SUMMARY OF SAFETY AND PROBABLE BENEFIT (SSPB)

I. GENERAL INFORMATION

Device Generic Name: Ablation System, High Intensity Focused Ultrasound (HIFU), Magnetic Resonance (MR)-Guided

Device Trade Name: Sonalleve MR-HIFU

Device Procode: QND

Applicant's Name and Address: Profound Medical Inc.
2400 Skymark Avenue, Unit #6,
Mississauga, Ontario L4W 5K5, Canada

Date(s) of Panel Recommendation: None

Humanitarian Device Exemption (HDE) Number: H190003

Humanitarian Use Device (HUD) Designation Number: 18-0401

Date of HUD Designation: December 18, 2018

Date of Notice of Approval to Applicant: November 27, 2020

II. INDICATIONS FOR USE

Sonalleve MR-HIFUis intended to be used for the treatment of osteoid osteomas in the extremities.

The indication for use statement is a subset of that which was granted for the HUD designation.

III. CONTRAINDICATIONS

- MR contraindications specified in the MR scanner's Instructions for Use, weight >140 kg (308 lbs), and MR contrast agents
- The target is located <1 cm from a nerve plexus, bladder, skin, or bowel
- The target is located <1 cm from the growth plate
- The target is located in the skull
- The target is located in unstable bone, impending fracture, or has been stabilized with metallic implants
- Scars that cannot be protected or surgical clips, implants, or prosthesis in the planned path of the ultrasound beam
- The patient is unable to tolerate a stationary position for the duration of the procedure

IV. WARNINGS AND PRECAUTIONS

The warnings and precautions can be found in the Sonalleve MR-HIFU System labeling.

V. DEVICE DESCRIPTION

The Sonalleve MR-HIFU System is designed to non-invasively deliver acoustic energy to prescribed locations. The system integrates a high intensity phased array focused ultrasound transducer with a Magnetic Resonance Imaging (MR or MRI) system and electromechanical transducer positioning system to deliver spatially and temporally controlled ultrasound energy to elevate tissue temperatures, and to ablate tissues non-invasively.

The Sonalleve MR-HIFU System is designed to be used with Philips Achieva and Ingenia 1.5T and 3.0T MR scanners and complies with the requirements of the applicable International Electrotechnical Commission (IEC) safety standards.

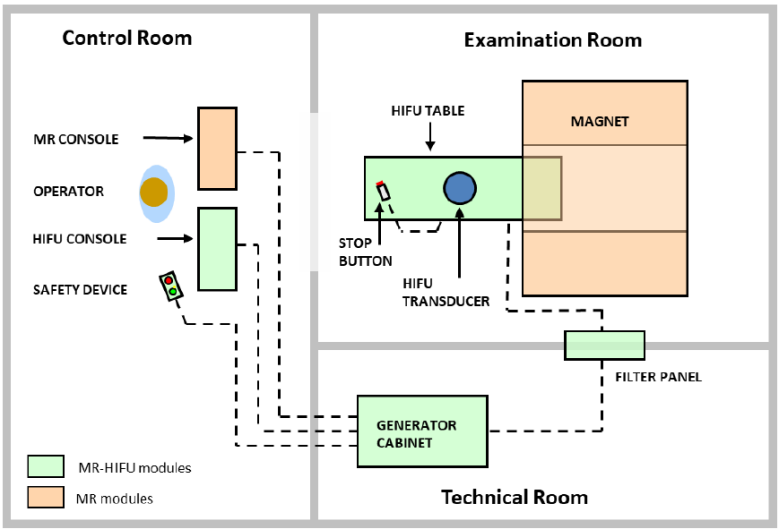

Figure 1: Sonalleve MR-HIFU System

The Sonalleve MR-HIFU therapy system consists of the following main components:

- Sonalleve Patient Table assembly - The Sonalleve Patient Table is a mobile patient support used for MR-HIFU therapy in an Achieva or Ingenia medical diagnostic MR system. The Patient Table is positioned to sit above the standard MR system Patient Support. It can be removed to enable normal diagnostic use of the MR scanner. The Sonalleve Patient Table (denoted as "HIFU TABLE" in Figure 1) and its parts are located in the examination room within the patient environment and include the following items:
    - Ultrasound transducer
    - Positioning mechanics
    - Matching electronics
    - Connector panel
    - Sonalleve Pelvis coil
    - Patient Emergency Stop Button (PESB)

- Pads, mattresses and straps for patient positioning
- Direct Skin Cooling device (DISC) – The Direct Skin Cooling (DISC) device is a device used to cool down the skin of the patient during HIFU treatment by circulating cooled water inside the DISC patient contact.

Figure 2: Sonalleve Patient Table.

- Sonalleve Generator Cabinet - The Sonalleve MR-HIFU System requires a separate cabinet for power distribution and the control driver electronics of the ultrasound transducer. The Sonalleve Generator Cabinet and its parts are located in the technical room. Electrically shielded cables connect the Generator Cabinet to the Patient Tabletop through a dedicated HIFU filter panel on the wall between the equipment and magnet rooms.

- Sonalleve Therapy Planning Console with a Safety Device - The Sonalleve Console is used for transferring the planning images from the MR scanner, planning of the sonication treatment, and the actual therapy sonication. It is located in the control room, with direct visibility to the examination room. A monitor and safety device are included with the Sonalleve Console. The operator can terminate the treatment at any point using the Safety Device if the operator detects a hazardous situation as an undesired heating pattern, or a malfunction in the equipment.

