Summary of Safety and Effectiveness Data

1.0 General Information

Device Generic Name	Sodium hyaluronate
Device Trade Name	Supartz™
Applicant's Name	SEIKAGAKU CORPORATION Tokyo, Japan
U.S. Representative	Quintiles, Incorporated 1300 North 17th Street, Suite 300 Arlington, VA 22209
PMA Number	P980044
Date of Notice of Approval to the Applicant	January 24, 2001

2.0 Indications for Use

SUPARTZ™ is indicated for the treatment of pain in osteoarthritis (OA) of the knee in patients who have failed to respond adequately to conservative non-pharmacologic therapy and simple analgesics, e.g., acetaminophen.

3.0 Contraindications

- Do not administer to patients with known hypersensitivity (allergy) to hyaluronan (sodium hyaluronate) preparations.
- Do not inject this product in the knees of patients with infections or skin diseases in the area of the injection site.

4.0 Warnings and Precautions

See labeling.

5.0 Device Description

SUPARTZ™ is a sterile, viscoelastic, non-pyrogenic solution of purified, high molecular weight sodium hyaluronate (620,000-1,170,000 daltons) having a pH of 6.8-7.8. The sodium hyaluronate is extracted from chicken combs. Sodium hyaluronate is a polysaccharide containing repeating disaccharide units of gluculoronic acid and N-acetylglucosamine. SUPARTZ™ is supplied in a 2.5 mL glass syringe. The contents of the syringe are sterile and non-pyrogenic. Each one mL of SUPARTZ™ contains 10mg of sodium hyaluronate dissolved in a physiological buffer (1.0% solution).

Each 2.5mL prefilled syringe of SUPARTZ™ contains:

Sodium Hyaluronate	25 mg
Sodium Chloride	21.25 mg
Dibasic Sodium Phosphate Dodecahydrate	1.343 mg
Sodium Dihydrogen Phosphate Dihydrate	0.04 mg
Water for Injection	q.s.

6.0 Alternative Practices and Procedures

For patients who have failed to respond adequately to conservative nonpharmacological therapy and simple analgesics, e.g., acetaminophen, alternative therapies to SUPARTZ™ include nonsteroidal anti-inflammatory drugs (NSAIDS); intra-articular corticosteroid or unmodified hyaluronan injections; avoidance of activities that cause joint pain; exercise; physical therapy; removal of excess fluid from the knee. For the patients who have failed the above treatments, surgical interventions such as arthroscopic surgery and total knee replacement surgery are also alternative treatments.

7.0 Potential Adverse Effects

The population of patients evaluated for the safety of SUPARTZ™ included all patients receiving at least one injection (619 SUPARTZ™; 537 control injection) in five controlled clinical trials. The most common adverse events (occurring in greater than 4% of SUPARTZ™-treated patients) were: arthralgia, defined as joint pain with no evidence of inflammation; arthropathy/arthrosis/arthritis, defined as joint pain with evidence of inflammation; back pain; pain (non-specific); injection site

reaction; headache; and injection site pain (See Table 1). There were no statistically significant differences in the incidence rates of these adverse events between the treatment and control groups.

Other adverse events occuring in 4% or less but not less than 1% of the SUPARTZ treated patients included upper respiratory tract infection, influenza-like symptoms, nausea, sinusitis, urinary tract infection, bronchitis, abdominal pain, diarrhea, inflicted injury, leg pain, discomfort in legs, dyspepsia, dizziness, rhinitis, and fall.

Of 8 allergic reactions reported, 5 occurred in the SUPARTZ™ group. All five events were classified as mild to moderate. These were: hayfever (2), reaction on face and neck, cutaneous reaction forearms and knees, and an undefined mild allergy reaction.

8.0 Marketing History

SUPARTZ™ has been commercially distributed in the following countries outside of the United States:

Japan

Korea

Sweden

Finland

Iceland

Austria

Italy

China

Portugal

Denmark

Spain

SUPARTZ™ has not been withdrawn from marketing in any country for any reason related to the safety and effectiveness of the device.

9.0 Summary of Preclinical Studies

The following is an overall review of the safety and activity testing of SPH (purified high molecular weight sodium hyaluronate extracted from rooster combs).

