Date of Approval: January 13, 2022

FREEDOM OF INFORMATION SUMMARY

ORIGINAL NEW ANIMAL DRUG APPLICATION

NADA 141-546

Solensia™

frunevetmab injection

Injectable Solution

Cats

Solensia™ is indicated for the control of pain associated with osteoarthritis in cats.

Sponsored by:

Zoetis Inc.

Executive Summary

Solensia™ (frunevetmab injection) is approved for the control of pain associated with osteoarthritis in cats. Frunevetmab is a felinized immunoglobulin G monoclonal antibody (mAb), which is a murine (mouse) antibody in which all regions of the mouse antibody are replaced with feline counterparts except for the complementarity-determining regions (the variable parts of the antibody that determine specific Ab binding). Monoclonal antibodies, such as frunevetmab, are a specific subclass of therapeutic proteins.

Frunevetmab binds to and blocks the effects of a neurotrophin called nerve growth factor (NGF) and also reduces the amount of NGF that binds to tropomyosin receptor kinase A (TrkA) and p75 neurotrophin receptor (p75NTR). Neurotrophins are a family of proteins that regulate the development, maintenance, and function of the nervous system of vertebrates. NGF specifically is involved in the normal development of sensory and sympathetic nerve fibers in developing animals. Both TrKA and p75NTR are activated by neurotrophins.

In vitro binding studies suggest that frunevetmab binds with high affinity to NGF but does not bind to other neurotrophins. NGF has been found to be elevated in osteoarthritic joints of multiple species. Following a noxious stimulus, the tissues of the injured joint release inflammatory cytokines and NGF. NGF binds to TrkA and p75NTR found on peripheral nerves, immune cells, endothelial cells, synoviocytes, and chondrocytes to induce peripheral sensitization, neurogenic inflammation, and increased pain perception. By blocking the effects of NGF, frunevetmab decreases signal transduction in these cell types and helps reduce pain perception.

Solensia™ is given by subcutaneous (SC) injection once a month and is dosed by weight range. Cats are given the full contents of 1 or 2 vials based on body weight to target a minimum dose of 1 mg/kg. Each vial contains 7 mg of frunevetmab.

Table 1. General Information

Proprietary Name	Established Name	Application Type and Number	Sponsor
Solensia™	frunevetmab injection	New Animal Drug Application (NADA) 141-546	Zoetis Inc.

Safety and Effectiveness

Because of the current limitations inherent in studies designed to evaluate the effectiveness of any drug intended to control chronic pain in cats, FDA used a weight of evidence approach to determine the effectiveness of Solensia™ to control pain associated with osteoarthritis in cats. The endpoints used to evaluate the effectiveness of Solensia™ were observer-reported measures conducted by either owners or veterinarians.

Exploratory Field Effectiveness Study

The sponsor conducted an exploratory field effectiveness study using a formulation of frunevetmab injection that was not the final market formulation of Solensia™ but was manufactured similarly. The study evaluated client-owned cats that had been

diagnosed with osteoarthritis in at least two joints or spinal segments based on clinical signs noted by the owner, the veterinarian's physical and orthopedic examinations, and radiographic confirmation. Enrolled cats were of both sexes, more than 6 months of age, of various weights and breeds, and had a total client-specific outcome measures (CSOM) score for pain of 7 or greater.

The CSOM score measured the degree of the cat's impairment due to pain based on three activities that the owner selected. For each activity, the owner considered the cat to be impaired compared to when the cat was normal (for example, jumping onto the couch, using the litter box, and grooming). Owners were asked to rate the degree of impairment associated with these specific activities using a five-point scale, from 1 (the cat had no problem with the activity) to 5 (the activity was impossible for the cat).

Cats received either frunevetmab injection or vehicle control. There were two frunevetmab groups in the study: one group was administered frunevetmab by SC injection two times, 28 days apart, and the other group was administered frunevetmab by intravenous (IV) injection followed by a SC injection 28 days later (this group was not part of the effectiveness evaluation). The control group received the vehicle control by IV injection on Day 0 followed by a SC injection on Day 28.

The total CSOM score was the primary outcome measure for determining effectiveness. On each assessment day, the cat's total CSOM score was calculated by summing the scores of the three owner-selected activities. The cat was considered a treatment success if (1) there was a 2-point reduction in the total CSOM score from Day 0 (before the first treatment), and (2) there was no increase in the CSOM score for any one activity. More cats were considered treatment successes in the treatment group that received two SC injections 28 days apart compared to the control group on all assessment days, but the difference was statistically significant only on Day 56.

Owners also completed a global assessment of their subjective impression of the cat's response to therapy (scored as an excellent, good, fair, or poor response). A cat was considered a treatment success if the owner reported a score of good or excellent. On Days 28 and 56, more cats in the treatment group that received two SC injections 28 days apart had higher global assessment scores compared to the control group.

During the orthopedic examination, the veterinarian evaluated the cat's pain in 21 locations on the limbs and spinal column and obtained a total orthopedic pain score using a five-point scale, from 1 (no pain or resentment on palpation) to 5 (the cat tried to escape or prevent manipulation of its limbs and spinal column). On Days 28 and 56, more cats in the treatment group that received two SC injections 28 days apart had lower (better) total orthopedic pain scores compared to cats in the control group. In addition, the decrease in the total orthopedic pain score from Day 0 (before the first treatment) was greater for cats in this treatment group compared to cats in the control group on Days 28 and 56.

The most frequently reported adverse reactions were digestive tract disorders, including vomiting and diarrhea, and skin disorders, including dermatitis, eczema,

and alopecia (some skin lesions were attributed to irritation from the collar the cats wore to record their movement as part of an exploratory effectiveness evaluation).

Confirmatory Field Effectiveness Study
The sponsor conducted a confirmatory field effectiveness study using the final market formulation of Solensia™. The study evaluated client-owned cats that had been diagnosed with osteoarthritis in at least two joints or spinal segments based on clinical signs noted by the owner, the veterinarian's physical and orthopedic examinations, and radiographic confirmation. Enrolled cats were of both sexes, were between 1.6 and 22.4 years old, of various weights and breeds, and had a total CSOM score for pain of 7 or greater.

Cats received either three SC injections of Solensia™ 28 days apart or vehicle control at the same dosage regimen. Similar to the exploratory field study, the primary outcome measure for determining effectiveness was the cat's total CSOM score on Days 28, 56, and 84 compared to Day 0 (before the first treatment). A cat was considered a treatment success if it had a 2-point reduction in the total CSOM score on Day 56 compared to Day 0. However, cats that had an increase in their CSOM score for any one activity (regardless of the total CSOM score) or that received rescue analgesia before Day 56 were considered treatment failures. More cats in the treatment group had a 2-point reduction in the total CSOM score compared to the control group on Days 28, 56, and 84, but the difference between the two groups was statistically significant only on Day 28. The average total CSOM score for the treatment group was also lower compared to the control group on all assessment days.

The owner's global assessment scores and the veterinarian's orthopedic examination scores were also evaluated to determine effectiveness. More cats in the treatment group had higher global assessment scores (owner-reported scores of good or excellent) compared to the control group on all assessment days. The pooled orthopedic examination scores from Days 28, 56, and 84 were slightly lower (better) in the treatment group compared to the control group for crepitus, effusion, pain, and thickening.