Principles of Operation

High Intensity Focused Ultrasound (HIFU) treatment is a non-invasive therapeutic technique that uses non-ionizing ultrasonic waves to heat tissue deep within the human body. The system uses an external ultrasound transducer to generate a focal beam to heat a target deep within the human body. This is called a sonication. The sonication causes a temperature rise that coagulates the target tissue. MR-guided HIFU (MR-HIFU) treatment is an image guided technique combining High Intensity Focused Ultrasound with real time monitoring of temperature change during the sonication.

The thermal MR images are used to calculate relative temperature maps that are monitored on the Sonalleve Console. The temperature maps are used to visualize the progress of the treatment and to control the duration of the sonication.

The essential performance of the Sonalleve MR-HIFU System is to deliver spatially and temporally controlled therapeutic ultrasound power into accessible and targeted tissues.

VI. ALTERNATIVE PRACTICES AND PROCEDURES

The Sonalleve MR-HIFU System is intended to be used for the treatment of osteoid osteoma. Osteoid osteoma is a benign painful bone tumor that occurs typically in the cortex of long bones of children and young adults [1]. The osteoid osteoma nidus is a highly vascularized central region that produces prostaglandins, causing local vasodilation, inflammation, and pain [2]. The pain, which characteristically worsens at night, commonly disrupting sleep [3]. In addition to pain, other signs and symptoms of osteoid osteoma include bony deformity, growth disturbance, and painful scoliosis [4].

Conventional procedures used in the treatment of Osteoid Osteoma

Pain associated with osteoid osteoma is initially treated by non-steroidal anti-inflammatory drugs (NSAIDs), such as ibuprofen. Treatment with NSAIDs may temporarily relieve pain in the short term but are associated with long-term toxicities [5]. Definitive treatment options for osteoid osteomas refractory to medical management are surgical resection or computed tomography-guided radiofrequency ablation (CT-RFA). Surgical resection has become less common today due to difficulty in intraoperative visualization of the lesion, which can lead to significant bone resection and collateral damage to surrounding tissue.

Morbidity is related to weakening of the remaining bone and prolonged recovery times with weight-bearing and mobility restrictions [6]. CT-RFA is a less invasive option than surgical resection. During CT-RFA, a needle is guided and advanced into the osteoid osteoma nidus under direct visualization with computed tomography (CT) imaging and heated to 90°C to ablate the nidus [4]. Thermal ablation of the nidus and adjacent periosteal nerves eliminates pain within a few days [1]. Although CT-RFA has a high success rate [7], the treatment is invasive and can potentially cause complications such as skin burn, nerve damage, infection and fracture. It also exposes patients and operators to ionizing radiation associated with the CT imaging guidance, which can have potential long-term negative effects, especially in growing children [8, 9].

VII. MARKETING HISTORY

The Sonalleve MR HIFU system is commercially marketed in the European Union (EU) jurisdictions. The Sonalleve MR HIFU has not been withdrawn from marketing for any reason relating to the safety and effectiveness of the device.

The Sonalleve MR-HIFU system has not been commercially marketed in the United States.

VIII. PROBABLE ADVERSE EFFECTS OF THE DEVICE ON HEALTH

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

- Mild/moderate muscle pain
- Leg pain
- Fatigue
- Foot pain

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

- Significant transient pain at the treated region
- Nausea
- Vomiting
- Swelling
- Skin burns
- Internal tissue thermal injury
- Radiating pain
- Fever
- Infection
- Back and shoulder pain
- Fracture at the site of bone lesion
- Damage to sciatic nerve or other nerve trunks
- Injury to internal organs, blood vessels, nerves near the tumor
- Worsening of existing pain
- Metabolic imbalance / tumor lysis syndrome
- Adverse drug reaction
- Cardio-respiratory depression
- Deep Vein Thrombosis
- Muscle Pain

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

IX. SUMMARY OF NON-CLINICAL STUDIES

A. Laboratory Studies

Electrical Safety and Electromagnetic Compatibility (EMC) Testing

Sonalleve MR-HIFU System has been designed and developed in accordance with requirements in the IEC 60601-1 family of standards, including basic safety, electromagnetic compatibility (EMC) and usability. Testing was performed by an accredited third-party test laboratory. The device was tested and based on the sponsor's specification of Essential Performance, passed all applicable sections. The system was also shown to comply with the particular standard IEC 60601-2-62 Medical electrical equipment – Particular requirements for basic safety and essential performance of high intensity therapeutic ultrasound (HITU) equipment.

Software Verification / Validation

Software verification and validation testing was conducted to test the Sonalleve MR-HIFU System software check program. Documentation was submitted by Profound Medical Inc. and found to be adequate. The software evaluation is based upon the documents provided. The documentation provided shows that the Sonalleve MR-HIFU System does not connect to any network and is a standalone system; therefore, cybersecurity is adequate.

Biocompatibility Testing

Sonalleve MR-HIFU system has materials that can contact the patient. Biocompatibility testing for the Sonalleve MR-HIFU System was conducted for the patient-contacting material. All biocompatibility testing was conducted in accordance with:

- ISO 10993-1: "Biological evaluation of medical devices – Part 1: Evaluation and testing" and
- Good Laboratory Practices Regulations

Table 1 below summarizes the biocompatibility tests conducted for the patient-contacting materials of the Sonalleve MR-HIFU system.

