AXON - SPINERY™

Clinical Study of SPINERY A novel Radio-Frequency Tumor Ablation Device for Spine Metastatic Tumors

(SPARTA STUDY)

Protocol #2020-01 (EU)

STUDY PROTOCOL

Version 7.0 – March 29th, 2022

Sponsor: Axon srl

Via Lepanto 84, 80045 Pompei (NA) – Italy

Summary of revision history

Revision	Date	Description
1.0	14 December 2020	Initial release
2.0	21 June 2021	a. Correction of clerical error in the primary safety endpoint b. Modified par. 6.1 replacing "Interim Analysis" with "Clinical Study Reports" c. Modified par. 6.3.2 with clarification and justification of exclusion criteria d. Modified par. 6.4.3 specifying actions to promote attendance of subjects to follow-up visits e. Modified par. 6.4.4 with clarification concerning device-related adverse events management f. Modified par. 6.5.2 giving details concerning reasons for withdrawal of participants from study treatment g. Modified par. 10.1 specifying that analysis will be performed according to Intention-to-treat principle h. Modified par. 10.4 replacing "Interim Analysis" with "Clinical Study Reports" i. Modified ANNEX 1 replacing Investigator Ospedale Santissima Trinità "Dr. Stefano Marcia" with "Dr. Stefano Marini" and his related email address.
3.0	6 August 2021	a. General revision of device denomination; b. Revision of monopolar needle codes and of components naming (drill and trocars) in par. 3;
4.0	8 October 2021	a. Modified par. 2, 4 and 6 to align SPINERY intended purpose and clinical study objectives. b. Modified exclusion criteria n°10 in the Synopsis and in par. 6.3.2 c. Modified Table A - Schedule of Visits and in par. 6.4.3, added the control of Concomitant pain medication at 1 Month follow-up d. Added par. 6.3.3 "Vulnerable populations" e. Added in par. 6.4.4 "Concomitant pain medications" info related to evaluation of concomitant pain medications f. Correction of clerical error in par. 6.4.4 "Brief Pain Inventory - BPI" g. Modified par. 6.5 "End of Trial" specifying time and duty of the Sponsor h. Modified par. 8.1.1 "Adverse Event", par. 8.1.2 Adverse Device Effect", par. 8.1.4 "Severe Adverse Event", par. 8.1.5 "Severe Adverse Device Effect", added par. 8.1.3 "Unanticipated Adverse Device Effect", par. 8.1.6 "Unanticipated Severe Adverse Effect" and par. 8.1.7 "Device Deficiency and Malfunction" i. Modified par. 8.2.2 "Reporting of a SAEs/ SADEs/ UADEs" to comply with national and european Regulations

		j. Modified par. 8.2.3 “Specific Adverse Device Effect” with indication to how minimize the risk of the study k. Modified Chapter 14 “Abbreviations” inserting OMED (Oral Morphine Equivalent Dose) l. Modified Chapter 15 “References”adding the following reference: “Patrick, D.L., Cleeland, C.S., von Moos, R. et al. Pain outcomes in patients with bone metastases from advanced cancer: assessment and management with bone-targeting agents. Support Care Cancer23, 1157–1168 (2015)”
5.0	1 December 2021	a. Added in Chapter 2 “Background and Rationale” more bibliography indications related to the the comparable efficacy of RF in pain reduction respect the standard therapy. b. Modified cap. 8.2.2 “Reporting of a SAEs/ SADEs/ UADEs” with correct indication of national regulations MDCG 2020-10/1 c. Added in Chapter 14 “Abbreviation” RT such as Radiotherapy d. Added in Chapter 15 “References” the new references mentioned in Chapter 2.
6.0	21 January 2022	a. Several minor editorial changes all over the text b. Revised the Investigational device description c. Added “Intended Purpose” (page 16) d. Added “Intended Clinical Performance” (page 16) e. Added table with expected dimensions of the ablated RF areas (page 17) f. Minor editorial changes to remove not-cooled monopolar needle (page 18) g. Updated “Primary Objectives” (page 19) h. Updated Inclusion Criteria (added points 2 and 3) with differentiation of two patients’ categories (page 23) i. Updated Inclusion Criteria (added point 4) with indication of the tumor size vs. RF ablation area (page 23) j. Updated Clinical Background and rationale (Chapter 2) k. Updated abbreviations (page 40) l. Updated references (page 41)
7.0	29 March 2022	a. Updated table with expected dimensions of the ablated RF areas (pag 17)

Statement of Confidentiality and Sponsor & Investigator Signatures

Study Title:	Clinical Study of SPINERY a novel Radio-Frequency Tumor Ablation Device for spine metastatic tumor ablation (SPARTA)
Protocol Number:	#2020-01 (EU)
Revision Number:	7.0
Date:	March 29th, 2022

I, the undersigned Investigator, am responsible for the conduct of the study at this site and agree to the following:

- I will conduct the study according to the protocol, the standard ISO 14155:2020, Good Clinical Practice, Declaration of Helsinki and all applicable regulatory authority requirements and national laws;
- I will not deviate from the protocol without prior written permission from the Sponsor and from the local and independent Ethics Committees, except where necessary to prevent any immediate danger to the subject;
- I have read and understand fully the Investigator's Brochure, and I am familiar with the investigational devices and their use according to this protocol;
- I have sufficient time to properly conduct and complete the trial within the agreed trial period, and I have available an adequate number of qualified staff and adequate facilities for the foreseen duration of the trial to conduct the trial properly and safely;

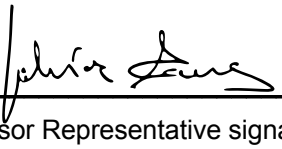
I will ensure, together with the Sponsor, that site personnel involved in the study conduct are adequately trained regarding the investigational devices, the present protocol and their responsibilities.

29/03/22 Mario Muto

Principal Investigator signature Date signed Printed name

Sponsor:

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



29/03/22 Salvatore Accardo

Sponsor Representative signature Date signed Printed name

1. SYNOPSIS

Title	**SPINERY A** novel **R**adio-Frequency **T**umor **A**blation Device Study (SPARTA)
Reference number	Protocol #2020-01 (EU)
Sponsor	Axon srl Via Lepanto 84, Pompei (NA) 80045 Italy
Version and date	Version 7 of March 29th, 2022
Investigational device	Axon SPINERY Radiofrequency Device with cooled bipolar and monopolar needles. SPINERY is a Radiofrequency (RF) device designed for local treatment of metastatic tumors localized in bone. The device is conceived to treat bone metastatic tumor areas using RF needles, with the aim of pain reduction. The RF needles are used single or in combinations to increase ablation efficacy. The SPINERY system consists in a RF generator connected to a 16G needle. The needles are bipolar or monopolar with cooling and equipped with two thermocouples (one distal to measure the center ablation temperature and one proximal to avoid hyperthermic damages to the healthy tissues. The procedure is conducted under Fluoroscopy imaging guidance.
Intended purpose	SPINERY is a Radiofrequency (RF) device designed for palliative treatment of patients with painful metastatic bone tumors involving vertebral bodies, sacrum, iliac crest and peri-acetabulum.
Intended clinical performance	SPINERY is a Radio-Frequency (RF) device designed for local treatments of metastatic bone tumors. In particular, SPINERY is conceived for: ● Pain reduction in patients affected by metastatic bone tumors involving the vertebral bodies, sacrum, iliac crest and peri-acetabulum, in patients with indication for Standard Therapy and in patients who have failed, not candidates or refuse Standard Therapy; ● Coagulation and ablation of bone tissue during interventional procedures including palliation of pain associated with metastatic lesions involving bone also in patients who have failed, not candidates or refuse Standard Therapy.
Principal investigator(s)	Prof. Mario Muto

	Azienda Ospedaliera di Rilievo Nazionale Antonio Cardarelli Via A. Cardarelli, 9 80131 Napoli (Italy)
Investigation site(s)	All sites are listed in Annex 1.
External organizations	CRO Advice Pharma Group Srl Address Via Giovanni Durando, 38 20158 Milano MI
Objectives and hypotheses	
Objective(s), primary and secondary	**Primary objectives:** 1. To demonstrate that SPINERY RF device is effective in short-term (3 months) pain reduction in patients affected by metastatic bone tumors involving the vertebral bodies, sacrum, iliac crest and peri-acetabulum with indication for standard therapy and in patients who have failed, not candidates or refuse standard therapy; 2. To demonstrate that SPINERY RF device is safe in the RF ablation treatment of metastatic bone tumors, without causing device-related adverse events including, in particular, nerve injury; **Secondary objectives:** 1. To demonstrate that SPINERY RF device is effective in long-term (up to 12 months) pain reduction in patients affected by metastatic bone tumors in the areas of vertebral bodies (thoracic and/or lumbar), sacrum, iliac crest and peri-acetabulum; 2. To demonstrate safety in relation to usability; 3. To demonstrate the procedural performance in terms of a short learning curve.
Hypotheses, primary and secondary	Primary hypothesis: - BPI Brief Pain Inventory scale performance in terms of palliative treatment: H0: $\mu c = 0$ HA: $\mu c \neq 0$ Where μc is the mean change from baseline to the 3-month visit in worst-pain score. No formal hypotheses for the remaining objectives.
Risks and anticipated adverse device effects to be assessed	Risks of innovative device SPINERY are the same of the state-of-the-art technology: - Carbonization - Post-operative pain

	- Limited/uncomplete treatment due to anatomical peculiarities - damage to surrounding tissue through iatrogenic injury - Nerve injury including thermal injury, puncture of spinal cord or nerve roots potentially resulting in radiculopathy, paresis, and paralysis - Pulmonary embolism - Hemothorax or pneumothorax - Infection - Unintended puncture - Hemorrhage - Hematoma
Design of the clinical investigation	
Clinical development stage	Pivotal confirmatory. Justification: pre-market study for demonstration of conformity of the device with the Essential Requirements for CE-marking.
Design type	Prospective, Single arm, Multicenter
Control group	No control group
Comparator (control device or treatment)	No comparator, on the other hand the clinical outcomes of this palliative treatment will be compared with the clinical data obtained with similar devices in similar clinical conditions.
Measures to minimize/avoid bias	- New technology bias is minimized through an adequate training to the Medical Operator - Low statistical bias is minimized through an adequate estimate of the number of patients in the treatment group as compared to the state of the art - Multicentric study to minimize usability bias
Primary endpoint(s)	- Change of Worst Pain Score expressed as average reduction of 2 BPI (Brief Pain Inventory) scores: Thoracic/Lumbar/ Peri-acetabulum/Iliac Crest/Sacrum RF Ablation [Time Frame: Baseline, 3 months]. Change in pain will be calculated as: μc = worst-pain 3-month – worst-pain baseline A negative average value for change in pain represents a lowering of the subject's pain score (an improvement, or reduction in pain) and a positive value represents an increase in the subject's pain score (a worsening or increase in pain). Worst pain score at the target treatment site will be collected from the BPI in the past 24 hours. - Completion (%) of the ablation procedure without device-related adverse events including in particular nerve injury [Timeframe: Post-procedure, 3 months]. All the analyses will be performed according to ITT and PPT principle.

