FDA Executive Summary

Prepared for the

Fall 2022 review by the

FDA's Pediatric Advisory Committee

H190003

Sonalleve MR-HIFU

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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, the peer-reviewed literature associated with the device, and post-market medical device reporting for adverse events. As this executive summary is the first report of the Sonalleve MR-HIFU device to the PAC since approval, the annual report data provided by the company covered a single year period (November 27, 2020 to November 23, 2021). The next safety review prepared for the PAC will attempt to include data covering a period from November 2021 to approximately 4-6 months prior to the respective PAC meeting, consistent with other HDE safety reviews for the PAC.

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

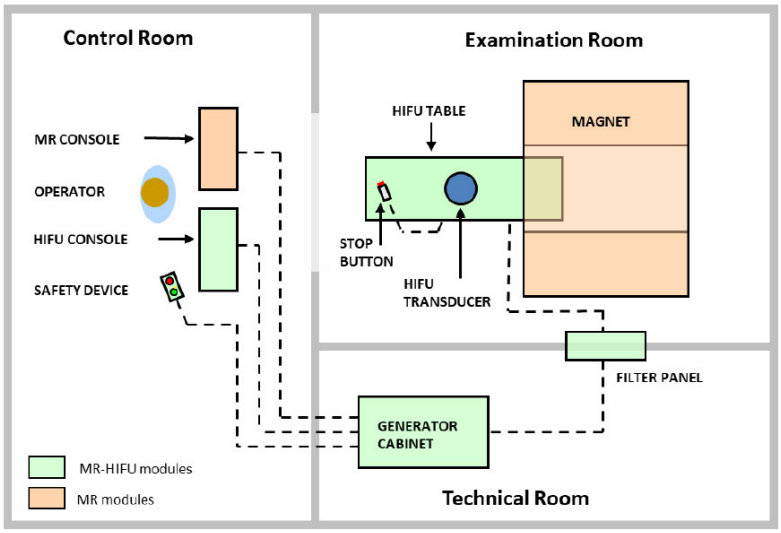

Figure 2: Schematic of main components of Sonalleve MR-HIFU System

- 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, 15 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:

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

Table 1: Reported adverse events in the Osteoid Osteoma study

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 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. 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.

For the annual reporting period between November 27, 2020, and November 23, 2021, Profound Medical Inc. treated a total of 6 additional patients under 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. All reported adverse events in these six patients were unlikely related or not related to the investigational device.

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.

VII. SYSTEMATIC LITERATURE REVIEW OF SAFETY IN THE PEDIATRIC POPULATION

Purpose

In preparation for the FDA PAC 2022 fall meeting, a literature review 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

A PubMed, Google Scholar, and Websearch literature search was performed covering the period between 2013, the first year in which FDA is aware of this technology being used for this indication as reported in literature, and May 2022. The HDE was approved on November 27, 2020. In addition, ongoing clinical trials (clinicaltrials.gov) were also reviewed.

Discussion

A literature search yielded the following distribution of articles by year for a total of 29 articles: 2013 (1), 2014 (1), 2016 (2), 2017 (3), 2018 (4), 2019 (4), 2020 (3), 2021 (7), and 2022 (4). Six clinical studies were identified in the ClinicalTrials.Gov database. Finally, information describing the applicant's clinical experience with the device since HDE approval was requested including safety, medical device reports (MDRs), data generated from post-market studies, and information (whether published or unpublished) that affects an evaluation of the safety of the device or that affect the statement of contraindications, warnings, precautions, and adverse reactions in the device's labeling.

Conclusion

Several clinical trials are enrolling. However, there were no recent newly published trial data and no newly reported safety concerns, or signals identified within the literature review.

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, conducted up to May 2022, did not result in any MDRs for the device.

MDR Summary

The MDR search raised no new safety concerns.

IX. SUMMARY

During the period between November 27, 2020, and November 23, 2021, Profound Medical Inc. treated a total of 6 additional patients under an approved pivotal study. Our review of the published literature and received MDRs for this HDE has not identified any new or unexpected risks for the pediatric population when compared to the pre-market data. Based on the available data, and considering the probable benefits and risks, FDA believes that the HDE remains appropriately approved for pediatric use.

Accordingly, FDA recommends continued surveillance and will report the following to the PAC in 2023:

- Annual distribution number
- Literature review
- MDR review