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# Feline Osteoarthritis Pain: Tools for Clinicians & Pet Owners

## KEY POINTS

- Owners should be educated that cats experience pain from OA, which impacts health, QOL, and behavior. Behavioral and QOL scores and mobility animations such as those available through Zoetis can be useful tools on educating owners how to recognize OA-associated pain (see ***Education & Diagnostic Tools***, next page).
- Using pain-specific questionnaires and performing feline-friendly, OA pain-specific examinations can help expedite a diagnosis of pain (see ***Education & Diagnostic Tools***, next page).
- **Solensia** (frunevetmab injection) is a breakthrough treatment for the control of feline osteoarthritis (OA) pain.

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Osteoarthritis (OA), a form of degenerative joint disease (DJD), is the most common cause of chronic pain in mammals, including cats. More than 90% of adult cats may have radiographic evidence of OA, with the presence/severity of disease expected to increase by >10% each year.[1]

Pain can be classified as either adaptive (physiologic) or maladaptive (pathologic). Adaptive pain facilitates tissue protection and healing, whereas maladaptive pain negatively impacts health, quality of life (QOL), and behavior, which can impact the human–animal bond, potentially leading to surrender or euthanasia of the pet.[2] OA is a nonhealing disease, with OA-associated pain having no protective benefit; thus, OA causes maladaptive pain that, without treatment, progressively worsens as peripheral and central sensitization and neuropathic pain develop.[1]

Although OA is not curable, if identified and treated early, the progression of the intensity of OA pain can be slowed, providing a prolonged period of controllable pain and good QOL (likely a normal lifespan). Because OA is more common in geriatric cats,[1,3] OA screening should begin when cats reach 7 to 10 years of age.

## Recognizing OA-Associated Pain

OA-associated pain may not be obvious—to owners and to veterinary teams.[4] Because cats are evolutionarily both predators and prey, their natural instinct is to hide any vulnerability that could increase predation, including pain. Tools such as checklists, animations, and videos can help owners and veterinary teams accurately recognize and assess pain associated with OA in cats.

### Tools for Owners

Although the expected prevalence of OA is similar between dogs and cats, cat owners may be less likely than dog owners to identify pain in their pet.[4] However, educating owners on the prevalence of OA-associated pain and available treatment options may make owners more likely to bring their cat to the clinic.[5]

Owner education starts with an understanding of feline behavior and mobility. Owners should understand that the clinical signs of OA-associated pain are rarely what is expected but the impact of pain (ie, pain-mediated changes in behavior, activity, and mobility) can still be identified. Behavior and activity changes related to urination/defecation, grooming, and social interactions (with humans and/or other pets) are often indicators of pain and, if not due to pain, could be due to other conditions that may require medical attention. Cats are largely sedentary, making pain-related mobility changes challenging to observe. Cats are also often semi-noc-

turnal, so owners may be sleeping when cats exhibit mobility changes. Feline OA is often idiopathic and bilateral as compared with canine OA, which is primarily secondary and unilateral.[6-8] Thus, classic limping as exhibited by dogs is unlikely to be exhibited by cats. In addition, cats also spend more time moving vertically (eg, jumping, climbing) as compared with dogs. Vertical mobility changes, which most owners do not know how to identify, are important indicators of OA-associated pain.

Checklists can be useful in a variety of settings, including medical diagnostics. Using checklists with specific pain-related behavior/activity questions can educate the owner on the potential presence of pain and expedite diagnosis by alerting the clinician to pain-related concerns (see ***Education & Diagnostic Tools***). Questions on a checklist should focus on the cat's behavior and activity. Mobility discussions should center on the cat's ability to jump and climb.

Videos and animations may help owners understand mobility in patients with OA, as the owner may more readily identify with observing the cat in motion. Detailed animations are available and can be effective diagnostic tools, comparing the movement of a cat with healthy, nonpainful joints with a cat with painful osteoarthritic joints as the cats climb up and down stairs, jump up and down, and jump to/from elevated surfaces, among others (see ***Education & Diagnostic Tools***). Providing mobility animations on the clinic website and/or social media can also be beneficial; they can also be displayed on TV or computer screens in the lobby or examination rooms.

Infographics describing changes in behavior-related pain are also available (see ***Education & Diagnostic Tools***). Clinicians should strive to be a pre-eminent resource for animal health information. Thus, infographics and questionnaires should be shared on the clinic website and/or social media and hard-copies made available in the clinic. Information regarding this material can also be included by audio in the clinic's on-hold phone recording.