Secondary endpoint(s)	- Change of Worst Pain Score: Thoracic/Lumbar/ Peri-acetabulum/Iliac Crest/Sacrum RF Ablation [Time Frame: 1 month, 12 months]. Worst pain score at the target treatment site will be collected at each timepoint from the Brief Pain Inventory (BPI) in the past 24 hours. - Usability endpoint: Technical success (ability to perform access to treatment site and perform ablation) and procedural success (ability to perform access to treatment site and perform ablation for one or more complete cycles as planned by the physician) without product specialist intervention [Timeframe: Post-procedure]; - Procedural endpoint: procedure time, number of procedural errors, number of procedural and technical success for the same surgeon [Time Frame: Post-procedure]; All analyses will be performed according to ITT and PPT principle.
Sample Size	52 subjects in a maximum of 10 sites
Follow-up	Baseline, Intra Procedure, Post procedure (within 24 hours), 1 month, 3 months and 12 months.
Duration of the clinical investigation	Upon obtaining informed consent, each subject will complete an Enrollment/Baseline visit, SPINERY procedure visit (Day 0), prior to discharge (within 24 hours), 1 month and 3 months clinic visits), and a final post-procedure study visit (12 months) for a total of 5 study related visits. The estimated time needed to enroll all subjects is approximately 6 months. The estimated time needed to obtain the CE Mark due to safe endpoints is 9 months (6 months for enrollment plus 3 months follow-up). The overall study duration, from first subject enrollment to last subject visit (including 12-month follow-up), is expected to last approximately 18 months. The completion of the study is defined as the approval of the Final Study Report and closure of all sites.
Inclusion criteria	1. Patients with painful metastatic malignant lesions involving bone; 2. Patients, candidates to standard therapy, in which the RF ablation can be performed in combination with the Standard Therapy in accordance with the Investigator's indications; 3. Patients who have failed, not candidates or refuse Standard Therapy (chemotherapy or radiotherapy); 4. Patients with metastatic tumor size compatible with the expected ablation dimensions as reported for SPINERY devices in the IFU;

	5. Patients with localized pain resulting from not more than two sites of symptomatic metastatic disease 6. Patients that do not have evidence of impending fracture 7. Patients with metastatic lesions targeted for treatment located in the thoracic and/or lumbar vertebral body(ies), peri-acetabulum, iliac crest, and/or sacrum - no restrictions on location of lesion; 8. Patients with BPI-Report worst pain score ≥4/10 at the target treatment site within the past 24 hours 9. Patients with Karnofsky score ≥ 40 at enrollment 10. Patients willing and able to provide a signed and dated informed consent, comply with the study plan, follow up visits and phone calls 11. Patients at least 18 years old at the time of informed consent
Exclusion criteria	12. Patients implanted with heart pacemaker or other implanted electronic device 13. Patients with previous mechanical bone stabilization in the vertebral body to be treated 14. Use of SPINERY in vertebral body levels C1-C7 15. Multiple myeloma, solitary plasmacytoma, or primary malignant lesions in the index vertebra or bone. 16. Active or incompletely treated local infection at the planned treatment site(s) and/or systemic infection. 17. Planned treatment site(s) accompanied by objective evidence of secondary radiculopathy or neurologic compromise. 18. Planned treatment site(s) associated with spinal cord compression or canal compromise requiring decompression. 19. Fractures due to prostatic cancer or other osteoblastic metastases to the spine. Metastatic lesions originating in the prostate that are osteolytic or of mixed origin are eligible for the study. 20. Pregnant, breastfeeding, or plan to become pregnant during the study duration. 21. Concurrent participation in another clinical study that may add additional safety risks and/or confound study results. 22. Any condition that would interfere with the subject's ability to comply with study instructions or might confound the study interpretation.

Table A - Schedule of Visits

	Enrollment Baseline	SPINERY Procedure (Day 0)[2]	Post-Procedure (within 24 hours)	1-Month Follow-up (±7 days)	3-Months Follow-up (±10 days)	12-Months Follow-up (±30 days)
Informed Consent Form[1]	X					
Inclusion/Exclusion Criteria	X					
Medical History with Demographics	X					
Physical Examination	X		X		X	
Karnofsky Performance Scale	X					
PI assessment of local tumor control (optional)		X		X	X	X
Concomitant pain medications	X	X	X	X	X	X
BPI (Short Form) – includes worst pain score in the past 24 hours	X			X	X	X
EQ-5D-5L[3]	X			X	X	X
Adverse Events Assessment	X	X	X	X	X	X
Deviations	X	X	X	X	X	X
Usability Assessment		X				
Tumoral lesion compatibility (clinical estimate)	X	X				

1) Informed consent must be obtained prior to performing any study-specific procedures.
2) Baseline Visit, Enrollment Visit and procedure can occur on the same day.
3) EQ-5D-5L is a standardized instrument for measuring generic health status

2. CLINICAL BACKGROUND AND RATIONALE

Painful bone metastases are a common cause of morbidity in patients with metastatic cancer, especially when combined with possible neural compression and pathologic fractures. Several solid cancers are associated with bone involvement, most often, prostate and breast, with 30% to 70% of cancer patients who develop bone metastases [1]. The skeletal system is the third most common site for cancer metastases, surpassed only by the lungs and liver. Many tumors, especially those of the breast, prostate, lungs, and kidneys, have a strong predilection to metastasize to bone, which causes pain, hypercalcemia, pathological skeletal fractures, compression of the spinal cord or other nervous structures, decreased mobility, and increased mortality. Metastatic cancer-induced bone pain is a type of chronic pain with unique and complex pathophysiology characterized by nociceptive and neuropathic components [2].

Falk et al. have studied the physiopathology of the cancer pain and especially the one caused by metastasis to bone, is a severe type of pain, and unless the cause and consequences can be resolved, the pain will become chronic. As detection and survival among patients with cancer have improved, pain has become an increasing challenge, because traditional therapies are often only partially effective. Until recently, knowledge of cancer pain mechanisms was poor compared with understanding of neuropathic and inflammatory pain states. Cancer-induced bone pain is a mixed-mechanism pain state exhibiting elements of both neuropathic and inflammatory pain, but with distinctive modifications to the tissue and nerves in the periphery as well as unique neurochemical changes at the spinal cord level. Thus, it is a complex syndrome involving inflammatory, neuropathic, ischemic, and cancer-specific mechanisms, often occurring at more than one site. Inflammatory infiltration occurs as a result of direct tissue damage caused by tumor growth as well as release of pain mediators by the cancer cells. The neuropathic component of the pain can result from cancer-induced damage to the sensory nerves caused by infiltration and/or compression by the tumor cells, tumor-induced hyperinnervation and stretching or denervation as the bone expands and degrades. In addition, neuropathy can arise as a subsequent consequence of therapeutic intervention, such as chemotherapy or surgery [3].

In the recent years many studies have been conducted to evaluate the efficacy of palliative pain treatments. Filippiadis et al. sustain that imaging-guided percutaneous techniques may act either indirectly or directly to provide significant pain alleviation and life quality improvement. Palliative treatment options include neurolysis, thermal ablation, bone consolidation, and high- intensity-focused ultrasound. Technical advantages of these procedures include the minimally invasive nature that can performed in the outpatient setting or with a short hospitalization, low complication rates, little to no interruption of systemic chemotherapy agents, and ability to combine with other palliative treatment options [4].

A number of different methods have been proposed for pain relief in cancer patients with bone metastases, including systemic analgesics, bisphosphonates, antitumor chemotherapy, radiotherapy, systemic radio-isotopes, local surgery and vertebroplasty [1,7,8], each one presenting with different indications, contraindications and complications.

Percutaneous, image-guided, "*in situ"* tumor ablation with a thermal energy source, such as a Radio-Frequency (RF), Laser or Microwave source, have been investigated for decades as an effective and minimally invasive approach in patients with a variety of primary and secondary malignant neoplasms, including tumors located

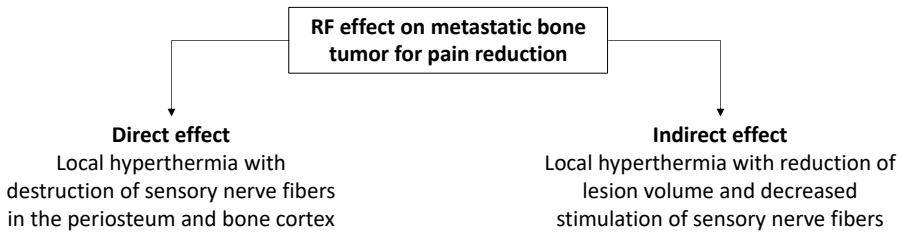
in the brain, musculoskeletal system, thyroid and parathyroid glands, pancreas, kidney, lung, liver, and breast [7]. This "*in-situ"* technique permits the destruction of tumors without necessitating their removal and in many cases can be used in place of more invasive and expensive surgical techniques. Moreover, the procedure can be performed in an outpatient setting, and gives a chance of treatment to patients who would not otherwise be considered candidates for surgery due to age, comorbidity, or extent of the disease [7].

Percutaneous radiofrequency (RF) ablation is an emerging, minimally invasive therapy for patients with metastatic bone disease who have not responded or have contraindications to radiotherapy [9]. The ablation probe, consisting of straight or expandable electrodes, is placed into the body through a sub-centimeter incision and directed into the tumor using imaging guidance. The electrodes deliver a high-frequency (375–500 kHz) alternating current into the lesion, which produces agitation of tissue ionic molecules that causes frictional heating (hyperthermia). Local tissue temperatures reach 60–100°C, causing protein denaturation and coagulative necrosis of the tumor.