Table 1: Biocompatibility testing for patient contacting materials of Sonalleve MR-HIFU system

Test	Method	Results
Cytotoxicity	Dulbecco's Modified Eagle's Medium (DMEM) elution, bicinchoninic acid (BCA)-staining	Non-cytotoxic
Acute dermal irritation / Corrosion	Acute dermal irritation / Corrosion	Pass

Test	Method	Results
Skin Sensitization	Local lymph node assay, polar and non-polar extracts	Pass
Acute Skin irritation	Acute (single exposure) skin irritation test in the rabbit	Pass
Irritation and delayed-type hypersensitivity	Epicutan test	Pass

B. Animal Studies

MR-HIFU laboratory tests have been conducted using the Sonalleve MR-HIFU system. The main objective of these studies was to investigate and validate the safety and treatment accuracy of the Sonalleve MR-HIFU technique. To meet the objectives, these studies combined simulations, thermal tests in laboratory settings, as well as pre-clinical animal studies in which *in vivo* and *ex vivo* pig thigh was ablated by MR-HIFU. In the animal studies, the accuracy of the volume ablation methodology and volumetric thermometry prediction using the Sonalleve MR-HIFU system was studied. Special attention was paid to the efficacy and safety of the volumetric heating method.

The animal study was intended to characterize thermal ablation of bone and correlate thermal dose threshold contours to histologically determined tissue damage. All ablations were performed using an 8 mm treatment target (i.e., a treatment cell); 1.2 MHz and 20 second sonication; and using 80W, 100 W and 160 W power settings. The histology results support the ability of the device to produce soft tissue thermal ablation consistent with the thermal dose contour dimensions. The study also showed that the temperature under the bone and inside the bone heats rapidly. Only a low amount of energy of about 1.4kJ is necessary to induce ablation around the cortical, which is 4 times less than soft tissue ablation parameters.

X. SUMMARY OF CLINICAL INFORMATION

The Sonalleve MR-HIFU system was reviewed under IDE submission G130041 and associated supplements. The device was studied for the ablation of osteoid osteomas in children, adolescents and young adults with 9 patients recruited and treated.

Feasibility study

The IDE G130041 included the protocol for the study "Safety and Feasibility of MR-guided High Intensity Focused Ultrasound (MR-HIFU) ablation of Osteoid Osteoma in Children" (ClinicalTrials.gov Identifier: NCT02349971).

Purpose/ Objective of study

This feasibility study was designed to evaluate the safety and feasibility of MR-HIFU ablation for osteoid osteoma (OO) in children. The safety was determined through clinical assessments and evaluation of toxicity and feasibility through technically successful

completion of treatment. The secondary objective was to provide an assessment of MR-HIFU ablation of OO in children through measurable clinical response (pain, distress and quality of life) as well as imaging response at 12 months. These included Visual Analogue Scale (VAS), Symptom Distress Scale (SDS), Patient-Reported Outcomes Measurement Information System (PROMIS) score and Pediatric Quality of Life Inventory (PedsQL v 4.0). In addition, pain medication or Non-Steroidal Anti-Inflammatory Drug (NSAID) use (frequency and dose) were recorded for the five days prior to treatment and for up to thirty days (or longer if needed) following treatment and compared.

Primary Objective:

To evaluate the safety and feasibility of MR-HIFU ablation of osteoid osteomas in children and young adults.

Secondary Objective:

To provide an assessment of MR-HIFU ablation of osteoid osteomas in children and young adults through measurable clinical and imaging response.

Controls

The pre-treatment baseline served as a control for the treated patient.

Inclusion / Exclusion Criteria

Table 2: Inclusion / exclusion criteria

Inclusion	Exclusion
Age: ≤ 25 years of age Diagnosis: • All patients with a clinical suspicion of OO based on presence of typical symptoms of localized nocturnal pain that is relieved by NSAIDs and unrelated to trauma or activity. • Typical imaging findings on CT and/or MRI. Plain radiographs and bone scans may be obtained by referring physicians and are helpful for confirming the clinical diagnosis but cannot be substituted for a CT or MRI. • Non-contrast enhanced or contrast enhanced CT studies are acceptable. • Contrast enhanced MRI studies should be performed.	• Clinically significant unrelated systemic illness, such as serious infections, hepatic, renal or other organ dysfunction, which in the judgment of the Principal or Associate Investigator would compromise the patient's ability to tolerate the general anesthetic required for the procedure. • Implant or prosthesis or scar tissue within the path of the HIFU beam. • Target <1 cm from nerve plexus, spinal canal, bladder, bowel • Target <1 cm of the growth plate (physis) • Lesion in the skull or vertebral body • Inability to undergo MRI and/or contraindication for MRI • Inability to tolerate stationary position during HIFU

• Tissue biopsy is not required Tumor location: • Target lesions can be located in any peripheral bone with acoustic accessibility. • Target lesions may be intracortical or juxtacortical in location. • Target lesions must be reachable within the normal safety margins of HIFU as specified in the instructions for use. Prior therapy: • Patients with prior unsuccessful surgical resection or RFA are eligible for enrollment. Laboratory: • Hemoglobin > 9 g/dL • Platelet count ≥75,000/μL (may receive transfusions) • Normal prothrombin time (PT), partial thromboplastin time (PTT) and international normalized ratio (INR) < 1.5 x upper limit of normal (ULN) (including patients on prophylactic anticoagulation) • Renal function: Age-adjusted normal serum creatinine (see the table below) OR a creatinine clearance ≥60 mL/min/1.73 m2 for safe contrast administration Adequate pulmonary function: Defined as no dyspnea at rest, and a pulse oximetry >94% on room air if there is clinical indication for determination.	• Patients currently receiving any investigational agents.