### Tools for Clinicians

In a study of 90 geriatric cats with radiographic changes of DJD, only 4 had DJD or arthritis mentioned in their medical records.[3] Although radiographic changes do not consistently predict the presence of pain, there is some correlation,[9] and it could therefore be assumed that >4 of these 90 cats were painful.

Identifying feline pain can be difficult for the clinician if not specifically investigated. Clinicians rarely observe a cat walking at the clinic as commonly occurs with dogs; thus, gait analysis is not typically a normal part of a non-pain–related examination. Having the owner explore checklists and mobility animations prior to the visit can increase the likelihood of pain being identified, as the owner's input will provide a template for pointed pain-related, cat-specific questions.

A feline-friendly musculoskeletal examination focused on joint-specific pain and mobility using gentle palpation and range of motion should be a part of any examination for patients in which pain is a potential problem and for every examination for cats >7 to 10 years of age. Detailed videos on feline-friendly, pain-focused musculoskeletal examinations in cats are available (see ***Education & Diagnostic Tools***) and include thorough evaluative descriptions of the patient and several joints, including the hip, stifle, tarsus, and elbow—common locations for feline OA. Asking the owner to video their cat at home can also help facilitate diagnosis, as mobility and behavior can be more accurately assessed when the cat is in an environment it is familiar with. Radiography can provide valuable information and is recommended; however, some patients will have radiographic lesions with no pain, and some patients may have pain that is worse than the radiographic evidence.[7,10] Regardless, pain should be the focus of treatment, not the radiographic changes.

## The New Science of OA Pain Management

Nerve growth factor (NGF) is a cytokine that has recently been recognized as a major factor in the generation, propagation, and sensation of pain.[11-13] Once released from damaged tissue, including tissue in an osteoarthritic joint, NGF rapidly escalates pain due to its impact on multiple pain pathway components, resulting in maladaptive pain.[11-13] NGF binds to tropomyosin receptor kinase A (trkA) and causes nociceptor sensitization, which can lead to hyperalgesia and/or allodynia; this is augmented by the release of other inflammatory mediators (eg, histamine, bradykinin) and additional NGF following NGF binding to trkA on proinflammatory cells (eg, mast cells). In addition, the NGF/trkA complex is internalized and transported to the neuronal cell body in the dorsal root ganglion, where it promotes the expression and/or upregulation of a variety of other pronociceptive ion channels and receptors, including transient receptor

## EDUCATION & DIAGNOSTIC TOOLS

- Feline Examination Videos: **felineOAexam.com**
- Feline OA Education Tools for Owners: **SolensiaVetTeam.com**
- Feline OA Owner Checklist: **catOAchecklist.com**
- The International Veterinary Academy of Pain Management: **ivapm.org**
- Role of Nerve Growth Factor in OA Pain: **thenewscienceofOApain.com**
- Zoetis Technical Bulletin: Current & Future State of Disease: **felineOApain.com**

potential vanilloid 1, which is integral for development of central sensitization.[11-13] Because of profound pronociceptive involvement and NGF's ability to rapidly produce both peripheral and central sensitization, NGF is an obvious target for the control of OA pain. Anti-NGF monoclonal antibodies bind to specific target molecules, including cytokines, and block the activity of the target. Specified (felinized and caninized) anti-NGF monoclonal antibodies are FDA-approved and can provide a first-line option for safe and effective management of OA pain.[14,15]

## Treatment of Feline OA

Analgesia is foundational to a multimodal OA treatment approach because it is multidimensional and offers a unique individual experience for feline patients. NSAIDs are an effective treatment option but are not approved in the United States for chronic use in cats and can cause adverse effects, including renal dysfunction, which is a common concern in cats.[16] Solensia™ (frunevetmab injection), a once-monthly monoclonal antibody injection for safe and effective control of feline OA pain, targets NGF, a key driver in OA pain progression, and is eliminated via normal protein degradation pathways like naturally produced antibodies, with minimal involvement of the liver or kidneys.[17] In a 3-month study, 77% of cat owners reported improvement in signs of pain when their cats were treated monthly with Solensia.* Nonpharmacologic treatment (eg, acupuncture, laser and physical therapy) should be considered for multimodal therapy. Although nutraceuticals and specific joint diets may be effective and could be added to the protocol as multimodal therapy, they have demonstrated little to no efficacy in cats. Most of these compounds are likely more effective at slowing disease progression, which may potentially delay the onset of worsening pain, than they are at providing analgesia directly. By targeting 1 of the key mediators in the feline OA pain pathway, Solensia helps keep OA pain from disrupting the unique bond cats share with their humans.