Adverse reactions related to Solensia™ included scabbing on the head and neck, dermatitis, and pruritis, but the skin lesions were not severe enough to require discontinuing the drug.

Weight of Evidence Approach
The two effectiveness studies described above used three clinical assessments that attempt to measure different aspects of pain associated with osteoarthritis in cats: (1) The CSOM measures the owner's assessment of the cat's impairment due to pain based on three activities that the owner selects; (2) the global assessment measures the owner's subjective impression of the drug's overall effect on the cat's clinical signs associated with osteoarthritis; and (3) the total orthopedic pain score measures the veterinarian's assessment of the cat's pain in its joints and spinal column.

In both studies, the owner's and veterinarian's assessments agreed that Solensia™ reduced pain associated with osteoarthritis more than the vehicle control did. There was a large disparity in the control group's CSOM results between the two studies

(47.1% success rate for the exploratory field effectiveness study versus 64.8% success rate for the confirmatory field effectiveness study on Day 56). The relatively high success rate of the control group in the confirmatory field effectiveness study likely contributed to the lack of statistical significance on Days 56 and 84. The high success rate in both studies' control groups (called the "placebo effect") is not unexpected. Because of the subjective nature of the endpoints used to evaluate the effectiveness of drugs intended to control pain, and the waxing and waning nature of the clinical signs of osteoarthritis over time, the placebo effect is usually relatively high in this type of study.

Taken together, the overall trend of the results in both studies supports the drug's effectiveness and the weight of the evidence demonstrates that Solensia™ is effective at controlling pain associated with osteoarthritis in cats.

Target Animal Safety
The sponsor conducted one laboratory safety study in young, healthy, intact cats. Female cats were not pregnant or lactating. Cats were administered Solensia™ by SC injection every 28 days for a total of 6 doses at 0 mg/kg, 2.8 mg/kg, 8.4 mg/kg, or 14 mg/kg.

Vomiting and diarrhea were observed sporadically in all groups. The highest frequency of vomiting occurred in the 2.8 mg/kg group. Clinically relevant skin findings included abrasions, alopecia, and scabs, mostly around the face and ears and at the injection site. One cat in the 2.8 mg/kg group developed an unusually severe skin lesion. This cat's persistent pruritus and prolonged skin healing were deemed potentially drug related. In all groups, no clinically significant changes were seen in body weight, food consumption, physical examination (other than the abnormal skin findings), and neurological examination.

Immunogenicity
All therapeutic proteins can trigger an immune response, including the production of antibodies that bind to the therapeutic protein. Such host-derived antibodies are also called anti-drug antibodies (ADAs). A subpopulation of ADAs, called neutralizing antibodies (NAbs), can inhibit the functional activity of the therapeutic protein and may decrease its effectiveness. If ADAs are produced, there are four basic possible outcomes:

1. ADAs bind to the therapeutic protein and have no subsequent impact on effectiveness or safety;
2. ADAs bind to the therapeutic protein and alter drug effectiveness (e.g., altered pharmacokinetic profile, reduced or lack of effectiveness from formation of NAbs);
3. ADAs bind to the therapeutic protein and cause adverse effects (e.g., allergenicity/hypersensitivity reactions); or
4. ADAs bind to the therapeutic protein and both (2) and (3) occur: alter drug effectiveness and cause adverse effects.

The sponsor assessed for the presence of anti-frunevetmab antibodies (ADAs) in cats using a screening and confirmatory assay approach. The formation of NAbs was not evaluated. In the two controlled studies in cats with osteoarthritis described above (the exploratory and confirmatory effectiveness studies), four out of 259 cats (1.5%)

that received monthly injections of Solensia™ developed anti-frunevetmab antibodies. One cat tested positive for anti-frunevetmab antibodies on Days 0, 28, 56, and 84. This cat had no detectable levels of Solensia™ in its plasma on Days 28 and 56 and was a treatment failure in the effectiveness analysis, suggesting that the anti-frunevetmab antibodies may have reduced Solensia™'s effectiveness in this cat. In the target animal safety study described above, no cats tested positive for anti-frunevetmab antibodies following Solensia™ administration.

The combined incidence of anti-frunevetmab antibody formation was 1.4% (4 of 283 total Solensia™-treated cats), in the 8-week and 12-week treatment periods in the field effectiveness studies and the 24-week treatment period in the target animal safety study. In these studies, the incidence of anti-frunevetmab antibody formation was low. Although these data show a limited impact of anti-frunevetmab antibody development on the safety and effectiveness of Solensia™ in cats, the available data are too limited to make definitive conclusions. It is unknown whether the incidence of anti-frunevetmab antibody formation increases with continued Solensia™ administration beyond the period evaluated in the effectiveness and target animal safety studies or whether any increase in incidence of anti-frunevetmab antibody formation would affect the safety and/or effectiveness of Solensia™.

Safety Warnings
Solensia™ should not be used in breeding cats or in pregnant or lactating queens because the drug may pass through the placental blood barrier and be excreted in milk. Women who are pregnant, may become pregnant, or are breastfeeding should take extreme caution to avoid accidental self-injection of Solensia™. It is well-established that NGF is important in the normal development of the fetal nervous system, and laboratory studies in nonhuman primates have shown that human anti-NGF mAbs can cause reproductive and developmental toxicity. Fetal abnormalities, increased rate of stillbirths, and increased postpartum fetal mortality were noted in rodents and nonhuman primates receiving anti-NGF mAbs.

In the case of accidental self-injection of Solensia™, a person may have hypersensitivity reactions, including anaphylaxis. Hypersensitivity reactions are more likely with a protein drug product such as Solensia™ than with non-protein drug products.

The safe use of Solensia™ with concurrent nonsteroidal anti-inflammatory drugs (NSAIDs) has not been established in cats. In clinical trials in people, rapidly progressing osteoarthritis (RPOA) has been reported in a small number of patients receiving humanized anti-NGF mAb therapy. The incidence of RPOA increased in those patients who were on long-term NSAID treatment in combination with an anti-NGF mAb. RPOA has not been characterized or reported in cats.

The safe use of Solensia™ was evaluated for 6 consecutive months, typical for a drug intended for chronic use. However, because of NGF's role in the normal development of sensory and sympathetic nerve fibers in developing animals, it is unknown whether delayed effects may occur beyond 6 months in young growing cats, or even in adult cats. Nonhuman primates receiving high doses of anti-NGF mAbs for 6 consecutive months had reduced cell size in postganglionic neuronal cell bodies. The cell bodies returned to normal size after discontinuing the anti-NGF mAb, suggesting that such long-term effects, should they occur, are likely reversable.

Conclusions
Based on the data submitted by the sponsor for the approval of Solensia™, FDA determined that the drug is safe and effective when used according to the labeling.

Table of Contents

I. GENERAL INFORMATION

A. File Number

NADA 141-546

B. Sponsor

Zoetis Inc.
333 Portage St.
Kalamazoo, MI 49007

Drug Labeler Code: 054771

C. Proprietary Name

Solensia™

D. Drug Product Established Name

Frunevetmab injection

E. Pharmacological Category

Monoclonal antibody

F. Dosage Form

Injectable solution

G. Amount of Active Ingredient

7 mg/mL

H. How Supplied

Single-use 4 mL glass vials

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

The full content of 1 or 2 vials based on body weight to target a minimum dosage of 0.45 mg/lb. (1 mg/kg) body weight, administered subcutaneously once a month.