Pharmacokinetics

The fate of radiolabeled, fluorescence-labeled, and unlabelled SPH was studied following intra-articular (ia), intraperitoneal (ip), subcutaneous (sc), and intravenous (iv) injection. Test species used were rats, rabbits, and primates.

Single injections of 20 or 100 mg/kg (ip), 60 mg/kg (sc), or 10 mg/kg (im) radiolabeled SPH were administered to rats; distribution and excretion were studied up to 192 hours following injection.. Peak plasma levels were achieved within 24 - 96 hours after treatment. From 120 - 192 hours after injection, 84 – 88% SPH was excreted in expired gas and urine, and SPH was widely and evenly distributed in various tissues.

Single ia injections of 1.93 mg/kg or 0.1 mg/kg SPH were administered to male rabbits. At 24 and 72 hours post-administration, low levels of radioactivity were found in the mesenteric lymph node. At 12 hours post-administration, low but detectable levels of radioactivity were observed in all tissues other than at the site of administration, where levels were highest. Radioactivity was found mainly in synovial fluid, joint capsule, synovial tissue, and ligament and muscle. The radioactivity decreased over time.

Rabbits were given ia injections of unlabelled SPH. Results indicated that injected hyaluronan was cleared from the joint with a half-life of approximately 20 hr. In a related experiment, fluorescein-labeled SPH was injected into the ia cavity of rabbits, with the joint examined microscopically at various timepoints after administration. Initially, the fluorescence was confined to the surface layer of the synovial tissue, but by the end of 24 hr fluorescence was well distributed through the tissues of all elements in the joint. Fluorescence was diminished but still present 72 hr after treatment.

A single dose of 1mg/kg SPH was given iv in the auricular vein of rabbits. Before 6 hours after administration, 98% of the radioactivity disappeared from the blood, and before 100 hours, 83% of the administered dose was excreted in the expired gas and urine. The high radioactivity observed in the liver and spleen was decreased at 100 hours after administration.

Radiolabeled 14C-SPH was administered to monkeys via ia injection into both the temporomandibular and knee joints. Plasma concentrations beginning 6 hr after injection reached the maximum concentration at 48 hr after injection to either joint. Radioactivity was still observed at 72 hrs in the synovial tissue and joint capsule. Radioactivity was noted in the liver, spleen, and kidneys at 19 hr post-injection. Most elimination was via expelled air with urinary and fecal excretion about 5 %.

Taken together, these studies indicate that in these models, exogenous SPH is widely distributed to tissues throughout the body, rapidly metabolized to low molecular weight saccharide compounds and excreted in expired gas and urine.

Toxicology

Acute Systemic Toxicity

SPH, as present in SUPARTZ™, has been administered to mice, rats, and rabbits by the oral, sc and ip routes at concentrations of 2 and 3% in saline. SPH of different average molecular weights ranging from 330,000 to 2,150,000 D has been administered as 2% solutions by ip injection to mice. The acute toxicity of products resulting from the incubation of SPH with hyaluronidase (HAase) has been evaluated in mice and rats following ip injection. Finally, pyrolysis products of SPH have also been evaluated for systemic acute toxicity in mice and rats by ip injection.

No mortality was seen following the administration of the maximum possible volumes of either the 2% or 3% solution of SPH by the oral or sc routes to mice, rats or rabbits. The oral doses administered in these studies ranged from 800 to 2,400 mg/kg and the sc doses ranged from 600 to 4,000 mg/kg. In comparison, the anticipated human dose of sodium hyaluronate for a 45 kg (100 lb) person, for example, is 0.55 mg/kg per ia injection. SPH administered ip produced some mortality in some groups. Sufficient mortality was observed in only two studies to allow the estimation of an LD50, which the results suggest is at least 1,500 mg/kg and probably greater than 2,000 mg/kg (2 g/kg).

In the study of the acute toxicity of hyaluronans having different average molecular weights, either 1 or 2 mice died in the high dose groups treated with hyaluronan having molecular weights of 540,000, 730,000, 1,000,000, 1,230,000 and 1,600,000. SUPARTZ™ has a molecualr weight of 620,000-1,170,000 D. No deaths were seen in animals treated with 330,000 or 2,150,000 molecular weight material nor in any animals treated with lower doses of any of the test materials. In the absence of a trend with molecular weight, it would appear that these materials had an equal degree of acute toxicity.

