

## **FREEDOM OF INFORMATION SUMMARY**

### **I. GENERAL INFORMATION**

#### **A. File Number**

NADA 141-038

#### **B. Sponsor**

Luitpold Pharmaceuticals, Inc.  
1 Luitpold Drive  
Shirley, NY 11967

#### **C. Proprietary Name**

Adequan® Canine

#### **D. Established Name**

polysulfated glycosaminoglycan (PSGAG)

#### **E. Dosage Form**

Each preserved multidose vial contains 5 mL of solution containing 100 mg PSGAG/mL.

#### **F. Dispensing Status**

Rx

#### **G. Dosage Regimen**

The recommended dose of Adequan® Canine is 2 mg/lb body weight (.02 mL/lb, or 1 mL per 50 lb), by intramuscular injection only, twice weekly for up to 4 weeks (maximum of 8 injections). Do not exceed the recommended dose or therapeutic regimen. Do not mix Adequan® Canine with other drugs or solvents.

#### **H. Route of Administration**

Intramuscular Injection

#### **I. Indication**

Adequan® Canine is recommended for intramuscular injection for the control of signs associated with non-infectious degenerative and/or traumatic arthritis of canine synovial joints.

## II. EFFECTIVENESS

### A. Dose Selection

Dose selection for Adequan® Canine was based on published studies concerning the use of polysulfated glycosaminoglycan in osteoarthritis models in dogs. The following studies support the selection of the 2 mg/lb body weight dose in dogs.

1. Hannan N., Ghosh, P., Bellenger, C., Taylor, T. "Systemic Administration of Glycosaminoglycan (Arteparon) Provides Partial Protection of Articular Cartilage from Damage Produced by Meniscectomy in the Canine." *J Orthop Res* 5, (1987), pp. 47-59. Sixteen dogs were enrolled in the study. Fourteen were subjected to bilateral meniscectomy of the stifle joint. Eight dogs received no additional treatment following meniscectomy. Six dogs were received subcutaneous treatment with Arteparon, a solution containing 50 mg/ml PSGAG, manufactured by Luitpold-Werk Munich, F.R.G., and labeled for use in humans. Arteparon was administered at a dose of 2 mg/kg (about 0.9 mg/lb) three times a week for 3 weeks, then 2 times a week for 23 weeks. Two dogs were subjected to arthrotomy only and served as sham operated controls. Histologically, the cartilage of drug treated dogs showed reduced surface fibrillation, diminished chondrocyte cloning, and maintenance of proteoglycan stain absorption (alcianophilia). The levels of proteoglycans and the hexuronate-protein ratios in the medial articular cartilage of the drug treated dogs were found to be comparable to sham operated controls, whereas these parameters in the non drug-treated meniscectomized group were depressed. These results indicate that Arteparon provided some protective effect to articular cartilage in the meniscectomized dogs.
2. Altman, R., Dean, D., Muniz, O., Howell, D. "Therapeutic Treatment of Canine Osteoarthritis with Glycosaminoglycan Polysulfuric Acid Ester" *Arthritis and Rheumatism*, 32:10, (1989), pp. 1300-1307. The Pond-Nuki model was used to create osteoarthritis of the right stifle joint in eighteen dogs. Eight control dogs received twice weekly intramuscular injections of saline for 4 weeks. The remaining 10 dogs received PSGAG (Arteparon) intramuscularly at 4 mg/kg twice weekly for 4 weeks. At necropsy, cartilage from the medial femoral condyle was analyzed for collagen integrity, hydroxyproline, uronic acid, active and total metalloproteinase, serine protease, and histopathology (Mankin Score). Condylar cartilage from animals treated with PSGAG demonstrated less cartilage swelling, less total and active metalloproteinase, and lower histological scores than were found in cartilage from saline-treated animals. These results show that PSGAG was able to suppress proteoglycan-degrading enzyme activity and maintain more normal-appearing cartilage.
3. The selected dose of 2 mg/lb body weight was shown to have an adequate margin of safety in dogs. Efficacy of the selected dose was confirmed in a clinical field trial. (Refer to Efficacy Studies and Animal Safety sections of FOI Summary.)

### B. Efficacy Studies

Adequan® Canine for the control of signs associated with non-infectious degenerative and/or traumatic arthritis in the dog has been evaluated in two studies: a study of the distribution of radiolabeled drug in canine serum, synovial fluid and articular cartilage,

and a controlled field trial. Effectiveness was also supported by a study published in a peer reviewed scientific journal.

1. Study 1

Title: Distribution of Tritium-Labeled PSGAG in Canine Serum, Synovial Fluid, and Articular Cartilage After Intramuscular Injection

a) Type of Study

This was a laboratory study designed to determine the distribution of tritium-labeled PSGAG in canine serum, synovial fluid and articular cartilage after a single intramuscular injection of 2 mg <sup>3</sup>HPSGAG per pound of body weight.

b) Names and Addresses of Investigators

The study was performed at the Boren Veterinary Teaching Hospital, College of Veterinary Medicine, Oklahoma State University in Stillwater, Oklahoma.