K. Route of Administration

Subcutaneous

L. Species/Class

Cats

M. Indication

Solensia™ is indicated for the control of pain associated with osteoarthritis in cats.

II. EFFECTIVENESS

A. Dosage Characterization

Frunevetmab is a felinized monoclonal antibody (mAb). It is a murine antibody in which all regions of the murine antibody are replaced with feline counterparts except for the complementarity-determining regions.

The minimum dose of 1 mg/kg administered once by SC injection every 28 days was selected for further evaluation based on the following studies.

Exploratory Single-Site Field Study
A randomized, double-masked, placebo-controlled, single-site field study (Study NV-02 Task Order #5) evaluated the effectiveness of frunevetmab in cats with naturally occurring osteoarthritis. Thirty-four cats were randomized at a ratio of 1:1:1 to treatment with a pilot formulation of frunevetmab (0.4 or 0.8 mg/kg body weight [BW]) or placebo. The dose of frunevetmab or placebo was administered SC once on Day 0. A CSOM score was recorded for each cat on Days 0, 21, 42, and 63. A cat was a treatment success if the total CSOM score improved by ≥ 2 compared to Day 0. A greater proportion of cats in both frunevetmab groups achieved treatment success compared to placebo at Day 21 but not at Days 42 or 63.

Exploratory Multi-Site Field Study
An exploratory field study (Study No. NV-02-11F15-005, described more fully below under substantial evidence of effectiveness) was conducted to evaluate the proposed minimum dose of 1 mg frunevetmab/kg BW administered IV or SC. Based on the results of the study, the minimum 1 mg/kg dose administered SC was chosen for further evaluation in the confirmatory field effectiveness study.

B. Substantial Evidence

Substantial evidence of effectiveness is demonstrated by the results of two field studies in cats with naturally occurring osteoarthritis (Study NV-02-11F15-005 and Study NV-02-11F16-001). These studies, taken together, establish the effectiveness of frunevetmab injection for the control of pain associated with osteoarthritis in cats.

Because of the limitations currently inherent in studies designed to evaluate the effectiveness of drugs intended to control chronic pain in cats, a weight of evidence approach was employed to determine if the overall evidence supported the conclusion that frunevetmab injection was effective for the control of pain associated with osteoarthritis in cats. The endpoints used to evaluate the effectiveness of frunevetmab injection for the control of osteoarthritic pain in cats are observer-reported measures conducted by either owners or veterinarians.

Study NV-02-11F16-001 found a significant difference in the CSOM scores between the frunevetmab-treated group and the control-treated group on Day 28 in favor of the frunevetmab-treated group, but the difference was not significant on Day 56 and Day 84. The lack of a significant difference between the two groups on Day 56 and Day 84 might suggest a lack of effect. However, the results of Study NV-02-11F15-005 support the effectiveness of frunevetmab injection on Day 56. Study NV-02-11F15-005 was conducted with a formulation of frunevetmab injection that was manufactured in a similar process to the final market formulation. Although manufacturing differences may have had an unknown impact on drug effectiveness, the results of the primary and secondary outcomes from the two studies, taken together, demonstrate substantial evidence of effectiveness despite each study's limitations.

1. Exploratory Field Effectiveness Study for Control of Pain Associated with Osteoarthritis in Cats

   Title: A Multi-center Exploratory Study to Evaluate the Effectiveness and Field Safety of Frunevetmab for the Control of Pain and Improvement in Mobility in Cats with Osteoarthritis (OA). (Study No. NV-02-11F15-005)

   Study Dates: October 2015 to May 2017

   Study Locations: Fourteen veterinary clinics in the United States from the following locations participated in this study.

   Decatur, IL
   Madison, WI‡
   Lake Worth, FL‡
   Bradenton, FL‡
   Quakertown, PA‡
   Farragut, TN‡
   Manchester, CT‡
   Lisle, IL
   Springfield, MO
   Morrisville, NC‡
   Altamonte Springs, FL
   Durham, NC‡
   Duluth, GA
   Denver, CO

   ‡ Clinical investigator also participated in Study No. NV-02-11F16-001

   Study Design: This was a multi-center, double-masked, randomized, placebo-controlled field study.

   Objective: The study evaluated the effectiveness and field safety of frunevetmab administered by SC injection two times at 28 day-intervals or by a single IV injection followed by a SC injection 28 days later for the control of pain associated with osteoarthritis in cats.

Study Animals: The study enrolled 126 client-owned cats with osteoarthritis (74 females; 52 males). Enrolled cats had been diagnosed with osteoarthritis in at least two joints or spinal segments based on owner history, physical examination, orthopedic examination, and radiography. The enrolled cats were older than 6 months of age, weighed 6.6 to 23.1 lbs. (3 to 10.5 kg), and were of various breeds or non-purebred.

Experimental Design: The cats were randomized at a ratio of 2:1 to receive frunevetmab injection or a vehicle control (85 cats in the frunevetmab group and 41 cats in the control group).

Treatment Groups:

Table II.1. Treatment Groups in Study No. NV-02-11F15-005

Treatment (Group)	**Vehicle control (Group 1)**	**Frunevetmab Injection (Group 2)**	**Frunevetmab Injection (Group 3)**
Day 0 Route	IV	IV	SC
Day 28 Route	SC	SC	SC
Dose	0 mg/kg	1.0 mg/kg	1.0 mg/kg
Total dose volume of frunevetmab or control[1]	1 or 2 mL	1 or 2 mL	1 or 2 mL
Total dose of frunevetmab (mg)[1]	0 mg	7 or 14 mg	7 or 14 mg

[1]Cats from 2.5 to 7 kg bodyweight were administered 1 mL of frunevetmab injection (7 mg frunevetmab per mL) or vehicle control. Cats from 7.1 to 14 kg bodyweight were administered 2 mL of frunevetmab injection (7 mg frunevetmab per mL) or vehicle control.

Inclusion Criteria: Client-owned cats that had been diagnosed with osteoarthritis in at least two joints or spinal segments based on clinical signs noted by the owner, the veterinarian's physical and orthopedic examination, and radiographic confirmation. Cats were in good general health or had stable chronic conditions that would not interfere with the study assessments. Cats were required to have a total CSOM score for pain of ≥ 7 (CSOM score described below).

Exclusion Criteria: Cats intended for breeding, pregnant or lactating female cats, or cats with conditions that would confound the study assessments or prevent completion of the study were excluded.

Drug Administration: The frunevetmab groups received a formulation of frunevetmab injection that was manufactured in a similar process to the final market formulation. The control group received the vehicle formulation (no active ingredient). Treatment administration occurred in the veterinary clinic at scheduled visits.

Measurements and Observations: Baseline physical examination, body weight, hematology, serum chemistry, urinalysis, immunological analysis, CSOM, Feline Musculoskeletal Pain Index (FMPI), activity monitoring (by collar), orthopedic examination, and orthopedic radiographs were obtained prior to the initial dose administration. FMPI and CSOM were reassessed by the cat owner on Days 14, 28, 42, and 56. Owners recorded the Owner Global Assessments on Days 28 and 56. The study veterinarian performed physical examinations, orthopedic examinations, and injection site evaluations on Days 28 and 56. Samples for hematology, serum chemistry, and urinalysis were collected on Day 56.