The devitalization of tissues leads to a lowering of perceived pain both directly through the destruction of periosteal nociceptors and indirectly by reducing tumor bulk. In fact, the proposed mechanisms by which RF ablation decreases pain may involve pain transmission inhibition by destruction of sensory nerve fibers in the periosteum and bone cortex; reduction of lesion volume with decreased stimulation of sensory nerve fibers; destruction of tumor cells that are producing nerve-stimulating cytokines (tumor necrosis factor-alpha [TNF-α], interleukins, etc.) and inhibition of osteoclast activity [10,11,12].

The pain control in oncology is an important clinical element interconnected with the adopted therapy as stated in the ESMO and NCCN Guidelines. Increasing evidence in oncology are showing that survival is linked to symptom control and that pain management contributes to broad quality-of-life improvement. To maximize patient outcomes, pain management is an essential part of oncologic management [5,13].

Bagla et al. [14] in their clinical study treated 50 patients and performed RF ablation in thoracic and lumbar vertebral bodies. FACT-BP (Quality of Life test) improved from 22.6 to 38.9 ($p < 0.001$). No complications related to the procedure were reported. In conclusion the RF ablation with cement augmentation safely and effectively reduces pain and disability rapidly, while increasing quality of life in patients suffering from vertebral body metastases.



According to preliminary results by Dupuy et al. [15], RF ablation can provide palliative treatment for patients with painful osseous metastases. Later on, Callstrom et al. [16] reported positive results in the treatment of 12 patients with severe pain, related to osteolytic metastasis, in whom RT or chemotherapy had previously failed, concluding that RF ablation provides an effective and safe alternative method of pain palliation in patients with osteolytic metastases. A multicenter clinical study involving 43 patients with painful osseous metastases showed again significant reduction of pain and decrease in the use of opioids, with only minor complications

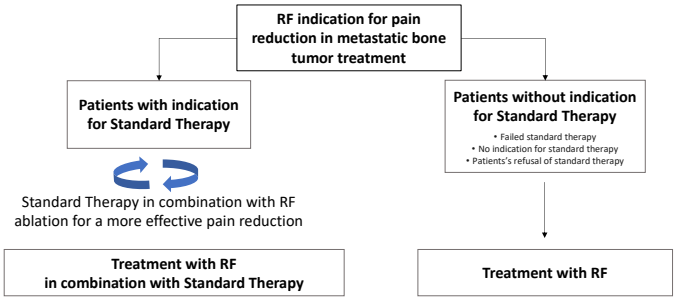
in patients with bone metastases who failed standard treatments [17]. Finally, CT-guided RF ablation proved to be effective for the treatment of painful bone metastases in a group of 30 patients. After treatment the authors observed a significant decrease, in the mean past-24-h, of Brief Pain Inventory (BPI) score for worst pain, average pain and pain interference during daily life (4.7, 4.8 and 5.3 units respectively) and a marked decrease (3 out of 30 patients at 4 and 8 weeks after treatment) in use of analgesics [9].

More recently Tomasian et al. [18] stated that in accordance with the latest NCCN Guidelines for adult cancer pain (version. 2019), thermal ablation may be considered for palliation of metastatic bone pain in the absence of an oncologic emergency when chemotherapy is inadequate and radiation therapy is contraindicated or not desired by the patient.

Many spinal tumors will continue to grow and cause pain after radiation therapy. Posterior vertebral body tumors will often progress and extend through the posterior cortex into the spinal canal, despite radiation therapy. As reported by Hillen et al. [18] RF ablation, in addition inducing pain relief, can often stop further progression of the posterior tumor extension and this RF technique does not hinder or delay the use of adjuvant therapies such as radiation therapy and may provide an alternative therapy for tumors not controlled with systematic chemotherapy or radiation therapy.

Other important works show the efficacy of RF even before RT. The study of Janjan [20] demonstrate that RT is active usually not before 6-8 weeks as analgesic and 10-12 weeks to recalcification. The author concludes saying that the treatment of painful metastases, the ablative treatment should be always performed before the RT because the analgesic effect of RF ablation is immediate compared to radiotherapy, whose undoubted effectiveness is usually obtained in the medium to long-term.

The same clinical evidences were observed by Di Staso [21] where 15 patients, treated with RF ablation followed by RT, were compared with a matched group (30 subjects) only treated by RT. Response at 12 weeks documented a pain relief in 53.3% and 16.6% of the subjects treated by RF-RT or RT respectively. The overall response rate at 12 weeks in pain relief was 93.3% in the group treated by RF-RT and 59.9% in the group treated by RT alone. Although recurrent pain was documented more frequently after RT (26.6%) than after RF-RT (6.7%) the results suggest that RF ablation before RT treatment is safe and more effective in pain reduction than RT alone.



In conclusion of this clinical literature review several aspects can be outlined in support to the role of RF ablation of metastatic tumors in bones with the aim to obtain a palliative pain reduction in patients:

1. The metastatic tumors of the vertebral bodies are very painful for the patients;
2. The RF ablation has been found to be effective, thanks to its local hyperthermia, destroying the sensory nerve fibers in the periosteum and bone cortex (direct effect);

3. The RF ablation has also an indirect effect expressed by the local reduction of the metastatic lesion reducing the stimulation of the sensory nerves;
4. The palliation of pain, obtained with RF ablation, is associated with a quick decrease in assumption of opioids and similar drugs for pain control;
5. The pain relief obtained by RF ablation is higher and pain is less recurrent than that one obtained with RT;
6. The RF ablation is also effective for the treatment of posterior vertebral body tumor expansion when standard therapy is not completely effective;
7. The RF ablation is clinically indicated for the pain relief in patients when the Standard Therapy fails, when it is contraindicated or when it is refused by the patient;
8. The RF ablation is clinically indicated in addition to RT since it promotes a faster pain symptoms relief without compromising the application of the Standard Therapy.

SPINERY is a Radio-Frequency (RF) device designed for local treatments of metastatic bone tumors.

The Intended Purpose is:

SPINERY is a Radiofrequency (RF) device designed for palliative treatment of patients with painful metastatic bone tumors involving vertebral bodies, sacrum, iliac crest and peri-acetabulum.

The SPINERY Intended Clinical Performance is:

- Pain reduction in patients affected by metastatic bone tumors involving the vertebral bodies, sacrum, iliac crest and peri-acetabulum, in patients with indication for Standard Therapy and in patients who have failed, not candidates or refuse Standard Therapy;
- Coagulation and ablation of bone tissue during interventional procedures including palliation of pain associated with metastatic lesions involving bone also in patients with indication for Standard Therapy who have failed, not candidates or refuse Standard Therapy.

The device is conceived to treat bone metastatic tumor areas using RF needles, with the aim of pain reduction. The RF needles are used single or in combinations to increase ablation efficacy. The SPINERY system consists in a RF generator connected to a handle carrying on a 16G needle. The RF needles are bipolar or monopolar with cooling and equipped with two thermocouples (one distal to measure the center ablation temperature and one proximal to avoid hyperthermic damages to the healthy tissues. The procedure is conducted under Fluoroscopy imaging guidance.

The peculiarity of this device is that, thanks to the availability of several accessories (electrodes), it provides physicians with the ability to plan the ablation volume in terms of shape and design a personalized shape and volume of the ablated area. This allows for a more individualized treatment, since a personalization of ablation area shape is not possible in the state of art technology, which allows only spherical ablation.

While the safety of the device is completely described thanks to compliance to international standards (safety tests reports and General Safety and Performance Requirements checklist are available as Annexes of Technical File on file at Axon), its clinical benefit needs further investigation on human subjects as the device is not completely equivalent to any other currently available on the market.

3. IDENTIFICATION AND DESCRIPTION OF THE INVESTIGATIONAL DEVICE

SPINERY is an active medical device intended for radiofrequency thermal ablation of metastatic bone tumors. SPINERY is a class IIb medical device as per rule 9 of Medical Device Regulation, annex VIII.

It is mainly composed by

- RF generator (Figure 1) for parameter control and treatment modulation; equipped with a peristaltic pump intended to allow the flow of cooling fluid inside RF electrode needles during ablation procedure. Footswitch is provided together with the generator.

Figure 1- SPINERY RF Generator

RF needle device composed by a handle with electrode needle (monopolar or bipolar) available in the following variants in order to offer an adequate treatment for many tumor shapes and dimensions:

- Monopolar needle 13 mm with irrigation and cooling, code SP-MI13
- Bipolar needle 7x4x7 mm with irrigation and cooling, code SP-BI0704
- Bipolar needle 10x5x10 mm with irrigation and cooling, code SP-BI1005

The 3 available variants (codes SP-MI13, SP-BI0704, SP-BI1005) consist of cooled needles capable of providing irrigation of tissue during ablation procedure. The needle is hollow and its inner space is divided into 3 concentric lumens:

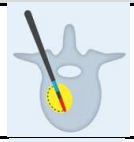
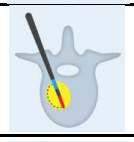
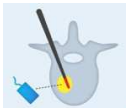
- The inner central lumen is used to distally deliver the irrigation solution to the tip of the RF needle; a hole on the needle tip allows the irrigation solution to reach tissues (the irrigation solution could be also delivered proximally through the insulation and irrigation cannula);
- The intermediate lumen is used to deliver a cooling fluid towards the proximal thermocouple;
- The outer external lumen returns the cooling fluid from the proximal thermocouple towards the cooling tubing circuit connected to the handle of the RF needle device; the cooling fluid is not intended to come in contact with patient tissues because it flows in a closed circuit.

The 3 needle variants SP-MI13, SP-BI0704 and SP-BI1005 also contain two thermocouples (distal thermocouple inside the ablation area and proximal thermocouple at the edge of ablation area) that permit

real-time monitoring of temperatures at the center of the ablation zone and at the edge of ablation area ensuring that no healthy tissue around tumor is damaged.