Michael Collier, DVM, DACVS (Study Director)  
Boren Veterinary Medical Teaching Hospital  
Oklahoma State University  
Stillwater, OK 74078

David Clark, DVM, DACVS (Principal Investigator)  
Boren Veterinary Medical Teaching Hospital  
Oklahoma State University  
Stillwater, OK 74078

Lawrence DeBault, Ph.D.  
Department of Pathology  
Oklahoma University Medical Center  
Oklahoma City, OK

Harold Thompson, Ph.D.  
U.S. Center for Toxicological Research  
Jefferson, AR

E. Wynn Jones, FRCVS, Ph.D. (Quality Assurance)  
101 Clairmont Circle  
Starkville, MS

c) Design of the Investigation

From a pool of ten mature healthy dogs, nine were selected as test animals. On study day -3, dogs received general anesthesia and a synovitis was induced by intraarticular injection of Complete Freund's Adjuvant (0.2 mL) in the left shoulder and stifle joints. This increased synovial fluid volume and thereby facilitated collection of synovial fluid, and induced synovial inflammation, a component of canine degenerative or traumatic joint disease.

On study day 0 or +1, the dogs were injected with 3HPSGAG at a dose of 2

mg/lb. Serum and synovial fluid samples from the left shoulder and stifle joints were collected prior to treatment and at 2, 6, 12, 24, 48, and 72 hours after injection of 3HPSGAG. Additional samples of synovial fluid from the left shoulder and stifle were collected prior to treatment and at 72 hours after treatment for determination of protein and hyaluronate levels. Seventy-two hours after treatment the dogs were humanely euthanized and articular cartilage samples collected from the left shoulder, left stifle, one elbow and one hip joint. Drug levels in these tissues, and in the serum and synovial fluid samples, were determined by scintillation analysis. All samples were shipped to the laboratory with coded labels to conceal the identity of the sample.

d) Results

Results of the serum and synovial fluid scintillation analyses are shown in Table 1. All values were converted from decays per minute to  $\mu\text{g}$  PSGAG/mL. Mean cartilage drug levels for each joint are shown in Table 2 and are expressed in  $\mu\text{g}$  PSGAG/g. Mean synovial fluid protein and hyaluronate levels in mg/mL are shown in Table 3.

Table 1 MEAN SERUM AND SYNOVIAL FLUID 3HPSGAG LEVELS IN  $\mu\text{g}$  PSGAG/ML

<b>TIME (HOURS)</b>	<b>SERUM</b>	<b>SYNOVIAL FLUID: SHOULDER</b>	<b>SYNOVIAL FLUID: STIFLE</b>
0	0	0	0
2	4.43	4.17	4.18
6	1.59	1.88	1.65
12	1.05	1.10	1.08
24	0.89	0.93	1.01
48	0.83	0.85	0.87
72	0.81	0.79	0.84

Table 2 MEAN ARTICULAR CARTILAGE 3HPSGAG LEVELS (72 HR) IN  $\mu\text{g}$  PSGAG/G

<b>JOINT</b>	<b>PSGAG LEVEL</b>
STIFLE (INDUCED SYNOVITIS)	0.17
SHOULDER (INDUCED SYNOVITIS)	0.16
HIP (NORMAL)	0.10
ELBOW (NORMAL)	0.08

Table 3: MEAN SYNOVIAL FLUID HYALURONATE AND PROTEIN LEVELS IN MG/ML

<b>JOINT</b>	<b>HOURL</b>	<b>PROTEIN</b>	<b>HYALURONATE</b>
SHOULDER	0	36.02	0.81
SHOULDER	72	31.56	0.80
STIFLE	0	38.36	0.87
STIFLE	72	32.93	0.86

e) Statistical Analysis and Conclusions

Initial and final mean synovial fluid hyaluronate and protein levels were

compared by t-test. The reduction in synovial fluid protein, an indicator of synovial inflammation, was significant in the shoulder joint ( $p = 0.04197$ ).

These data indicate that, after an intramuscular injection of PSGAG at 2 mg/lb in dogs, PSGAG reaches synovial fluid within 2 hours and detectable levels are maintained in synovial fluid and articular cartilage for up to 72 hours. These findings support efficacy of the proposed dose and twice weekly dosing interval. The significant reduction of synovial fluid protein in the shoulder also supports the efficacy of the drug.

f) Adverse Reactions

No adverse reactions to the PSGAG treatment were noted.

2. Study 2

Title: Controlled Field Trial

a) Type of Study

This trial was a blinded, placebo-controlled field trial to determine the efficacy and safety of Adequan® Canine at a dose of 2 mg per lb body weight, administered intramuscularly, twice weekly for 4 weeks, under conditions routinely encountered in 3 small animal veterinary practices in the United

States.

b) Names and Addresses of Investigators

Center 1  
Al Atkinson, DVM, ABVP  
Lone Star Veterinary Hospital  
3870 Mission Blvd. Suite D6  
Oceanside, CA 92056

Center 2  
Larry Anson, DVM, DACVS  
Veterinary Referral Clinic  
5035 Richmond Road  
Bedford Heights, OH 44146

Center 3  
Paul Dean, DVM, DACVS  
Bradford Park Veterinary Hospital  
1255 E. Independence  
Springfield, MO 65804