Statistical Methods: The primary analysis for effectiveness was a comparison of the proportions of treatment success in each group using methods appropriate for binary outcomes (the GLIMMIX procedure in SAS), assuming a binomial distribution and logit link. The model included treatment group as a fixed effect with site and treatment group by site interaction as random effects. The experimental unit was the individual cat. Statistical significance was evaluated at a two-sided alpha equal to 0.05.

Results:

CSOM: The total CSOM score was the primary outcome measure for determining effectiveness. The total CSOM score measured the degree of pain-associated impairment recognized by the owner using three owner-selected activities that were impaired compared to when the cat was considered normal (e.g., jumping onto the couch, use of litter box, grooming). Owners were asked to be very specific and to indicate both the places and the times when the activities were impaired. Owners were asked to rate the degree of impairment associated with these very specific activities. A five-point scale was used for each activity:

1 = no problem
2 = mildly problematic
3 = moderately problematic
4 = severely problematic
5 = impossible

The score for each activity was summed to determine the total CSOM score. An individual cat was considered a treatment success on an assessment day if they achieved a 2-point reduction in total CSOM score from Day 0 (scored prior to first treatment administration) and no increase in any individual CSOM activity. Frunevetmab injection was considered effective if there was a higher percentage of successful cases in the frunevetmab-treated group compared to the control group, and the difference was statistically significant ($\alpha = 0.05$).

There was a significant difference ($p < 0.05$) between the CSOM scores in the SC-SC frunevetmab group and the placebo group on Day 56 (see Table II.2).

Table II.2. Least Squares (LS) Mean Percent Success for CSOM Assessments for SC-SC Frunevetmab Injection and Control Groups Including Only Study Sites With at Least 2 Evaluable Cases Per Treatment Group

Study Day	Percent Success Frunevetmab Injection[1]	Percent Success Control[1]	p-value
14	61.8	60.6	0.924
28	68.6	55.9	0.304
42	73.5	55.9	0.162
56	80.0	47.1	0.020

[1]LS mean

Owner Global Assessment: The owner made a Global Assessment of their subjective impression regarding the success of the treatment in controlling clinical signs of osteoarthritis in their cat. The owner's impression of the response to therapy was scored as excellent, good, fair, or poor as described below. An individual cat was considered a treatment success if they received a score of good or excellent:

Table II.3. Owner Global Assessment Scoring Options

Score	Descriptor
Excellent	Clinical signs of osteoarthritis were eliminated or reduced to an inconsequential level.
Good	Clinical signs of osteoarthritis were substantially [at least 50%] reduced.
Fair	Clinical signs of osteoarthritis were minimally [less than 50%] reduced.
Poor	Clinical signs of osteoarthritis were unaffected by therapy.

The Owner's Global Assessment on Day 28 and Day 56 showed a higher success rate in the SC-SC frunevetmab group than in the control group (see Table II.12. Owner Global Assessment results in Study NV-02-11F15-005 below).

Orthopedic Examinations: During the orthopedic exam, the veterinarian examined and graded all four limbs and the spinal column to obtain the Total Orthopedic Pain Score. The following scoring system was used:

Pain (based on palpation)

1. No resentment; normal amount of movement or wriggling
2. Mild withdrawal; mildly resists
3. Moderate withdrawal; body tenses; may orient to site; may vocalize or hiss or bite
4. Orients to site; forcible withdrawal from manipulation; may vocalize or hiss or bite
5. Tries to escape or prevent manipulation; bites/hisses; marked guarding of area

The mean Total Orthopedic Pain Score in the SC-SC frunevetmab group was less on Day 28 and Day 56 than in the control group, and the decrease in mean Total Orthopedic Pain Score from the screening (baseline) score was greater in the SC-SC frunevetmab group on Day 28 and Day 56 than in the control group (see Table II.15. Mean Veterinary Assessed Total Orthopedic Pain Scores in Study NV-02-11F15-005 below).

Adverse Reactions: Safety was evaluated in 126 cats (85 frunevetmab, 41 control) during the study through the review of treatment-emergent adverse events, clinical pathology results, and physical examination. The most frequently reported adverse reactions were digestive tract disorders including vomiting and diarrhea, and skin disorders including dermatitis/eczema and alopecia (some skin lesions were attributed to irritation from the collar the cats wore to record their movement).

Conclusion: Although this study was an exploratory study using a non-final formulation, this study, when paired with the results from Study NV-02-11F16-001 (described below), provides evidence that the administration of frunevetmab injection at a minimum dose of 1.0 mg/kg BW subcutaneously 28 days apart is safe and effective for the control of pain associated with osteoarthritis in cats. See full discussion below in 'Weight of the Evidence'.

2. Field Effectiveness Study for Control of Pain Associated with Osteoarthritis in Cats

Title: A Multi-center Study to Evaluate the Effectiveness and Field Safety of Frunevetmab for the Control of Pain Associated with Osteoarthritis (OA) in Cats. (Study No. NV-02-11F16-001)

Study Dates: October 6, 2016 to October 16, 2017

Study Locations: Twenty-one veterinary clinics in the United States from the following locations participated in this study.

Bristol, CT	Liverpool, NY
Manchester, CT‡	Durham, NC‡
Bradenton, FL‡	Greensboro, NC
Lake Worth, FL‡	Morrisville, NC‡
Duluth, GA	Harrisburg, PA
Chicago, IL	Quakertown, PA‡
Franklin, IN	Columbia, SC
Terre Haute, IN	Farragut, TN‡
Catonsville, MD	Madison, WI‡
Canton, MI	Milwaukee, WI
Kentwood, MI	

‡ Clinical investigator also participated in Study No. NV-02-11F15-005

Study Design: This was a multi-center, double-masked, randomized, placebo-controlled field study.

Objective: The study evaluated the effectiveness and field safety of Solensia™ (frunevetmab injection) administered by SC injection three times at 28 day-intervals for the control of pain associated with osteoarthritis in cats.

Study Animals: The study enrolled 275 client-owned cats with osteoarthritis (152 spayed females, 123 castrated males). Enrolled cats had been diagnosed with osteoarthritis in at least two joints or spinal segments based on clinical signs noted by the owner, physical examination, orthopedic examination, and radiography. The enrolled cats were 1.6 to 22.4 years old, weighed 5.5 to 25.1 lbs. (2.5-11.4 kg), and were of various breeds or non-purebred.

Experimental Design: The cats were randomized at a ratio of 2:1 to receive Solensia™ (frunevetmab injection) or a vehicle control (182 cats in the frunevetmab group and 93 cats in the control group). This study was conducted in accordance with Good Clinical Practice.

Treatment Groups:

Table II.4. Treatment Groups and Dose of Solensia™ and Control Products

Group	Treatment	Dose	Total dose volume[1]	Total dose of frunevetmab (mg)[1]
1	Vehicle Control	0 mg/kg	1 or 2 mL	0 mg
2	Solensia™ (Frunevetmab Injection)	1.0 mg/kg	1 or 2 mL	7 or 14 mg

[1]Cats from 2.5 to 7 kg bodyweight were administered 1 mL of Solensia™ (7 mg frunevetmab per mL) or vehicle control. Cats from 7.1 to 14 kg bodyweight were administered 2 mL of Solensia™ (7 mg frunevetmab per mL) or vehicle control.