Number of subjects

Nine (9) subjects were enrolled and treated. Gender and target location is described in the table below:

Table 3: Subject gender and target location

Subject ID	Gender	Location	Category	Bone Depth (mm)
OO27-0001	Male	Tibia	Cortical	14.0
OO27-0002	Female	Femur	Cortical	2.7
OO27-0003	Male	Femur	Intramedullary	3.3
OO27-0004	Male	Phalanx	Subortical/intramedullary	2.3
OO27-0005	Male	Femur	Cortical	11.3
OO27-0006	Female	Talus	Cortical	0.0
OO27-0007	Male	Tibia	Cortical	2.3
OO27-0008	Male	Tibia	Cortical	3.6
OO27-0009	Male	Calcaneus	Cortical	2.4

Study period

First subject's first visit: 16-Jan-2015
Last subject's last visit: 22-Dec-2017

Patient discontinuation

One subject discontinued at 28 days post treatment due to lack of response from MR-HIFU.

Patient complaints

Other than the reported adverse effects, there were no other patient complaints.

Device failures and replacements:

No device failures. None of the treatments were interrupted.

Statistical analysis

Adverse effects and toxicities were summarized descriptively and tabulated based on the type, severity, and relationship to treatment. Patient-reported VAS pain score, sleep disruption, and medication use were summarized.

Adverse events

In total, 15 adverse events were reported in the Osteoid Osteoma study. No serious adverse event were reported. Two of the nine treated subjects did not experience any adverse events. All of the adverse events were transitory. One patient developed minor focal bruising at the

edges of the treatment window, which was attributed to inadequate padding at this location. This bruising was visible but caused minimal discomfort and resolved without additional treatment within1 week. The complete list of reported adverse events is presented in the table below:

Table 4: Adverse events

Subject ID	Adverse Event	Relationship to Study Device	Grade	Serious adverse event
OO27-0001	Fatigue	Possibly	Mild	No
	leg pain	Probably	Moderate	No
	nausea	Unlikely	Mild	No
OO27-0002	bruising (bilateral shins)	Unlikely	Mild	No
	leg pain	Possibly	Moderate	No
OO27-0003	leg pain	Probably	Moderate	No
OO27-0005	muscle pain	Probably	Mild	No
	nausea	Unlikely	Mild	No
OO27-0006	foot pain	Possibly	Mild	No
	laryngeal inflammation	Unlikely	Mild	No
	back pain	Unlikely	Mild	No
OO27-0008	headache	Not related	Moderate	No
	back pain	Not related	Moderate	No
	nausea	Not related	Mild	No
OO27-009	peripheral sensory neuropathy	Unlikely	Mild	No
	peripheral motor neuropathy	Unlikely	Mild	No

Visual Analogue Scale (VAS)

All 9 patients were included in this analysis for pre-treatment, day 7, and day 28. One patient left the study after day 28, and one patient missed the 6 month visit, so at month 6 the number of patients with data was 7, and at month 12 the number of patients with data was 8. The median pre-treatment score was 2, and the median score decreased to 0 at day 7 and did not increase at any time points measured afterward.

Non-parametric trend test between VAS and time

- Kendall tau-b correlation coefficient = -0.3978 ($p = 0.0026$).

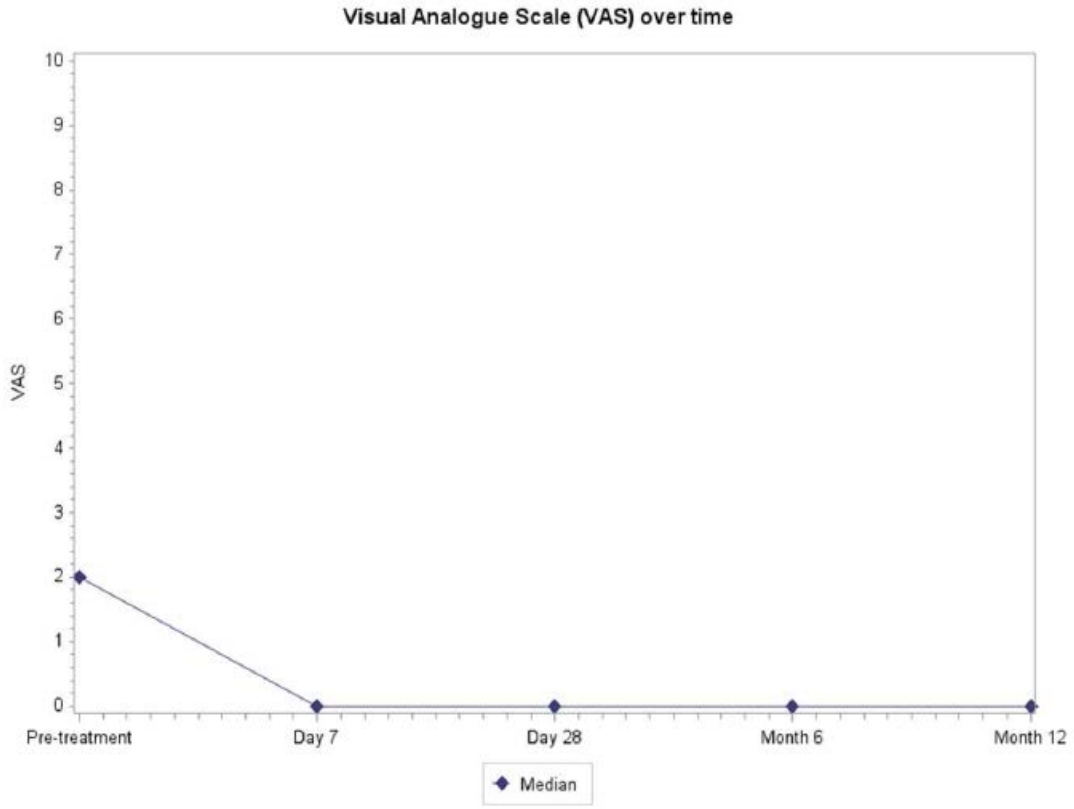

Figure 3: VAS over time.