Quality Assurance  
E. Wynn Jones, FRCVS, Ph.D.  
101 Clairmont Circle  
Starkville, MS

c) Design of the Investigation

The study was a blinded, placebo-controlled field trial. Dogs presented to the investigators with lameness and pain secondary to radiographically detectable traumatic or degenerative joint diseases in 1 or 2 joints were eligible for the study. The dogs were assigned to treatment group A or B by a computer generated randomization schedule. Group A received 0.9% saline solution and group B received Adequan® Canine at 2 mg/lb of body weight. Investigators administering treatments and conducting orthopedic exams were unaware of the dog's treatment group assignment. All treatments were administered intramuscularly twice weekly for 4 weeks (8 injections total). The test products were provided in coded vials; the dose for both test products was 0.02 mL per pound of body weight.

The health of the dogs was determined and monitored by a physical examination at the time of each visit and by a complete blood count, blood urea nitrogen and serum creatinine determination prior to treatment and at

the final examination. The investigators also recorded all potential adverse reactions to the experimental therapy.

d) Inclusion Criteria:

Any age, breed, or sex

score of grade 1 or higher on the radiographic scoring scale

demonstrated gait changes characteristic of traumatic or degenerative joint disease and lameness score of at least 2 (lameness at a walk and trot

combined) on at least 1 limb

demonstrated pain on manipulation of the affected joint(s) as well as limitation of the range of motion

functional disability score of 2 or higher

e) Exclusion Criteria:

dogs which had received NSAID or Adequan® therapy within 10 days or corticosteroid therapy within 30 days of entrance into study

dogs which were known or suspected to have septic arthritis

dogs which had concomitant lameness of neurologic origin

dogs which had been subjected to corrective surgery such as pelvic osteotomy or total hip replacement

dogs which had an abnormal BUN or creatinine or suspected bleeding disorder

dogs which had any systemic illness or infectious diseases which compromised the dog's general health

dogs which had more than 2 joints clinically affected

An orthopedic examination was performed prior to treatment, at the time of injection 5, and approximately 1 week after the final injection. The following parameters were assessed for each lame limb and scored:

Lameness at a walk - scored 0-6

0= no detectable lameness

1= intermittent weight bearing lameness

2= persistent weight bearing lameness

3= persistent weight bearing lameness; intermittent non-weight bearing lameness

4= persistent non-weight bearing lameness

5= ambulatory only with assistance

6= non-ambulatory

Gait analysis at a trot - scored 0 to 6, using lameness at walk scale above

Pain on manipulation of limb - scored 0 to 2

0 = no pain

1 = mild pain (dog attempted to withdraw limb)

2 = severe pain ( dog attempted to withdraw limb, cried out or attempted to bite)

Range of motion - scored 0 to 3

0 = no limitation in range of motion

1 = pain only at full range of motion

2 = pain at less than full range of motion

3 = pain at any attempt to manipulate the joint

Functional Disability - scored 0 to 4



0 = activities of daily living were normal  
1 = dog was stiff after periods of inactivity but normal after warming up  
2 = dog could not tolerate strenuous prolonged exercise  
3 = dog was unable to climb stairs, jump into car without assistance  
4 = quality of daily living was severely compromised; dog had difficulty rising, sitting up, or lying down

Radiographic Scoring:

0 = normal joint  
1 = radiographic evidence of instability; no degenerative change  
2 = mild degenerative change (occasional osteophytes)  
3 = moderate degenerative change (osteophytes, subchondral sclerosis)  
4 = severe degenerative change (osteophytes, subchondral sclerosis, remodeling of bone)

Clinician's Subjective Response:

very poor dog's condition worse than when treatment started  
poor dog's condition is essentially unchanged  
fair slight improvement in the parameters of the orthopedic score  
good readily apparent improvement in the parameters of the orthopedic score  
excellent dog's condition is normal or as near normal as could be expected

