permitted concurrent therapy. Please refer to section 8.4 for information on specific supplemental treatments for this protocol.

7 SUBJECT POPULATION

7.1 Subject Selection

This study can fulfill its objectives only if appropriate subjects are enrolled. The following eligibility criteria are designed to select subjects for whom cryoablation therapy is considered appropriate. All relevant medical and non-medical conditions should be taken into consideration when deciding whether cryoablation therapy is suitable for a particular subject.

7.2 Inclusion Criteria

Eligible subjects for this study must meet all of the following criteria:

7.2.1 18 years of age or older

7.2.2 Metastatic disease involving bone with metastatic disease previously confirmed by prior biopsy;
or
Metastatic disease involving bone previously confirmed on imaging (e.g. CT or MRI) with known (biopsied) primary disease (primary bone cancer is excluded)

7.2.3 Current analgesic therapies have failed, the subject is not a candidate for, OR the subject is not experiencing adequate pain relief from current pain therapies (e.g. radiation, analgesics)

7.2.4 The 'worst pain' in the last 24 hours must be reported to be 4 or above on a scale of 0 (no pain) to 10 (pain as bad as subject can imagine)

7.2.5 Pain must be from one painful metastatic lesion involving the bone that is amenable to cryoablation with CT (additional less painful metastatic sites may be present)

7.2.6 Cryoablation should be performed within 14 days of screening visit

7.2.7 If taking hormonal therapy, use should be stable (no changes within 4 weeks prior to the cryoablation procedure)

7.2.8 Karnofsky Performance Status (KPS) score ≥60

7.2.9 Life expectancy ≥ 3 months

7.2.10 No debilitating medical or psychiatric illness that would preclude giving informed consent or receiving optimal treatment and follow-up

7.2.11 Known coagulopathy or bleeding disorders are controlled

7.3 Exclusion Criteria

Subjects not eligible for participation in this study include those who have any of the following:

7.3.1 Primary cancer is leukemia, lymphoma, or myeloma

7.3.2 Tumor involves a weight-bearing long bone of the lower extremity with the tumor causing > 50% loss of cortical bone

7.3.3 Has undergone prior surgery at the tumor site or the index tumor has undergone previous surgery or ablation treatment

7.3.4 Prior radiation therapy of the index tumor <3 weeks prior to the screening visit

7.3.5 Index tumor causing clinical or radiographic evidence of spinal cord or cauda equina compression/effacement

7.3.6 Anticipated treatment of the index tumor that would require iceball formation within 0.5 cm of the spinal cord, brain, other critical nerve structure, large abdominal vessel (possibly achieved with additional maneuvers such as hydrodissection)

7.3.7 Index tumor involves the skull

7.3.8 Currently pregnant, nursing, or wishing to become pregnant during the study

7.3.9 Serious medical illness, including any of the following: uncontrolled congestive heart failure, uncontrolled angina, myocardial infarction, cerebrovascular event within 6 months prior to the screening visit

7.3.10 Concurrent participation in other studies that could affect the primary endpoint

8 STUDY PROCEDURES

The study schedule of events and the specific procedures performed at each visit are shown in Table 1, Schedule of Events. Each subject will undergo a total of 9 visits, including a screening visit, the procedure visit, 7 post-operative visits. In the event the subject is not able to return for office follow up visits, the follow up assessment may be conducted via telephone. More visits may be required if medically necessary.

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Table 1: Schedule of Study Events

Procedures	Screening	Baseline Assessment[b] (within 24 hrs of cryo)	Procedure [a]	W 1[d] ±5 days	W 4[d] ± 12 days	W 8[d] ± 12 days	W 12[d] ± 12 days	W 16[d] ± 12 days	W 20d ± 12 days	W 24 [d,e] ± 12 days
Informed Consent	X									
Inclusion/Exclusion	X									
Medical Comorbidities	X									
Targeted Medical History	X									
Demographics	X									
Pain Medication Assessment	X[c]	X		X	X	X	X	X	X	X
KPS	X[c]	X		X	X	X	X	X	X	X
BPI-SF Question #3	X[c]									
BPI-SF		X		X	X	X	X	X	X	X
Tumor characteristics			X							
Cryoablation Procedure			X							
Safety Assessments			X	X	X	X	X	X	X	X

[a] The procedure is recommended to be performed within 14 days of the screening visit.

[b] The Baseline Assessment should be completed within 24 hours prior to the cryoablation procedure. Evaluation of the inclusion/exclusion criteria should be re-evaluated prior to the cryoablation procedure to ensure criteria are met.

[c] In the event the screening visit is completed within 24 hours of the cryoablation procedure, a separate BPI-SF #3 is not required. Complete the BPI-SF, KPS, and Pain Medication Assessment per the Baseline Assessment requirement.

[d] In the event a subject is unable to return for a scheduled office visit follow up, the visit may be conducted via telephone.

[e] Week 24/Study Completion or Early Termination

8.1 Screening

The screening period begins after informed consent has been obtained. The screening visit allows the investigator to assess a subject's eligibility for this study. Medical records from prior to the signed informed consent date may be used to confirm eligibility.

The following assessments will be collected:

- BPI- Question 3 only (worst pain in last 24 hours)
- KPS
- Comorbidities
- Demography
- Targeted medical history
- Review inclusion/exclusion criteria
- Documentation of pain medication (opioid and/or NSAID) and reason for use

8.2 Baseline

The following items will be completed within 24 hours prior to the cryoablation procedure and will serve as baseline information for all applicable protocol directed evaluations.