Figure 2 - SPINERY Cooled Bipolar Needle

The expected dimensions of the RF ablation areas, obtained with SPINERY system during in-vivo sessions treating healthy vertebral bodies, are below summarized (see also IFU):

Needle code	Type of ablation *	Electrode/s lenght	Distal thermocouple temperature Td**	Proximal thermocouple temperature range Tp***	Expected ablation dimensions L1xL2xL3****	Expected ablation area size	Expected ablation volume size	Power range****	Total ablation time
SP-BI0704		7 mm (intra-electrodes distance of 4 mm)	90°C	31-44°C	17 x 10 x 10 mm	134 mm^2	890 mm^3	6-15 W	6:00 min
SP-BI1005		10 mm (intra-electrodes distance of 5 mm)	90°C	31-44°C	22 x 12 x 12 mm	207 mm^2	1.658 mm^3	6-15 W	6:00 min
SP-MI13 + Neutral plate		13 mm	90°C	31-44°C	15 x 8 x 8 mm	94 mm^2	503 mm^3	6-15 W	6:00 min

(*) Type of expected ablation based on in-vivo test data. The experimental animal model should be considered informative but not prescriptive in the sizing of the target volumes, as these are healthy and non-metastatic biological tissues, the bone tissue is homogeneous and confined within the bone theca of the cortical bone of the vertebra.
(**) All the ablation parameters shown in the table refer to the target ablation temperature of 90 ° C detected by the distal thermocouple Td (ablation ramp that provides 3 levels of heating).
(***) Temperature range of the proximal thermocouple detected upon reaching the target ablation temperature of 90°C (detected by Td).
(****) Expected ablation dimensions that also include the portion of tissue called the transition crown of ablation, which is about 2-3 mm.
For the calculation of the ablation volume it is assumed that the size of L3 is equal to the size of L2.
(*****) Power range automatically delivered by the generator during the target temperature maintenance period of 90°C (2 minutes)

NOTES:

- The ablation area and volumes in a bipolar or monopolar double needle configuration are strongly influenced by the relative distance between the electrodes.
- The ablation area in a double bipolar crossed needle configuration may have a different geometric shape from the ellipse. It can switch from partially overlapping double ellipsoids (distant electrodes) to a more rounded ablation area (nearby electrodes) depending on the relative distance between the electrodes.

Table 1 - SPINERY system expected ablation dimensions

Accessories that can be described as follows:

- Connection cooling tubing to connect the handle with the cooling solution, code SP-CS and code SP-CD;
- Bone access accessories:
- Drill;
- Diamond tip trocar;
- Oblique tip trocar;
- Introducer;
- Insulation and irrigation cannula;
- Syringe to inject irrigating solution through the needle lumen or through insulation and irrigation cannula;
- Footswitch;
- Connection for neutral plates;

Figure 3 - SPINERY RF system and accessories

4. OBJECTIVES

SPINERY is a Radio-Frequency (RF) device designed for the pain reduction in patients with metastatic bone tumors. In particular, SPINERY is intended for:

- Pain reduction in patients affected by metastatic bone tumors involving the vertebral bodies, sacrum, iliac crest and peri-acetabulum, in patients with indication for Standard Therapy and in patients who have failed, not candidates or refuse Standard Therapy;
- Coagulation and ablation of bone tissue during interventional procedures including palliation of pain associated with metastatic lesions involving bone also in patients with indication for Standard Therapy and in patients who have failed, not candidates or refuse Standard Therapy.

The main objective of this pre-marketing study is to demonstrate the safety and efficacy of SPINERY RF device in the palliative treatment of patients with metastatic bone tumors in the areas of vertebral bodies (thoracic and/or lumbar), sacrum, iliac crest and peri-acetabulum and to prove the conformity of this device with the Essential Requirements for CE-marking [Medical Device Regulation 2017/745].

4.1. Primary Objectives

- To demonstrate that SPINERY RF device is effective in short-term (3 months) pain reduction in patients affected by metastatic bone tumors involving the vertebral bodies, sacrum, iliac crest and peri-acetabulum with indications for standard therapy in patients who have failed, not candidates or refuse standard therapy;
- To demonstrate that SPINERY RF device is safe in the RF ablation treatment of metastatic bone tumors, without causing device-related adverse events including in particular nerve injury;

4.2. Secondary Objectives

- To demonstrate that SPINERY RF device is effective in long-term (12 months) pain reduction in patients affected by metastatic bone tumors in the areas of vertebral bodies (thoracic and/or lumbar), sacrum, iliac crest and peri-acetabulum.
- To demonstrate safety in relation to usability;
- To demonstrate the procedural performance in terms of a short learning curve.

5. ENDPOINTS

5.1. Primary Endpoints

The primary endpoints of the study are:

- Change of Worst Pain Score expressed as average reduction of 2 BPI (Brief Pain Inventory) scores: Thoracic/Lumbar/ Peri-acetabulum/Iliac Crest/Sacrum RF Ablation [Time Frame: Baseline vs. 3 months];

  Change in pain will be calculated as:
  μc = worst-pain 3-month – worst-pain baseline
  A negative average value for change in pain represents a lowering of the subject's pain score (an improvement, or reduction in pain) and a positive value represents an increase in the subject's pain score (a worsening or increase in pain)
  Worst pain score at the target treatment site will be collected from the BPI in the past 24 hours.

- Completion (%) of the ablation procedure without device-related adverse events including in particular nerve injury [Timeframe: Post-procedure, 3 months].

5.2. Secondary Endpoints

- Change of Worst Pain Score: Thoracic/Lumbar/ Peri-acetabulum/Iliac Crest/Sacrum RF Ablation [Time Frame: Baseline vs. 1 month and 12 months];

  Worst pain score at the target treatment site will be collected from the Brief Pain Inventory (BPI) in the past 24 hours.

- Usability endpoint: Technical success (ability to perform access to treatment site and perform ablation) and procedural success (ability to perform access to treatment site and perform ablation for one or more complete cycles as planned by the physician) without product specialist intervention [Timeframe: Post-procedure];
- Short learning curve endpoint: procedure time, number of procedural errors, number of procedural and technical success for the same surgeon [Time Frame: Post-procedure];

6. TRIAL DESIGN

6.1. Summary of trial design

This is a prospective, single arm, uncontrolled multicenter study to assess the safety and effectiveness of SPINERY RF device in reducing pain in adult patients affected by metastatic bone tumors.

The trial design was defined in order to provide information regarding the clinical benefit of pain reduction; this clinical benefit is obtained thanks to the clinical performance of the device to provide coagulation and ablation.

Upon obtaining the informed consent, each subject will complete an enrollment/baseline visit, followed by treatment with SPINERY RF (Day 0); patients will then be visited immediately after the procedure (prior to hospital discharge within 24 hours), and after 1 month, 3 months and 12 months from the procedure, for a total of 5 study related visits.

The estimated time needed to enroll all subjects is approximately 6 months. The estimated time needed to obtain the CE Mark due to safe endpoints is 9 months (6 months for enrollment plus 3 months follow-up).
The overall study duration, from first subject enrollment to last subject visit (including 12 month follow-up), is expected to last approximately 18 months. The completion of the clinical study is defined as the approval of the Final Study Report and closure of all sites. Nevertheless, Clinical Study Reports at completion of each follow-up timeframe are expected in order to evaluate the evolution of the clinical study in relationship to the safety, the occurrence of clinical events and accomplishment of the Study Endpoints.
The following Clinical Study Reports will be issued during the clinical Study:

1. At completion of each planned study timeframe for all patients:
   - **a.** Postoperative, at achievement of primary safety endpoint;
   - **b.** 1 month, at achievement of the first timeframe of the secondary endpoint concerning the change of worst pain score;
   - **c.** 3 months (the primary endpoint) for CE mark purposes, at achievement of primary efficacy endpoint;
   - **d.** 12 months at achievement of the second timeframe of the secondary endpoint concerning the change of worst pain score;
2. In case of request from Ethical Committees or Competent Authority.

Planning of the Clinical Study Reports is summarized in the following table:

Timeframe of analysis	Endpoint	Expected clinical report content

Postoperative	Primary safety endpoint	Number of device-related adverse events observed
1 month	First secondary endpoint at the first timeframe (1 month)	Data on change of worst pain score after 1 month from the procedure
3 months	Primary efficacy endpoint	Data on change of worst pain score after 3 months from the procedure
12 months - Final Clinical Report	First secondary endpoint at the second timeframe (12 months)	Data on change of worst pain score after 12 months from the procedure

Table 2 - Clinical Report Plan

6.2. Study Flowchart

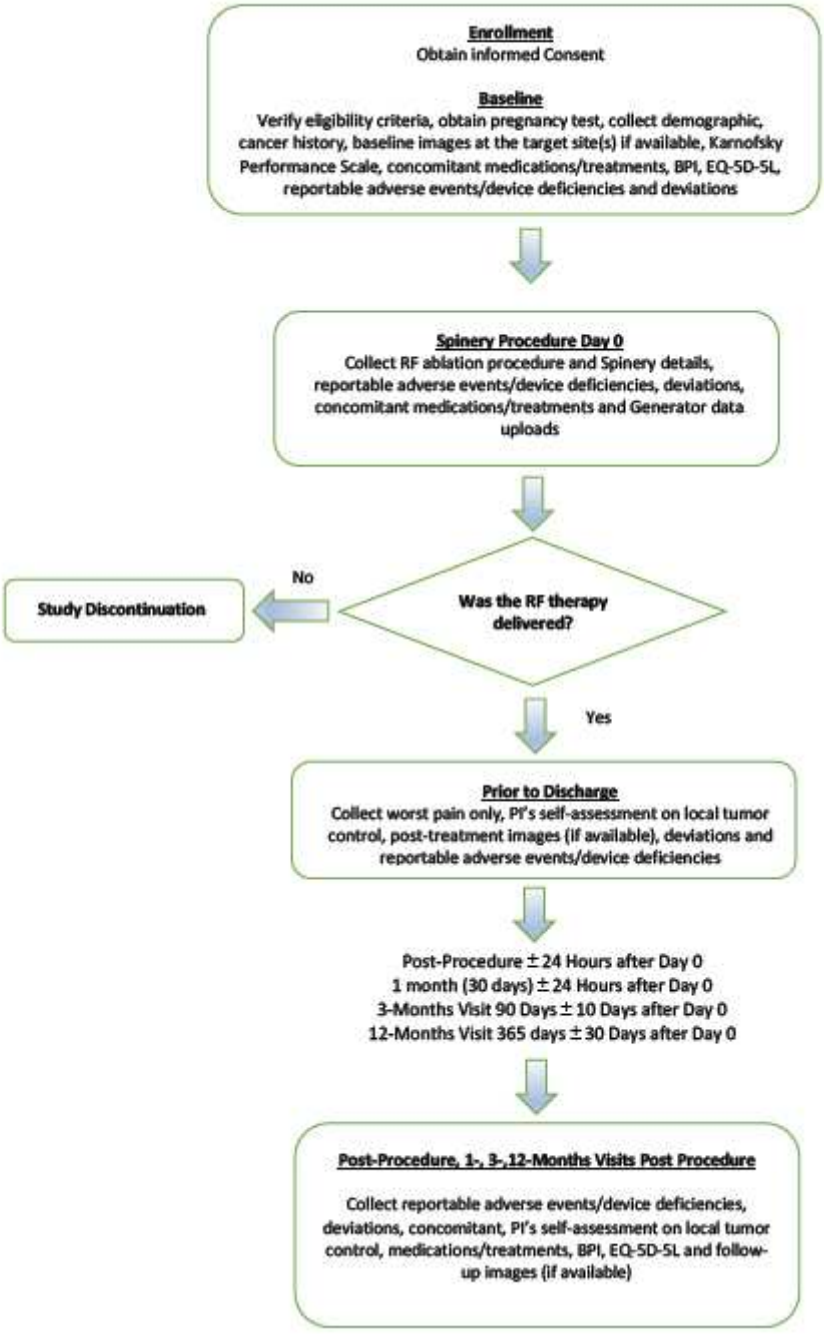


Figure 4 - Clinical Study Flowchart

6.3. Study population

The study population consists of adult patients with metastatic bone tumors undergoing radiofrequency tumor ablation with the SPINERY RF device.