Chronic toxicity

Two studies were conducted to determine the results of long-term exposure to SPH. In one study, SPH was administered to rats by ip injection of 15, 30 or 60 mg/kg daily for 6 months. Approximately two thirds of the animals were sacrificed at the end of the treatment period while the remaining third were allowed to recover for 5 weeks before they were sacrificed and examined. Seven animals out of the 80 in the two highest dose groups died during the study. Four of these deaths were definitely attributable to injection errors. Mortality was only seen in the two highest dose groups. Animals in the highest dose group (60 mg/kg) consumed less food and displayed an increased incidence of retinal hemorrhage compared to control animals. No consistent compound related histopathological findings were present. The 60/mg/kg dose was an effect level and the 30 mg/kg dose was considered to be a no effect level.

In the other study, SPH was administered to beagle dogs (7 dogs/sex/group) by intra-articular injection of 2, 6, or 12 mg/kg two times per week for 3 months (2 dogs/sex/group) or 6 months (5 dogs/sex/group). The dogs treated for 3 months and 3 dogs/sex/group from those treated for 6 months were sacrificed and examined at the end of the treatment periods, while 2 dogs/sex/group were allowed to recover for 3 months after the 6 month treatment regimen. No histopathologic or grossly observable abnormalities were detected in any of the treated animals. No dogs died during the study. This study indicated that under the conditions of the study, SPH was not toxic at the highest dose tested (12 mg/kg).

Subacute toxicity

In a subacute toxicity study, SPH was administered to rats by ip injection at doses of 27, 40, 60, and 90 mg/kg once per day for 4 weeks. One half of the rats were sacrificed 2 weeks after the final dose, with the remainder sacrificed 4 weeks after the final dose. The two highest doses in this study were associated with significant changes in hematological and clinical chemistry parameters. Histopathological changes were not evident in the tissues of treated animals. The lowest effect level in this study was 60 mg/kg and 40 mg/kg was a no effect level.

Subchronic toxicity

The subchronic toxicity of SPH was evaluated in two studies. The first study involved daily treatment of rats by ip injection of 15, 30, or 60 mg/kg SPH for three months followed by a 35 day recovery period for half of the animals. In the second study, rabbits were given intra-articular injections of SPH of 2, 4, or 8 mg/kg SPH twice per week for 3 months. Half of the rabbits in the

control and highest dose groups were allowed to recover for 1 month following the last dose. All rabbits in the other groups were sacrificed and examined at the end of the treatment period.

No mortality was associated with treatment in either of these studies. In the rat study, alterations in hematologic and clinical chemistry parameters were found at the two highest dose levels. Slight histopathological changes in the renal tubules were also noted at these doses. In the rabbit study there were no clear-cut compound related changes observed in any treatment group. The lowest effect level in the rat study was 30 mg/kg and 15 mg/kg was the no effect level. In the rabbit study, the highest dose tested (8 mg/kg) was a no effect level.

Reproductive Toxicity

The reproductive toxicity of SPH has been investigated in four nonclinical studies. In three of these studies the effects of sc administered SPH in three different phases of the reproductive process were examined. In the first one, male and female rats were treated with SPH prior to mating. In the second, SPH was administered to pregnant female rats during days 7 to 17 of gestation. In the third, SPH was administered to pregnant female rats beginning on day 17 of gestation and continued until weaning. In addition to the rat studies, a standard teratology study was conducted in rabbits with ip administration of SPH.

The results of these studies indicated that in all cases there was no significant effect on reproductive performance or outcome. Fertility, viability, and developmental parameters were unaffected. Slight increases in the incidence of minor skeletal anomalies in fetuses of dams treated with the highest doses were most likely attributable to maternal effects of the treatment.

Mutagenicity/Genotoxicity

The genetic toxicity of SPH and its pyrolysis products was evaluated in four in vitro genetic toxicity bioassays. SPH and its pyrolysis products were tested for their ability to induce reverse mutations in various tester strains of Salmonella typhimurium (Ames test) in the presence and absence of a microsomal metabolic activation system. SPH did not induce a significant increase in the number of revertant colonies in any of these strains.