Symptom Distress Scale

The SDS is a 10 item scale which asks patients about feelings about appearance, ability to get around, tiredness, quality of sleep, current feeling, pain, appetite, nausea, bowel movements, and concentration. Each question is on a scale from 1 to 5 where 1 equals the absence of or normal symptoms, and 5 equals the worst possible symptoms.

All 9 patients were included in this analysis for pre-treatment, day 7, and day 28. One patient left the study after day 28, and one patient missed the 6 month visit, so at month 6 the number of patients with data was 7, and at month 12 the number of patients with data was 8.

Symptom Distress Scale scores range from 10 to 25. The median symptom distress score at pre-treatment was 15, and decreased to 11 at the twelve month follow-up. At pre-treatment, patients were most likely to report mild problems with pain, tiredness and not sleeping well (median score of 2). The median score for all other symptoms at pre- treatment was 1.

Non-parametric trend test between SDS Score and Time

- Kendall tau-b correlation coefficient = -0.3747 (p=0.0023).

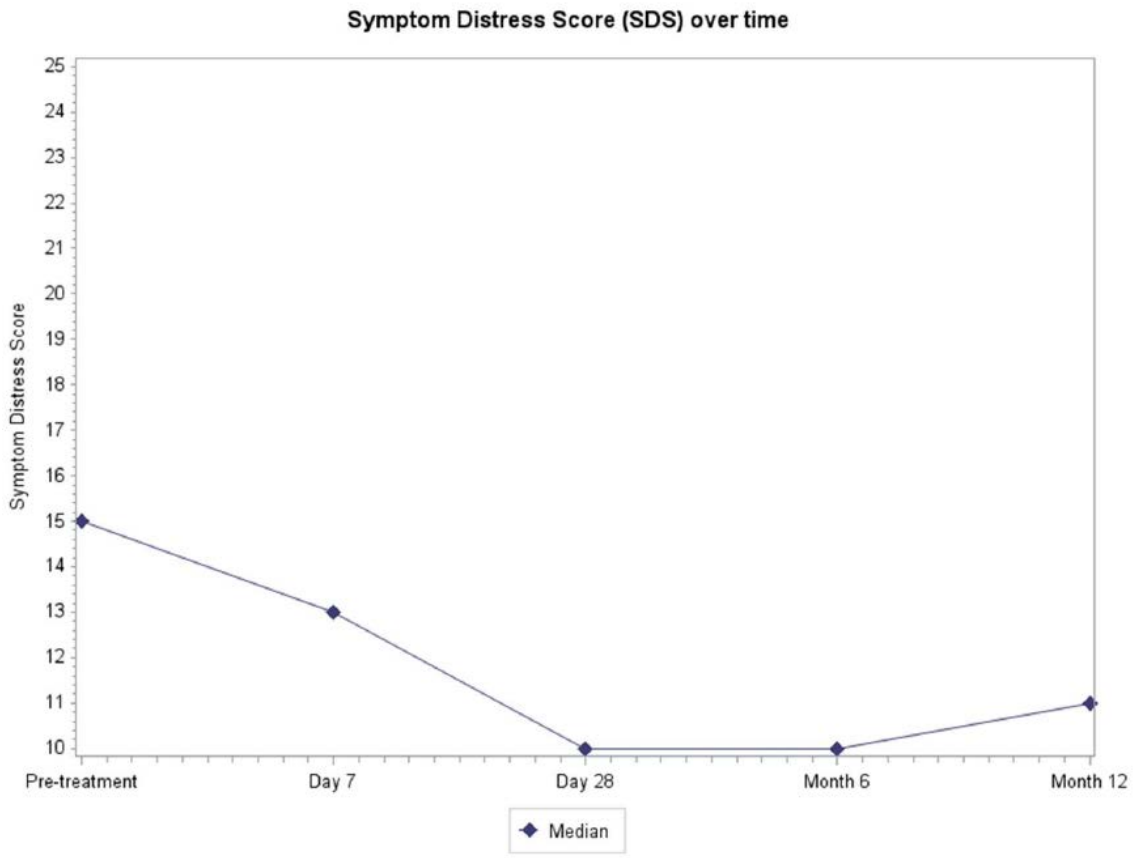

Figure 4: SDS over time.

PROMIS Pediatric Pain Interference

The Pediatric PROMIS Pain Interference short form was designed to measure the impact of pain on different aspects of life in pediatric patients between 8 and 17 years of age. Raw scores are converted to standardized t scores with a possible ranging from 34 to 78, a mean of 50, and a standard deviation of 10.

Paired T-test between mean score at pre-treatment and mean at 12 month follow-up:

- Difference between means = 20.24; 95% CI: (12.9250, 27.55), p = 0.0003.

