P970010

Summary of Safety and Effectiveness

General Information

Device Generic Name	Carbonated Apatite Cement, fracture stabilization adjunct
Device Trade Name	Norian® SRS® Skeletal Repair System® Cement
Applicant's name:	Norian Corporation 10260 Bubb Road Cupertino, CA 95014-4166
PMA Number:	P970010
Date of Panel Recommendation:	October 9, 1998
Date of Notice of Approval:	December 23, 1998

Indications for Use

Norian SRS Cement is indicated as an adjunct for fracture stabilization in the treatment of low impact, unstable, metaphyseal distal radius fractures in cases where early mobilization (cast for 2 weeks, then removable splint for 2–4 weeks) is indicated.

Use of Norian SRS Cement alone in highly comminuted fractures is not indicated.

Device Description

Norian SRS Cement is an injectable, moldable cement that hardens in vivo forming a carbonated apatite of low crystalline order and low solubility that is slowly resorbed in vivo. Norian SRS Cement is provided sterile for single use in a Reactants Pack of solution (sodium phosphate) and powder (calcium phosphate) that is mixed together prior to use. The materials are mixed in a reusable, automated mixer designed to be used with the Reactants Pack or in a mortar and pestle by hand.

The mixer, also available from Norian, uses a consistent pressure roller to mix the solution with the powder and then to eject the resulting paste into a tube. The tube is removed from the Reactants Pack aseptically and placed in a delivery device. A needle is attached to the delivery device, and the paste injected into prepared voids. In the event that an automated mixer is not available, the solution and powder can be mixed into a paste by hand with a mortar and pestle and then packed into the Reactants Pack tube for injection into the site using the delivery device.

Norian SRS Cement is intended for adjunctive stabilization for distal radius fractures by filling the voids between the bone fragments of a reduced fracture and then hardening. The cement can be implanted over a five-minute interval (Implant Period) at room temperature during which the paste is injectable and then remains manipulatable for two minutes (Work Period) at body temperature after implantation. The paste begins to harden within a two-minute work period and sets in approximately 10 minutes. Norian SRS Cement continues to cure and becomes pure carbonated apatite. After 24 hours in situ, the device reaches a maximum compressive strength of approximately 50 MPa. Norian SRS Cement is gradually resorbed over time. Figure 1 illustrates the implant, working, and setting periods and temperatures associated with Norian SRS Cement.

Norian SRS Cement is available in 5 cc and 10 cc packages. The packages provide these approximate amounts of usable paste after mixing in order to fill different void sizes.

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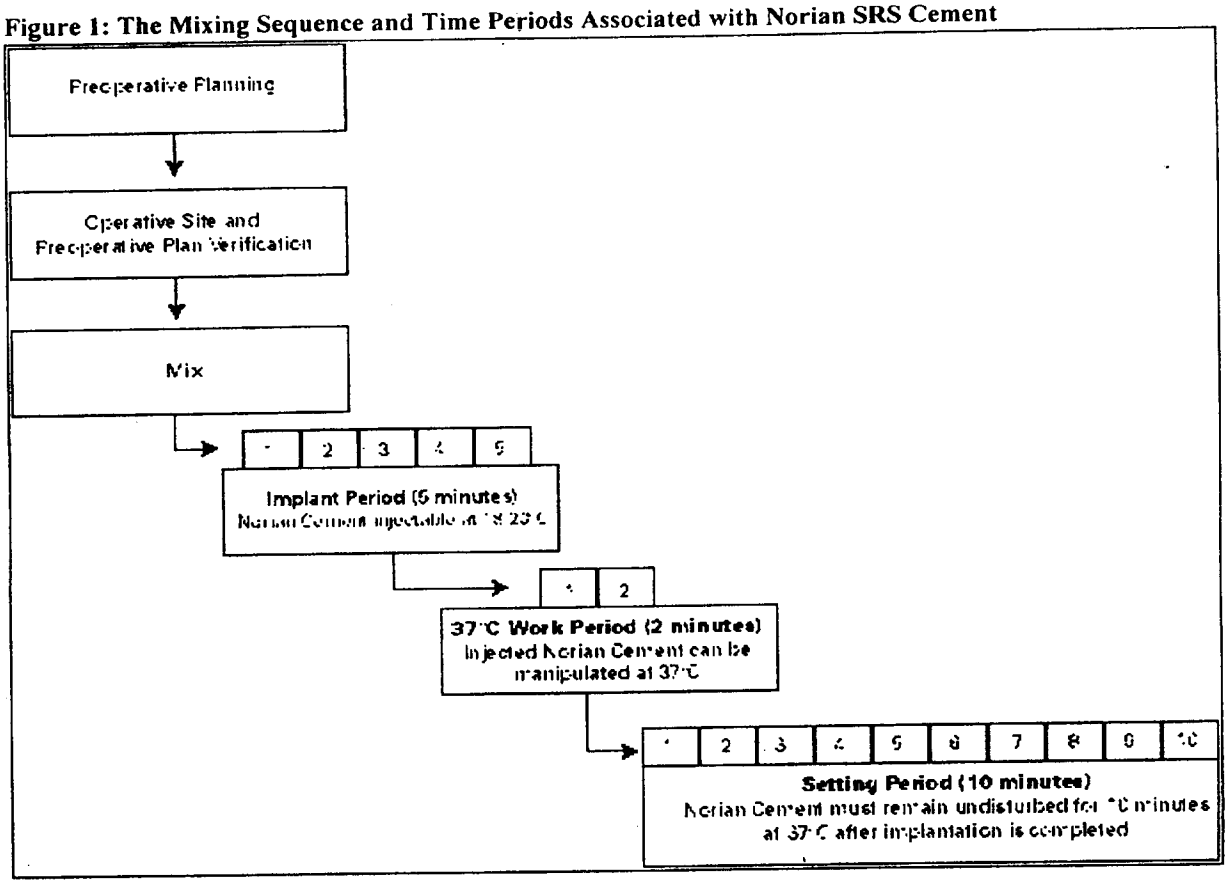
Figure 1: The Mixing Sequence and Time Periods Associated with Norian SRS Cement



Contraindications

Norian SRS Cement should not be used:

- in the presence of active or suspected infection
- in diaphyseal fractures
- as a substitute for external fixation

Precautions

Long Term Effects

- The long-term effects of extraosseous Norian SRS Cement or intra-articular Norian SRS Cement (material injected into the joint space) are unknown. Arthritis may be a possible complication of intra-articular Norian SRS Cement.
- The long-term refracture rate of patients with Norian SRS Cement is unknown.