Mice injected with a 2% solution of SPH ip at doses of 250, 500, and 1,000 mg/kg did not show an increase in the frequency of polychromatocytes with micronuclei at 24, 48, or 72 hr post-treatment.

Finally, the incubation of SPH with hamster lung cells in the presence and absence of a microsomal metabolic activation system did not result in an increase in the frequency of chromosomal aberrations in the treated.

Sensitization/Immunogenicity

SPH was administered to mice, rats, guinea pigs, and rabbits by intradermal, im or intra-articular injection. Endpoints examined included delayed dermal sensitization, passive systemic anaphylaxis, delayed cutaneous anaphylaxis and other miscellaneous tests designed to indicate the presence of antibodies or cellular response. In three studies, sera from animals that had been treated with SPH by continuous administration for periods of 3 or 6 months were heat inactivated and tested for their ability to produce a passive cutaneous anaphylactic response in guinea pigs. The data show that SPH is not immunogenic or a skin sensitizer.

Hemolysis

The potential hemolytic effects of SPH were evaluated using an in vitro rabbit blood method. Incubation of various concentrations of SPH in saline with rabbit erythrocytes indicated that SPH solution produced no greater hemolysis when compared to the saline control.

Pyrogenicity

The pyrogenicity of SPH was tested using a method in accordance with the Guideline on Validation of the Limulus amoebocyte lysate test. All 3 lots of SPH tested met the criteria for passing the test, and did not produce a pyrogenic response.

Implantation Tests

Several studies were conducted to evaluate the activity of SPH in animal models of human OA of the knee. In one, SPH was administered by intra-articular injection to rabbits whose knees had been immobilized in a cast for 8, 14 or 28 days. In another study, hyaluronan preparations of average molecular weights ranging from 200,000 to 1,100,000 D were injected in the same rabbit model to determine whether there was a relationship between effectiveness and average molecular weight. In the third study, SPH was used to treat rabbits in which OA was induced by surgical removal of ligaments and cartilage. The results of these studies indicated that SPH, with a molecular weight $\geq$ 500,000 D, increased the mobility of the immobilized rabbit knee.

Irritation

The irritant potential of SPH following im injection in rabbits was studied. Gross examination of the injection sites 2 and 7 days after injection revealed no evidence of inflammation or tissue damage. Histopathological examination revealed a mild infiltration of macrophages in one study and a mild infiltration of macrophages and neutrophils with slight bleeding at the injection site in the other study 2 days following treatment. There were no histopathological changes at the injection sites in either

study 7 days after treatment. These studies indicate that SPH does not cause significant implantation site irritation in this model system.

Cytotoxicity

The potential cytotoxicity of SPH was evaluated in a study in which HeLa cells were cultured in the presence of SPH at concentrations ranging from 1 to 1,000 ug/mL for up to 5 days. SPH had no effect on cell proliferation or morphology in this assay.

10.0 Summary of Clinical Studies

Study Design

Since 1978, 18 clinical studies have been completed in which the safety and/or effectiveness of SUPARTZ™ for the treatment of osteoarthritis (OA) of the knee were studied. These clinical studies vary in trial design and execution. Of the 18, 5 studies were prospective, randomized, double-blind, placebo-controlled, and multi-center, and were used to determine safety and effectiveness as assessed individually and in an integrated analysis. These 5 studies were performed in Australia, France, Germany, Sweden and United Kingdom.

Basic entry (inclusion/exclusion) criteria are described for all studies (See Table 2). All studies required patients to have symptomatic OA and be in the age range between 40 and 70 to 80 years (depending on the study). For two studies it was not stated that patients must be willing to discontinue current OA therapy. Two other studies had additional criteria of morning stiffness, and/or crepitation, and/or age greater than 50 years.

Regarding exclusion criteria, all five studies prohibited intra-articular injections within 3-6 months prior to the study start. Four of the five studies shared the following exclusion criteria: primary or other joint disease, severe joint effusion, severe false alignment, and moderate or severe instability. Three of the five studies prohibited bilateral OA of the knee, lower extremity joint replacement, severe overweight or obesity, surgery or arthroscopy within the past 6-12 months, and participation in a clinical trial/use of investigational product within previous 1-3 months. Some exclusion criteria were unique to one study: one study designated certain therapies as exclusion criteria; another study did not allow bone attrition, previous intra-articular knee fracture, or abnormal hematology or clinical chemistry; and a third study designated coxarthrosis as an exclusion criteria.