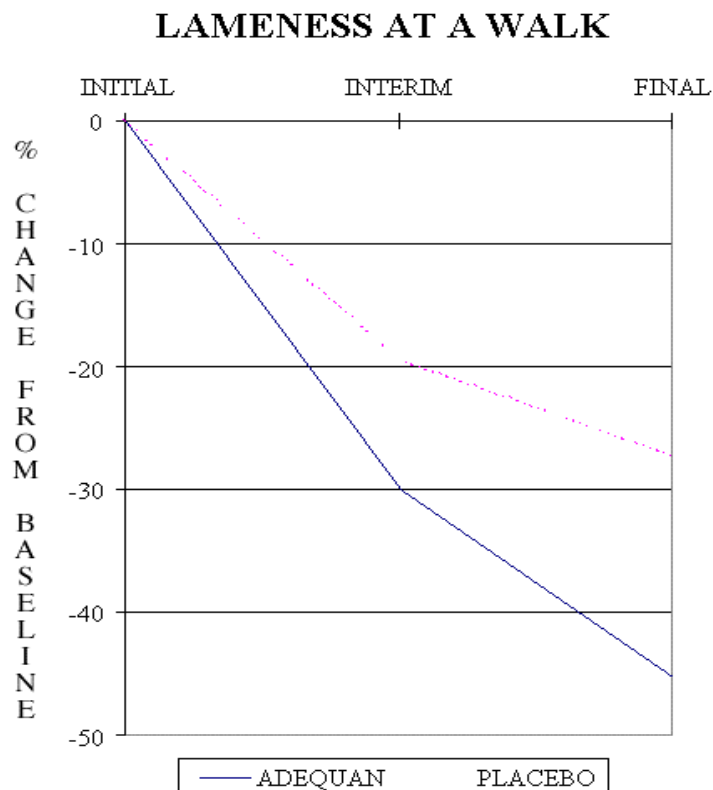
f) Results

The final data analysis included data from 71 limbs in 51 dogs. Of these, 35 limbs in 24 dogs were in the Adequan® Canine treated group, and 36 limbs in 27 dogs were in the placebo treated group. The joints evaluated included hips, stifles, shoulders, hocks and elbows.

The mean percent change from baseline for each parameter and for the total orthopedic scores are shown in Graphs 1-7. Negative percent change from

baseline reflects an improvement in the parameter evaluated; that is, a decrease in the score for that parameter.

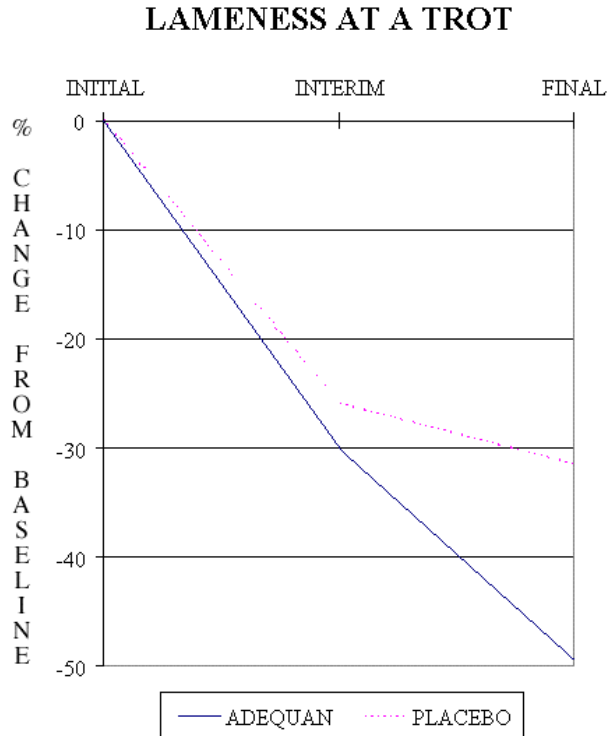
Graph 1: Lameness At A Walk



Graph 1 shows the percentage change in lameness score from prior to treatment with Adequan or placebo to one week after final treatment. A decrease in the lameness score reflects an improvement in the dog's lameness. Three time periods were evaluated: initial (prior to treatment with Adequan or placebo), interim (after the 5th injection of Adequan or placebo), and final (one week after the 8th injection of Adequan or placebo). Dogs

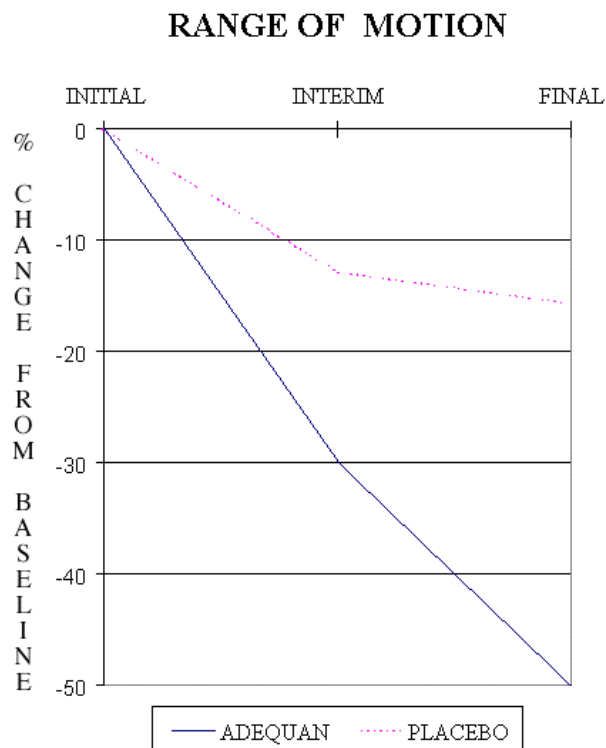
treated with Adequan show a greater decrease in lameness score at a walk than placebo treated dogs at both the interim and final time points.

Graph 2: Lameness at a Trot



Graph 2 shows the percentage change in lameness score from prior to treatment with Adequan or placebo to one week after final treatment. A decrease in the lameness score reflects an improvement in the dog's lameness. Three time periods were evaluated: initial (prior to treatment with Adequan or placebo), interim (after the 5th injection of Adequan or placebo), and final (one week after the 8th injection of Adequan or placebo). Dogs treated with Adequan show a greater decrease in the lameness score at a trot than placebo treated dogs at both the interim and final time points.