External Fixation

The safety and effectiveness of early removal of external fixation when used with Norian SRS Cement has not been established.

General

- Familiarity with the surgical principles for cementing fractures, mixing instructions, instrumentation, injection technique, Implant Period, 37°C Work Period, Setting Period and Cure Period are required prior to treatment (see Figure 1).
- Because Norian SRS Cement must be implanted within 5 minutes from the end of mixing, the surgeon should develop a preoperative plan. This requires understanding the method, sequence, and estimated volume of Norian SRS Cement needed to fill the fracture void.

- If more than one Reactants Pack is required, the total volume (not to exceed 40cc) of Norian SRS Cement should be implanted within the 2 minute 37°C Work Period. Disturbing the initial Norian SRS Cement after 2 minutes may damage the construct.
- The Norian SRS Cement Reactants Pack should be equilibrated to 18 –23 C prior to mixing.
- If the Implant Period (5 minutes from end of mixing process) elapses and the Norian SRS Cement has not been implanted into the patient, the remaining paste must be discarded and a new Reactants Pack mixed.
- The safety and effectiveness of Norian SRS Cement in contact with adjacent allograft, acrylic, silicone, or polymer materials has not been established.
- In the event that the seal of the Reactants Pack is breached during mixing, proper eye protection and surgical gloves should be worn when cleaning up the components. Seek medical attention if the components are ingested or inhaled. If skin or eye contact occurs, do the following and seek medical attention if irritation occurs:
  Skin exposure: Wash area with soap and water.
  Eye exposure: Flush thoroughly with running water.
- Norian SRS Cement is for single use only, and should not be resterilized.
- Unused Norian SRS Cement should be discarded. Before disposal of a Reactants Pack, mix according to the directions for use to render the contents pH neutral.

Sterility

The Norian SRS Cement Reactants Pack is supplied sterile and non-pyrogenic. This product is sterilized by gamma irradiation. Do not resterilize. This product is intended for Single Use Only. Sterile product packaging should be inspected and if compromised, the product must be assumed non-sterile and appropriately discarded.

Use in Specific Populations

The safety and effectiveness of Norian SRS Cement has not been established in:

- multi-fragmentary intra-articular fractures that extend into the diaphysis and/or significant ligamentous disruption (scapholunate instability)
- fractures requiring open surgical reduction or bone grafting
- traumatic open injuries of the injured wrist which are predisposed to infection
- patients with compromised health (e.g., abnormal calcium metabolism, metabolic, vascular, or severe neurological disease, infection, immunologic deficiencies)
- patients who are skeletally immature
- pregnant or nursing women
- patients undergoing concurrent radiotherapy or chemotherapy treatment

Alternative Practices and Procedures

A variety of treatment options for low impact, unstable, metaphyseal distal radius fractures are available. Treatment options include casting, pins and casting, external fixation with or without pins, and open reduction with internal fixation.

Marketing History

Initial commercial use of Norian SRS Cement began in the Netherlands in 1994. It has been used throughout Europe since January 1997. It is available for marketing in Australia and Canada. Norian SRS Cement has not been withdrawn from these markets due to any device safety or effectiveness concerns.

Potential Adverse Events

Multicenter Clinical Trial

Norian SRS Cement was investigated in a prospective multicenter clinical trial including a total of 323 patients (161 patients treated with Norian SRS and 162 patients conventionally treated). The adverse events reported to be related to the fracture or treatment are listed in Table 1.

Table 1: Incidence of Complications on Per Patient Basis

Complication[a]	Norian SRS Cement			Control
	Total (n=161)	Extraosseous Norian SRS[b] (n=112)	Without Extraosseous Norian SRS (n=49)	Total (n=162)
Loss of Reduction[c]	46 (28.6%)	41 (36.6%)	5 (10.2%)	40 (24.7%)
Infection, (pin or K-wire)	3 (1.9%)[d]	2 (1.8%)	1 (2.0%)	25 (15.4%)[d]
Neuropathy[e]	8 (5.0%)	6 (5.4%)	2 (4.1%)	6 (3.7%)
Carpal Tunnel Syndrome[f]	4 (2.5%)	4 (3.6%)	0 (0.0%)	8 (4.9%)
RSD/Sudeck's	7 (4.3%)	6 (5.4%)	1 (2.0%)	8 (4.9%)
Tendinopathy[g]	6 (3.7%)	5 (4.5%)	1 (2.0%)	6 (3.7%)
Tendon Rupture	6 (3.7%)	5 (4.5%)	1 (2.0%)	2 (1.2%)
Infection, osteomyelitis	1 (0.6%)	1 (0.9%)	0 (0.0%)	0 (0.0%)
Pain	4 (2.5%)	4 (3.6%)	0 (0.0%)	10 (6.2%)
Swelling	2 (1.2%)	2 (1.8%)	0 (0.0%)	1 (0.6%)
Intra-articular Norian SRS Cement[h]	4 (2.5%)	4 (3.6%)	0 (0.0%)	NA
Other[i]	9 (5.6%)	6 (5.4%)	3 (6.1%)	13 (8.0%)
Total Patient Complications[j]	100 (62.1%)	86 (76.8%)	11 (22.4%)	119 (73.5%)
Total Patients Experiencing ≥ 1 Complication	74 (46.0%)	63 (56.3%)	11 (22.4%)	82 (50.6%)

