FDA Executive Summary

Prepared for the

Fall 2024 review by the

FDA's Pediatric Advisory Committee

Sonalleve MR-HIFU

(H190003)

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I. INTRODUCTION

In accordance with the Pediatric Medical Device Safety and Improvement Act, this review provides a safety update based on the post-market experience with the use of the Sonalleve MR-HIFU (Magnetic Resonance – High Intensity Focused Ultrasound) device as a treatment for osteoid osteomas in the extremities of pediatric patients.

The Sonalleve MR-HIFU System is designed to non-invasively deliver acoustic energy to targeted anatomy. The system combines a high energy ultrasound transducer, a MR imaging system, and a targeting system to deliver position and time-controlled ultrasound energy. The focused ultrasound energy raises tissue temperatures until the targeted tissue is ablated. MR-guided HIFU treatment is an image-guided technique combining High Intensity Focused Ultrasound with real-time monitoring of temperature change during the sonication.

The purpose of this review is to provide the Pediatric Advisory Committee (PAC) with post-market safety data, so that the committee can advise the Food and Drug Administration (FDA) on any probable safety concerns associated with the use of this device in children. This executive summary will include summaries of the pre-market clinical study, post-market experience in an ongoing pivotal study, the peer-reviewed literature associated with the device, and post-market medical device reporting for adverse events. This executive summary provides updated information covering data from November 2021 to July 2024.

II. INDICATIONS FOR USE

The Sonalleve MR-HIFU System is intended to be used for the treatment of osteoid osteomas in the extremities.

III. BRIEF DEVICE DESCRIPTION

The Sonalleve MR-HIFU system (Figure 1) is designed to non-invasively deliver acoustic energy to prescribed locations. The system integrates a high intensity phased array focused ultrasound transducer with an MR-imaging 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 Therapy 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 Tablet 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 2) and its parts (see below) are located in the examination room within the patient environment.
    - Ultrasound transducer
    - Positioning mechanics
    - Matching electronics
    - Connector panel
    - Sonalleve Pelvis coil
    - Patient Emergency Stop Button
    - Pads, mattresses, and straps for patient positioning
    - Direct skin cooling device

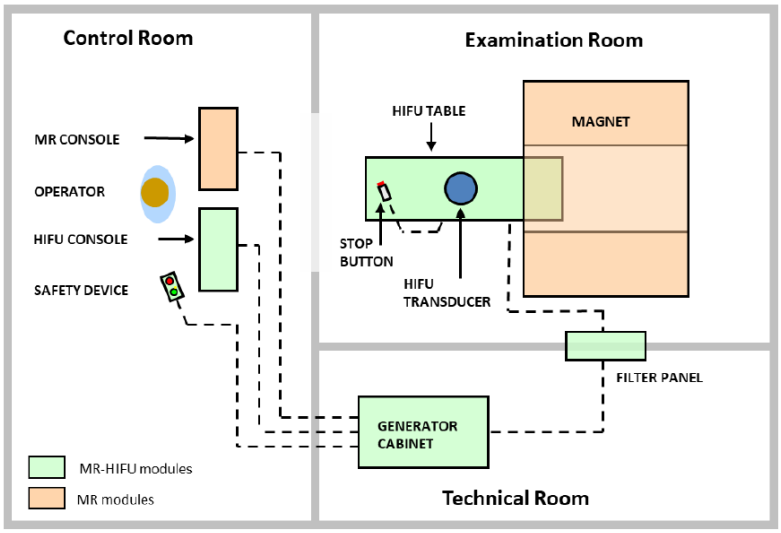

Figure 2: Schematic of main components of Sonalleve MR-HIFU System

- Sonalleve Generator Cabinet - The Sonalleve MR-HIFU Therapy 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 technical and examination 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.

IV. REGULATORY HISTORY

On December 18, 2018, the Sonalleve MR-HIFU received designation as a Humanitarian Use Device (HUD). On November 27, 2020, the Humanitarian Device Exemption (HDE) application was approved by the Center for Devices and Radiological Health of the Food and Drug Administration.

V. PRE-MARKET DATA: CLINICAL INVESTIGATION

Summary of Clinical Study:

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

The study was entitled "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 score and Pediatric Quality of Life Inventory (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.