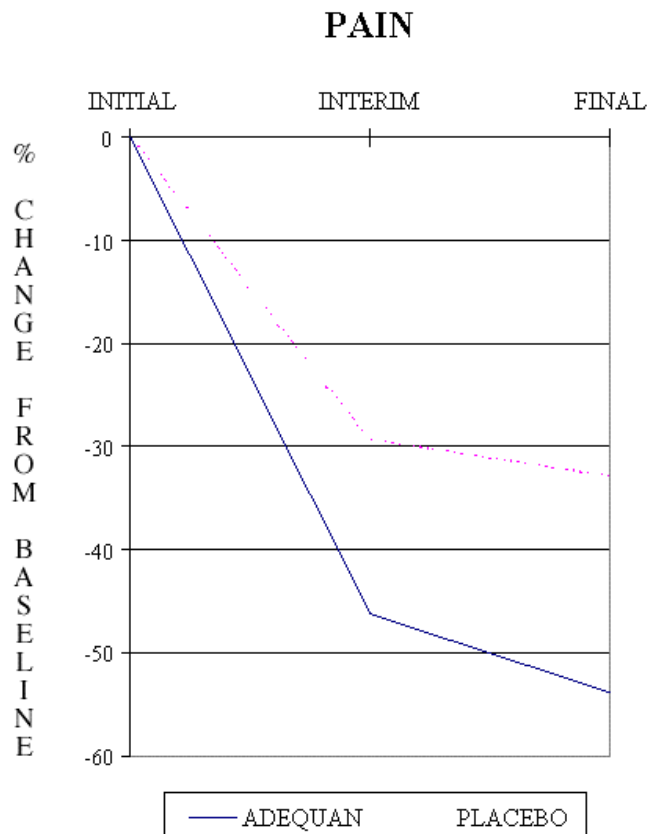
Graph 3: Range of Motion



Graph 3 shows the percentage change in range of motion scores in dogs prior to treatment with either Adequan or placebo to one week after final treatment in dogs evaluated for range of motion. A decrease in the range of motion score reflects an improvement in the dogs range of motion of the evaluated joint. Dogs treated with Adequan show a greater improvement in the range of

motion score than placebo treated dogs at both the interim and final time points.

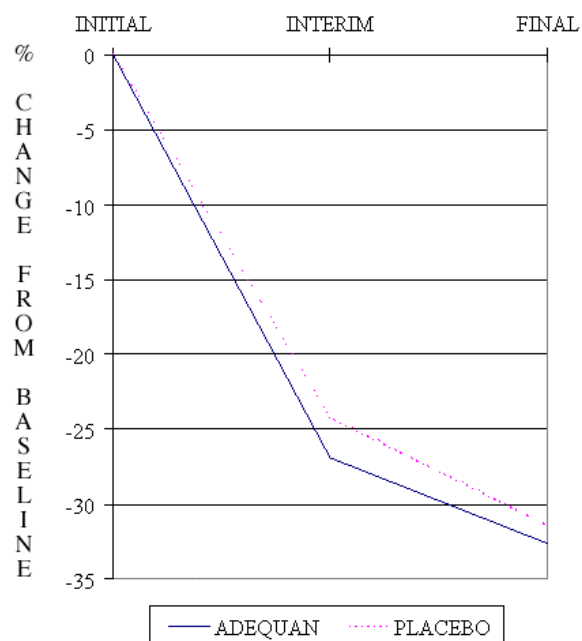
Graph 4: Pain on Manipulation of limb



Graph 4 shows the percentage change in pain score from prior to treatment with Adequan or placebo to one week after final treatment in dogs evaluated for pain on manipulation of affected limb. A decrease in the pain score reflects an improvement in exhibition of signs of pain when affected joint was manipulated. Dogs treated with Adequan show a greater decrease in the pain on manipulation score than placebo treated dogs at both the interim and final time points.