6.3.1. Inclusion criteria

Participants are eligible to enroll in the study only if *all* the following criteria apply:

1. Patients with painful metastatic malignant lesions involving bone;
2. Patients, candidates to standard therapy, in which the RF ablation can be performed in combination with the Standard Therapy in accordance with the Investigator's indications;
3. Patients who have failed, not candidates or refuse Standard Therapy (chemotherapy or radiotherapy);
4. Patients with metastatic tumor size compatible with the expected ablation dimensions as reported for SPINERY devices in the IFU;
5. Patients with localized pain resulting from not more than two sites of symptomatic metastatic disease;
6. Patients that do not have evidence of impending fracture;
7. Patients with metastatic lesions targeted for treatment located in the thoracic and/or lumbar vertebral body(ies), peri-acetabulum, iliac crest, and/or sacrum - no restrictions on location of lesion;
8. Patients with BPI-Report worst pain score ≥4/10 at the target treatment site within the past 24 hours;
9. Patients with Karnofsky score ≥ 40 at enrollment;
10. Patients willing and able to provide a signed and dated informed consent, comply with the study plan, follow up visits and phone calls;
11. Patients at least 18 years old at the time of informed consent.

6.3.2. Exclusion criteria

Participants are excluded from the study if *any* of the following criteria apply:

12. Patients implanted with heart pacemaker or other implanted electronic device;
13. Patients with previous mechanical bone stabilization in the vertebral body to be treated;
14. Use of SPINERY RF device in vertebral body levels C1-C7;
15. Multiple myeloma, solitary plasmacytoma, or primary malignant lesions in the index vertebra or bone;
16. Active or incompletely treated local infection at the planned treatment site(s) and/or systemic infection;
17. Planned treatment site(s) accompanied by objective evidence of secondary radiculopathy or neurologic compromise;
18. Planned treatment site(s) associated with spinal cord compression or canal compromise requiring decompression;
19. Fractures due to prostatic cancer or other osteoblastic metastases to the spine. Metastatic lesions originating in the prostate that are osteolytic or of mixed origin are eligible for the study;
20. Pregnancy, breastfeeding, or plan to become pregnant during the study duration;
21. Concurrent participation in another clinical study that may add additional safety risks and/or confound study results;
22. Any condition that would interfere with the subject's ability to comply with study instructions or might confound the study interpretation.

Exclusion criteria have been identified thanks to literature review concerning RF ablation contraindications[1]:

- Criterion nr. 9 originates from the possibility of interferences between SPINERY and the implanted electronic device, which might be damaged by RF emission
- Criteria nr. 10-12-13-14-15-16 specify pathologies and conditions, which might confound study results interpretation
- Criterion nr. 11 originates from the incompatibility of vertebral bodies C1-C7 with SPINERY procedure in terms of shape and limited dimensions
- Criteria nr. 17-18 have been included for ethical reasons and to guarantee subjects' protection
- Criterion nr. 19 refers in general to subject's conditions which, according to physician's assessment, might not allow to comply with study procedures and/or might confound results interpretation

6.3.3. Vulnerable populations

In this Clinical Investigation no vulnerable subjects will be enrolled. The vulnerable subjects are those described in the ISO 14155:2020 (paragraphs 3.55 and 5.7) and in MDR 2017/745 (Annex XV, Chapter II, paragraph 3.6.3).

[1] Cazzato et al, Spinal Tumor Ablation: Indications, Techniques, and Clinical Management, Tech Vasc Interv Radiol, 2020 Jun;23(2):100677; Thanos et al., Radiofrequency ablation of osseous metastases for the palliation of pain, Skeletal Radiol. 2008 Mar;37(3):189-94; Moynagh et al., Thermal Ablation of Bone Metastases, Semin Intervent Radiol. 2018 Oct;35(4):299-308; Study protocol "OPuS One Clinical Investigation Plan" of clinical study "OsteoCool Tumor Ablation Post-Market Study (OPuS One)"

6.4. Study procedures

6.4.1. Informed Consent

The Investigator is responsible for and will obtain informed consent from each subject in the study, in accordance with the UNI EN ISO 14155, and the current version of the Declaration of Helsinki.
All subjects invited to participate in the study are entitled to make their voluntary decision based on all currently available information provided to them by the Investigator/designee.
The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

The participant must personally sign and date the latest approved version of the informed consent form before any study specific procedures are performed.

The Principal Investigator(s) at each site will ensure that the participant is given full and adequate oral and written information about the nature, purpose, possible risk(s) and benefit(s) of the study. The participant must also be notified that he/she is free to discontinue from the study at any time. The participant will be allowed as much time as wished to consider the information, and the opportunity to question the Investigator, their general physician or other independent parties to decide whether they will participate in the study. Written Informed Consent will then be obtained by means of dated signature of the participant and of the person who presented and obtained the informed consent. The person who obtained the consent must be suitably qualified and experienced and have been authorized to do so by the Principal Investigator. A copy of the signed Informed Consent will be given to the participant; the original signed form will be retained at the study site.

6.4.2. Eligibility Assessment

Eligible subjects are recruited among patients with metastatic bone tumors referred to one of the clinical centers. Potential participants are evaluated before enrollment based on inclusion and exclusion criteria.

6.4.3. Schedule of visits

Following signature of the informed consent, participants are enrolled in the study and perform the following study phases, as detailed in Table 1.

Enrollment and baseline visit. The eligibility criteria required by the protocol for participant's enrolment are assessed and evaluated and a comprehensive visit is performed to collect baseline parameters.

SPINERY Procedure. Patients are treated with RF ablation using SPINERY device. The use of bipolar or monopolar cooled needles or their combination is at physicians' discretion. More information is available in the instruction for use provided to each site.

Follow-up. Patients are followed-up within 24 hours from the RF ablation procedure, before the hospital discharge, and then after 1 month, 3 months and 12 months from the procedure.

	Enrollment Baseline	**SPINERY procedure (Day 0)[2]**	**Post-Procedure (within 24 hours)**	**1 month Follow-up (± 7 days)**	**3 Months Follow-up (±10 days)**	**12 Months Follow-up (±30days)**
Informed Consent Form[1]	X					
Inclusion/Exclusion Criteria	X					
Medical History with Demographics	X					
Physical Examination	X		X		X	
Karnofsky Performance Scale	X					
PI assessment of local tumor control (optional)		X		X	X	X
Concomitant pain medications	X	X	X	X	X	X
BPI (Short Form) – includes worst pain score in the past 24 hours	X			X	X	X
EQ-5D-5L[3]	X			X	X	X
Adverse Events Assessment	X	X	X	X	X	X
Deviations	X	X	X	X	X	X
Usability Assessment		X				
Tumoral lesion compatibility (clinical estimate)	X	X				
1) Informed consent must be obtained prior to performing any study-specific procedures. 2) Baseline Visit, Enrollment Visit and procedure can occur on the same day. 3) EQ-5D-5L is a standardized instrument for measuring generic health status						

Table 3 - Scdule of Visits

The attendance of subject to follow-up visits will be promoted by agreeing in advance on the schedule of visits with each subject. In addition, each subject will be contacted by phone a few days before the scheduled follow-up visit by the center to remember the need and the importance of attending the forthcoming control visit.

6.4.4. Description of the assessments

The following assessments are performed during the study, at different timepoints according to Table 1.

Medical History with Demographics

Relevant cancer medical history and demographic information will be collected at the Baseline visit and reported on the applicable eCRFs.

Physical Examination

Complete physical examination includes, at a minimum, assessments of the skin, lymph nodes, respiratory system, abdomen, cardiovascular system, musculoskeletal system, genitourinary system, ear/nose/throat, measurement of height (in cm) and weight (in Kg).

Karnofsky Performance Scale

The Karnofsky Performance Scale Index classifies patients as to their functional impairment. This can be used to compare effectiveness of different therapies and to assess the prognosis in individual patients.
Functional status is assessed by the physician. The KPS ranges from 100 to 0, where 100 is “perfect” health and 0 is death. The lower the Karnofsky score, the worse the survival prognosis for most serious illnesses.
Not applicable for subjects with benign bone tumors.

PI Assessment of local tumor control

After procedure and during the follow-up, the PI can decide to assess the local control

Concomitant pain medications

All over-the-counter, prescription medication and/or herbal supplements used for palliative purposes are recorded on CRFs.

The specific concomitant medications listed below should be documented as concomitant medications and will be updated at each visit:

- Osteoporosis medication(s): Antiresorptive medications (e.g., bisphosphonates, parathyroid hormone (PTH), calcitonin), calcium, and vitamin D.
- Steroid(s): any steroid use, including steroid inhalers
- Oral narcotics in the last 24 hours. This information will be converted to oral morphine equivalent dose (OMED) (including transdermal patches)

Response rate at 3 months post RF ablation is defined in Table 6-1. Complete Response (CR) and Partial Response (PR) will be considered as treatment response.
Pain Progression (PP) and Indeterminate Response (IR) will be considered as treatment non-response.