a. Some patients reported more than one complication. Patients are reported with each type of complication only once.
b. Continued radiographic presence in 29 of 112 patients (26%) at their last visit.
c. There was statistically significantly greater ($p<0.0006$) loss of reduction in the extraosseous Norian SRS Cement group compared to the patients without extraosseous Norian SRS Cement. The control patients had statistically significantly greater loss of reduction compared to the Norian SRS Cement patients without extraosseous Norian SRS Cement ($p=0.0301$). The extraosseous Norian SRS Cement group had statistically significantly greater loss of reduction than the control group ($p=0.0336$). Patients treated with Norian SRS Cement experienced a greater loss of radial length (mean=4.5±4.0 mm) than those treated with conventional fixation (mean=3.7±4.0mm), although this difference was not statistically significant.
d. The proportion of infection was greater for the control patients due to external fixation pin tract infections (18/25); Norian SRS Cement patients did not initially receive external fixation as treatment. Infections were determined by the physician and not necessarily based on cultures.
e. Includes dysesthesia, paresthesia, radial nerve symptoms, ulnar nerve symptoms, and median nerve symptoms. One control patient had a median nerve dysfunction as a pre-existing event.
f. One control patient had carpal tunnel syndrome as a pre-existing condition.
g. Includes tendon weakness, tendonitis, stenosing tenosynovitis, and tendon adhesion.
h. Continued radiographic presence at 12 months in all 4 patients.
i. Includes cellulitis, shoulder bursitis, shoulder impingement, shoulder pain, pin problems, ulna fractures, thumb fracture, ulnar styloid nonunion, fall onto treated wrist, minor trauma to wrist.
j. The proportions of total complications between the total Norian SRS Cement patient population and the control patient population were not statistically significantly different from each other. The proportions of total complications in the extraosseous Norian SRS Cement patients and in the control patients were not statistically significantly different from each other. The proportions of total complications were significantly lower for the Norian SRS Cement patients without extraosseous material compared to patients with extraosseous Norian SRS cement ($p<0.0001$).

Potential Complications

Other local complications may occur, such as:

- Wound complications such as edema, hematoma, tenderness, redness, and drainage
- Device fracture
- Device migration
- Secondary fractures
- Nonunion or malunion

Summary of Preclinical Studies

In Vitro Investigations:

A summary of the preclinical bench studies is provided in Table 2 below.

Table 2: Summary of Preclinical Bench Studies

Test	Test Method	Results
Injection	Modified ASTM F451-86	Norian SRS Cement was found to be injectable using hand pressure intraoperatively during the working period under expected clinical conditions.
Intrusion	Modified ASTM F451-86	Norian SRS Cement was found to be injectable using hand pressure intraoperatively during the working period under expected clinical conditions (intrusion into a void of similar size to the porosity of cancellous bone).
Static Compression	Modified ASTM F451-86	The average compressive strength of tested Norian SRS Cement samples was ≥ 50 MPa upon setting for 24 hours. Testing out to 10 minutes curing time revealed an average compressive strength of 10 MPa, suggesting that minor compressive manipulation of the fracture site may occur without fracturing the SRS material.
pH	Modified ASTM E70-90	The average pH of curing Norian SRS Cement was within the biologically acceptable levels of 6.4 to 8.4.
Solubility	Modified ASTM E1148-87	The low solubility of Norian SRS Cement was demonstrated after 568 hours of immersion in phosphate-buffered saline solution in biologically simulated conditions (37°C and pH=7.4) demonstrating that the material does not dissolve extensively under conditions of 37°C and pH=7.4..
Temperature	Modified ASTM F451-86	The temperature from within and around a bolus of curing Norian SRS Cement maintained biologically compatible temperatures (< 42°C).
Compressive Fatigue Strength	Modified ASTM F451-86	The endurance limit for Norian SRS Cement for 1 million compression cycles was within a range of 5 to 10 MPa.
Diametral Compressive Strength (Tensile Strength)	Modified ASTM C1273-95a	The average tensile strength of Norian SRS Cement was approximately 2.2 MPa.
Flexural Strength (3- and 4- point bending)	Modified ASTM 1161-94; Modified ASTM D790-92	The average flexural strength of tested samples was 7.3 and 5.0 MPa in 3- and 4- point bending experiments, respectively.
Flexural Fatigue (4-point bending)	Modified ASTM 1161-94; Modified ASTM D790-92	The endurance limit for Norian SRS Cement for 1 million flexural cycles was within a range of 1.3 to 1.8 MPa.
Fracture Toughness	Modified ASTM E399-90	The mean fracture toughness of Norian SRS Cement was 0.06 MPa/m^2 and 0.14 MPa/m^2 using the chevron notch and disc-shaped compact tension tests, respectively.
Initiation to Set and Set Time (Indentation Test)	Modified ASTM C403/M-95; Modified ASTM C266-99	At 37°C, Norian SRS Cement set in 10 minutes sufficiently to resist a 90-lb indentation load (corresponding to a compressive strength of approximately 10 MPa).
Mineralogy Testing	X-ray diffraction; Fourier Transform Infrared Spectroscopy; carbon coulometry	After mixing the powder and liquid components together, Norian SRS Cement became a carbonated apatite with approximately 5% carbonate by weight. The degree of crystalline order (perfect crystal size) of Norian SRS Cement was approximately 200 Å when calculated using x-ray diffraction.

ASTM (American Society for Testing and Materials) Standards referenced:
F 451-86: Standard specification for acrylic bone cement
E 70-90: pH of aqueous solutions with the glass electrode
E 1148-87: Measurement of aqueous solubility
C 1273-95: Tensile strength of monolithic advanced ceramics at ambient temperatures
C 1161-94: Flexural strength of advanced ceramics at ambient temperature
D 790-92: Flexural properties of unreinforced and reinforced plastics and electrical insulating materials
E 399-90: Plane-Strain Fracture Toughness of Metallic Materials
F 403 and F 403 M-95: Time setting of concrete mixtures by penetration resistance
C 266-99: Standard Test Method for Time of Setting of Hydraulic-Cement Paste by Gillmore Needles

Biocompatibility

Norian SRS Cement was tested for biocompatibility in accordance with ISO (International Standards Organization) 10993.