Graph 5: Functional Disability

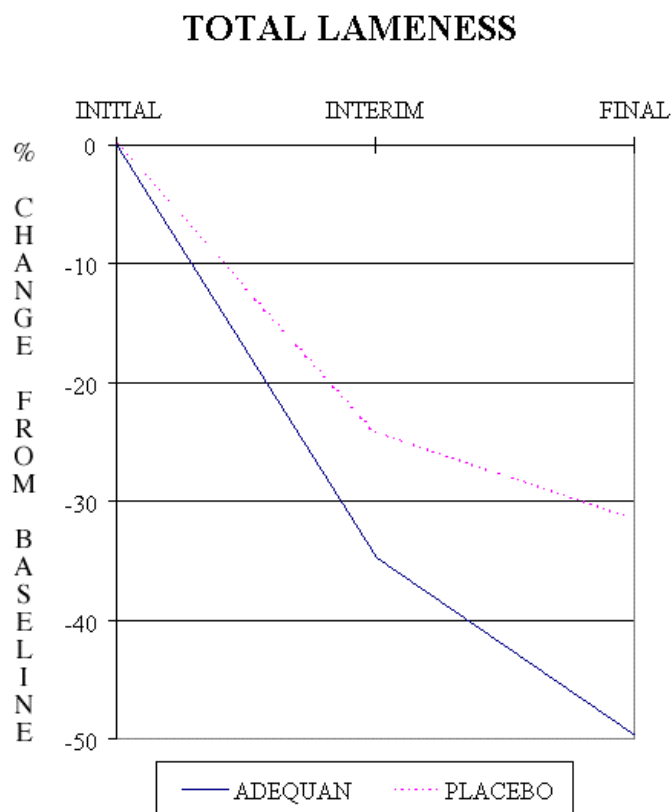
### DISABILITY



Graph 5 shows the percentage change in functional disability score from prior to treatment with Adequan or placebo to one week after final treatment in dogs. A decrease in the disability score reflects an improvement in quality of life. Three time periods were evaluated: initial (prior to treatment with Adequan or placebo), interim (after the 5th injection of Adequan or placebo), and final (one week after the 8th injection of Adequan or placebo). Dogs

treated with Adequan show a greater decrease in the functional disability score than placebo treated dogs at both the interim and final time points.

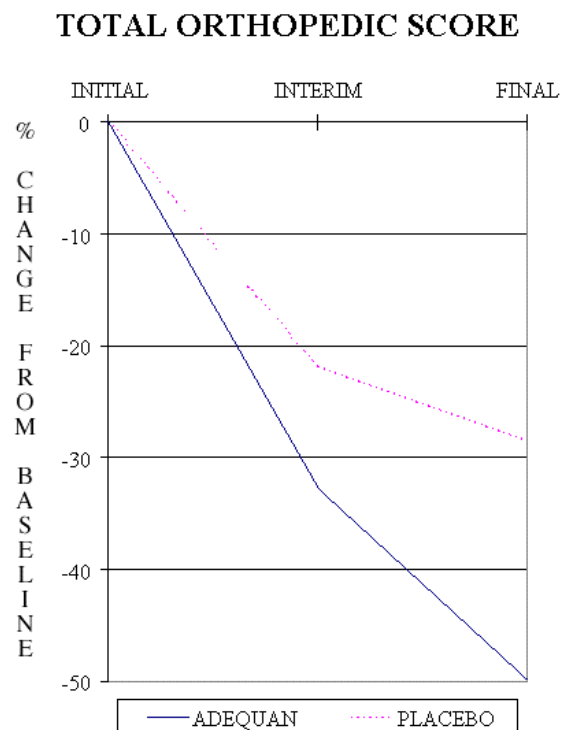
Graph 6: Total Lameness



Graph 6 shows the percentage change in total lameness score from prior to treatment with Adequan or placebo to one week after final treatment in dogs evaluated for lameness. A decrease in the lameness score reflects an improvement in overall lameness. Dogs treated with Adequan show a greater

decrease in the total lameness score (at a walk and trot combined) than placebo treated dogs at both the interim and final time points.

Graph 7: Total Orthopedic Score



Graph 7 shows the percentage change in total orthopedic score from prior to treatment with Adequan or placebo to one week after final treatment. The total orthopedic score is a sum of scores for each variable reflected in Graphs 1-5. Adequan had a greater decrease in total Orthopedic Score than placebo treated dogs at both the interim and final time points.

The graphs show a trend toward greater improvement in the Adequan® Canine treated group versus the placebo group for all parameters at both the



interim and the final evaluations. The trend is most distinct for range of motion, lameness at a trot, and total orthopedic score at the final evaluation.

g) **Statistical Analysis and Conclusions**

Analysis of variance (ANOVA) was performed on the percent change from baseline values at the interim and final evaluations.

The p-values for dose effect for variables expressed as percent change from baseline are shown below.

<b>Parameter</b>	<b>Interim</b>	<b>Final</b>
Lameness/Walk	0.367	0.173
Lameness/Trot	0.716	0.053
Range of Motion	0.156	0.007
Pain	0.305	0.221
Disability	0.076	0.252
Total Lameness	0.323	0.063
Total Orth. Score	0.180	0.025

A statistically significant improvement for Adequan® treated dogs was noted in range of motion and total orthopedic score, where the p-values for dose effect were < 0.05. For lameness at a trot, dose effect approached significance, with p = 0.053. An additional evaluation of the data dichotomized all dogs into responders or non-responders to treatment. A responder dog was defined as one for which all limbs evaluated showed a greater than 30% improvement over baseline values. The percent responders/ non-responders in each treatment group was evaluated using frequency tables and Fisher's Exact Test.

Percent Responders (Experimental Unit: Dog)

<b>Group</b>	<b>Interim</b>	<b>Final</b>
Placebo	37	33
Adequan® Canine	50	67
P- Value	0.405	0.0025

h) **Adverse Reactions**

Statistical analysis of the pre-treatment and post-treatment laboratory data revealed no treatment related effects on hematology parameters, on blood

urea nitrogen (BUN), or creatinine. The following potential adverse reactions were recorded:

- a. preputial bleeding (1 incident; the investigator did not believe the bleeding was related to the experimental treatment)
- b. transient injection site pain (1 incident)
- c. transient diarrhea (1 incident each in 2 dogs)

### 3. Published Literature Reference

Altman, R., Dean, D., Muniz, O., Howell, D. "Therapeutic Treatment of Canine Osteoarthritis with Glycosaminoglycan Polysulfuric Acid Ester" *Arthritis and Rheumatism*, 32:10, (1989), pp. 1300-1307.