- BPI Questionnaire
- KPS
- Documentation of pain medication (opioid and/or NSAID) and reason for use

8.3 Cryoablation Procedure

Pre-procedure labs may be performed per institutional standard of care. It is recommended the cryoablation be performed within 14 days of the screening visit. Extension beyond this timeframe may be necessary since this is a chronically ill population.

Typically, two freeze-thaw cycles will be used. The cryoablation needles will use compressed argon gas through the Joule-Thomson effect to produce extremely low temperatures within the target tumor(s). Antibiotics (per site standard of care) may be given at the investigator's discretion.

The following data will be collected at the time of the procedure or prior to discharge, as applicable:

- Tumor location and description
- Tumor size measured by two methods:
  - 3-dimensional measurements (cm) and
  - Greatest trans-axial diameter (cm)
- Number and type of cryoablation needles used
- Freeze and thaw times, per cycle
- Estimation of % tumor ablation during procedure
- Concomitant procedures

- Number and type of intraoperative complication(s)
  - Severity of complication(s)
- Duration of hospital admittance/stay
- Safety assessments

8.3.1 Cryoablation Needle Testing

Before anesthesia inducement of the subject, all cryoablation needles should be tested in accordance with the Galil Medical cryoablation system User Manual to confirm their freezing function and structural integrity.

8.3.2 Cryoablation Needle Placement

A Galil Medical cryoablation system will be used per the manufacturer's guidelines. Galil Medical's cryoablation needles will be placed using image guidance in a pattern necessary to fully freeze the target tumor. Image-guided ablation of bone metastases may be performed under general anesthesia or moderate sedation.

8.3.3 Freezing Procedure

Once freezing has been initiated, the cryoablation procedure will be monitored with imaging to visualize iceball growth, to ensure the ablation zone is adequately frozen and adjacent anatomical structures are protected. As the freezing continues, the ice formations from each of the cryoablation needles coalesce so the targeted portions of the ablation zone are frozen. Throughout the phases of the procedure, the ablation zone should be monitored under imaging guidance at intervals deemed appropriate by the investigator. Typically when the leading edge of the ice has reached at least 5 mm beyond the tumor periphery, the freezing process should be stopped. Typically, two freeze-thaw cycles should be utilized. Freeze and thaw cycle times may vary depending on the size and iceball coverage of the tumor and proximity to adjacent critical structures. Passive or active thaw should be carried out between freeze cycles. Following the last freeze cycle, a brief active thaw should be utilized prior to attempting to remove the needle(s).

The low-density changes within the tissue should be measured to approximate the size of the ablated region. Hemodynamic monitoring should be done in compliance with national and local standards.

8.4 Recurrent Tumor Pain/New Tumor Pain

Additional targeted therapies (cryoablation, RFA, MWA, HIFU, radiation, surgery, etc.) are not permitted on an index tumor per this protocol. If the investigator feels additional targeted therapy is appropriate, the subject will be discontinued from the study.

If a new painful tumor is identified during the follow-up period, targeted therapies (cryoablation, RFA, MWA, HIFU, radiation, surgery, etc.) are permitted, provided that the region of identifiable pain may be clearly distinguished from the region/tumor treated during the initial cryoablation procedure.

Other therapies, including pain medications and chemotherapy are permitted.

8.5 Weeks 1, 4, 8, 12, 16, 20, and 24 Post-Procedure Follow-up

In the event that a subject cannot return for an office visit, the subjects should be contacted by telephone. Subjects will be assessed at the above intervals to complete the following assessments:

- BPI
- Pain medication (opioid and/or NSAID) and reason for use in the prior 24 hours prior to the visit
- KPS
- Additional new bone metastases
- Overall tumor burden
- Any additional therapies the subject may have started for bone metastases (index tumor or new metastases)
- Safety Assessment

8.6 Study Completion or Early Termination

The 24 week visit will be the final visit for subjects undergoing a single cryoablation procedure. Subjects who request Early Termination from the study will be asked to return for a final visit to complete the above assessments if possible.

Subjects may be considered "lost to follow-up" after 3 unsuccessful attempts to contact the subject with one contact being a registered letter to the last known address of the subject. Site should document all attempts to contact the subject in the source documents.

9 ASSESSMENTS

9.1 Demography

Demographic information will be collected from the subject during the screening visit. The information will consist of age at the time of enrollment, race, ethnicity and gender.

9.2 Targeted Medical History

Targeted medical history information must be obtained from each subject entering the study. Obtaining accurate medical history is necessary to ensure documented baseline health status and to ensure that subjects meet study entry criteria.

9.3 Biopsy

A biopsy of a tumor(s) in the bone(s) metastasized from another primary disease may be obtained at the discretion of the treating investigator per his/her standard practice.

9.4 Pain Scale and Quality of Life

The Brief Pain Inventory (BPI) Short Form is a standardized scale for consistently capturing patient reported symptom assessments. This two-page form uses numerical rating scales to measure both pain severity and the resulting functional interference caused by pain. The BPI provides a list of descriptors to help the patients

report the pain. Subjects rate the pain at its "worst," "least," and "average" in the last 24 hours, as well as "now," using a numerical rating scale that ranges from 0 (no pain) to 10 (pain as bad as you can imagine). Subjects rate the amount of interference from pain on a scale of 0 (does not interfere) to 10 (completely interferes) regarding the following areas: general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life.[44] See Appendix C.