Inclusion Criteria: Client-owned cats that had been diagnosed with osteoarthritis in at least two joints or spinal segments based clinical signs noted by the owner, the veterinarian's physical and orthopedic examination, and radiographic confirmation. Cats were in good general health or had stable chronic conditions that would not interfere with the study assessments. Cats were required to have a CSOM score for pain of ≥ 7.

Exclusion Criteria: Cats that were intended for breeding, or pregnant or lactating female cats, or cats with conditions that would confound the study assessments or prevent completion of the study.

Drug Administration: The frunevetmab group received the final market formulation of Solensia™ (frunevetmab injection). The control group received the vehicle formulation (no active ingredient). Treatment administration occurred in the veterinary clinic at scheduled visits.

Measurements and Observations: Baseline physical examination, body weight, hematology, serum chemistry, urinalysis, immunological analysis, CSOM,

orthopedic examination, and orthopedic radiographs were obtained prior to the initial dose administration. CSOM and Owner Global Assessments were evaluated by the cat owner on Days 28, 56, and 84. The veterinarian completed physical examination, orthopedic examination, and injection site evaluation on Days 28, 56, and 84. Hematology, serum chemistry, and urinalysis were evaluated on Day 84. Samples for immunological assessment were collected on Days 28, 56, and 84. A follow-up telephone call was made on Day 112.

Statistical Methods: The primary analysis for effectiveness was a comparison of the proportions of treatment success in each group using methods appropriate for binary outcomes (the GLIMMIX procedure in SAS), assuming a binomial distribution and logit link. The model included treatment group as a fixed effect with site and treatment group by site interaction as random effects. The experimental unit was the individual cat. Statistical significance was evaluated at a two-sided alpha equal to 0.05.

Results:

CSOM: Effectiveness was determined by the owner's evaluation of CSOM at Days 28, 56, and 84 compared to baseline (Day 0, before treatment). The primary effectiveness outcome for measuring treatment success was defined as a reduction of at least 2 in the total CSOM score on Day 56 compared with the score at baseline (Day 0, before treatment). However, cats that had an increase in any individual CSOM activity (regardless of the total CSOM score), or that received rescue analgesia prior to Day 56, were considered treatment failures. The proportion of cats considered treatment successes based on the owner CSOM assessment was greater in the Solensia™ group compared to the control group on all assessment days. The difference between the two groups was significant only at Day 28.

Table II.5. LS Mean Percent Success for CSOM Assessments by Treatment Group and Study Day

Day	Percent Success Solensia™ Group[1]	Percent Success Control Group[1]	p-value
28	66.9	51.6	0.0243
56	75.1	64.8	0.0925
84	76.5	67.3	0.1293

[1]LS Mean

Total CSOM Scores: The comparison of the mean total CSOM Scores was a secondary effectiveness variable. The total mean CSOM scores were lower in the Solensia™ group compared to the control group at Days 28, 56, and 84.

Table II.6. Summary of Total CSOM Scores: LS Means and Standard Error

Day	Total CSOM Scores Solensia™ Group LS Mean (Standard Error)	Total CSOM Scores Control Group LS Mean (Standard Error)
28	8.13 (0.2110)	8.83 (0.2803)
56	7.08 (0.2281)	7.93 (0.3067)
84	6.76 (0.2347)	7.46 (0.3161)

Owner Global Assessment Score: The Owner Global Assessment score was a secondary variable. The Owner Global Assessment score was based on the owner's subjective impression regarding the success of the treatment in controlling clinical signs of osteoarthritis in their cat. The owner's impression of the response to treatment was scored as Excellent, Good, Fair, or Poor (defined above under Study NV-02-11F15-005). Cats in the Solensia™ group had a higher percent of excellent and good scores compared to the control group on Days 28, 56, and 84.

Table II.7. Summary of the Owner Global Assessment Scores

Day	Group	N	% Excellent	% Good	% Fair	% Poor
28	Solensia™	178	6.18	33.15	44.38	16.29
28	Control	92	2.17	28.26	40.22	29.35
56	Solensia™	172	14.53	44.77	23.84	16.86
56	Control	87	4.60	43.68	27.59	24.14
84	Solensia™	164	25.00	39.63	20.12	15.24
84	Control	83	16.87	40.96	16.87	25.30

Orthopedic Examination Scores: The orthopedic examination scores were a secondary effectiveness endpoint. The mean pooled scores from Days 28, 56, and 84 were slightly lower (better) in the Solensia™ group compared to the control group for crepitus, effusion, pain, and thickening.

Table II.8. Summary of Orthopedic Examination Scores Pooled Across Days 28, 56, and 84

Variable	Group	LS Mean (Standard Error of the Mean)
Crepitus Total	Solensia™	17.26 (0.15)
Crepitus Total	Control	17.34 (0.17)
Effusion Total	Solensia™	14.43 (0.07)
Effusion Total	Control	14.45 (0.09)
Pain Total	Solensia™	27.79 (0.54)
Pain Total	Control	28.90 (0.61)
Thickening Total	Solensia™	16.44 (0.21)
Thickening Total	Control	16.49 (0.23)

Clinical Pathology: There were no clinically relevant differences in clinical pathology results between the Solensia™ and control groups.

Adverse Reactions: Safety was evaluated in 275 cats (182 Solensia™, 93 control) that received at least one treatment dose during the study. One hundred thirteen cats in the Solensia™ group (62.1%) and 45 cats (48.4%) in the control group had at least one adverse reaction during the study.

Table II.9. Adverse Reactions in the Field Effectiveness Study NV-02-11F16-001

Adverse Reactions	Solensia™ N=182[1] (%)	Control N=93[1] (%)
Vomiting	24 (13.2%)	10 (10.8%)
Injection site pain[2]	20 (10.9%)	13 (14%)
Diarrhea	12 (6.6%)	5 (5.4%)
Abnormal behavior and behavioral disorders[3]	12 (6.6%)[4]	5 (5.4%)[5]
Renal insufficiency[6]	12 (6.6%)	4 (4.3%)
Anorexia	12 (6.6%)	4 (4.3%)
Lethargy	11 (6.0%)	3 (3.2%)
Dermatitis	11 (6.0%)	1 (1.1%)
Alopecia	10 (5.5%)	2 (2.2%)
Dehydration	8 (4.4%)	0 (0.0%)
Lameness[7]	8 (4.4%)	2 (2.2%)
Pruritus	7 (3.8%)	0 (0.0%)
Weight loss	6 (3.3%)	5 (5.4%)
Scabbing on head/neck	6 (3.3%)	1 (1.1%)
Gingival disorder	5 (2.7%)	0 (0.0%)
Bacterial skin infection	4 (2.2%)	1 (1.1%)
Otitis externa	4 (2.2%)	0 (0.0%)

[1]If an individual cat experienced the same event more than once, only the first occurrence is reported.
[2]The control product was the vehicle without active ingredient.
[3]Behavior abnormal for the individual cat
[4]Individual cats had at least one of the following behavior changes: anxiety (1), hiding (1), hypersomnia (1), inappropriate urination (5), sleeping with owner (1), vocalization (3), increased aggressive behavior (1).
[5]Individual cats had at least one of the following behavior changes: anxiety (2), disorientation (1), inappropriate urination (2), and vocalization (1).
[6]Worsening of existing disease
[7]New lameness or worsening of previous lameness

Conclusions: Although this study failed to demonstrate treatment success based on the established primary effectiveness outcome measure, when paired with Study NV-02-11F15-005 above, this study provided evidence that the subcutaneous administration of Solensia™ (frunevetmab injection) at a minimum dose of 1.0 mg/kg BW every 28 days is safe and effective for the control of pain associated with osteoarthritis in cats. See full discussion below in 'Weight of the Evidence'.