- Cytotoxicity
- Systemic toxicity
- Acute Intracutaneous Reactivity
- Mutagenicity
- Hemolysis
- Muscle Implantation
- Sensitization
- Heavy Metals

The material passed each of these biocompatibility tests. In addition, chronic toxicity was assessed from the results of a long-term canine study. This study revealed no chronic toxicity associated with the implantation of Norian SRS Cement based on clinical observation, gross pathology, histopathology of the organs and implantation sites, and hematology. All evaluations demonstrated no abnormal pathologic changes and normal serum calcium and phosphorous levels. In addition, carcinogenicity testing was deemed not necessary based data from other sources (i.e., mutagenicity testing, pre-clinical testing, literature) that suggest the materials used in the product are not carcinogens. Furthermore, the device does not contain any foreign extractable or degradation products. Data from Fourier Transform Infrared Spectroscopy (FTIR) was provided to demonstrate that all potentially carcinogenic substances were eliminated during the manufacturing of the device. Data from rabbit pyrogenicity testing showed the device to be non-pyrogenic.

Extra-articular Distal Radius Fracture Biomechanics

Biomechanical testing of human cadaveric radii with extra-articular fractures of the distal radius, similar to those treated in the multicenter clinical trial demonstrated a statistically significant increase in load carrying capacity of fractured radii following Norian SRS Cement implantation.

Intra-articular Distal Radius Fracture Biomechanics

Biomechanical testing of human cadaveric radii, with intra-articular fractures of the distal radius, demonstrated a significant increase in fracture construct stability upon compression loading when Norian SRS Cement was used compared to conventional K-wire fixation. The fractures were similar to those treated in the distal radius fracture multicenter clinical trial.

The Extra-articular and Intra-articular Distal Radius Fracture Biomechanics studies were preformed using precursor formulations of the Norian SRS Cement. These data were determined to be applicable to the final device.

In Vivo Investigations:

The animal investigations were performed on a precursor formulation of the Norian SRS Cement. FDA determined that the data obtained from these studies were relevant as supporting information for the final Norian SRS Cement formulation used clinically. The precursor formulation is also referred to as Norian SRS Cement.

Primate Pilot Study

A pilot study was performed using a non-human primate model to evaluate casted fractures of the distal radius and the response to Norian SRS Cement. Bilateral distal radius fractures were created in three monkeys and treated with SRS (with or without reduction). Radiographic evaluation was performed every 2 weeks until sacrifice at 12 weeks, at which time histologic and mechanical evaluations were performed. The results, although limited to those from a few animals only, did not reveal any adverse safety or effectiveness results related to the use of Norian SRS Cement. The study was not pursued with additional animals for reasons associated with difficulty in creating reproducible fractures similar to distal metaphyseal fractures in humans.

Canine Study

Seventy-six skeletally mature canines were implanted with Norian SRS Cement in metaphyseal bone defects in the tibial plateau and distal femur. For early evaluation, 14 animals each were sacrificed at 24 hours, or at 2, 4, 8, and 16 weeks postoperatively. Long term data were collected from one animal each sacrificed at 32 and 78 weeks, with an additional four animals followed for 4.5 years. Whole bone torsional strength, compressive

strength, histologic, and radiographic analyses were performed after increasing periods of mechanical loading and bone incorporation.

Early histologic findings demonstrated Norian SRS Cement to be a biocompatible material with no adverse host tissue response. Bone apposition to exposed Norian SRS Cement surfaces was noted within two weeks of implantation. Osteoclastic cell-mediated remodeling was noted at the periphery of the Norian SRS Cement in the early time periods. The new bone deposition and remodeling of Norian SRS Cement resulted in re-establishment of the cortical walls between 4 and 8 weeks. The histologic finding of healing coincided with mechanical findings of healing determined by re-establishment of whole bone torsional strength by 8 weeks.

Histologic analyses of the 32 and 78-week specimens demonstrated continued remodeling of the remaining Norian SRS Cement. Osteoclastic cell-mediated resorptive cutting cones, vascular infiltration, new bone deposition, and cement remodeling lines similar to that of native skeletal remodeling processes were seen adjacent to and throughout the remaining Norian SRS Cement at each time period. Prior to sacrifice of the remaining four animals (4.5 years), the animals were examined clinically. None of the animals demonstrated pain or difficult movement with the experimental limbs, and all measures of physical health were normal. Biomechanical tests between the Norian SRS Cement and contralateral sides were similar, including the long-term (4.5 year) results. Histologically, variable amounts of remodeled Norian SRS Cement were evident in the implanted sections in a pattern similar to native bone.

Summary of Multicenter Clinical Study

A clinical study of Norian SRS Cement was conducted under an approved Investigational Device Exemptions (IDE) application. Five patients were enrolled in the feasibility portion of the study and treated with Norian SRS Cement. All patients maintained reduction for up to six months and revealed outcomes that were clinically consistent with those associated with standard treatment reported in the literature. The percutaneous administration of Norian SRS Cement was without serious or unanticipated complications. Additionally, results from six patients enrolled in a separate study outside the United States were presented. These patients had similar outcomes compared to the U.S. feasibility study patients and provided additional information about early cast removal, although the follow-up period was relatively short. These data, combined with the non-clinical data, supported initiation of a multi-center U.S. clinical study.

The prospective multicenter, randomized portion of the study was initiated in January 1995, and enrollment was completed in June 1997. The study protocol was limited to 25 centers and a total of 324 subjects to be evaluated and reported on at 3 and 12 months postoperatively.

Objective

The purpose of this study was to demonstrate the safety and effectiveness of Norian SRS Cement in the treatment of low impact, unstable and/or displaced metaphyseal distal radius fractures. The study was designed to demonstrate Norian SRS Cement superiority to the control group in the primary endpoints of radial length loss and grip strength 3 months after surgery.