Treatment Response	Complete Response (CR)	A worst pain score of 0 with no concomitant increase in daily oral morphine equivalent dose (OMED) within the last 24 hours.
	Partial Response (PR)	Pain reduction of 2 or more on a scale of 0-10 without increase in OMED, or OMED reduction of 25% in the last 24 hours or more from baseline without an increase in pain.
Treatment Non-response	Pain Progression (PP)	Increase in pain score of 2 or more above baseline worst pain score with stable OMED, or an increase of 25% or more in OMED within the last 24 hours compared with baseline with the worst pain score stable or 1 point above baseline.
	Indeterminate Response (IR)	Any response that is not captured by the complete response, partial response, or pain progression definitions.

Table 4 – Pain Response Table

Brief Pain Inventory (BPI)

The Brief Pain Inventory short form is a 9-question self-administered questionnaire used to evaluate the severity of a patient's pain and the impact of this pain on the patient's daily functioning. The patient is asked to rate their worst, least, average, and current pain intensity, list current treatments and their perceived effectiveness, and rate the degree to which pain interferes with general activity, mood, walking ability, normal work, relations with other people, sleep, and enjoyment of life. Each patient is instructed to rate their pain by circling the one number that best describes their pain at its worst in the last 24 hours on a 11-point scale (no pain = 0, pain as bad as you can imagine = 10).

The worst pain question in the BPI will be used to evaluate the pain severity:

The BPI pain interference, as defined in question 9, is typically scored as the mean of the seven interference items (general activity, mood, walking ability, normal work, relations with other people, sleeping, and enjoyment of life). The mean can be used if more than 50% or 4/7 of the total items has been completed.

The general pain question (Question #1), pain map (Question #2) and the medication question (Question #7) will not be used in this study. The removal of these questions does not affect the validity of the questionnaire and was approved by the BPI author Charles S. Cleeland, PHD

The BPI can be completed by the subject, by in-person interview or by phone interview by the Principal Investigator or qualified (delegated) designee.

European Quality of Life - Five Dimensions (EQ-5D-5L)

The European Quality of Life – Five Dimensions (EQ-5D), version 5L, is a standardized measure of health status developed by the EuroQol Group and a widely used validated tool to determine health-related quality of

life. The EQ-5D-5L consists of two sections, the descriptive system and the EQ visual analogue scale (EQ VAS).

The EQ-5D descriptive system consists of 5 dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression. Each dimension has 5 levels of severity: no problems, slight problems, moderate problems, severe problems and extreme problems. The subjects are asked to indicate their health status by selecting the most appropriate statement in each of the 5 dimensions.

The EQ VAS records the respondent's self-rated health on a 20 cm vertical, visual analogue scale with endpoints labelled as 'the best health you can imagine' and 'the worst health you can imagine'. This information can be used as a quantitative measure of health as judged by the individual respondents.

The EQ-5D can be completed by the subject, in-person interview, or by phone interview by the Principal Investigator or qualified (delegated) designee.

Adverse Events Assessment

Any adverse event meeting the definition of device, therapy and/or procedure related, as well as all device deficiencies that occur from enrollment through subject discontinuation from the study will be collected.

All device, therapy and/or procedure-related adverse events will be collected for this study from enrollment to the end of the study, including events related to:

- The device components and/or procedure (Bone Access Kit, Probe, generator, etc.)
- Surgery or anesthesia regarding the initial or repeat procedure

Any adverse event due to the device, detected during the ablation procedure and/or during follow-up, will be recorded and evaluated through a dedicated case report form. The case report form will include at least the following information: date of the event, diagnosis or description of the event, severity assessment, treatment, outcome and date of resolution. The investigator is responsible for the detailed recording of the adverse event through the dedicated case report form and for the communication of the adverse event to the Sponsor.

The clinical course of each adverse event will be followed by the physician until resolution or until the subject's participation in the study is discontinued.

Deviations

Protocol deviations are digressions from the written protocol defined as an event where the clinical investigator or site personnel did not conduct protocol-required procedures according to the study protocol. Protocol deviations are to be pre approved by Axon study personnel and the IRB/EC (as required) unless the deviation is necessary to protect the health, safety, or welfare of a subject in an emergency situation. The investigator or delegated site personnel should immediately contact the designated Axon study personnel to discuss the impact of the potential deviation; prior approval of deviations should be documented. Prior approval is generally not required if the deviation is due to an emergency circumstance or an unforeseen circumstance that is beyond the investigator's control; however, these deviations should be reported to Axon and the IRB/EC (as required) after site personnel become aware of the deviation. All protocol deviations must be reported on the Protocol Deviation eCRF after the site's awareness of the deviation.

The sponsor may choose to terminate the study at a site for failure to follow the written protocol and investigator agreement.

Usability Assessment

At the end of the procedure the Investigator will fill-in a SPINERY device usability Case Report Form.

Tumoral lesion dimension

Subjects will be exposed to a small amount of radiation that they will receive during the study. The amount of this radiation cannot be determined in advance. For example, during the initial procedure, fluoroscopy or CT may be used according to standard of care at the site or an Investigator may order pre-operative or post-operative x-ray films or CT scans to assess the dimension of lesions/tumors. These images are routinely performed according to the standard of care; therefore, no additional radiation risk is associated with participation in this clinical study.

6.5. End of trial

The 'end of study' (also known as 'study completion date') is defined as the date of the last visit of the last participant in the study. When adequate data has been collected or when the clinical investigation is terminated for any reason, each Investigator will be notified in writing. This letter will describe briefly the status of the study and will inform the Investigator of any remaining responsibilities he/she may have with regards to the study. A study closeout visit may also be conducted.

Sponsor will notify the applicable Regulatory Agencies, all IRBs and Principal Investigators within 30 working days of the completion or termination of the investigation. A final report will be submitted within 6 months.

6.5.1. Early study termination

The Sponsor may suspend or prematurely terminate either the clinical investigation in an individual investigation site or the entire clinical investigation for significant and documented reasons.

The Sponsor is supported by an independent DSMB in the study review and to recommend any modification or study termination for any perceived safety concern based on clinical judgment, including but not limited to, a higher than anticipated rate for any component of the primary endpoint, device failures resulting in adverse events, or unexpected SAEs.

Possible reasons for early study termination include:

- The discovery of an unexpected, significant, or unacceptable risk to the subjects enrolled in the study
- A decision on the part of the Sponsor to suspend or discontinue the development of the device
- unexpected device malfunction whose root cause can be traced to major design pitfalls
- suboptimal efficacy in the first 30% of enrolled participants

In case of early termination of the clinical investigation all Principal Investigators, associated Competent Authorities and ECs will be notified in writing, and will be informed with a report on the reasons for the early termination. The Principal Investigator will inform the subjects and their Primary Care Physician by sending a letter, which will include their contact information for questions or concerns.

A principal Investigator, EC, or regulatory authority may suspend or prematurely terminate participation in a clinical investigation at the investigation sites for which they are responsible.

6.5.2. Withdrawal of Participants from Study Treatment

Each participant has the right to withdraw from the study at any time. In addition, the investigator may discontinue a participant from the study at any time if the investigator considers it necessary for any reason including:

- Pregnancy

- Ineligibility (either arising during the study or retrospective having been overlooked at screening)
- Significant protocol deviation
- Significant non-compliance with study requirements
- An adverse event which requires treatment discontinuation, such as adverse events related to complications during anesthesia procedure performed before RF ablation treatment, leading to the impossibility to treat the subject with SPINERY (for example inability of the patient to tolerate required level of anesthesia)
- An adverse event which results in inability to continue to comply with study procedures, that is any adverse event, which is related or not to SPINERY device and impedes the subject from attending to scheduled follow-up visits
- Disease progression which results in inability to continue to comply with study procedures, because it requires reintervention through ablation or other treatments in order to stop the progression; possible reintervention might not allow to conclude study procedures and might confound results interpretation
- Need for a second ablation procedure with SPINERY RF device or other similar devices, as per clinical judgment
- Consent withdrawn
- Lost to follow up

If a participant is withdrawn due to an AE/SAE, every attempt will be made by the investigator to obtain follow-up information about the AE/SAE until resolution or a determination that the AE/SAE will not be resolved.
If the participant withdraws consent for disclosure of future information, the sponsor may retain and continue to use any data collected before such a withdrawal of consent.
If a participant withdraws from the study, he/she may request destruction of any samples taken and not tested, and the investigator must document this in the site study records.

6.5.3.Site Discontinuation

The Sponsor has the right to terminate the study or terminate enrollment and remove all appropriate study materials from the study site for the following reasons:

1. It becomes apparent that patient enrollment is unsatisfactory as to quality (violations of inclusion or exclusion criteria) or enrollment rate;
2. The completion of the CRFs is inaccurate, incomplete or considerably delinquent; and
3. There are repeated, uncorrected protocol violations.

All patients treated with the study device before the Site discontinuation will be followed according to the study protocol.

6.5.4.Source Data

Source documents are original documents, data, and records from which participants' CRF data are obtained. These include, but are not limited to, hospital records (from which medical history and previous and concurrent medication may be summarized into the CRF), clinical and office charts, laboratory and pharmacy records, diaries, microfitches, radiographs, and correspondence. All documents are stored safely in confidential conditions at the study site.

7. TREATMENT OF TRIAL PARTICIPANTS

7.1. Description of Study Intervention(s)

Description of the device and of study intervention(s) is reported in the Investigator Brochure.

The physician may decide that cementoplasty (i.e., Vertebroplasty or Kyphoplasty) is required after the ablation procedure. This information will be collected during the procedure and during any subsequent follow-up procedures.

In the treatment of metastases involving weight-bearing bones – such as the spine or acetabulum – cement is routinely instilled after RFA into the ablation cavity for stabilization or prevention of pathologic fractures [Wallace 2015]. Even when a gross pathologic fracture is not evident, cementoplasty may contribute to pain relief by stabilizing trabecular microfractures [Heran 2006]. The exothermic reaction from polymethyl methacrylate polymerization is also thought to cause destruction of pain fibers at the margins of the ablation zone [Lane 2001, Weill 1996]. Because the risk of cementoplasty is low, it is routinely performed after ablation at many institutions [Wallace 2015, Wallace 2016, Anchala 2014, Hillen 2014]. The risk of symptomatic extravasation may be reduced through the use of ultrahigh viscosity cement [Wallace 2016].