3. Weight of the Evidence

Study NV-02-11F15-005 and Study NV-02-11F16-001 taken together demonstrate the effectiveness of Solensia™ (frunevetmab injection) for the control of pain associated with osteoarthritis in cats.

Client Specific Outcome Measure Results:

The CSOM was the primary outcome measure in Study NV-02-11F16-001 and provided the strongest evidence for the effectiveness of Solensia™. Tables II.10[1] and II.11[2] provide the LS mean success rates for the frunevetmab injection and the control groups on Day 28 (both studies), Day 42 (Study NV-02-11F15-005 only), Day 56 (both studies), and Day 84 (Study NV-02-11F16-001 only). Additionally, Figure II.1 shows the study results graphed across time for the frunevetmab and control groups in studies NV-02-11F16-001 and NV-02-11F15-005. As the results show, the success rates in the Solensia™ groups in the two studies were very similar on Days 28 and 56. Despite the differences in study design and possible manufacturing differences, the consistency of the results between the two studies supports drug effectiveness.

Table II.10. LS Mean CSOM Success Rate by Day in Study NV-02-11F15-005 Including Only Study Sites With at Least 2 Evaluable Cases Per Treatment Group

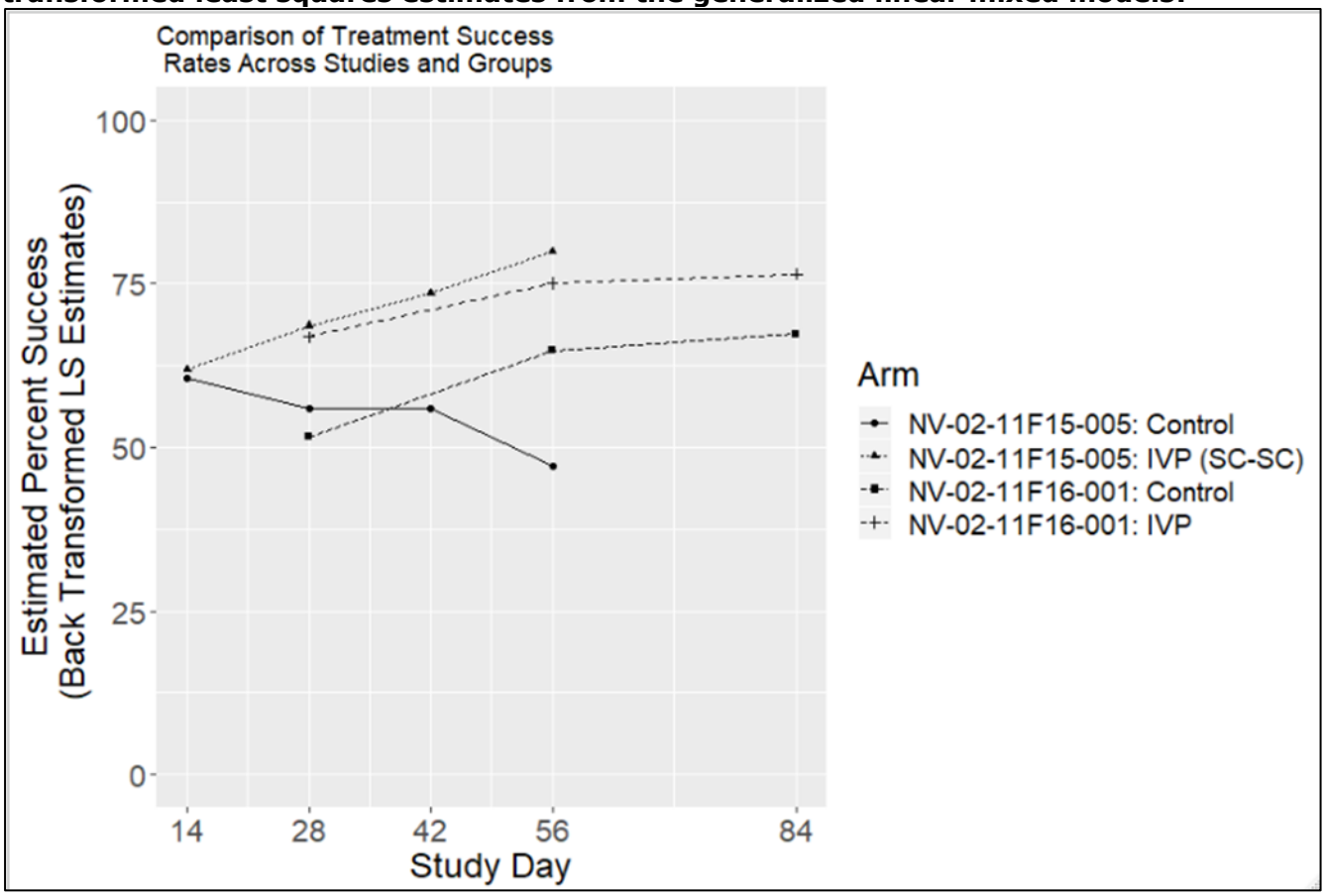
CSOM Assessment Day	Percent Success Frunevetmab Group	Percent Success Control Group
Day 28	68.6	55.9
Day 42	73.5	55.9
Day 56	80.0	47.1

Table II.11. LS Mean CSOM Success Rate By Day in Study NV-02-11F16-001

CSOM Assessment Day	Percent Success Frunevetmab Group	Percent Success Control Group
Day 28	66.9	51.6
Day 56	75.1	64.8
Day 84	76.5	67.3

[1] Same as Table II.2 above, provided here for comparison
[2] Same as Table II.5 above, provided here for comparison

Figure II.1. Comparison of success rates by treatment groups in studies NV-02-11F15-005 and NV-02-11F16-001. The success rates were calculated as the back transformed least squares estimates from the generalized linear mixed models.



In Figure II.1, IVP stands for the Solensia™ group.

The consistency of owners' responses across time in the two studies was further evaluated to account for the variable nature of pain associated with osteoarthritis across time. At each time point sampled, more owners of cats that received frunevetmab injection than owners of cats that received control recorded improved activity after treatment. Additionally, the consistency of owners' responses among individual cats in each study was assessed. For this, the percent of cats with CSOM data at 3 consecutive timepoints (Study NV-02-11F15-005: Days 28, 42, and 56; Study NV-02-11F16-001: Days 28, 56, and 84) was compared across treatment groups. Table II.12 provides the numerical results and shows that more owners of cats that received frunevetmab injection observed improvement in their cat's activity at 3 consecutive timepoints than owners of cats that received control. These results support the conclusion that frunevetmab injection improved pain control in cats.