Inclusion and Exclusion Criteria

The following inclusion and exclusion criteria were used for patient selection.

Inclusion Criteria:

- An unstable and/or displaced unilateral distal radius fracture resulting from a low energy impact
- An extra-articular fracture classified as AO Type A2.1, A2.2, A3.1, A3.2, and A3.3 or an intra-articular fracture classified as AO Type Cl.1, Cl.2, Cl.3, C2.1, and C2.2. Preselected treatment would consist of closed reduction with either casting or external fixation with or without the use of percutaneous K-wires (AO type A1, A2.3, all Type B, C2.3 and C3 fractures were not included).
- Male or female, 45 years of age or older
- Living independently and ambulatory at the time of injury
- Treatment administered within 5 days of injury
- Agreement to return for the specified follow-up evaluations
- Signed written informed consent

- Anatomic reduction within 2 mm of radial length, a volar angle of 0-28°, volar cortical alignment, and normal joint congruity

Exclusion Criteria:

- A multi-fragmentary intra-articular fracture extending into the diaphysis or significant ligamentous disruption (i.e., scapholunate instability)
- A Smith's fracture (i.e., volar displacement) or Barton's fracture (i.e., shearing)
- Open surgical reduction or bone grafting required
- A nondisplaced or stable fracture
- A previous wrist fracture in the injured limb within the last 12 months
- A concomitant limb fracture, ipsilateral ulnar fracture (excluding ulnar styloid process), an open fracture, nerve or blood vessel injury, or hard or soft tissue infection at the operative site
- Radiotherapy or chemotherapy
- A clotting disorder treated with anticoagulant therapy (e.g., heparin, coumadin)
- Medications known to affect skeletal metabolism or a metabolic disorder known to affect the skeleton, other than osteoporosis
- Physically or mentally compromised and unable to perform functional examinations
- A prisoner, a transient, or a history of alcohol or drug abuse within the last 12 months

Investigator Participation

Twenty-three centers (20 domestic, 2 European, and 1 Canadian) enrolled 323 patients. All institutions received IRB approval prior to study initiation. Prior to study initiation, investigators and participating research personnel were trained in Norian SRS Cement surgical technique, postoperative evaluation procedures, data collection, and adverse event reporting. Prior to patient enrollment, all sites were provided with a computer-generated randomization assignment.

Patient Population and Demographics

A total of 323 patients were randomized to Norian SRS Cement (161 patients) or control fracture stabilization (162 patients). The demographics and baseline characteristics were similar in both treatment groups. Overall there were 272 (84%) females and 32 (16%) males enrolled into the study. There was a significantly higher proportion (p=0.0447) of males in the Norian SRS Cement group (19.9%) compared to the controls (11.7%). The two treatment groups were evenly matched for average age which was 63.6 years overall. Nearly 90% of the population were Caucasians. There was no difference in the hand dominance split between the Norian SRS Cement group and the control group, and there was an approximately even split between dominant and non-dominant hand injuries. Using Chi square analysis, there were no other differences detected between the two groups for any of the other demographic variables: preselected treatment methods, fracture severity, medical history, and AO classification.

Table 3: Patient Characteristics

Characteristic	Norian SRS Cement	Control	p-value
Gender [Frequency (%)]			0.0447
Female	129 (80.1%)	143 (88.3%)	
Male	32 (19.9%)	19 (11.7%)	
Age (years)			0.8945
Mean ±SD	63.5 ± 11.0	63.6 ± 11.5	

Evaluation Schedule

Preoperatively patients were assessed clinically and radiographically. Once patients were enrolled, they were asked to return for clinical and radiographic assessment at 1, 2, 4, and 6-8 weeks, and 3, 6, and 12 months postoperatively. Functional range of motion assessments were obtained for study patients after their initial immobilization was removed. This occurred at 2 weeks for the experimental group at the time the cast was removed and replaced with a removable splint, and between 6 and 8 weeks for the control group.

Patient Accountability

All enrolled patients were accounted for at all evaluation time points where radiographic and clinical assessments were obtained as shown in Table 4.

Table 4: Number of Patients Accounted For

Number of Patients with Results	Norian SRS Cement (n=161)							Control (n=162)						
	1 wk	2 wk	4 wk	6-8 wks	3 mos	6 mos	12 mos	1 wk	2 wks	4 wks	6-8 wks	3 mos	6 mos	12 mos
Expected[a]	161	160	159	159	158	156	150	162	162	162	161	159	155	154
Evaluated[b]	157	157	155	157	153	140	134	156	157	154	159	150	145	138
Missed[c]	3	2	4	1	3	10	2	6	5	7	0	5	8	2
Pending[d]	0	0	0	0	0	0	9	0	0	0	0	0	1	9
Lost to F/U[e]	0	0	0	1	1	4	2	0	0	0	2	3	0	2
Withdrawn[f]	1	1	0	0	1	2	1	0	0	1	0	1	1	2
Deceased[g]	0	0	0	0	0	0	2	0	0	0	0	0	0	1

a. the number of patients who have reached that time point and are not deceased, withdrawn, or lost to follow-up
b. the number who actually returned for evaluation
c. the number who did not return for an evaluation at that time point and are not deceased, withdrawn, or lost to follow-up
d. the number where data either was not due or was expected and not received at each time point
e. the number who can no longer be contacted or are unable to return at that time point
f. the number of patients who elected to withdraw from the study at each time point
g. the number of subjects who died during that time point

Study Design and Analyses

Randomization

Patients were asked to participate prior to knowledge of the type of treatment that they would receive, i.e., investigational or control. Patients who met the inclusion criteria were enrolled and randomized to Norian SRS Cement or control fracture stabilization based on four parameters, i.e., fracture type, hand of injury, bone mineral density, and designated treatment method. Designated treatment method was based on the physician's assessment of how they would manage the patient, i.e., with external fixation or with a cast. Patient enrollment was stratified to ensure equal distribution of these four parameters, and these were equally matched between treatment groups. After randomization, patients were not masked to the treatment that they received.