Although this is a subjective measure, it is determined to be the most appropriate tool to use for the outcome measures. The treatment goal in subjects with painful bone metastases is usually palliative pain control. Since the objective of this study is not focusing on treating/curing the bone metastases or the original tumor source, this scale is relevant in assessing the outcome.

9.5 Physical Performance

Physical function assessments will be measured using the standardized scale from the Karnofsky Performance Status (KPS). The KPS is a standard way of measuring the ability of cancer patients to perform ordinary tasks. The scores range from 0 to 100. A higher score means the patient is better able to carry out daily activities. KPS may be used to determine a patient's prognosis, to measure changes in a patient's ability to function. (See Appendix D)

9.6 Self-assessed Overall Treatment Effect (OTE)

Overall treatment effect will be assessed based on the subject's opinion of the effect (better, same, worse) the cryoablation procedure has had on their well-being. The subject will be asked to the compare their well-being at each follow up visit compared to the previous visit or telephone call.

9.7 Imaging

As outlined in this protocol, all subjects will have an initial confirmation of metastases involving bone using CT, MRI, or US prior to cryoablation. The cryoablation procedure will be completed under imaging guidance. Follow-up imaging is at the discretion of the investigator.

10 ENGINEERING, MANUFACTURING, HANDLING AND ACCOUNTABILITY

10.1 Manufacturing, Packaging and Labeling

The Galil Medical cryoablation system and needles are manufactured, packaged and labeled according to current Good Manufacturing Practices (cGMP) and applicable international, national and local regulations, laws, and guidelines.

10.2 Handling and Storage

The Galil Medical cryoablation system and needles, necessary equipment, and disposables are handled and stored according to Galil Medical's specifications.

10.3 Recall of Device

The Galil Medical cryoablation system is designed and built in accordance to IEC 60601-1, 3rd edition standard performance and safety specifications for surgical medical instruments. Any recall of the system will be done in accordance with applicable international, national and local legislation and guidelines, as well as the sponsor's requirements.

11 STATISTICAL ANALYSIS

11.1 General Methods

This is a prospective, single-arm study designed to evaluate the effectiveness, durability, and safety of Galil Medical's cryoablation system and needles for the palliative treatment of metastatic tumors involving bone.

11.2 Sample Size

A 2 point reduction from baseline in worst pain score is considered to be clinically meaningful. The expected device performance is at least a 3.2 point reduction from baseline in mean worst pain score and the expected standard deviation is 2.7. With these assumptions, PASS 13 software was used to compute a sample size for a one-sample T-test with superiority by a margin:

> A sample size of 42 achieves 80% power to detect superiority using a one-sided t-test when the margin of superiority is -2.0 and the true difference between the mean and the reference value is -3.2. The data are drawn from a single population with a standard deviation of 2.7. The significance level (alpha) of the test is 0.025.

With an attrition rate at 8-weeks estimated to be 30%, the total treated study sample size will be approximately **60 subjects**, with continued enrollment until at least 42 evaluable subjects have reached 8 weeks. This sample size will be considered clinically sufficient to give indications of device effectiveness.

11.3 Missing Data

Missing data will be prospectively minimized through training of the participating investigator and site staff, and through appropriate clinical trial management. Every effort will be made to collect all data points in the study. All subject data that is available on subjects who drop out during the course of the study will be included where possible.

Sensitivity analyses will be performed on the primary efficacy endpoint using two methods of missing data imputation: multiple imputation and last observation carry forward.

11.4 Analysis Populations

Intent-to-Treat (ITT) analyses will be performed on all subjects with a Galil Medical cryoablation system as the attempted treatment. Endpoints will also be evaluated using per protocol population (PP).

11.4.1 General Analysis

Data will be analyzed using descriptive statistics. Continuous variables (e.g., age) will be summarized by the number of subjects, mean, standard deviation, median, interquartile range, minimum and maximum. Categorical variables (e.g., race) will be summarized by frequencies and percentages of subjects in each category.

11.4.2 Primary Efficacy Endpoint

The endpoint for this study will be measured as follows: assessment of the effectiveness of cryoablation associated with palliation of pain in subjects with metastatic lesions involving bone by measuring the average difference of pre- and post-treatment worst pain in 24 hours from baseline to 8 week follow-up interval as measured Brief Pain Inventory (BPI) scale. A mean difference of 2 points reduction is considered clinically significant.

Calculations:

- 8-Week follow-up minus baseline worst pain will be calculated for each subject.
- Mean change over all subjects will be calculated.
- The mean reduction in pain at 8-weeks will be evaluated for clinical meaning

To be considered clinically meaningful the 95% confidence interval's upper bound on the mean reduction in worst pain score must be less than -2.

Subjects without missing endpoint data will be considered completers. Intent-to-Treat Completers (ITTC) analysis as well as Per-Protocol Completers (PPC) analysis will be supplemented by missing data sensitivity analyses. Sensitivity analyses will be performed on the primary efficacy endpoint using two methods of missing data imputation: multiple imputation and last observation carry forward. These imputation methods will be employed on both the ITT and PP populations resulting two additional outcome analyses: Intent-to-Treat Imputed (ITTI) and Per-Protocol Imputed (PPI). Of the four analyses, the primary hypothesis test will be considered the ITTI analysis with multiple imputation.