Injection Procedure and Schedule

All patients in these studies (including those injected with the control) received arthrocentesis of the knee prior to an injection of SUPARTZ™ or vehicle (phosphate buffered saline) or, in the German study only, a dilute (1%) form of the SUPARTZ™ formulation. The French study included an additional treatment arm: 3 SUPARTZ™ injections followed by 2 injections of the control per patient. (Table 3 describes the study design and the treatment/ followup schedules.). Each study group received five 2.5 ml intra-articular injections one week apart and had a 13 week follow-up period. The treatment regimen consisted of 5 weekly injections in all studies. Paracetamol was used as a rescue medication in all studies except in the UK study where Co-proxamol (325mg of paracetamol with 32.5mg of dextropropoxyphane) was used. In all cases there was a pre-study evaluation or screening visit and effectiveness was based on evaluations after treatment completion: at 13 weeks in all studies, and three studies continued with evaluations at 17, 20 and/or 25 weeks, respectively.

Measures of Effectiveness

Table 3 provides details of the primary and secondary effectiveness parameters used in each study. The Lequesne Index, although a primary measure of effectiveness in only three studies (France, Germany, and Sweden), was common to all five studies. It was used for the integrated analysis of effectiveness across all five studies. The primary measure used in the other two studies was the WOMAC Index in Australia, and VAS pain ratings in the United Kingdom. All studies included an investigator global assessment; four studies included a patient global assessment and four studies a VAS pain score. All studies assessed rescue medication use.

Results

Patient Population and Demographics

The demographics of study participants were comparable across treatment groups with respect to age, sex, mean body mass index, and baseline scores, with the exception of gender in the German study (see Table 4). Analgesic and anti-inflammatory drug use during the studies was also examined with no noteworthy differences between treatment groups (see Table 5).

Individual Study Results

The WOMAC was the primary outcome measurement in the Australian study. None of the other studies used the WOMAC index. The Australian protocol defines the primary measure of efficacy as the patient's assessment of their current level of pain, stiffness, and disability according to the

WOMAC scale. Scores were to be recorded at Weeks 6, 10, 14, and 18 (week numbers represent weeks since the study started, which was one week before the first injection). All patients who received at least one injection were to be included in the analysis. The ITT population consisted of 108 SUPARTZ™ patients and 115 placebo patients. A repeated measures analysis of covariance of mean reduction from baseline over weeks 6, 10, 14, and 18 revealed a statistically significant difference between the treatment groups (at the α=0.05 level) with respect to WOMAC pain and WOMAC stiffness scores (mean reduction of 2.72 in SUPARTZ™ vs. 2.23 in the active control (p=0.045), and mean reduction of 1.37 in SUPARTZ™ vs. 0.99 in the active control (p=0.024), respectively). For WOMAC disability, the difference between treatment groups approached statistical significance (improvement in physical function scores of 9.21 in SUPARTZ™ vs. 7.51 in the active control (p = 0.064)). See Table 6A.

Other primary measure analyses, not including Lequesne score, are as follows: The results for Germany of the paracetamol consumption performed as a non-parametric ranking procedure (stratified Wilcoxon rank-sum test), over weeks 1-5, are SUPARTZ™ = 0.85 and Control = 0.89 (p > 0.05). The results for Sweden and UK for the protocol-specific primary analysis = VAS ratings as analysis of covariance (ANCOVA) at weeks 1-5, 13 and 20 (Sweden), and repeated measures analysis of variance (ANOVA), over weeks 10, 14, and 18, (UK) are the following: SUPARTZ™ = 10.11 and Control = 9.76 for Sweden (p > 0.05); and SUPARTZ™ = 13.47 and Control = 12.89 for UK (p > 0.05). Medication use results are presented in Table 5.

The results for each individual study of analysis of the Lequesne score as repeated measures analysis of covariance (ANCOVA) of mean reduction from baseline over all visits at or following the 5 week visit are presented in table 6B. Statistically significant differences between groups were demonstrated in only the Australian and UK studies. In the Swedish study, the results are not statistically significant and the active control is numerically slightly better than SUPARTZ™.