Patients who were randomized to Norian SRS Cement did not receive external fixation. Norian SRS Cement patients who had been designated as needing external fixation received a cast and Norian SRS Cement only.

Treatment Method – Investigational vs. Control

The use of K-wires was optional for both treatment groups. Norian SRS Cement patients were stabilized using Norian SRS Cement and a cast for 2 weeks, followed by a splint for 2 to 4 weeks (20–22 hours per day). Patients in the control group received a cast or external fixation for 6–8 weeks. See Table 5. Hand exercises were started at 2 weeks for the Norian SRS Cement patients and at 6–8 weeks for the control patients.

Study Endpoints

The endpoint for evaluation of the functional parameters was 3 months. Patients were evaluated for radiographic and clinical parameters postoperatively through 12 months. Radiographs were digitized, measured electronically, and then evaluated by an independent radiologist and an independent orthopedic surgeon. Investigators, not masked to treatment type, completed the remainder of the clinical evaluations. All range-of-motion evaluations were conducted by a physical and occupational therapist.

Table 5: Immobilization Time

Treatment Group	Immobilization Method	Immobilization Time (days)
Norian SRS Cement	Cast (n=161)	15.8 ± 5.6
Control	Cast (n=108)	40.3 ± 12.7
Control	External Fixator (n=54)	44.8 ± 8.2

Effectiveness Analyses

Effectiveness variables were divided into primary, secondary, and ancillary outcomes according to the protocol. Outcomes were either functional or radiographic measures and are listed in Table 6. Outcome success, as described in the protocol, was determined using the 3 month endpoint.

Table 6: Functional and Radiographic Effectiveness Outcomes

Importance	Functional	Radiographic
Primary	Grip Strength	Radial Length
Secondary	Flexion Extension Pronation Supination Radial Deviation Ulnar Deviation	Volar/Dorsal Angle Dorsal Angle Ulnar Variance Radial Shift Joint Alignment
Ancillary	Quality of Life/SF-36 HSQ Hand Use Finger Range of Motion Edema	Fracture Healing (Gap)

Primary (Functional) Endpoint: Grip Strength

Grip strength was assessed clinically using a Jamar dynamometer at all postoperative time points beginning at 6-8 weeks. Three assessments were obtained for the treated and the uninjured hand at each interval. The average of the treated side was then expressed as a value of the uninjured hand and normalized for dominance. Successful grip strength was defined as regaining at least 10% grip strength in the injured hand compared with the gripping ability of the uninjured hand at the 3 month postoperative time point. Please see Table 7 for the grip strength means and success rates for 3 and 12 months. Although the immobilization time was less for the Norian SRS Cement patients, the grip strength for both groups was similar at 3 and 12 months.

Table 7: Primary Outcome Results -Grip Strength

Grip Strength	3 Months		12 Months	
	SRS	Control	SRS	Control
Number of patients	146	138	130	134
Mean (% of contralateral) ±SD	58.6 ± 24.5	57.3 ± 35.1	88.8 ± 24.3	89.4 ± 23.0
Success[a]	100%	98%	100%	100%

a. Individual patient success for grip strength was defined as regaining at least 10% grip strength in the injured hand compared to the contralateral.

Primary (Radiographic) Endpoint: Radial Length

Radial length, the distance from the distal tip of the radial styloid to the distal ulnar articular surface, was assessed radiographically from standard PA radiographs postoperatively at 1, 2, 4, and 6-8 weeks and at 3, 6, and 12 months postoperatively. Radial length was assessed for the treated and uninjured wrists, and then compared. Successful radial length maintenance was defined in the protocol as less than 5 mm difference between the two sides. Results are provided in Table 8. Norian SRS Cement patients experienced a greater loss of radial length at 3 and 12 months than those treated with conventional fixation, although this difference was not statistically significant based on repeated measures analysis and univariate analysis at these time points.

Table 8: Primary Outcomes Results – Loss of Radial Length

Loss of Radial Length	3 Months		12 Months	
	SRS	Control	SRS	Control
Number of patients	143	143	129	136
Mean (mm)±SD	4.7 ± 4.3	4.0 ± 4.3	4.5 ± 4.0	3.7 ± 4.0
Success[a]	65%	66%	63%	65%

a. Successful radial length maintenance for each patient was defined as less than 5 mm difference between the injured and the contralateral sides.

Primary Outcomes Results by Designated Treatment Method

An analysis was conducted to evaluate each of the treatment groups by the designated treatment method (cast or external fixation). Prior to randomization in this trial, physicians were asked to determine how they would manage the patient –with external fixation or with a cast. All patients were then randomized. Patients who were randomized to Norian SRS Cement did not receive external fixation. Norian SRS Cement patients who had been designated as needing external fixation received a cast and Norian SRS Cement only.

For the primary clinical outcome of grip strength, the results revealed no statistically significant differences in grip strength between the groups at 3 and 12 months for either cast or external fixation designated treatment methods. For the primary radiographic parameter of radial length loss, there was statistically significantly greater radial length loss at 12 months for Norian SRS Cement patients designated for external fixation compared to the control patients who received external fixation. For patients designated for cast treatment at randomization, the clinical and radiographic results were similar to those for patients designated for external fixation, with the exception that there were no significant differences between Norian SRS Cement patients and control patients in terms of radial length loss. See Table 9.

Table 9: Grip Strength and Radial Length Loss by Designated Treatment Method

Outcome	Designated External Fixation[a]		Designated Cast[a]	
	SRS	Control	SRS	Control
Grip Strength at 3 Months Mean (% contralateral) ±SD	58.8 ± 20.6	57.3 ± 42.5	58.5 ± 26.3	57.3 ± 31.0
Radial Length Loss at 12 Months Mean (mm) ±SD	4.4 ± 3.8[b]	1.9 ± 3.3[b]	4.5 ± 4.1	4.5 ± 4.0

a. Designated Treatment Method was used as one of the randomization parameters.
b. Statistically significant (p=0.0019 using an unpaired student's t-test).