11.4.3 Safety Endpoints

The safety endpoint for this study is to assess the incidence and severity of intraoperative events, post-operative adverse events, serious adverse events and unanticipated adverse device effects.

Point estimates and two-sided Exact 95% confidence intervals will be generated for procedural related events in the following categories:

- Intra-operative events
- Post-operative adverse events
- Serious adverse events
- Unanticipated adverse device effects

The safety analysis will be performed on the per-protocol population. No formal statistical hypothesis testing will be performed for safety endpoints.

11.4.4 Intra-procedural data

Initial cryoablation procedure information including the type of procedure, tumor size, cryoablation needle type and the number of each type of needle used, freeze and thaw times, and how ice formation encompasses the tumor will be summarized.

11.4.5 Other Analyses

Kaplan-Meier, T-Tests and other appropriate statistical tests may be performed on various parameters depending on the data collected during the study.

11.4.6 Poolability Analyses

Though individual treatments may vary (needle used, number of needles used, and freeze/thaw times, etc.), it is expected that data will be poolable across study sites since all sites and investigators will follow a common protocol with identical inclusion/exclusion criteria (same population) and outcome assessment. The primary efficacy endpoint will be evaluated by study site.

12 DATA MANAGEMENT

12.1 Data Collection

Data will be collected using a web-based electronic data capture (EDC) system. The system will be fully validated and compliant with FDA 21 CFR Part 11 Guidance. Participating sites will enter all subject data collected during the conduct of the protocol into the EDC system using the electronic case report forms (eCRFs) developed for each stage of the study.

All sites will receive training on the proper use of the system and the data collection expectations for this protocol. A Galil Medical representative will train each site on how to create a new subject, enter data into the eCRFs, edit/update data on existing eCRFs, resolve queries and approve/sign-off on each form/completed eCRF.

12.2 Data Processing

To help minimize data entry errors, the EDC system will include real-time edit checks that will identify potential data issues at the time of entry. These edit checks will display on-screen messages when triggered so that the investigator or data entry designee can immediately review the potential data issue and address it before leaving the system.

All eCRFs will be reviewed by a Galil Medical representative to check for completeness and potential unresolved data entry issues. A Galil Medical representative will generate queries within the system for open data issues and follow-up with each site, as necessary, to resolve key data element issues.

The investigator will review all eCRFs entered and will approve each eCRF for a subject via electronic signature within the EDC system. The database will be subject to periodic interim analyses based on key study milestones (e.g. adverse event assessments and primary endpoint after completed by all participating subjects). Prior to each milestone analysis, a Galil Medical representative will work with each site to ensure a data set that is as complete and accurate as possible. At the conclusion of the study, the database will undergo a final review and then be locked. No changes will be allowed in the database after the final lock without the written authorization of the appropriate Galil Medical management team members.

13 MONITORING AND AUDITING PROCEDURES

Participating sites will be managed remotely via regular telephone/email contact and routine monitoring visits will be conducted. When necessary, site visits will be performed by an authorized representative from Galil Medical, and will be conducted according to the monitoring plan and applicable FDA and GCP guidelines.

In addition, sites may be subject to an audit visit by Galil Medical, the FDA or a local regulatory authority. If such a site audit occurs, the investigator agrees to provide access to all pertinent subject records, eCRFs and other site documents deemed necessary to complete the audit visit.

By signing the Study Agreement, the investigator grants permission to authorized representatives of Galil Medical to conduct on-site monitoring visits for the purpose of reviewing the collected study data and to review site procedures employed in the conduct of this study.

It is important that the investigator(s) and their relevant personnel are available during the monitoring visits and possible audits or inspections and that sufficient time is devoted to the process.

14 SAFETY ASSESSMENTS

All related, potentially related, or unknown to be related adverse events (AEs), serious adverse events (SAEs) and unanticipated adverse device effects (UADEs) that occur within 30 days after the cryoablation procedure is performed will be recorded. A related event is one in which the investigator determines there is a reasonable possibility that the procedure/study device caused or contributed to an adverse event. The AEs, SAEs and UADEs identified will be followed until resolution or for a period of 6 months.

14.1 List of Definitions

Adverse Event (AE)

An adverse event is defined as any untoward or unfavorable medical occurrence in a human subject, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with the subject's participation in the research, whether or not considered related to the subject's participation in the research. According to this protocol, only those related, potentially related, or unknown to be related (to the cryoablation procedure) adverse events will be collected. Adverse events which are related to a pre-existing condition or treatment of that condition (noted in subject records as existing prior to the cryoablation procedure) will not be documented as adverse events. All AEs (as specified above) must be recorded in the electronic database. A description of the event, including the start date, resolution date, action taken and the outcome should be provided, along with the investigator's assessment of the relationship between the AE and the study procedures.

The anticipated cryoablation related adverse events and their corresponding Common Terminology Criteria for Adverse Events (CTCAE) Terms are listed in Appendix B.

Serious Adverse Event (SAE)

Category 4 or higher of the CTCAE guidelines and/or the following ICH definitions will be used in the protocol as applicable. According to this protocol, only those related, potentially related, or unknown to be related (to the cryoablation procedure) serious adverse events will be collected.

- Results in Death
- Is Life-threatening

  Note: the term 'life threatening' in the definition of serious refers to an event in which a subject was at immediate risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it were more severe.