Adverse Events

In total, 16 adverse events were reported in the Osteoid Osteoma study. No serious adverse events 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 within one week. The complete list of reported adverse events in the Osteoid Osteoma study is presented in Table 1 below:

Table 1: Reported adverse events in the Osteoid Osteoma study

Subject ID				
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

Summary of Results

Clinical response showed significant overall improvement (P = 0.0002, Friedman). Pain resolution was demonstrated by improvement in the median VAS score, which decreased from 2 to 0 (P < 0.01, Dunn post hoc test) by day 28 after HIFU treatment. The mean pre-treatment score was 2.8, and the mean score decreased to 0.4 at day 7, 0.2 at day 28, 0.3 at month 6, and 0.3 at month 12. 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. Additional patient reported outcome results are presented in the H190003 Summary of Safety and Probable Benefit (https://www.accessdata.fda.gov/cdrh_docs/pdf19/H190003B.pdf).

Conclusion

The results showed 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 assessment. This patient later underwent radiofrequency ablation (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.

VI. POST-MARKET DATA: ANNUAL DISTRIBUTION NUMBER

Section 520(m)(6)(A)(ii) of the Food, Drug, and Cosmetic Act (FD&C Act) allows HDEs indicated for pediatric use to be sold for profit as long as the number of devices distributed in any calendar year does not exceed the annual distribution number (ADN). On December 13, 2016, the 21st Century Cures Act (Pub. L. No. 114-255) updated the definition of ADN to be the number of devices "reasonably needed to treat, diagnose, or cure a population of 8,000 individuals in the United States." The approved ADN for Sonalleve is no more than 8,000 treated patients per year.

Per updated information provided for the reporting period between November 2022 and November 2023, Profound Medical Inc. has treated a total of 15 patients since initiation of a pivotal study for ablation of painful osteoid osteoma in children and young adults (ClinicalTrials.gov Identifier: NCT04658771) as approved in IDE G130041/S022. No serious adverse event or unanticipated device-related adverse event has been reported in this study.

An application for the Sonalleve MR-HIFU for the treatment of osteoid osteoma received CE mark in August 2020. No serious adverse events have been reported in the European Union (EU) for treatment of osteoid osteoma using the Sonalleve MR-HIFU.

No Sonalleve MR-HIFU devices have been shipped or sold since initial HDE approval.

VII. REVIEW OF SAFETY IN THE PEDIATRIC POPULATION

Purpose

In preparation for the FDA PAC 2024 fall meeting, a review of literature, ongoing clinical trials, and medical device reports (MDRs) was conducted to address the following question: what adverse events are reported in the literature associated with the use of MR-HIFU for any indication in the pediatric population (<22 years old).

Methods

1. A PubMed, Google Scholar, and web-search literature search was performed covering the period between 2013 and July 15, 2024. The HDE was approved on November 27, 2020.
2. In addition, ongoing clinical trials (ClinicalTrials.gov) were also reviewed regarding the status of MR-HIFU osteoid osteoma studies, as well as any available interim information on adverse events that may have been reported for these ongoing studies.
3. We requested information from the study's (IDE G130041/S022/NCT04658771) Principal Investigator regarding ongoing clinical experience with the device with particular focus on safety and adverse events.
4. We reviewed MDRs, data generated from post-market studies, and information (whether published or unpublished) relevant to device safety and labeling (contraindications, warnings, precautions, and adverse events) (please refer to Section VIII).

Discussion

A literature search yielded the following distribution of relevant articles by year for a total of 40 articles: 2013 (1), 2014 (1), 2015 (1), 2016 (2), 2017 (3), 2018 (4), 2019 (4), 2020 (3), 2021 (8), 2022 (4), 2023 (1), and 2024 (8). Published clinical studies and reviews reported favorable treatment outcomes with no significant safety concerns.

Six clinical studies of MR-HIFU for osteoid osteoma were identified in the ClinicalTrials.gov database (3 active, 2 completed, and 1 of "unknown status"). Further details regarding these studies are provided in Table 2 below. The Principal Investigator for NCT04658771 reported closure of trial enrollment on June 13, 2024, due to funding limitations but the study remains

open for data analysis and publication of results. NCT04658771 enrolled a total of 16 subjects and treated 15 (1 screen failure). The final three subjects were enrolled in 2023. The most common adverse events that could be related to treatment (bone pain, muscle cramping) resolved with one exception. One other trial (NCT02923011) is active in the United States with an anticipated completion date of December 31, 2024.