Primary Effectiveness Outcomes: Conclusion

Patients treated with Norian SRS Cement demonstrated similar functional and radiographic results based on the primary effectiveness variables when compared to the control patients. For the subgroup of patients designated for external fixation, the Norian SRS Cement patients who received Norian SRS Cement and cast only had greater radial length loss than the control.

Secondary (Functional) Endpoints

Secondary functional endpoints included flexion, extension, pronation, and supination. These parameters were measured at 6-8 weeks, 3 months, 6 months and 12 months postoperatively using a standard goniometer. The Norian SRS Cement treated group was also evaluated at the 2- and 4-week time points. Percentage values were obtained by comparing the treated side to the uninjured side. Success for each of the range of motion (ROM) parameters was defined as regaining at least 10% of the contralateral side.

Table 10: Percentage and Proportion of Successful Secondary Endpoints

Successful Outcomes by Treatment		3 Months		12 Months	
		%	n	%	n
Flexion	Norian SRS	100	147/147	99	127/128
	Control	100	136/136	100	130/130
Extension	Norian SRS	99	146/147	100	128/128
	Control	99	134/136	100	130/130
Pronation	Norian SRS	100	147/147	100	128/128
	Control	100	137/137	100	129/129
Supination	Norian SRS	99	146/147	99	127/128
	Control	99	135/136	100	129/129

Ulnar and radial deviation were also defined as secondary functional endpoints; however, success and failure were not defined for these endpoints. Reported measurements were expressed as a percentage of the contralateral side. Descriptive statistics for the 3- and 12-month endpoints are provided in Table 11. There

were no significant differences between the Norian SRS Cement treatment group and the control treatment group for ulnar or radial deviation. These measurements improved over time for both treatment groups.

Table 11: Descriptive Statistics for Ulnar Deviation and Radial Deviation

Descriptive Statistics by Treatment		3 Months		12 Months	
		SRS	Control	SRS	Control
Ulnar Deviation	N	147	136	128	130
	mean (%) ± SD	74.4 ± 34.0	75.9 ± 33.9	85.2 ± 34.5	90.1 ± 41.9
Radial Deviation	N	147	136	128	130
	Mean (%) ± SD	94.1 ± 46.8	88.3 ± 61.7	106.5 ± 45.3	111.5 ± 64.3

Secondary (Radiographic) Endpoints

Secondary endpoints included volar/dorsal angle, ulnar variance, radial shift, and articular step-off measured at 1, 2, 4, and 6-8 weeks, and at 3, 6, and 12 month postoperative time points using standard PA and lateral view radiographs. Measurements of the treated side were subtracted from the uninjured side for all the parameters, except for articular step-off which measured the difference in the alignment of the articulating surfaces in millimeters from the central axis of the wrist.

Success for the secondary endpoints was specified for fracture healing, volar/dorsal angle (change and anatomic dorsal angle), and articular step-off. Radiographic evidence of a fracture gap less than 3 millimeters at the 3-month postoperative time point was considered successful fracture healing. Success for the volar/dorsal angle was defined as less than 20 degrees of change in the volar or dorsal directions and less than 10 degrees of dorsal angle. Success for articular step-off was defined as less than 2 millimeters. Successful secondary endpoint results for the 3 and 12-month endpoints are provided in Table 12. There were no significant differences between the control and Norian SRS patients at any time point.

Table 12: Percentage and Proportion of Successful Secondary Radiographic Outcomes

Successful Outcomes by Treatment		3 Months		12 Months	
		%	n	%	n
Fracture Healing (gap)	Norian SRS	99	148/149	100	127/127
	Control	99	143/144	100	133/133
Volar/Dorsal Angle change	Norian SRS	71	103/146	69	90/131
	Control	70	99/141	77	102/132
Dorsal Angle	Norian SRS	70	106/151	68	91/133
	Control	72	104/144	79	108/136
Joint Alignment /Step off	Norian SRS	100	150/150	100	132/132
	Control	99	143/144	100	137/137

Secondary Effectiveness Endpoints Conclusions

There were no differences found between the Norian SRS Cement group and the control group at 3 and 12 month time points.

Ancillary Endpoints

Functional ancillary endpoints included quality of life as measured by the Health Status Questionnaire, hand use, quality of life directly related to wrist and hand activities using a hand usage questionnaire, finger range of motion, and edema. Success for these endpoints was not defined; however, mean Physical and Mental Component Summaries (PCS, MCS) from the Health Status Questionnaire are provided in Table 13. The results for both treatment groups were similar.

Table 13: Mean Physical Component Summary (PCS) and Mean Mental Component Summary (MCS), Composite Measurements of the Health Status Questionnaire

Treatment	Mean Score[a]	6 Months	12 Months
Norian SRS	PCS	48	47
	MCS	55	54
Control	PCS	48	48
	MCS	53	54

a. Calculated by composing the eight aggregate scales for the Health Status Questionnaire, averaging these for the treatment group, and then transforming into a z-score and using a validated coefficient to arrive at the MCS and PCS scores. Data was not collected for the 3 months time point.

The single radiographic ancillary endpoint was qualitative assessment of fracture healing, where the determination was made by an independent radiologist that the fracture was healed. Both groups showed an equivalent proportion of fracture healing at 3 and 12 months (see Table 14).

Table 14: Percentage and Proportion of Fractures Healed

Treatment	3 Months		12 Months	
	%	n	%	N
Norian SRS	96	140/146	100	127/127
Control	97	140/145	100	133/133

Safety Analyses

Safety analyses included all patients regardless of the completeness of their follow-up data or length of follow-up. Reported complications can be found in this summary in the Potential Adverse Effects section. Overall, no difference was detected between the Norian SRS Cement treated group (100 events) and the control group (119 events). The only statistical difference noted between groups was for the subgroup of Norian SRS Cement patients with extraosseous material: in this subgroup there was a statistically significantly greater loss of reduction compared to the control group.