- Requires inpatient hospitalization or prolonged existing hospitalization

  Note: complications that occur during hospitalization are AEs. If a complication prolongs hospitalization or fulfills any other serious criteria, the event is serious. Hospitalization for elective treatment of a preexisting condition that did not worsen from baseline is not considered to be an AE.

- Results in persistent or significant disability/incapacity

  Note: the term disability means a substantial disruption of a person's ability to conduct normal life functions. This definition is not intended to include experiences of relatively minor medical significance (e.g., uncomplicated headache, nausea, vomiting, diarrhea, influenza, or accidental trauma) that may interfere or prevent everyday life functions, but do not constitute a substantial disruption.

- Results in permanent impairment of a body structure or body function or requires surgical intervention to prevent permanent impairment of a body structure of body function
- Leads to fetal distress, fetal death or a congenital anomaly/birth defect
- Important medical events that may not be immediately life threatening, or result in death or hospitalization but may jeopardize the subject or may require intervention to prevent one of the outcomes listed in the definition above should also usually be considered serious

  Note: Examples of such events are intensive treatment in an emergency room or at home for allergic bronchospasm, blood dyscrasias, or convulsions that do not result in hospitalization; or development of drug dependency or drug abuse.

Unanticipated Adverse Device Effect (UADE)

Unanticipated adverse device effect is any serious adverse effect on health or safety, any life-threatening problem or death caused by, or associated with a device, if that effect, problem, or death was not previously identified in nature, severity, or degree of incidence in the application; or any other unanticipated serious problem associated with a device that relates to the rights, safety, or welfare of subjects.

14.2 Causality Assessment

The investigator's assessment of causality must be provided for all adverse events (serious and non-serious). An investigator's causality assessment is the determination of whether there exists a reasonable possibility that the procedure or study device caused or contributed to an adverse event. If the investigator's final determination of causality is unknown and the investigator does not know whether or not the procedure or study device caused the event, then the event will be handled as "related to procedure or study device" for reporting purposes. If the investigator's causality assessment is "unknown but not related to procedure or study device," this should be clearly documented on study records.

The investigator will evaluate AEs/SAEs/UADEs using the following guidelines:

- Description of event (if the event consists of multiple signs and symptoms, a diagnosis should be recorded rather than each sign and symptom)
  - Record term and grade according to the CTCAE 4.03 grading criteria
- Onset date
- Stop date (if available)
- Seriousness
  - The investigator must determine whether or not the AE meets the definition of serious as noted above. If the event is serious, the investigator must inform the Sponsor within 24 hours of knowledge of the event.
- Relationship to Study Procedure or Study Device
  - The investigator must make a causality assessment for all AEs and decide whether there is a reasonable possibility the AE was caused by the procedure or study device.
  - If there is a valid reason to suspect a causal relationship between the AE and the procedure or study device, the AE should be considered "related or possibly related" to the procedure or study device.
- Outcome
- Action Taken

14.3 Recording Related AEs

All related, potentially related, or unknown to be related adverse events must be recorded on the eCRF. The investigator will review all documentation (e.g., hospital progress notes, laboratory, or diagnostic reports) relative to the event and record all relevant information regarding an AE in the eCRF.

14.4 Recording and Reporting Related SAEs and UADEs

Any related, potentially related, or unknown to be related serious adverse events must be reported by the investigator within **24 hours** of learning of the event. The site must maintain adequate documentation of timely event reporting.

Reporting of SAEs and UADEs may be done via telephone at [redacted] or via E-mail at [redacted]

A Galil Medical clinical representative will work with the investigator to complete the SAE report. The investigator or designee must forward the requested follow-up information to the Galil Medical clinical representative as the event continues and/or resolves.

Investigators are required to submit to the Institutional Review Board (IRB)/Independent Ethics Committee (IEC) and Galil Medical a report of any UADE occurring during an investigation as soon as possible, but in no event later than 10 working days after the investigator learns of the effect. The site must maintain adequate documentation of timely event reporting.

Delegated study personnel are to enter the SAE/UADE information into the eCRF EDC system.

It is the responsibility of the investigator to inform the IRB/IEC of SAEs/UADEs as required by local procedure. Galil Medical is responsible for relaying adequate information on SAEs/UADEs to all investigators participating in this study as well as to the FDA and other regulatory authorities.

14.5 Grading of Toxicity

Grading of toxicity will be done according to Common Terminology Criteria for Adverse Events (CTCAE, version 4.03). See anticipated adverse events in Appendix B.

15 PRODUCT COMPLAINTS

In the event of a Galil Medical cryoablation system or needle complaint, the investigator should contact the Galil Medical Customer Service Department at:

US	[redacted]
Europe	[redacted]
Israel	[redacted]

16 INVESTIGATOR REQUIREMENTS

16.1 Study Initiation

Prior to enrolling subjects in this study, the investigator must provide the following documents to Galil Medical:

- Signed and dated Study Agreement

- Signed and dated Protocol Signature page
- Signed and dated Financial Disclosure
- Signed and dated Site Training Form
- A copy of the written IRB/IEC approval of the protocol
- IRB/IEC membership roster or assurance letter
- A copy of the written IRB/IEC approval of the Informed Consent Form
- A copy of the abbreviated curriculum vitae of the investigator
- A copy of the investigator's medical license or number

Participating site staff must also complete an initiation/training session with a Galil Medical Clinical Representative. The session will include a review of the protocol, discussion of the informed consent process, an overview of the study procedures and a practice session with the EDC system.