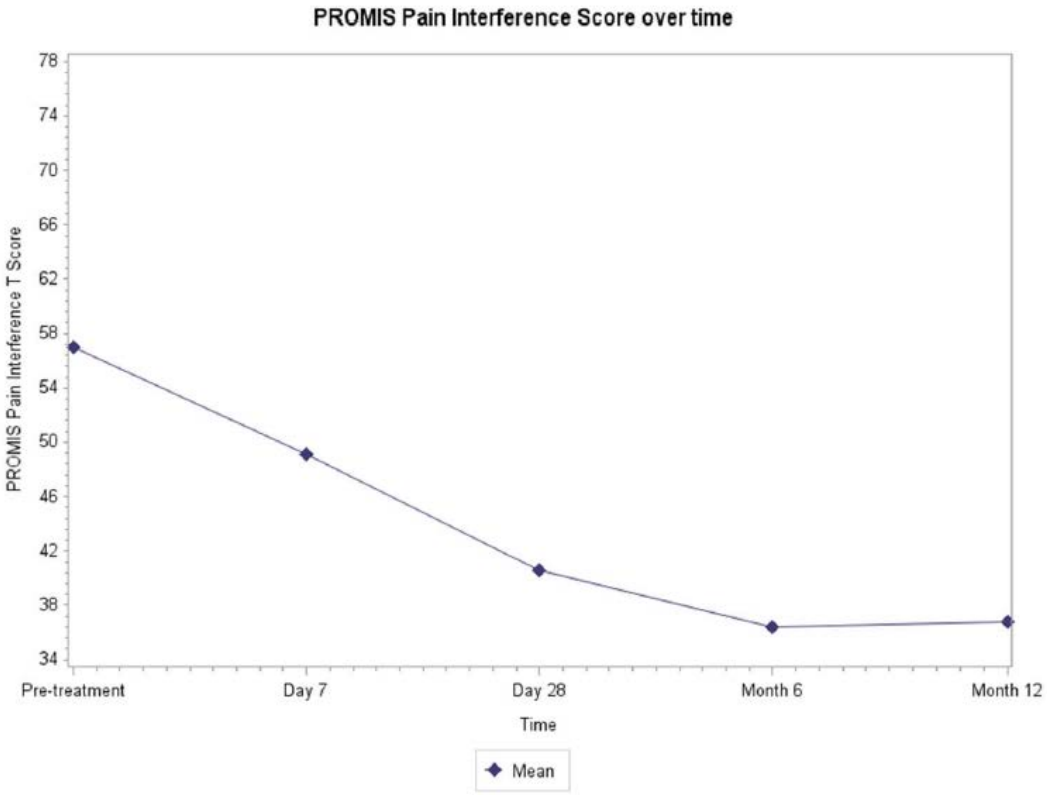

Figure 5: PROMIS over time.

Pediatric Quality of Life Inventory (PedsQL v 4.0)

These inventories consist of 4 scales: physical health scale, emotional health scale, social health scale, and school functioning scales. Each item is scored on a 5 point Likert scale from 0 (Never) to 4 (Almost Always).

The raw Total Scale Score is the mean of all the items in the entire inventory. The median of all patient and parent total scale scores were taken at each time point. The patient score decreased significantly over time.

Non-parametric trend test between Median Total Scale Score and Time

- Kendall tau-b correlation coefficient for patient score = -0.52619; p <0.0001
- Kendall tau-b correlation coefficient for parent score = -0.44769; p= 0.0011

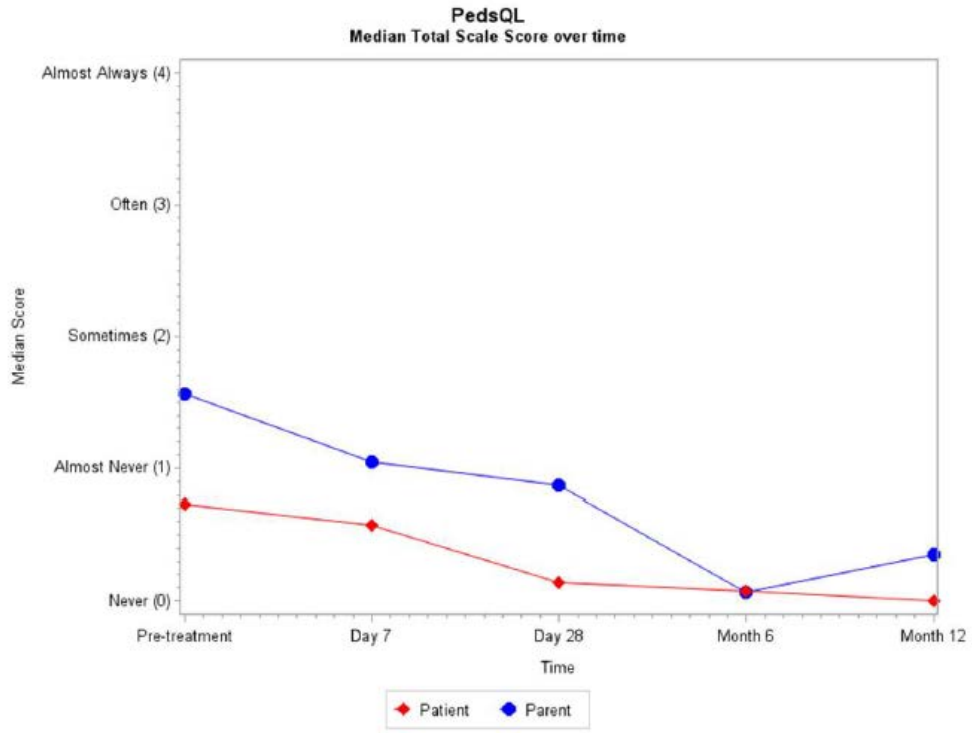

Figure 6: PedsQL over time.