Integrated Analysis

An integrated longitudinal analysis was conducted to examine results across all five studies. See Table 6C. This method of analyzing data with repeated measurements takes into account the correlation structure of the repeated measurements and examines the effects of treatment over time. The integrated longitudinal analysis showed a reduction in the total Lequesne score of 2.68 in the SUPARTZ™ treatment groups compared to a reduction in the total Lequesne score of 2.00 in the

control groups (p=0.0026). The 95% confidence interval for the difference of the reduction in total Lequesne score between SUPARTZ™ and control is (0.56, 0.79).

Summary of Results

The difference in reduction in total Lequesne scores between the SUPARTZ™ treated group and the control group is 0.68, which is statistically significant in the integrated analysis (p=0.0026). Additionally, the Australian study shows a significant difference between SUPARTZ™ and control in both the WOMAC pain (p=0.045) and stiffness (p=0.024) scores and Lequesne total scores (p=0.0114).

11.0 Conclusions Drawn from Studies

These 5 studies provide reasonable assurance of the safety and effectiveness of SUPARTZ™ for the treatment of pain in OA of the knee in patients who have failed to respond adequately to conservative non-pharmacological therapy and simple analgesics (e.g., acetaminophen). There were no statistically significant differences in the incidence rates of adverse events for any of the controlled studies. For all studies, very few adverse effects were reported. Reported events were primarily localized effects of mild to moderate severity and resolved when treatment ended.

12.0 Panel Recommendations

In accordance with the provisions of sections 51 5(c)(2) of the act as amended by the Safe Medical Devices Act of 1990, this PMA application was not referred to the Orthopedic and Rehabilitation Devices Panel, an FDA advisory committee, for review and recommendation because the information in the PMA substantially duplicates information previously reviewed by this panel.

13.0 CDRH Decision

On January 24, 2001, CDRH approved a single course of 5 intra-articular SUPARTZ™ injections for the treatment of pain in OA of the knee in subjects who have not responded adequately to conservative non-pharmacological therapy and simple analgesics (e.g., acetaminophen).

14.0 Approval Specifications

Directions for Use: See labeling.

Hazards to health from use of the device: See indication, contraindications, warnings, precautions and adverse events in the labeling.

Postapproval Requirement and Restrictions: See approval order.

Table 1: Adverse Events Occuring in > 4% of SUPARTZ™-treated Patients

Integrated Safety Database	SUPARTZ™ (N=619)		Control (N=537)	
	N	%	N	%
Arthralgia	110	17.8%	95	17.7%
Arthropathy/Arthrosis/Arthritis	68	11.0%	57	10.6%
Back Pain	40	6.5%	26	4.8%
Pain (non-specific)	37	6.0%	26	4.8%
Injection Site Reaction*	35	5.7%	18	3.4%
Headache	27	4.4%	23	4.3%
Injection Site Pain	26	4.2%	22	4.1%

*Includes application/injection site reaction, injection site inflammation, and purpura injection site

Table 2: Entry Criteria

Study	Inclusion				Exclusion
	Baseline pain level	Duration of pain prior to study entry	Unilateral versus bilateral	Radiologic criteria	Effusion
Australia	Not specified	≥ 3 months	Unilateral or predominantly unilateral**	Evidence of one or more of the following features in an x-ray taken during the previous 6 months: femorotibial osteophytes, osteosclerosis of the femoral or tibial endplates, or joint space narrowing	> 50 ml
France	Lequesne total score = 4 – 12 Global pain ≥ 35 mm on VAS	≥ 3 months	Unilateral or Predominantly unilateral**	Narrowing of femorotibial space > 20% and < 90% in at least 1 of the appropriate angles and or OA and/or osteocondensation, and/or geode(s)	Severe (tight, distending effusion)
Germany	Moderate to medium*	Not specified	Unilateral or bilateral	Osteophytes	> 100 ml
Sweden	Not specified	Not specified	Unilateral	Knee flexion angle of 10 – 15°; 50 – 100% obliteration (= 400 mm) of the joint space (standing radiographs) without any bone erosion	Not specified
United Kingdom	Moderate*	> 3 months	Unilateral or predominantly unilateral**	Femorotibial osteophytes	> 50 ml