Table 2: Related Clinical Studies (ClinicalTrials.Gov)

#	Title	Status	Study Results	Last Update	Study Completion	Locations	Study Number
1	MR-HIFU Treatment of Painful Osteoid Osteoma	Active, not Recruiting	No Results Posted	01/25/24	06/30/25*	Children's National Hospital, Washington, District of Columbia, United States	NCT04658771
2	Comparative Effectiveness of MRgFUS Versus CTgRFA for Osteoid Osteomas	Recruiting	No Results Posted	07/17/23	12/31/24*	Stanford Medical Center, Palo Alto, California, United States | UCSF Imaging Center, San Francisco, California	NCT02923011
3	Safety and Feasibility of MR-Guided High Intensity Focused Ultrasound (MR-HIFU) Ablation of Osteoid Osteoma in Children	Completed	No Results Posted	03/11/22	10/03/20	Children's National Hospital, Washington, District of Columbia, United States	NCT02349971
4	MRI-guided Focused Ultrasound: Feasibility Study for the Treatment of Bone Metastases and Osteoïd Osteoma	Recruiting	No Results Posted	05/17/23	06/01/24*	CHU de Strasbourg, Strasbourg, France	NCT04803773
5	MR-Guided High Intensity Focused Ultrasound for Pain Management Of Osteoid Osteoma & Benign Bone Tumors in Children and Adults	Completed	No Results Posted	05/03/24	10/18	The Hospital for Sick Children, Toronto, Ontario, Canada	NCT02618369
6	Non-invasive Focal Therapy for Osteoid Osteoma	Unknown status	No Results Posted	11/27/14	12/15	Alessandro Napoli, Rome, Italy	NCT02302651

*Estimated

Conclusion

Three clinical trials are active and should be completed by 2026. Our review identified no new safety concerns or signals.

VIII. MEDICAL DEVICE REPORTS

Overview of Manufacturer and User Facility Device Experience Database

Each year, the FDA receives several hundred thousand MDRs of suspected device-associated deaths, serious injuries, and malfunctions. The FDA database houses MDRs submitted to the FDA by mandatory reporters (manufacturers, importers, and device user facilities) and voluntary reporters such as health care professionals, patients, and consumers. The FDA uses MDRs to monitor device performance, detect potential device-related safety issues, and contribute to benefit-risk assessments of these products. MDRs can be used effectively to:

- Establish a qualitative snapshot of adverse events for a specific device or device type
- Detect actual or potential device problems used in a "real world" setting/environment, including:
    - Rare, serious, or unexpected adverse events
    - Adverse events that occur during long-term device use
    - Adverse events associated with vulnerable populations
    - Off-label use
    - Use error

Although MDRs are a valuable source of information, this passive surveillance system has limitations, including the potential submission of incomplete, inaccurate, untimely, unverified, or biased data. In addition, the incidence or prevalence of an event cannot be determined from this reporting system alone due to potential under-reporting of events and lack of information about frequency of device use. Because of this, MDRs comprise only one of the FDA's several important post-market surveillance data sources. Other limitations of MDRs include, but are not necessarily limited to:

- MDR data alone cannot be used to establish rates of events, evaluate a change in event rates over time, or compare event rates between devices. The number of reports cannot be interpreted or used in isolation to reach conclusions about the existence, severity, or frequency of problems associated with devices.
- Confirming whether a device actually caused a specific event can be difficult based solely on information provided in a given report. Establishing a cause-and-effect relationship is especially difficult if circumstances surrounding the event have not been verified or if the device in question has not been directly evaluated.
- MDR data are subject to reporting bias, attributable to potential causes such as reporting practice, increased media attention, and/or other agency regulatory actions.
- MDR data do not represent all known safety information for a reported medical device and should be interpreted in the context of other available information when making device-related or treatment decisions.

MDRs Associated with the Sonalleve MR-HIFU Device

An MDR search for the product code 'QND' (associated with the Sonalleve device), for 'Sonalleve' and 'Profound' in the MDR database did not result in any MDRs for the device.

MDR Summary

The MDR search raised no new safety concerns.

IX. SUMMARY

As of July 2024, Profound Medical Inc. has enrolled sixteen patients, with one screen failure, in an ongoing pivotal study. Fifteen patients have received seventeen treatments (in total) including two re-treatments. This approved pivotal study is for treatment of painful osteoid osteoma in children and young adults (Osteoid Osteoma phase II). Our review of the published literature, ongoing clinical studies, and received MDRs since the time of approval of the HDE has not identified any new or unexpected risks for the pediatric population when compared to the pre-market data.

FDA concludes that the Sonalleve MR-HIFU device intended to be used for the treatment of osteoid osteomas in the extremities does not pose an unreasonable or increased risk of illness or injury, and that the probable benefit to health continues to outweigh the risk of injury or illness. Accordingly, FDA recommends continued surveillance and will report the following to the PAC in 2025:

- Annual distribution number
- Literature review
- Ongoing studies
- MDR review