PedsQL - Physical Health Summary Score

The Physical Health Summary Score is the mean of the items on the Physical Functioning Scale. The median patient and parent scores were taken at each time point.

Non-parametric trend test between Median Physical Health Summary Score and Time

- Kendall tau-b correlation coefficient for patient score = -0.55324 ($p < 0.0001$).
- Kendall tau-b correlation coefficient for parent score = -0.45349 ($p = 0.0025$).

PedsQL - Psychosocial Health Summary Score

The Psychosocial Health Summary Score is the mean of all of the items in the Emotional, Social, and School Functioning scales.

Non-parametric trend test between Median Psychosocial Health Score and Time

- Kendall tau-b correlation coefficient for patients = -0.44889 ($p = 0.0004$).
- Kendall tau-b correlation coefficient for parents = -0.36264 ($p = 0.0093$).

PedsQL - Item Scores driving change in total score and summary scores

For patient respondents, the items in the physical health summary score which had the highest median scores were "participating in a sports activity or exercise" (median =3 or

"often"), running (median = 2 or "sometimes"), and having hurts or aches (median = 2 or "sometimes"). The psychosocial item with the highest median score at pre-treatment was "trouble sleeping" on the emotional scale (median = 2, "sometimes").

For parent respondents the items in the physical functioning scale which had the highest median scores at pre-treatment were "Having hurts/aches" (median = 4 "almost always"") "Participating in sports activity or exercise" (median = 3.5 between "often" and "almost always"), "Walking more than one block" (median 3 "often"). The psychosocial items which had the highest median scores at pre-treatment were "feeling angry" (median =2 "sometimes"), "trouble sleeping" (median =2 or "sometimes), "worrying about what will happen" (median =2 or "sometimes") on the emotional scale; and "forgetting things" (median =2 or "sometimes) in the school scale.

Summarized below are problems with "participating in sports activity or exercise" "running" "walking" and "having hurts or aches" items.

Non-parametric trend test between Median "Problems with participating in sports activity or exercise" item

- Kendall tau-b correlation coefficient for patients = -0.57374 ($p < 0.0001$).
- Kendall tau-b correlation coefficient for parents = -0.35766 ($p = 0.0206$).

Non-parametric trend test between Median "Problems with running" item

- Kendall tau-b correlation coefficient for patients = -0.46077 ($p < 0.0009$).
- Kendall tau-b correlation coefficient for parents = -0.41448 ($p = 0.0057$).

Non-parametric trend test between Median "Problems with walking" item

- Kendall tau-b correlation coefficient for patients = -0.4622 ($p = 0.0011$).
- Kendall tau-b correlation coefficient for parents = -0.31132 ($p = 0.0430$).

Non-parametric trend test between Median "Having hurts or aches" item

- Kendall tau-b correlation coefficient for patients = -0.49164 ($p = 0.0004$).
- Kendall tau-b correlation coefficient for parents = -0.48080 ($p = 0.0013$).

Non-parametric trend test between Median "Problems with Trouble Sleeping" item

- Kendall tau-b correlation coefficient for patients = -0.48242 ($p = 0.0006$).
- Kendall tau-b correlation coefficient for parents = -0.41573 ($p = 0.0060$).

Summary of results

Clinical response showed significant overall improvement ($P = 0.0002$, Friedman). Pain resolution was shown as median VAS score, which decreased from 6 to 0 ($P < 0.01$, Dunn

post hoc test) by day 28 after HIFU treatment. There was clear reduction in NSAID use; 8 of 9 patients were no longer taking medication after HIFU therapy. Furthermore, patients reported improvement in sleep quality following treatment. Pain-associated sleep interruption decreased significantly following MR-HIFU ablation (P = 0.0013, Friedman). The number of patients with pain-related sleep disruption decreased from 8 to 1.

Conclusion:

The results show that MR-HIFU ablation of painful osteoid osteoma can provide a complete clinical response and lasting pain resolution. No serious treatment-related adverse events were observed in any of the 9 patients who underwent MR-HIFU. All treatments were performed on an outpatient basis without overnight admission. The minor focal bruising due to inadequate padding at edges of the HIFU treatment window can be addressed by ensuring that adequate padding and careful positioning are applied.

MR-HIFU ablation was feasible in all 9 patients who consented to this treatment. The single patient with partial clinical response following MR-HIFU ablation had an osteoid osteoma located in the medullary cavity of the femur, rather than the cortex. Post treatment MRI in this patient showed that periosteal nerves were ablated but the nidus remained viable. This explains partial improvement but not complete resolution of symptoms in this patient at the 1- month follow-up. This patient later underwent RFA. On the other hand, one patient who had previously undergone unsuccessful surgical resection and RFA demonstrated a complete clinical response after MR-HIFU ablation.

Pediatric Extrapolation

In this HDE application, existing clinical data was not leveraged to support approval of a pediatric patient sub-population. Pediatric data was generated by the clinical investigation to support the indicated osteoid osteoma patient population.