16.2 Informed Consent Form

A sample Informed Consent Form (ICF) will be provided to each site. Any requested changes to the ICF must be reviewed and approved by Galil Medical prior to submission to an IRB/IEC.

An approved ICF, including HIPAA language, must be signed by each subject, or the subject's legally authorized representative, before any study procedures are completed. The investigator or designee must also sign and date the ICF to document the process as well as noting the process in the source. A copy of the ICF must be given to each subject, or the subject's legally authorized representative. The original signed ICF is to be kept with the subject's study records and must be made available for review upon request during any on-site monitoring or audit visits.

Prior to signing the ICF, the subject, or the subject's legally authorized representative, will be provided with an oral overview of the study. This overview will include a discussion of the study's purpose and objectives, the scope and duration of participation and the disclosure that the subject may withdraw from the study at any time without consequence. All questions from the subject or his/her legally authorized representative are to be answered before the ICF is signed.

16.3 Institutional Review Board/Independent Ethics Committee

This protocol, the Informed Consent Form (ICF) and relevant supporting information must be submitted to an Institutional Review Board / Independent Ethics Committee (IRB/IEC) before a site is initiated for participation. Approval from the IRB/IEC must be obtained before any study assessments are performed. IRB/IEC approval shall be documented in a letter to the investigator, clearly identifying this protocol, the documents reviewed and the date of approval. This protocol will be conducted in accordance with applicable local regulatory and IRB/IEC requirements.

The investigator is responsible for keeping his/her local IRB/IEC apprised of the progress of the study and of any protocol changes, as necessary. Galil Medical will be responsible for updating the study's central IRB/IEC, if applicable.

Investigators are required to notify their local IRB/IEC of all Serious Adverse Events (SAEs) and all Unexpected Adverse Device Events (UADEs). Investigators under the jurisdiction of the study's central IRB/IEC are required to promptly notify Galil Medical of such events so that they can notify the central IRB/IEC.

The investigator will be responsible for obtaining annual IRB/IEC approval and renewal throughout the duration of the study.

16.4 Protocol Amendments

This protocol will only be altered by written amendments. Administrative changes that do not impact subject participation in the study may be made without any further approvals.

Any change that would require alteration of the Informed Consent form must receive approval from all persons or designees who approved the original protocol and from the IRB/IEC prior to implementation. Following approval, the protocol amendment(s) will be distributed to all protocol recipients with instructions to append them to the protocol.

16.5 Record Retention

All source documents, records and reports related to data provided to this study will be retained by the investigator in accordance with applicable FDA regulations, ICH and GCP guidelines for at least two (2) years following closure of the study. The investigator will take measures to ensure that these essential documents are not accidentally damaged or destroyed. No records should be disposed of without the written approval of Galil Medical.

17 STUDY COMMITTEES

An independent Medical Monitor will be designated to ensure the safety of subjects throughout the duration of the study through regular review and analysis of the safety data.

18 STUDY ADMINISTRATION

Galil Medical will make necessary efforts to ensure that this study is conducted in compliance with all applicable regulatory requirements.

18.1 Study Registration

Information about this study will be registered and updated on www.clinicaltrials.gov.

18.2 Study Discontinuation

Galil Medical reserves the right to terminate this study at any time. Reasons for terminating may include the following:

- Unsatisfactory enrollment
- Inability to ensure consistent follow-up data collection
- Other ethical or clinical considerations

18.3 Discontinuation of a Study Site

Galil Medical reserves the right to discontinue a site's participation in this study at any time. Possible reasons for discontinuation include:

- Site's discontinuation of the use of Galil Medical's cryoablation products
- Slower than agreed to study enrollment
- Non-compliance with study procedures

- Poor data quality
- Multiple or severe protocol violations without justification and prior approval
- Insufficient documentation and/or follow-up of SAEs and UADEs

19 CONFIDENTIALITY/PUBLICATION OF STUDY RESULTS

This clinical study is confidential and should not be discussed with individuals outside of the study. Additionally, the information in this document and from the study may contain secrets and commercially sensitive information that is confidential and may not be disclosed unless such disclosure is required by federal or state law or regulations. Subject to the foregoing, this information may be disclosed only to those persons involved in this study that have a need to know, but all such persons must be instructed not to further disseminate this information to others.

The data may be used now and in the future for presentation or publication at the sponsor's discretion or for submission to governmental regulatory agencies. All reports and communications relating to subjects in the study will identify each subject only by the subject's initials and by the subject's study number. Final study data will be posted to www.clinicaltrials.gov according to the regulatory posting requirements.

20 STUDY COMPLETION

The investigator will complete and report the study in satisfactory compliance with the protocol. It is agreed that, for any reasonable cause, either the investigator or the sponsor, Galil Medical, may terminate this study, provided a written notice is submitted at a reasonable time in advance of intended termination. If the study is terminated for safety reasons, the investigator will be notified immediately by telephone, followed by written instructions for study termination notification of the IRB/IEC.

21 PROTOCOL DEVIATIONS AND EXCEPTIONS

The investigator should not implement any deviation from or changes of the protocol without agreement by the sponsor and prior review and documented approval from the IRB/IEC of an amendment, except where necessary to eliminate an immediate hazard(s) to study subjects.