#### a) Type of Study

This was a laboratory trial to evaluate the efficacy of intramuscular PSGAG injections in the treatment of canine osteoarthritis created using the Pond-Nuki model.

#### b) Names and Addresses of the Investigators

Roy D. Altman, MD  
Veterans Administration Medical Center  
University of Miami School of Medicine  
Miami, FL  
David D. Dean, Ph.D.  
University of Miami School of Medicine  
Miami, FL

Ofelia E. Muniz, D.Sc.  
University of Miami School of Medicine  
Miami, FL

David S. Howell, MD  
University of Miami School of Medicine  
Miami, FL

#### c) Design of the Investigation

Eighteen mixed breed dogs were subjected to anterior cruciate ligament transection of the right leg, creating an unstable stifle joint. The contralateral (left, unoperated) leg served as a normal control. Following surgery, the dogs were allowed to ambulate for 4 weeks. Eight dogs were designated as controls and were treated with twice weekly intramuscular injections of saline for 4 weeks. The remaining 10 dogs received PSGAG at 4 mg/kg twice weekly for 4 weeks. Following completion of the injections, the dogs were allowed to ambulate an additional 4 weeks. At week 12 following cruciate transection surgery, all dogs were euthanized and necropsied. Cartilage from the medial femoral condyle was analyzed for collagen integrity, hydroxyproline, uronic

acid, active and total metalloproteinase, serine protease, and histopathology (Mankin Score).

The test product used was Arteparon, a solution containing 50 mg/ml PSGAG, manufactured by Luitpold-Werk Munich, F.R.G., and labeled for use in humans.

d) Results

Condylar cartilage from animals treated with PSGAG demonstrated less cartilage swelling, less total and active metalloproteinase, and lower histological scores than were found in cartilage from saline-treated animals. PSGAG at the dose tested (4 mg/kg or about 1.8 mg/lb twice weekly for 4 weeks) was able to suppress cartilage matrix degrading enzyme activity and maintain a more normal appearing cartilage.

e) Adverse Reactions

There were no apparent adverse reactions to PSGAG treatment in the dogs.

f) Conclusions

The data from this study support the efficacy of the proposed dose and treatment regimen for Adequan® Canine for the treatment of canine arthritis.

### **III. ANIMAL SAFETY**

The safety of the proposed dose regimen of Adequan® Canine has been evaluated by an intramuscular subacute toxicity study in dogs.

1. Safety Study

Title: Intramuscular Subacute Toxicity Study in Dogs

a) Type of Study

This trial was a subacute toxicity study of intramuscularly administered PSGAG in beagle dogs.

b) Name and Address of the Investigator

Mr. Harold Chesterman, Study Director  
Huntingdon Research Centre  
P.O. Box 2  
Huntingdon, Cambridgeshire, PE18 6ES, England

c) Design of the Investigation

Thirty-two adult beagle dogs (16 of each sex) served as test animals. After a 4 week acclimation period, the dogs were stratified by sex and weight and assigned to 4 groups of 4 males and 4 females each. The control group

received injections of 0.9% saline. The remaining 3 groups received 5 mg, 15 mg, or 50 mg PSGAG per kg of body weight.

The test product used in this study was supplied by the study's sponsor, Luitpold-Werk, as powdered, dry, white PSGAG. The raw material was reported to be identical in composition to that used in the final formulation of Arteparon, the sponsor's human-labeled PSGAG product. The powder was reconstituted by the researchers with 0.9% physiologic saline to create 1%, 3%, and 10% solutions. All concentrations were administered at doses of 0.5 mL/kg.

All treatments were administered by intramuscular injection twice weekly for 13 weeks. These groups represented approximately 1, 3, and 10 times the recommended dose of Adequan® Canine (2 mg/lb) and the duration of the treatment regimen was approximately 3 times the recommended 4 week duration for Adequan® Canine. Necropsies were performed 24 hours after the final treatment.

Parameters assessed throughout the study included clinical signs, mortality, body weight, food consumption, and water consumption. Ophthalmoscopy, hematology, clinical chemistry, and urinalyses were evaluated prior to therapy and during weeks 6 and 12. Terminal studies included gross post-mortem examination, bone marrow smear, organ weight, and histopathology evaluation

d) Results

Clinical signs: Transient injection site pain was noted on one occasion each in three 50 mg/kg dogs and one 15 mg/kg dog.

Mortalities: One 50 mg/kg dog was euthanized after development of a large hematoma during week 12 of the treatment. Except for an elevated serum

alanine aminotransferase (ALT, SGPT), all terminal findings related to the hematoma.

Body weight: All groups continued to gain weight throughout the study. No overall group differences were detected. Reduced weight gain was detected in the 50 mg/kg females.

Food and water consumption: No drug or dose related effects were detected.

Ophthalmoscopy: No drug or dose related effects were detected.