* Definition not specified in protocol

**Predominantly unilateral means that even in the case of bilateral disease it is possible for the patient to identify one predominant knee that is affected, as reported by the investigator

Table 3: Prospective, Randomized Clinical Studies of Symptomatic OA Patients – Study Design

Study	Control	Effectiveness Parameters	Evaluation Timepoints	Protocol-Specified Analysis Plan for Primary Effectiveness Analysis	Concurrent OA therapy
Australia	Arthrocentesis Injection with phosphate buffered saline	Primary – WOMAC pain, stiffness, and disability Secondary – Lequesne, Paracetamol Consumption, Investigator Global Assessment, Patient Global Assessment	Week 0, 1*, 2, 3, 4, 5, 6, 10, 14, 18	Repeated measures analysis of covariance (ANCOVA) of mean reduction from baseline for WOMAC pain, stiffness, and disability, over weeks 6, 10, 14, and 18.	Paracetamol Rescue
France**	Arthrocentesis Injection with phosphate buffered saline	Primary – Lequesne Secondary – VAS Ratings, Paracetamol Consumption, Investigator Global Assessment	Screen, Day 0*, 7, 14, 21, 28, 35, 60, 90	Analysis of variance (ANOVA) of mean reduction from baseline for Lequesne scores, at days 35, 60, and 90.	Paracetamol Rescue
Germany	Arthrocentesis Injection with a dilute (1%) formulation of SUPARTZ™	Primary – Lequesne, Paracetamol Consumption Secondary – VAS Ratings, Investigator Global Assessment, Patient Global Assessment	Week 0, 1*, 2, 3, 4, 5, 6, 10, 14	1. Repeated measures ANCOVA of mean reduction from baseline for Lequesne scores, over weeks 4, 5, and 6. 2. Non-parametric ranking procedure applied to mean reduction from baseline for paracetamol consumption, over weeks 1-5.	Paracetamol Rescue
Sweden	Arthrocentesis Injection with phosphate buffered saline	Primary – Lequesne, VAS Ratings for knee function, knee pain, range of motion, and activity level Secondary – Paracetamol Consumption, Investigator Global Assessment, Patient Global Assessment	Week -1, 0*, 1, 2, 3, 4, 5, 13, 20	ANCOVA of mean reduction from baseline for both Lequesne scores and VAS pain ratings, at weeks 1-5, 13, and 20.	Paracetamol Rescue
United Kingdom	Arthrocentesis Injection with phosphate buffered saline	Primary – VAS Pain Ratings Secondary – Lequesne, Paracetamol Consumption, Investigator Global Assessment, Patient Global Assessment	Week 0, 1*, 2, 3, 4, 5, 6, 10, 14, 18, 26	Repeated measures ANOVA of mean VAS pain ratings, over weeks 10, 14, and 18.	Co-Proxamol Rescue

*First injection given

**This study had 3 treatment arms: 3 injections of SUPARTZ™, 5 injections of SUPARTZ™, control

Table 3: Prospective, Randomized Clinical Studies of Symptomatic OA Patients – Study Design

Table 4: Patient* Demographics by Treatment Group

Country	# of Centers	# of Patients			Age (Mean)	% Female	BMI	Baseline Total Lequesne
		Total	SUPARTZ™	Control				
Australia	17	223	108	115	A = 62.4 C = 63.0	A = 56.5 C = 61.7	A = 29.5 C = 29.2	A = 12.1 C = 13.0
France	54	254	(5) 87 (3) 87	80	A (5) = 64.7 A (3) = 63.9 C = 65.2	A (5) = 60.9 A (3) = 73.6 C = 68.8	A (5) = 27.4 A (3) = 28.3 C = 28.5	A(5) = 9.8 A(3) = 9.8 C = 10.1
Germany	25	208	102	106	A = 62.0 C = 60.5	A = 70.6** C = 56.6	A = 26.2 C = 26.8	A = 10.5 C = 9.6
Sweden	8	239	119	120	A = 58.5 C = 58.0	A = 55.5 C = 55.8	A = 27.7 C = 27.2	A = 9.9 C = 9.6
UK	19	231	116	115	A = 60.8 C = 61.6	A = 60.3 C = 53.9	A = 28.7 C = 28.2	A = 13.5 C = 13.5
Total	123	1155	619	536***				