The investigator should document and explain any deviation from the approved protocol. The reasons for it and, if appropriate, the proposed protocol amendments should be submitted to the sponsor for agreement, the IRB/IEC and to the regulatory authority (when applicable).

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22 APPENDIX A: ABBREVIATIONS

Acronym	Definition
AE	Adverse Event
BPI	Brief Pain Inventory - Short Form
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events
EDC	Electronic Data Capture
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
GCP	Good Clinical Practices
HIPAA	Health Insurance Portability and Accountability Act
ICF	Informed Consent Form
ICH	International Conference on Harmonization
IRB/IEC	Institutional Review Board/Independent Ethics Committee
KPS	Karnofsky Performance Status
MRI	Magnetic Resonance Imaging
SAE	Serious Adverse Event
UADE	Unanticipated Adverse Device Effect

23 APPENDIX B: ANTICIPATED ADVERSE EVENTS ASSOCIATED WITH CRYOABLATION

Common Terminology Criteria for Adverse Events v 4.03 (CTCAE)

Adverse Event	CTCAE TERM
Allergy/ acute inflammatory reaction	Anaphylaxis
Angina/coronary ischemia	Acute coronary syndrome
Bladder injury	Intraoperative urinary injury
Blood and lymphatic disorders	Blood and lymphatic disorders, other specify
Bowel injury	Intraoperative gastrointestinal injury
Cardiac arrest	Cardiac arrest
Cardiac disorders	Cardiac disorders – Other, specify
CSF leakage	Cerebrospinal fluid leakage
Death not otherwise specified (NOS)	Death NOS
Ecchymosis/bruising	Bruising
Fever	Fever
Fracture	Fracture
Hematoma	Hematoma
Hypotension	Hypotension
Hypothermia	Hypothermia
Injection site reaction	Injection site reaction
Injury, poisoning and procedural complications - Other, specify	Injury, poisoning and procedural complications - Other, specify
Infections and infestations	Infections and infestations – Other, specify
Intraoperative arterial injury	Intraoperative arterial injury
Intraoperative endocrine injury	Intraoperative endocrine injury
Intraoperative hemorrhage	Intraoperative hemorrhage
Intraoperative hepatobiliary injury	Intraoperative hepatobiliary injury
Intraoperative musculoskeletal injury	Intraoperative musculoskeletal injury
Intraoperative neurological injury	Intraoperative neurological injury
Intraoperative renal injury	Intraoperative renal injury
Intraoperative skin injury	Intraoperative skin injury
Intraoperative splenic injury	Intraoperative splenic injury
Intraoperative venous injury	Intraoperative venous injury
Myocardial infarction	Myocardial infarction
Nausea	Nausea

Neuralgia	Neuralgia
Pain at needle site	Pain
Paresthesia (e.g., nerve injury)	Paresthesia
Pleural effusion	Pleural effusion
Pneumothorax	Pneumothorax
Postoperative hemorrhage	Postoperative hemorrhage
Pulmonary embolism	Thromboembolic event
ARDS	Adult respiratory distress syndrome
Pulmonary failure/hypoxia	Hypoxia
Radiculitis	Radiculitis
Respiratory Failure	Respiratory failure
Sepsis	Sepsis
Skin burn/Frostbite	Burn
Skin infection	Skin infection
Soft tissue infection	Soft tissue infection
Swelling/localized edema	Localized edema
Stroke	Stroke
Thrombosis/thrombus/embolism	Thromboembolic event
TIA	Transient ischemia attack
Tumor pain	Tumor pain
Ureteral injury (spine cases)	Intraoperative urinary injury
Urinary incontinence	Urinary incontinence
Vasovagal reaction	Vasovagal reaction
Vomiting	Vomiting
Wound complication (e.g., hernia)	Wound complication
Wound dehiscence	Wound dehiscence
Wound infection (e.g., abscess)	Wound infection

24 APPENDIX C: BRIEF PAIN INVENTORY (BPI)

STUDY ID# _____ HOSPITAL # _____

DO NOT WRITE ABOVE THIS LINE

Brief Pain Inventory (Short Form)

Date: ____/____/____ Time: ____

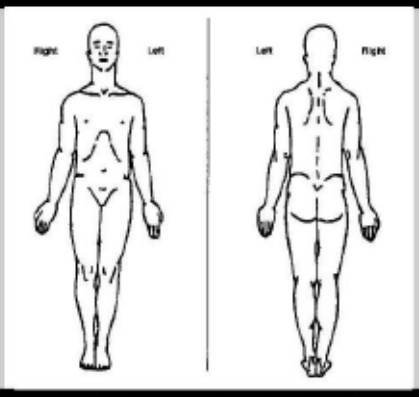
Name: _____ _____ _____

Last First Middle Initial

1. Throughout our lives, most of us have had pain from time to time (such as minor headaches, sprains, and toothaches). Have you had pain other than these every-day kinds of pain today?

1. Yes 2. No

2. On the diagram, shade in the areas where you feel pain. Put an X on the area that hurts the most.



3. Please rate your pain by circling the one number that best describes your pain at its worst in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

4. Please rate your pain by circling the one nuimber that best describes your pain at its least in the last 24 hours.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

5. Please rate your pain by circling the one number that best describes your pain on the average.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

6. Please rate your pain by circling the one number that tells how much pain you have right now.

0	1	2	3	4	5	6	7	8	9	10
No Pain										Pain as bad as you can imagine

7. What treatments or medications are you receiving for your pain?

8. In the last 24 hours, how much relief have pain treatments or medications provided? Please circle the one percentage that most shows how much relief you have received.