Table II.12. Percent of Cats Successful on 3 Consecutive Timepoints based on CSOM (Study NV-02-11F15-005: Days 28, 42, and 56; Study NV-02-11F16-001: Days 28, 56, and 84)

Study	Frunevetmab Group	Control Group
NV-02-11F15-005	63.9% (23/36)	35.1% (13/37)
NV-02-11F16-001	56.0% (94/168)	42.9% (39/91)

Figure II.1 and Tables II.10 and II.11 also show the large disparity in the control group's CSOM results between studies NV-02-11F16-001 and NV-02-11F15-005. The higher percent success in the control group in Study NV-02-11F16-001 compared to Study NV-02-11F15-005 likely contributed to the lack of statistical significance in Study NV-02-11F16-001 on Days 56 and 84. Although the specific causes for this amount of difference in the percent success of the control group between these two studies was not determined, the high rate of success in the control groups is not unexpected. Because of the subjective nature of the endpoints used to evaluate the effectiveness of drug products for the control of pain and the waxing and waning of osteoarthritis clinical signs across time, the success rate in the control group (termed the "placebo effect") is usually relatively high in studies for the control of pain associated with osteoarthritis. Because of the limitations inherent in the study design and in the CSOM, secondary endpoints were evaluated to determine if they supported the conclusion of drug effectiveness.

Owner Global Assessment Results:

The results of the Owner Global Assessment also favored the frunevetmab group. Success was defined as a score of either good or excellent. In Study NV-02-11F15-005 and in Study NV-02-11F16-001, at each time point evaluated, the success rate in the frunevetmab group was higher than the success rate in the control group (see Table II.13 and Table II.14). Thus, more owners of cats that received frunevetmab injection than owners of cats that received the control reported that their cat's clinical signs of osteoarthritis were reduced by at least 50% or more. These results corroborate the findings in the CSOM and support the effectiveness of frunevetmab.

Table II.13. Percent of owners that reported their cat's clinical signs of osteoarthritis were reduced by at least 50% on the Owner Global Assessment in Study NV-02-11F15-005

Study Day	Frunevetmab Injection (%)	Control (%)
Day 28	63.2	26.3
Day 56	71.1	32.4

Table II.14. Percent of owners that reported their cat's clinical signs of osteoarthritis were reduced by at least 50% on the Owner Global Assessment results in Study NV-02-11F16-001

Study Day	Frunevetmab Injection (%)	Control (%)
Day 28	39.3	30.4
Day 56	59.3	48.3
Day 84	64.6	57.8

Total Orthopedic Pain Score Results:

Finally, in both Study NV-02-11F15-005 and Study NV-02-11F16-001, the mean veterinary-assessed Total Orthopedic Pain Score decreased more in the frunevetmab group than in the control group, as seen in Table II.15 and Table II.16. In Study NV-02-11F16-001, although the mean Total Orthopedic Pain Score at baseline (Screening) was higher in the frunevetmab group than in the control group, it was lower in the frunevetmab group than in the control group after treatment. These results indicate a larger decrease in Total Orthopedic Pain Score for the cats that received frunevetmab injection than for cats that received the control. As with the Owner Global Assessment results, these results support the CSOM results and provide further evidence for the effectiveness of frunevetmab.

Table II.15. Mean Veterinary Assessed Total Orthopedic Pain Scores in Study NV-02-11F15-005

Study Day	Frunevetmab Injection, SC only group (Change from baseline)	Control Group (Change from baseline)
Screening	31.88	32.25
Day 28	27.08 (-4.8)	28.03 (-4.22)
Day 56	25.69 (-6.19)	27.75 (-4.5)

Table II.16. Mean Veterinary-Assessed Total Orthopedic Pain Scores in Study NV-02-11F16-001

Study Day	Frunevetmab Injection Group (Change from baseline)	Control Group (Change from baseline)
Screening	34.11	33.6
Day 28	28.68 (-5.43)	29.1 (-4.5)
Day 56	27.52 (-6.59)	28.67 (-4.93)
Day 84	27.29 (-6.82)	28.54 (-5.06)

Conclusion:

The outcomes measured in Study NV-02-11F16-001 and Study NV-02-11F15-005 show a greater effect in the frunevetmab injection group than in the control group. The three clinical assessments used in these studies attempt to measure different aspects of pain associated with osteoarthritis in cats. The CSOM measures an owner's assessment of their cat's pain-

associated impairment in performing three tasks or activities. The Owner's Global Assessment measures the owner's assessment of the drug's overall effect on the clinical signs associated with osteoarthritis. Lastly, the Total Orthopedic Pain Score is the veterinarian's assessment of pain in 21 locations on the limbs and spinal column. In both studies, the owner's and veterinarian's assessments agreed that frunevetmab injection reduced pain associated with osteoarthritis more than the control. Although the numerical results differed between the studies, the overall trend supported the effectiveness of frunevetmab injection. Therefore, the weight of the evidence from these two studies demonstrates substantial evidence of effectiveness of Solensia™ (frunevetmab injection) for the control of pain associated with osteoarthritis in cats.

4. Immunogenicity:

   All therapeutic proteins have the potential for immunogenicity, including the production of antibodies that bind to the therapeutic protein and may decrease effectiveness. Such host-derived antibodies are also termed anti-drug antibodies (ADA). Monoclonal antibodies such as frunevetmab are a specific subclass of therapeutic proteins, and therefore have the potential to cause the cat to produce ADAs against frunevetmab.

   The presence of binding antibodies to frunevetmab in cats was assessed using a screening and confirmatory assay approach. In the two controlled field studies in cats with osteoarthritis described above (Study NV-02-11F15-005 and Study NV-02-11F16-001), 4 out of 259 cats that received Solensia™ once monthly for 2 or 3 months developed ADAs. One cat tested positive for ADAs on Days 0, 28, 56, and 84. This cat had non-detectable plasma drug concentration levels of Solensia™ on Days 28 and 56, and was a treatment failure in the effectiveness analysis, suggesting that the ADAs may have reduced Solensia™'s effectiveness in this cat. No assessment for neutralizing antibodies was performed.

III. TARGET ANIMAL SAFETY

The safety of Solensia™ (frunevetmab injection) was demonstrated in a well-controlled laboratory study using 7- to 8-month-old, healthy cats. The purpose of the study was to demonstrate the safety of Solensia™ in cats when used according to label instructions.

A. Margin of Safety Study

Title: Target Animal Safety Study of NV-02 in Cats. (Study No. NV-02-11F16-004)

Study Dates: October 2016 to December 2018

Study Location: Stouffville, ON, Canada

Study Design:

Objective: To demonstrate a margin of safety of frunevetmab injection in laboratory cats when administered SC once every 4 weeks for 6 consecutive doses at 0X (0.0 mg/kg BW), 1X (2.8 mg/kg BW), 3X (8.4 mg/kg BW), and 5X (14.0 mg/kg BW) the high end of the inherent dosage range (1 to 2.8 mg/kg BW).

Study Animals: Thirty-two (16 male, 16 female) healthy, intact domestic short hair cats between 7 to 8 months of age on Day 0, weighing 2.7 to 4.7 kg at study enrollment. Female cats were non-pregnant and non-lactating.

Experimental Design: Cats were randomly allocated to one of four treatment groups of 8 cats per group (4 per sex). The study was conducted under Good Laboratory Practices (GLP).

Drug Administration: Cats were administered Solensia™ (frunevetmab injection) or vehicle control SC via a 22-gauge needle. Six doses were administered at 28-day intervals on Days 0, 28, 56, 84, 112, and 140.