Hematology: A statistically significant reduction of prothrombin time and platelet counts in the 50 mg/kg group at week 12 was detected.

Clinical Chemistry: Significantly increased serum alanine aminotransferase (ALT, SGPT) values in the 50 mg/kg group and cholesterol values in the 15 and 50 mg/kg groups were noted at weeks 6 and 12.

Urinalysis: No drug or dose related effects were detected.

Terminal studies: Grossly, injection site hemorrhage was noted in all treated groups and in 1 control dog. Cut surface of the liver appeared granular in three of the 50 mg/kg dogs. There were significant increases in liver and kidney weights in the 50 mg/kg group and significant increases in kidney weights in the 15 mg/kg group. Treatment related changes in the liver, kidneys and mesenteric lymph nodes were detected histologically in the 15 and 50 mg/kg groups. Histologically, intramuscular inflammation, hemorrhage, and degeneration were seen in all 3 PSGAG treated groups; the incidence and severity appeared dose related.

e) Statistical Analysis and Conclusions

Significant statistical findings are summarized in Table 4.

Table 4 SIGNIFICANT FINDINGS: SUBACUTE TOXICITY STUDY IN DOGS

PARAMETER	SIGNIFICANT FINDING	P VALUE
Body Weight	SUPPRESSION OF WEIGHT GAIN 50 mg/kg group Females	<0.05 William's Test
Platelet Count	SIGNIFICANT REDUCTION <sup>&amp;127</sup> ; Week 12 50 mg/kg group	<0.05 William's Test
Prothrombin Time	SIGNIFICANT REDUCTION <sup>&amp;127</sup> ; Week 12 50 mg/kg group	<0.01 William's Test
ALT (SGPT)	SIGNIFICANT INCREASE Week 6 50 mg/kg group	<0.01 William's Test
ALT (SGPT)	SIGNIFICANT INCREASE Week 12 50 mg/kg group	<0.01 William's Test
Cholesterol	SIGNIFICANT INCREASE Week 6 15 mg/kg group	<0.05 William's Test
Cholesterol	SIGNIFICANT INCREASE Week 12 15 mg/kg GROUP	<0.01 William's Test
Cholesterol	SIGNIFICANT INCREASE Weeks 6 and 12 50 mg/kg group	<0.01 William's Test
Liver Weight	SIGNIFICANT INCREASE 50 mg/kg group	<0.05 William's Test
Kidney Weight	SIGNIFICANT INCREASE 50 mg/kg group	<0.01 William's Test

These data indicate that the proposed dosage regimen for Adequan® Canine (2 mg/lb body weight twice weekly for 4 weeks) is unlikely to produce adverse effects in dogs. At higher doses and for longer treatment periods, effects on the kidney, liver, and blood coagulation are possible. These results indicate the drug should be used with caution in dogs with known or suspected bleeding, renal, or hepatic disorders. f) Adverse Reactions:

In the 5 mg/kg dose group, no adverse reactions were noted. Abnormal hemorrhage was noted in one 50 mg/kg group dog and transient injection site pain was noted in one of the 15 mg/kg dogs and three 50 mg/kg dogs.

## 2. Reproductive Safety

The following statement will appear on the product labeling:

**"Reproductive Safety:** Studies to establish the safety of Adequan® Canine in breeding dogs have not been conducted."

## IV. HUMAN FOOD SAFETY

### A. Human Safety Relative to Food Consumption

Data on human safety pertaining to consumption of drug residues in food were not required for the approval of this NADA. This drug is to be labeled for use in dogs, which are non-food animals.

## **B. Human Safety Relative to Possession, Handling, and Administration**

Human safety relative to possession, handling and administration is addressed by the following statement on the product labeling:

**"Warning:** Keep this and all medication out of the reach of children."

## **V. AGENCY CONCLUSIONS**

The data submitted in support of this NADA satisfy the requirements of Section 512 of the Federal Food, Drug, and Cosmetic Act (FFDCA), and 21 CFR Part 514. Dose selection for Adequan® Canine was based on published studies concerning the use of polysulfated glycosaminoglycan in osteoarthritis models in dogs. The selected dose of 2 mg/lb was shown to have an adequate margin of safety in dogs, and was confirmed in a clinical field trial. These data demonstrate that Adequan® Canine, when used according to the conditions set forth in the labeling, is safe and effective.

Under section 512(c)(2)(F)(ii) of the FFDCA, this approval for non food producing animals qualifies for THREE years of marketing exclusivity beginning on the date of approval because the application contains substantial evidence of the effectiveness of the drug involved, or studies of animal safety required for the approval of the application and conducted or sponsored by the applicant.

In order to select cases for the appropriate use of Adequan® Canine, the diagnosis of non-infectious degenerative and/ or traumatic arthritis and associated lameness must be established. Only a veterinarian, suitably qualified by training and experience, can establish the diagnosis. Special studies, such as radiographs, are generally required for definitive diagnosis. Therefore, Adequan® Canine is classified as a prescription drug.

The format of this FOI Summary document has been modified from its original form to conform with Section 508 of the Rehabilitation Act (29 U.S.C. 794d). The content of this document has not changed.