7.2. Maintenance and storage of device

Maintenance and storage of the device are described in dedicated sections of Investigator Brochure and Instruction for Use.

7.3. Concomitant Medication

There are no restrictions to prior or concomitant medications before or during the study. The specific concomitant medications listed below should be documented as concomitant medications and will be updated at each visit:

- Osteoporosis medication(s): antiresorptive medications (e.g., bisphosphonates, parathyroid hormone (PTH), calcitonin), calcium, and vitamin D.
- Steroid(s): any steroid use, including steroid inhalers
- Oral narcotics in the last 24 hours. This information will be converted to oral morphine equivalent dose (OMED) (including transdermal patches)

8. SAFETY REPORTING

8.1. Definitions

8.1.1. Adverse Event (AE)

An adverse event is defined in ISO 14155:2020 as any untoward medical occurrence, unintended disease or injury, or untoward clinical signs (including abnormal laboratory findings) in subjects, users or other persons, whether or not related to the investigational medical device and whether anticipated or unanticipated.

All adverse events, regardless of severity, associated with the use of the SPINERY device will be reported on the adverse event CRF.

8.1.2. Adverse Device Effect (ADE)

An adverse device effect is defined in ISO 14155:2020 as an adverse event related to the use of an investigational medical device.

This definition includes adverse events resulting from insufficient or inadequate instructions for use, deployment, implantation, installation, or operation, or any malfunction of the investigational medical device.

8.1.3. Unanticipated Adverse Device Effect (UADE)

An Unanticipated Adverse Device Effect (UADE) is defined as any serious adverse effect on health or safety, or any life-threatening problem caused by, or associated with, the SPINERY device, the effect of which was not previously identified in nature, severity or degree of incidence in the study protocol or any other unanticipated serious problem associated with the study device that relates to the rights, safety or welfare of subjects.

In the event of an unanticipated adverse device effect, the Investigator and/or other professional personnel in attendance will undertake whatever therapy is indicated. If an unanticipated adverse device effect occurs, the Investigator will submit a report to Sponsor and the IRB as soon as possible but no later than ten (10) working days (or as indicated by applicable regulations) after the Investigator learns of the event. The nature and causes of the problem will be reported and any treatment that is administered due to the event will be described in detail. This information will be reported on the Adverse Event CRF and documents from the medical records will be provided to the Sponsor.

It is the responsibility of the Sponsor/Manufacturer to conduct an evaluation (including discussions with the Investigator) of the event and, with respect to the applicable regulations, to determine if it is an unanticipated adverse device effect. If the event is an unanticipated adverse device effect, the Sponsor must notify all participating Investigators and the reviewing IRB within ten (10) working days (or as indicated by applicable regulations) of receiving notification of occurrence of the event.

If the Sponsor determines that an adverse device effect presents an unreasonable risk to the patient population, study enrollment shall be terminated. Termination will occur no later than five (5) working days after the determination is made and no later than 15 working days after the initial notification by the Investigator. A terminated investigation will not resume without approval from the local Competent Authority and the IRB.

8.1.4.Serious Adverse Event (SAE)

A serious adverse event (SAE) is defined in ISO 14155:2020 as an adverse event that led to any of the following:

a) led to death,

b) led to serious deterioration in the health of the subject, that either resulted in

1) a life-threatening illness or injury, or

2) a permanent impairment of a body structure or a body function, or

3) in-patient or prolonged hospitalization, or

4) medical or surgical intervention to prevent life-threatening illness or injury or permanent impairment to a body structure or a body function,

5) chronic disease

c) led to fetal distress, fetal death or a congenital abnormality or birth defect including physical or mental impairment

Planned hospitalization for a pre-existing condition, or a procedure required by the CIP, without serious deterioration in health, is not considered a serious adverse event.

To ensure no confusion or misunderstanding of the difference between the terms "serious" and "severe", which are not synonymous, the following note of clarification is provided:

The term "severe" is often used to describe the intensity (severity) of a specific event (as in mild, moderate, or severe myocardial infarction); the event itself, however, may be of relatively minor medical significance (such as severe headache). This is not the same as "serious," which is based on patient/event outcome or action criteria usually associated with events that pose a threat to a participant's life or functioning. Seriousness (not severity) serves as a guide for defining regulatory reporting obligations.

8.1.5.Serious Adverse Device Effects (SADE)

A serious adverse device effect (SADE) is defined in ISO 14155:2020 as an adverse device effect that has resulted in any of the consequences characteristic of a serious adverse event.

8.1.6.Unanticipated Serious Adverse Device Effect (USADE)

An unanticipated serious adverse device effect (USADE) is an effect which by its nature, incidence, severity or outcome has not been identified in the current version of the risk analysis report.

Note: Anticipated serious adverse device effect (ASADE) is an effect which by its nature, incidence, severity or outcome has been identified in the risk analysis report.

8.1.7.Device Deficiency and Malfunction

Device deficiency and malfunction information will be collected throughout the study. Device deficiencies (event, date of onset, severity, duration, and relationship) will be recorded on the applicable CRFs.

A device deficiency is defined in ISO 14155:2020 as an inadequacy of a medical device with respect to its identity, quality, durability, reliability, usability, safety or performance.

A device malfunction is a failure of the investigational medical device to perform in accordance with its intended purpose when used in accordance with the instructions for use or CIP, or IB.

8.2. Reporting procedures

8.2.1. Reporting of an AE

All AE(s) and ADE(s) occurring during the study observed by the investigator or reported by the participant, whether or not attributed to the device under investigation are recorded on the CRF as specified in the protocol.

The following information should be recorded: description, date of onset and end date, severity, assessment of relatedness to device, other suspect drug or device and action taken. Follow-up information should be provided as necessary.

The relationship of AEs to the device is assessed by a medically qualified investigator or by the sponsor/manufacturer and is to be followed up until resolution or the event is considered stable.

All ADE(s) that result in a participant's withdrawal from the study or are present at the end of the study, should be followed up until a satisfactory resolution occurs.

Where relevant, any pregnancy occurring during the clinical study and the outcome of the pregnancy, should be recorded and followed up for congenital abnormality or birth defect.

8.2.2. Reporting of a SAEs/ SADEs/ UADEs

All SAE/SADE/UADEs must be reported to the study Sponsor Axon as soon as possible and no later than 2 days after the Investigator first learns of the event.

Adverse events will be recorded on the applicable CRFs (event, date of onset, severity, duration, relationship to device and procedure) by the Investigator or designee and will be followed until they are adequately resolved or explained.

Notification of adverse events to Axon may be completed via telephone, fax, email, or through the electronic database (EDC). Reportable adverse events will be submitted to the applicable EC and regulatory authorities per national and local reporting regulations and requirements and timeframes. Adverse event reporting must comply with national regulations of each European Country where the investigation is conducted. Axon will comply with any specific country requirements regarding adverse event reporting.

The Sponsor will report SAEs to the Competent Authorities as applicable according to national regulations MDCG 2020-10/1. Reporting will include report table, quarterly SAE summary reports, and any applicable national formats for reporting individual SAEs as applicable.

The Principal Investigator is required to report all Device-Related, Procedure-Related and Serious Adverse Events to the Sponsor. Adverse events will be recorded on the Adverse Event CRF and may or may not be device or operative site related. Adverse events that are associated with the procedure are included in the paragraph 8.2.3 and defined in the Guidelines for clinical investigation ISO14155:2020. All adverse events, regardless of severity, associated with the use of the SPINERY device will be reported on the adverse event CRFs.

The contact information for Axon is below:

Axon srl

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8.2.3. Specific Adverse Device Effect (ADE)

The following ADE should be carefully assessed as they are recognized as possible ADE for SPINERY based on the state of the art of other medical devices:

- Carbonization
- Post-operative pain
- Limited/uncomplete treatment due to anatomical peculiarities
- Damage to surrounding tissue through iatrogenic injury
- Nerve injury including thermal injury, puncture of spinal cord or nerve roots potentially resulting in radiculopathy, paresis, and paralysis
- Pulmonary embolism
- Hemothorax or pneumothorax
- Infection
- Unintended puncture
- Hemorrhage
- Hematoma

Unanticipated adverse device effects can occur. If they do occur, they will be handled as discussed in paraph 8.1.3.

Aside from the risks listed above, there are no known gender-specific risks associated with the use of the SPINERY device. Minimization of the risks will be accomplished by selection of patients who are appropriate candidates for this device and by careful selection of Investigators and centers that have appropriate experience with this type of procedure. Also, intervention techniques, peri-interventional and post-interventional, will be those that are typically used in each study center.

9. MONITORING PLAN

The study will be monitored on a regular basis by the CRO's adequately qualified and trained clinical Monitors throughout the study period to ensure the proper conduct of the clinical Investigation.
The purposes of study monitoring are to verify that the rights and well-being of study subjects are protected, that the reported study data are accurate, complete and verifiable against the source documents, and that the study is conducted in accordance with the current clinical investigation plan, Good Clinical Practice guideline (UNI EN ISO 14155) and applicable regulatory requirements.
During the monitoring visits, Monitors will verify the following, including but not limited to: subject informed consent, subject's eligibility, safety data and reporting, quality of source documents and CRF data against subject's medical records. If inconsistencies are found, the corresponding corrections to the CRF data will have to be made by the Investigator or designated person. Monitors will also check subject compliance, accrual, study product handling, including dispensing procedures and accountability logs, delegation of responsibilities within the Investigator's team, relevant communications with family doctors, if any, ancillary

equipment and facilities, etc. The Investigator and other site staff involved in the study must allocate enough time to the Monitor at these visits. Additionally, due to the COVID-19 pandemic, site monitoring visits may not be feasible; in that case, a remote monitoring strategy will be implemented.

Upon request by the Sponsor, on-site study audits may be conducted in order to ensure the study is in compliance with GCP, applicable regulatory requirements, and the clinical investigation plan. The auditing activities may also be conducted after study completion.

The Investigator agrees to allow Sponsor/auditors/CRO monitors to have direct access to his/her study records for review, being understood that they are bound by professional secrecy, and as such will not disclose any personal identity or personal medical information.

Regulatory Authorities may wish to conduct on-site inspections (during the study or after its completion). If a Regulatory Authority notifies the Investigator of an inspection or visits the site unannounced for purposes of conducting an inspection, the Investigator must inform the Sponsor and CRO immediately. The Investigator will make all efforts to facilitate the conduct of the audits and inspections giving access to all necessary facilities, data and documents.