0%	10%	20%	30%	40%	50%	60%	70%	80%	90%	100%
No Relief										Complete Relief

9. Circle the one number that describes how, during the past 24 hours, pain has interfered with your:

A. General Activity

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

B. Mood

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

C. Walking Ability

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

D. Normal Work (includes both work outside the home and housework)

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

E. Relations with other people

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

F. Sleep

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

G. Enjoyment of life

0	1	2	3	4	5	6	7	8	9	10
Does not Interfere										Completely Interferes

25 APPENDIX D: KARNOFSKY PERFORMANCE STATUS (KPS)

The Karnofsky Performance Status allows patients to be classified as to their functional impairment. This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients.

KARNOFSKY PERFORMANCE STATUS SCALE DEFINITIONS	RATING (%)	CRITERIA
Able to carry on normal activity and to work; no special care needed.	100	Normal no complaints; no evidence of disease.
	90	Able to carry on normal activity; minor signs or symptoms of disease.
	80	Normal activity with effort; some signs or symptoms of disease.
Unable to work; able to live at home and care for most personal needs; varying amount of assistance needed.	70	Cares for self; unable to carry on normal activity or to do active work.
	60	Requires occasional assistance, but is able to care for most of his personal needs.
	50	Requires considerable assistance and frequent medical care.
Unable to care for self; requires equivalent of institutional or hospital care; disease may be progressing rapidly.	40	Disabled; requires special care and assistance.
	30	Severely disabled; hospital admission is indicated although death not imminent.
	20	Very sick; hospital admission necessary; active supportive treatment necessary.
	10	Moribund; fatal processes progressing rapidly.
	0	Dead

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26 *APPENDIX E:* INSTRUCTIONS FOR MORPHINE EQUIVALENT DAILY DOSE (MEDD)

INSTRUCTIONS FOR MORPHINE EQUIVALENT DAILY DOSE (MEDD)

Translate the dose and route of each of the opioids the patient has received over the last 24 hours to parenteral morphine equivalent using a standard conversion table (see below).

MEDD initial: It is the 24hr opioid dose before the physician meets with the patient. (Using the conversion table found online which has the MEDD factors). i.e midnight-midnight.

MEDD final: The final 24 hrs opioid dosage that the patient receives.
•Discharged: Take the last complete 24hr period the patient received opioid dosage before discharge.
•Death: Take the last complete 24hr period that the patient was alive for and use that as the final MEDD dosage.

MORPHINE EQUIVALENT DAILY DOSE (MEDD) CONVERSION TABLE

MEDICATION	ROUTE	MEDD FACTOR	MEDICATION	ROUTE	MEDD FACTOR
CODEINE	IM	0.1	METHADONE	IV	8
CODEINE	PO	0.05	METHADONE	PO	4
CODEINE	R	0.05	METHADONE	R	4
CODEINE	SC	0.1	METHADONE	SC	8
DIAMORPHINE	PO	0.65	MORPHINE	EP	3
DIAMORPHINE	SC	1.3	MORPHINE	IT	30
DIAMORPHONE	EP	3.9	MORPHINE	IM	1
DIAMORPHONE	IT	39	MORPHINE	IV	1
FENTANYL	EP	0.3	MORPHINE	PO	0.4
FENTANYL	IT	3	MORPHINE	R	0.4
FENTANYL	PO	0.05	MORPHINE	SC	1
FENTANYL	SL	0.05	OXYCODONE	PO	0.63
FENTANYL	IV	0.1	OXYCODONE	SC	1.5
FENTANYL	SC	0.1	PROPOXYPHENE	IM	0.167
FENTANYL	TD	0.1	PROPOXYPHENE	IV	0.167
HYDROCODONE	PO	0.4	PROPOXYPHENE	PO	0.08
HYDROMORPHONE	IM	5	PROPOXYPHENE	R	0.08
HYDROMORPHONE	IV	5	PROPOXYPHENE	SC	0.167
HYDROMORPHONE	PO	2	PROPOXYPHENE	TD	0.167
HYDROMORPHONE	SC	5	SUFENTANIL	SC	1
HYDROMORPHONE	EP	15	SUFENTANIL	IV	1
HYDROMORPHONE	IT	150	SUFENTANIL	PO	0.5
LEVO-DROMORAN	SC	5	SUFENTANIL	SL	0.5
MEPERIDINE	EP	0.3	TRAMADOL	PO	0.05
MEPERIDINE	IT	3	TRAMADOL	SC	0.1
MEPERIDINE	IM	0.1			
MEPERIDINE	IV	0.1			
MEPERIDINE	PO	0.05			
MEPERIDINE	SC	0.1			
METHADONE	EP	24			

Note:
1. MEDD calculation: [DOSE] × [MEDD_FACTOR]
2. Abbreviation list

PO	Oral
IM	Intramuscular
IV	Intravenous
SC	Subcutaneous
SL	Sublingual
R	Rectal
EP	Epidural
IT	Intrathecal
TD	Transdermal

palliative.org/NewPC/_pdfs/tools/INSTRUCTIONs**MEDD**.pdf

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