Patient Outcome

For a patient to be considered an overall study success, the patient must have met all of the success criteria and none of the failure criteria. The success rates for the functional endpoints, the radiographic endpoints, and combined (functional and radiographic) overall are provided in Table 15.

Table 15: Functional, Radiographic, and Combined Overall Percentage and Proportion of Success

Successful Outcomes by Treatment		3 Months		12 Months	
		%	n	%	N
Functional	Norian SRS	99	145/147	99	128/130
	Control	96	134/140	100	135/135
Radiographic	Norian SRS	50	76/151	47	62/133
	Control	48	69/145	52	72/138
Combined Overall	Norian SRS	49	74/152	46	61/134
	Control	42	62/147	46	63/138

Conclusions Drawn from the Studies

The results of the clinical study showed the immobilization time for the Norian SRS Cement patients could be as short as 2 weeks (followed by a removable splint for 2-4 weeks), without statistically significant differences compared to the control group for either primary endpoint (i.e., grip strength or radial length loss) at the 3- and 12-month evaluations. A direct comparison of immobilization times cannot be made,

however, since the study protocol dictated that Norian SRS Cement patients have their casts removed at 2 weeks (followed by a removable splint for 2-4 weeks), and that control patients have their casts removed at 6-8 weeks.

The clinical study also showed that patients with extraosseous Norian SRS exhibited a greater loss of reduction compared to Norian SRS patients without extraosseous Norian SRS. Patients with extraosseous SRS also exhibited greater loss of radial length than either Norian SRS patients without extraosseous SRS or control treated patients. Furthermore, the clinical study showed that at both 3 and 12 months, the SRS patients designated as needing external fixation, but who underwent SRS and cast treatment alone, exhibited greater loss of radial length than SRS patients not designated as needing external fixation.

The frequency and type of complications that occurred between the Norian SRS Cement and control group were similar, with the exception that for the subgroup of Norian SRS Cement patients with extraosseous material, there was a statistically significantly greater loss of reduction compared to the control group.

Although the clinical study did not achieve its original objective of demonstrating Norian SRS Cement superiority compared to the control group, for the primary endpoints of radial length loss and grip strength, the data show the device is safe and effective for a selected group of patients when used as indicated. Given the similar performance between Norian SRS Cement and the control group in these effectiveness parameters, and considering the similar adverse event profile, it was determined that the early immobilization (cast for 2 weeks, then removable splint for 2–4 weeks) afforded by Norian SRS Cement would provide a clinical benefit to some patients, without exposing them to undue additional risk.

Panel Recommendation

On October 9, 1998, the Orthopedic and Rehabilitation Devices Panel recommended approval of the Norian SRS Cement as an adjunct for fracture stabilization in the treatment of unstable, distal radius fractures in cases where early mobilization is indicated. The panel recommended several labeling changes as conditions of approval: (1) that the labeling include the data on loss of radial length and extraosseous Norian SRS Cement; (2) that it warn about the unknown long-term effects of intra-articular SRS Cement; (3) that it address their expressed concern about using Norian SRS alone to treat highly comminuted fractures; and (4) that it state that Norian SRS Cement is not a substitute for external fixation. The panel also recommended a training plan to surgeons that would address how to use the material appropriately based on information learned in the clinical investigation, such as the increased potential for extraosseous Norian SRS Cement to adversely affect patient outcome.

In addition, the panel requested a PMA post-approval study for long-term safety evaluation of all patients, with additional follow-up to be collected on the four patients with intra-articular Norian SRS Cement. The panel also raised concerns regarding the continued presence of extraosseous Norian Cement and the unknown long-term effects, and recommended these patients be followed until there is no material present radiographically.

CDRH Decision

CDRH agreed with the Panel's recommendations regarding the data in the PMA and the appropriate patient population for treatment with the Norian SRS Cement. CDRH concluded that Norian SRS Cement is safe and effective when used as an adjunct for fracture stabilization in the treatment of low impact, unstable, metaphyseal distal radius fractures in cases where early mobilization (cast for 2 weeks, then removable splint for 2–4 weeks) is indicated, and that Norian SRS Cement is not indicated alone for use in highly comminuted fractures.

CDRH agreed with the Panel's recommendations that the PMA be approved subject to conditions, and concurred with the conditions recommended by the Panel, with an additional condition that an animal study be performed to investigate the long-term effects of intra-articular injection of Norian SRS Cement. This animal study was required to provide sufficiently long-term data (i.e., five-year rabbit model data) to assess whether intra-articular injection of Norian SRS Cement adversely affects the joint. This animal

study will allow for controlled intra-articular injection of the material, as well as the necessary follow-up to assess long-term effects on the joint. This data will be used to supplement the human clinical information on patients with intra-articular Norian SRS Cement requested by the Panel.

Norian Corporation submitted information that adequately addressed each of the conditions of approval identified above. The company submitted revised labeling and a physician-training plan. In addition, the applicant agreed to conduct post-approval clinical studies on the patients enrolled in the study, as well as the above-mentioned animal study. Goals of the post-approval clinical study are to further evaluate the safety and effectiveness of Norian SRS Cement, to assess the long-term risk of refracture associated with the use of the device, and to further evaluate patients with extraosseous Norian SRS Cement present at the time the study was completed, until there is no material present radiographically.

CDRH determined that, based on the submission of modified labeling and a physician-training plan, and the applicant's agreement to conduct post-approval studies, the application was approvable without further conditions.

FDA inspections completed on November 21, 1997, and November 10, 1998, determined the manufacturing facilities to be in compliance with the Good Manufacturing Practices Regulation.

CDRH issues an approval order for the stated indication for the applicant's PMA for Norian SRS Cement on December 23, 1998.

Approval Specifications

Directions for Use: See labeling.

Hazards to Health from Use of the Device: See indications, contraindications, warnings, precautions, and adverse events in labeling.

Post-approval Requirements and Restrictions: See approval order.