XI. FINANCIAL DISCLOSURE

The Financial Disclosure by Clinical Investigators regulation (21 CFR 54) requires applicants who submit a marketing application to include certain information concerning the compensation to, and financial interests and arrangement of, any clinical investigator conducting clinical studies covered by the regulation. The clinical study included 11 investigators. None of the clinical investigators had disclosable financial interests/arrangements as defined in sections 54.2(a), (b), (c), and (f). The information provided does not raise any questions about the reliability of the data.

XII. SAFETY AND PROBABLE BENEFIT ANALYSIS

A. Probable Benefit Conclusions

The clinical results supports the probable benefit of Sonalleve MR-HIFU for the ablation of painful osteoid osteoma. All treatments were performed on an outpatient basis without

overnight admission. The treatment is feasible and can provide a complete clinical response and lasting pain resolution. Nine subjects (7 male, 2 female; 16 ± 6 years) were treated with MR-HIFU without technical difficulties or any serious adverse events. There was a significant decrease in their median pain scores 4 weeks within treatment (6 vs 0, P < .01). Total cessation of analgesics was achieved in 8 of 9 patients after 4 weeks.

There is statistical evidence supporting the effect of the treatment. This can be observed in each of the pain Visual Analogue Scale (VAS), Symptom Distress Scale (SDS), Patient-Reported Outcomes Measurement Information System (PROMIS) score and Pediatric Quality of Life Inventory (PedsQL) scales. The majority of HIFU-treated patients exhibited complete response, i.e., complete symptom resolution. Clinical response is comparable with standard of care treatment with low reintervention. This study shows that MR-HIFU treatment of osteoid osteoma refractory to medical therapy is feasible and can provide probable benefit to patients.

B. Safety Conclusions

No serious treatment-related adverse events were observed in any of the 9 patients who underwent Sonalleve MR-HIFU System treatment. The reported device-related adverse events are acceptable and not unexpected. Non-serious adverse events (i.e., minor complications) reported for Sonalleve MR-HIFU OO therapy in scientific literature were few in number and transitory in nature, and included mild swelling, mild stiffness, skin redness, and minor bruising related to inadequate tabletop padding. The mild and moderate adverse events such as fatigue and muscle pain are transient.

While a low risk for potential heat-related nerve or skin damage exists with HIFU, this risk can be mitigated through the use of MRI thermometry that provides real time temperature maps of both the target region as well as nearby vulnerable structures such as neurovascular bundles. This is corroborated by a meta-analysis review of available literature reporting no serious adverse events, and only very few non-serious adverse events, for 117 MR-HIFU treated OO patients in the scientific literature.

The minor focal bruising due to inadequate padding at edges of the HIFU treatment window can be addressed by ensuring that adequate padding and careful positioning are applied. In addition, the Sonalleve MR-HIFU system includes a Direct Skin Cooling Device (DISC) to maintain low skin temperatures during HIFU therapy, further mitigating the risk for skin burns.

C. Probable Benefit-Risk Conclusions

The treatment of Osteoid Osteoma using Sonalleve reported no serious adverse events during the study. The mild and moderate adverse events are transient and resolved uneventfully. The probable benefit outweighs the probable risk of injury from Sonalleve use in osteoid osteoma therapy, taking into account the probable risks and benefits of currently available devices or alternative forms of treatment. An important difference compared to CT guided radiofrequency ablation (RFA) is that MR-HIFU is non-invasive

and free from ionizing radiation whereas RFA ablation is an invasive procedure with exposure to ionizing radiation, which can have potential long-term negative effects, especially for growing children.

Patient Perspective

Patient perspectives considered during the review included:

> This submission either did not include specific information on patient perspectives or the information did not serve as part of the basis of the decision to approve or deny the HDE for this device.

The clinical data support reasonable assurance of the safety and probable benefit of the Sonalleve HIFU system in a pediatric and young adult population with osteoid osteoma.

D. Overall Conclusions

The extent of uncertainty is moderate due to:

- A small number of treated subjects with treatments limited to the extremities;
- Absence of a prespecified study protocol including prespecified study endpoints, enrollment criteria, protocolized treatments, and follow-up requirements;
- The potential for selection bias because survey completion by operators was voluntary;
- A single arm dataset without a concurrent or a historical control group or a prespecified performance goal;
- Absence of blinded adjudication of events using prespecified event definitions; and
- Limited follow-up information on treated patients.

The data in this application support the reasonable assurance of safety and probable benefit of this device when used in accordance with the indications for use. The Sonalleve MR-HIFU System can effectively ablate osteoid osteomas, the probability of harm is low (per the limited clinical data), and the totality of the clinical information provides a reasonable assurance of safety and probable benefit.

Therefore, it is reasonable to conclude that the probable benefit to health from using the device for the target population outweighs the risk taking into account the probable risks and benefits of currently available devices or alternative forms of treatment when used as indicated in accordance with the directions for use.

XIII. PANEL RECOMMENDATION

This HDE was not taken to a meeting of the Orthopedics and Rehabilitation Devices Panel because the HDE did not raise any unanticipated safety issues and raised no new clinical issues with respect to currently available devices of similar technology.

XIV. CDRH DECISION

CDRH has determined that, based on the data submitted in the HDE, the Sonalleve MR-HIFU System will not expose patients to an unreasonable or significant risk of illness or injury and the probable benefit to health from using the device outweighs the risks of illness or injury. CDRH issued an approval order on November 27, 2020.

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

XV. APPROVAL SPECIFICATIONS

Directions for use: See the device labeling.

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

Post-approval Requirements and Restrictions: See approval order.

XVI. REFERENCES

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