Any result or information arising from the inspection will be immediately communicated by the Investigator to the Sponsor. The Investigator will take all appropriate measures required by the Sponsor to implement corrective actions for all problems found during audits or inspections.

Study monitoring procedures are described in detail in a dedicated document “Monitoring plan”.

10. STATISTICS

10.1. Description of Statistical Methods

All the analyses will be performed according to ITT principle.

The PPT analysis will be performed as secondary.

Sample size calculation was performed using the “proc power” in SAS v.9.4 software (Cary, NC, USA).

10.2. Number of Participants

Approximately 52 patients will be enrolled in the study.

A sample size of 36 successfully treated subjects who complete the 3-months period of follow-up will allow to detect a difference between the pre-treatment and post-treatment means of worst pain score collected from the BPI equal to 2 points (e.g., from 7 to 5 points), assuming that the SD of the scores is equal to 3 and the correlation between measurements at different time periods is 0.3, and with two-tailed alpha = 0.05 and study power of 0.90. Such a 2-points difference is considered as the minimally important difference for the worst pain rating of the BPI (Corli O et al, 2010: p.51; *Misurare il dolore nel paziente con cancro nella ricerca e nella clinica;* Mathias SD et al, 2011; 9:72-78; J Support Oncol). Taking into account about 30% of patients’ attrition from treatment through the pain assessment at 3 months, 52 subjects will be enrolled in the study. Sample size calculation was performed using the “proc power” in SAS v.9.4 software (Cary, NC, USA).

10.3. Measures to minimize/avoid bias

The following measures have been implemented in order to minimize avoid/bias:

- New technology bias is minimized through an adequate and thorough training to the surgeon;
- Low statistical bias is minimized through an adequate estimate of the number of patients in the treatment group as compared to the state of the art;

- Multicentric study to minimize usability bias.

10.4. Clinical Study Reports

Clinical study reports will be issued at the completion of the following timeframes on all patients:

- Postoperative, at achievement of primary safety endpoint;
- 1 month, at achievement of the first timeframe of the secondary endpoint concerning the change of worst pain score;
- 3 months (the primary endpoint) for CE mark purposes, at achievement of primary efficacy endpoint;
- 12 months at achievement of the second timeframe of the secondary endpoint concerning the change of worst pain score (Final Clinical Report);

Statistical analysis will be performed at 1-month, 3-months and 12-months intervals on BPI worst pain score results and change as compared to baseline values.

11. ETHICS

11.1. Ethics Review and conduct of the study

The study will be performed in accordance with ethical principles that have their origin in the Declaration of Helsinki and are consistent with ICH/Good Clinical Practice and any applicable regulatory requirements.

The protocol, the informed consent form and any participant information sheet or proposed advertising material must be approved or given a favorable opinion in writing by an Ethics Committee (EC) and by the relevant Competent Authority, as appropriate. Initial EC/Competent Authority approval, and all materials approved by the EC for this study including the patient consent form and recruitment materials must be maintained by the Investigator and made available for inspection.

The Principal Investigator is responsible for informing the EC of any amendment to the protocol in accordance with local requirements and for providing the EC with any progress reports or notification of any reportable SADE, according to local regulations and guidelines.

11.2. Participant Confidentiality

In order to ensure data protection, participants will be assigned a unique identifier. Any participant records or datasets that are transferred to the sponsor will contain the identifier only; participant names or any information which would make the participant identifiable will not be transferred. The participant must be informed that his/her personal study-related data will be used by the sponsor in accordance with local data protection law. The level of disclosure must also be explained to the participant. The participant must be informed that his/her medical records may be examined by Clinical Quality Assurance auditors or other authorised personnel appointed by the sponsor, by appropriate EC members, and by inspectors from regulatory authorities.

11.3. Data Quality Assurance

All participants' data relating to the study will be recorded on printed or electronic CRF unless transmitted to the sponsor or designee electronically (e.g., laboratory data). The investigator is responsible for verifying that data entries are accurate and correct by physically or electronically signing the CRF.

The investigator must maintain accurate documentation (source data) that supports the information entered in the CRF.

The investigator must permit study-related monitoring, audits, EC review, and regulatory agency inspections and provide direct access to source data documents.

The sponsor or designee is responsible for the data management of this study including quality checking of the data.

12. FINANCING AND INSURANCE

Investigators and sub-investigators will provide the sponsor with sufficient and accurate financial information as requested to allow the sponsor to submit complete and accurate financial certification or disclosure statements to the appropriate regulatory authorities. Investigators are responsible for providing information on financial interests during the course of the study and for 1 year after completion of the study.

An insurance policy must be put in place to cover participants' visits conducted at the investigating sites**.**

13. PUBLICATION POLICY

The results of this study may be published or presented at scientific meetings. If this is foreseen, the investigator agrees to submit all manuscripts or abstracts to the sponsor before submission. This allows the sponsor to protect proprietary information and to provide comments.

The sponsor will comply with the regulatory requirements for publication of study results. In accordance with standard editorial and ethical practice, the sponsor will generally support publication of multicenter studies only in their entirety and not as individual site data. In this case, a coordinating investigator will be designated by mutual agreement.

All information obtained as a result of the study will be regarded as confidential.

The results of the clinical study will be documented in an integrated clinical study report according to UNI EN ISO 14155.

14. ABBREVIATIONS

AE	Adverse Event
ADE	Adverse Device Event
BPI	Brief Pain Inventory
CIP	Clinical Investigation Plan ('Protocol')
CR	Complete response
CRF	Case Report Form
CT Scan	Computerized Tomography
EC	Ethics Committee
eCRF	Electronic Case Report Form
EQ-5D-5L	Standardized instrument for measuring generic health status
EQ VAS	European Quality Visual Analogue Scale
IR	Indeterminate Response
IRB/IEC	Institutional Review Board/Independent Ethics Committee
ITT	Intention To Treat
KPS	Karnofsky Performance Scale
MDR	Medical Device Regulation
OMED	Oral Morphine Equivalent Dose
PI	Principal Investigator
PP	Pain Progression
PPT	Per Protocol Treatment
PR	Partial Response
PTH	Parathyroid Hormone
RF	Radiofrequency
RT	Radiotherapy
RFA	Radiofrequency Ablation
SADE	Serious Adverse Device Event
SAE	Serious Adverse Event
UADE	Unexpected Adverse Device Event

15. REFERENCES

1. Dupuy DE, Goldberg SN. Image-guided radiofrequency tumor ablation: challenges and opportunities. II. J Vasc. Interv Radiol. 2001;12:1135–1148.
2. Zajaczkowska R, et al. Bone Pain in Cancer Patients: Mechanisms and Current Treatment. Int. J. Mol. Sci. 2019, 20, 6047.
3. Falk S et al. Pain and Nociception: Mechanisms of Cancer-Induced Bone Pain. J Clin Oncol 32:1647-1654.
4. Filippiadis D, et al. Percutaneous Management of Cancer Pain. Current Oncology Reports (2020) 22:43.
5. Coleman R, et al. Bone health in cancer: ESMO Clinical Practice Guidelines. Annals of Oncology. 2020; 31:12; 1650-1663.
6. NCCN guideline. Adult Cancer Pain. Version 1.2021 – February 26, 2021.
7. Gazelle GS, Goldberg SN, Solbiati L, Livraghi T. Tumor Ablation With Radio-Frequency Energy. Radiology.2000; 217:433–466.
8. Rosenthal DI, Hornicek FJ, Torriani M, Gebhardt MC, Mankin MJ. Osteoid osteoma: percutaneous treatment with radiofrequency energy. Radiology. 2003; 229:171–175.
9. Thanos L, Mylona S, Galani P, et al. Radiofrequency ablation of osseous metastases for the palliation of pain. Skeletal Radiol. 2008;37(3):189-194.
10. Wallace AN, Huang AJ, Vaswani D, et al. Combination acetabular radiofrequency ablation and cementoplasty using a navigational radiofrequency ablation device and ultrahigh viscosity cement: technical note. Skeletal Radiol. 2016;45(3):401–405.
11. Lane MD, Le HBQ, Lee S, et al. Combination radiofrequency ablation and cementoplasty for palliative treatment of painful neoplastic bone metastasis: experience with 53 treated lesions in 36 patients. Skeletal Radiol. 2011;40(1):25–32.
12. Cleeland CS, Gonin R, Hatfield AK, et al. Pain and its treatment in outpatients with metastatic cancer. N. Engl. J. Med. 1994;330(9):592–596.
13. NCCN Guidelines Version 2.2016: Adult Cancer Pain: Clinical Practice in Oncology.
14. Bagla S et al. Multicenter Prospective Clinical Series Evaluating Radiofrequency Ablation in the Treatment of Painful Spine Metastases. Cardiovasc Intervent. Radiol. 2016 v39 p1289-1297.
15. Dupuy DE, Safran H, Mayo-Smith WW, Goldberg SN. Radiofrequency ablation of painful osseous metastatic disease (abstract) Radiology. 1998;209(P):389.
16. Callstrom MR, Charboneau JW, Goetz MP, et al. Painful metastases involving bone: feasibility of percutaneous CT and US guided radiofrequency ablation. Radiology. 2002;224:87–97.
17. Goetz MP, Callstrom MR, Charboneau JW, et al. Percutaneous image-guided radiofrequency ablation of painful metastases involving bone: a multicenter study. J Clin Oncol. 2004;22(2):300–306.
18. Tomasian A, Jennings JW. Percutaneous Minimally Invasive Thermal Ablation of Osseous Metastases: Evidence-Based Practice Guidelines. American Journal of Roentgenology Pub Date: 2020-05-26, DOI: 10.2214/ajr.19.22521).
19. Hillen TJ, Anchala P, Friedman MV, Jennings JW. Treatment of metastatic posterior vertebral body osseous tumors by using a targeted bipolar radiofrequency ablation device: technical note. Radiology. 2014 Oct;273(1):261-7.

20. Janjan, N.A. (1997), Radiation for bone metastases. Cancer, 80: 1628-1645.
21. Di Staso M, Zugaro L, Gravina GL et al. A feasibility study of percutaneous radiofrequency ablation followed by radiotherapy in the management of painful osteolytic bone metastases. Eur Radiol 21, 2004–2010 (2011).
22. Medical Device Regulation 2017/745.

ANNEX 1

Investigation Site List

Principal Investigators and Sites

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