*All ITT Patients
** Percent female was statistically significantly higher in the SUPARTZ™ group
*** One patient is excluded from this table since no efficacy data was collected/available
A = SUPARTZ™ (5) = 5 Injections, France
C = Control (3) = 3 Injections, France

Table 5: % Distribution of Patients* Using Analgesic and Anti-inflammatory Drugs by Treatment Group

Medication	Country									
	Australia Total #s of Patients SUPARTZ™ = 108 Control = 115		France Total #s of Patients SUPARTZ™ = (5) 87 / (3) 87 Control = 80		Germany Total #s of Patients SUPARTZ™= 102 Control = 106		Sweden Total #s of Patients SUPARTZ™ = 119 Control = 120		UK Total #s of Patients SUPARTZ™ = 116 Control = 115	
	n	%	n	%	n	%	n	%	n	%
Aspirin										
SUPARTZ™	5	4.6%	2	2.3%	1	1.0%	29	24.4%	9	7.8%
SUPARTZ™ (3)**			3	3.4%						
Control	10	8.7%	0	0.0%	1	0.9%	37	30.8%	15	3.0%
Paracetamol***										
SUPARTZ™	85	78.7%	74	85.1%	73	71.6%	59	49.6%	108	93.1%
SUPARTZ™ (3)**			74	85.1%						
Control	97	84.3%	71	88.8%	81	76.4%	56	46.7%	106	92.2%
Codeine Compounds										
SUPARTZ™	25	23.1%	18	20.7%	0	0%	19	16.0%	56	48.3%
SUPARTZ™ (3)**			18	20.7%						
Control	30	26.1%	21	26.3%	0	0%	24	20.0%	46	40.0%
Dextropropoxyphene										
SUPARTZ™	0	0.0%	0	0%	0	0%	11	9.2%	0	0%
SUPARTZ™ (3)**			0	0%						
Control	2	1.7%	0	0%	0	0%	20	16.7%	0	0%
NSAIDs										
SUPARTZ™	42	38.9%	47	54.0%	1	1.0%	59	49.6%	41	35.3%
SUPARTZ™ (3)**			41	47.1%						
Control	49	42.6%	49	61.3%	1	0.9%	48	20.0%	48	41.7%
Methylprednisolone										
SUPARTZ™	2	1.9%	0	0%	0	0%	0	0%	0	0%
SUPARTZ™ (3)**			0	0%						
Control	5	4.3%	0	0%	0	0%	0	0%	0	0%

*All ITT Patients, patients with multiple types of medication use are counted for each type of medication

**All studies had 5 SUPARTZ™ injections. In the French study, there was an additional treatment arm with 3 SUPARTZ™ injections.

***Includes paracetamol consumption as provided per protocol as rescue medication, as well as any additional paracetamol use.

Table 6A: Australia Study Results for WOMAC (Pain, Stiffness, & Disability) as Repeated Measures Analysis of Covariance (ANCOVA) of Mean Reduction from Baseline Over Weeks 6, 10, 14, and 18

Treatment	Pain	Stiffness	Disability
SUPARTZ™	2.72*	1.37*	9.21
Control	2.23	0.99	7.51

* = p-value < 0.05

Table 6B: Individual Study Results for Lequesne Score as Repeated Measures Analysis of Covariance (ANCOVA) of Mean Reduction from Baseline Over All Visits at or Following the 5 Week Visit

Study	SUPARTZ™ (5 Injections)	SUPARTZ™ (3 Injections)	Control
Australia	2.85*		1.98
France	3.08	3.14	2.64
Germany	3.87		2.74
Sweden	1.68		1.77
UK	2.19*		1.53

* = p-value < 0.05

Table 6C: Integrated Analysis (All Five Studies) for Lequesne Score as Repeated Measures Analysis of Covariance (ANCOVA) of Mean Reduction from Baseline Over All Visits at or Following the 5 Week Visit

Study	SUPARTZ™	Control
All Studies	2.68*	2.00

* = p-value < 0.05