Table III.1. Dose of Solensia™ (Frunevetmab Injection) and Control

Treatment Group	Number of cats	Subcutaneous dosage (mg/kg)
Vehicle control [0X]	4 male 4 female	0
Solensia™ [1X]	4 male 4 female	2.8
Solensia™ [3X]	4 male 4 female	8.4
Solensia™ [5X]	4 male 4 female	14.0

Measurements and Observations:

Clinical observations were conducted twice daily. Injection sites were evaluated daily. Body weights were monitored weekly. Food consumption was measured daily. Physical and neurological examinations, clinical pathology (hematology, serum chemistry), and urinalyses were performed prior to treatment, monthly, and prior to the end of the study. Gross pathology and histopathology were evaluated. Frunevetmab plasma levels were determined from plasma collected during the first and fifth dosing intervals. Immunogenicity assessments were determined from plasma collected during each dosing interval.

Statistical Methods: Body weight, average weekly food consumption, and continuous clinical pathology data were analyzed using a linear mixed model for repeated measures with dose, sex, day, dose-by-sex, sex-by-day, dose-by-day, and dose-by-sex-by-day terms in the model as fixed effects, and animal identification as the subject in the repeated statement. Where appropriate, a baseline covariate was included in the model. Clinical, physical, and neurological

observations, and unscheduled observation findings were summarized with a data listing and frequency distributions by treatment and time point. For organs collected for both sexes, organ weight, organ weight relative to final body weight, and organ weight relative to brain weight were analyzed using a linear mixed model with dose, sex, and the dose-by-sex interaction as fixed effects.

Summary statistics (mean, standard deviation, minimum, maximum, and number of animals) for males and females within each dose group at each study day were provided for all quantitative variables.

Categorical outcomes were summarized by counts and percentages. Profile plots of body weight, food consumption, and all continuous clinical pathology, and physical examination variables for each individual animal from baseline to study completion were provided.

Results: There were no clinically significant changes noted in body weight, food consumption, and neurological examinations. Plasma frunevetmab levels were less than dose proportional, and there were no ADA positive cats following Solensia™ administration in this study.

The most common findings included vomiting and diarrhea observed sporadically in all groups. The highest frequency of vomiting occurred in the 1X group. Clinically relevant skin findings included abrasions, alopecia, or scabs mostly around the face and ears. These findings were noted in three 1X cats, three 3X cats, and one 5X cat. Another 1X cat developed a 2 cm ventral neck lesion following clipping and blood collection on Day 87. Although the initial irritation appeared related to the clipping, the unexpectedly severe and persistent pruritus and prolonged recovery were deemed possibly drug related. The ulcerated skin lesion healed when self-trauma was prevented, which included the placement of an e-collar for the remainder of the study. There were no clinically significant changes noted on physical examination other than the abnormal skin findings.

Injection Sites

Responses to injection included occasional flinching associated with injections, most frequently noted during the first administration across all dosing groups. Occasionally, scabs, small abrasions, or spots of alopecia were observed at the injection sites in all dosing groups. A few cats had transient swelling at injection sites in all groups.

Clinical Pathology and Observations

At the end of study, one control cat, one cat in the 1X group, one cat in the 3X group, and three cats in the 5X group had a white blood cell count below the lower end of the reference range.

The mean serum creatinine values in females were significantly different and numerically higher in the 5X group compared to controls ($P < 0.10$). Creatinine values on Day 28 were significantly different and numerically higher ($P = 0.0239$) in the 1X group compared to the control group. On Day 112, values were significantly different and numerically higher ($P = 0.0443$) in the 5X group

compared to the control group. Creatinine values did not exceed the reference ranges in cats of either sex at any time point.

The mean serum globulin values in males were significantly different and numerically higher in the 1X and 3X group as compared to controls ($P < 0.10$). Globulin values did not exceed the reference ranges in cats of either sex at any time point.

One 1X cat had mild bilirubinuria on Day 43. This cat had dark urine and hematuria diagnosed at Days 43 to 45. The cat responded to a canned prescription urinary diet and recovered. There was no evidence of a urinary tract infection on the urinalysis. This cat also vomited food, bile, or hair on three days and had diarrhea or dark, tarry stools on two days.

Body tremors and shivering were noted in one 3X cat on Day 28. Another 3X cat had mild bilirubinuria on Day 83 and orange colored urine. This cat also had elevated serum lactate dehydrogenase activity at 3 time points.

There was one 5X cat that had mild bilirubinuria at the end of the study with lipid sediment. This cat also had focal hepatic lipidosis (6 X 10 X 15 mm) on histopathology.

There was one 1X cat with mild focal discoloration of the left tibiofemoral joint cruciate ligament on gross pathology. There was no correlative pathology on microscopic examination. No lameness was reported in this cat or any cat over the course of this study.

Ovary to brain weight ratios were significantly different and numerically higher ($P < 0.10$) in the 3X and 5X groups compared to controls. Thyroid/parathyroid to brain weight ratios (across males and females) were significantly different and numerically higher ($P < 0.10$) in 1X and 3X groups compared to controls.

Conclusion: Solensia™, administered to healthy 7- to 8-month-old cats, at 1, 3, or 5 times the high end of the inherent dose band, was safe when administered subcutaneously once every four weeks for six consecutive doses.

IV. HUMAN FOOD SAFETY

This drug is intended for use in cats. Because this new animal drug is not intended for use in food-producing animals, CVM did not require data pertaining to drug residues in food (i.e., human food safety) for approval of this NADA.

V. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to Solensia™:

Not for use in humans. Keep out of reach of children.

Hypersensitivity reactions, including anaphylaxis, could potentially occur in the case of accidental self-injection.

In case of accidental self-injection, seek medical advice immediately and show the package leaflet or the label to the physician.

Pregnant women, women trying to conceive, and breastfeeding women should take extreme care to avoid accidental self-injection.

The importance of NGF in ensuring normal fetal nervous system development is well-established and laboratory studies conducted on nonhuman primates with human anti-NGF antibodies have shown evidence of reproductive and developmental toxicity.

VI. AGENCY CONCLUSIONS

The data submitted in support of this NADA satisfy the requirements of section 512 of the Federal Food, Drug, and Cosmetic Act (FD&C Act) and 21 CFR part 514. The data demonstrate that Solensia™, when used according to the label, is safe and effective for the control of pain associated with osteoarthritis in cats.

A. Marketing Status

This product may be dispensed only by or on the order of a licensed veterinarian (Rx marketing status). Adequate directions for lay use cannot be written because professional expertise is required to properly diagnose pain associated with osteoarthritis in cats, administer the injection, and monitor the safe use of the product, including treatment of any adverse reactions.

B. Exclusivity

The exclusivity provisions of section 512(c)(2)(F) of the FD&C Act do not apply to this drug because under section 106 of the Generic Animal Drug and Patent Term Restoration Act (Pub.L. 100-670), FDA cannot approve an abbreviated new animal drug application (ANADA) for a new animal drug that is primarily manufactured using recombinant DNA, recombinant RNA, hybridoma technology, or other processes involving site specific gene manipulation techniques. Therefore, a sponsor cannot submit an ANADA to market a generic version of this drug.

C. Patent Information

For current information on patents, see the Green Book Reports in the Animal Drugs @ FDA database.