## Conclusion

OA can cause maladaptive, potentially excruciating, pain in cats. Although owners may struggle to identify pain in their cat, educating owners on the prevalence of OA-associated pain and available treatment options may make owners more likely to bring their cat to the clinic. Education can be provided through numerous resources, such as posters, questionnaires, and mobility animations. Providing education to owners through these means can also help expedite a diagnosis of OA, as pointed questions regarding changes in behavior and mobility can help more quickly identify pain. Incorporating these tools can help both the owner and the clinician more readily identify feline OA-associated pain, thus improving patient quality of life and helping cats get back to their normal.

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*67% of cats in the placebo group experienced improvement in signs of pain.

# Solensia™
(frunevetmab injection)

## 7 mg/mL

**Feline anti-nerve growth factor monoclonal antibody for subcutaneous injection in cats only.**

**Single-Use Vial**

**CAUTION**
Federal law restricts this drug to use by or on the order of a licensed veterinarian.

**DESCRIPTION**
SOLENSIA (frunevetmab injection) is a sterile injectable solution containing 7mg/mL of frunevetmab in histidine buffer (10 mM L-histidine monohydrochloride, 5% D-sorbitol, 0.01%polysorbate 20, adjusted to pH 6.0 by HCl/NaOH, quantity sufficient to 1 mL by Water for Injection.). Frunevetmab is a felinized immunoglobulin G monoclonal antibody (mAb), a murine antibody in which all regions of the mouse antibody are replaced with feline counterparts except for the complementarity-determining regions. Frunevetmab binds to nerve growth factor (NGF) to block NGF's effects. Such mAbs are commonly referred to as anti-NGF mAbs.

**INDICATION**
SOLENSIA is indicated for the control of pain associated with osteoarthritis in cats.

**DOSAGE AND ADMINISTRATION**
Cats should be dosed by weight range according to the Dosing Chart (Table 1) below. Cats are given 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. Aseptically withdraw the total dose into a single syringe and administer immediately.

The product does not contain a preservative. The full content of each vial is for single use only. Once punctured, contents of the vial should be used immediately and any remaining solution should be discarded.

**Table 1. Dosing Chart**

| Weight of Cat (lb.) | Weight of Cat (kg) | Volume | Number of Vials* |
|---|---|---|---|
| 5.5-15.4 | 2.5-7 kg | 1 mL | 1 |
| 15.5-30.8 | 7.1-14 kg | 2 mL | 2 |

*1 mL frunevetmab injection per vial

**CONTRAINDICATIONS**
SOLENSIA should not be administered to cats with known hypersensitivity to frunevetmab.

SOLENSIA should not be used in breeding cats or in pregnant or lactating queens because it may pass through the placental blood barrier and be excreted in milk. Fetal abnormalities, increased rates of stillbirths and increased postpartum fetal mortality were noted in rodents and primates receiving anti-NGF mAbs.

**WARNINGS**
**User SafetyWarnings**
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.

**PRECAUTIONS**
Administration of mAbs may be associated with hypersensitivity reactions and delayed hypersensitivity reactions. If anaphylaxis or other hypersensitivity reaction occurs, discontinue use and institute appropriate therapy.

Administration of SOLENSIA may be associated with scabbing on the head and neck, dermatitis, and pruritus; however, pre-approval data suggest that these signs do not require cessation of SOLENSIA administration (see **ADVERSE REACTIONS** and **TARGET ANIMAL SAFETY**).

Evaluations were not made to determine if interactions occurred between SOLENSIA and veterinary vaccines.

Treatment with SOLENSIA may result in the formation of anti-frunevetmab antibodies and potentially the loss of product effectiveness (see **Immunogenicity**).

The safe use of SOLENSIA with concurrent non-steroidal anti-inflammatory drugs (NSAIDs) has not been established in cats. In human clinical trials, rapidly progressing osteoarthritis (RPOA) has been reported in a small number of patients receiving humanized anti-NGF mAb therapy. The incidence of these events increased in human patients receiving NSAID treatment long term in combination with an anti-NGF mAb. RPOA has not been characterized or reported in cats.

SOLENSIA has not been evaluated in cats less than 7 months or 5.5 lbs.

Long term effects, which may occur more than 6 months after the use of SOLENSIA, have not been evaluated. Primates receiving high doses of anti-NGF mAbs had reduced cell size in postganglionic neuronal cell bodies. The change in cell body size returned to normal after anti-NGF mAb administration was discontinued. NGF is involved in the normal development of sensory and sympathetic nerve fibers in developing animals. This may be important with use of SOLENSIA in young growing cats.

The safe use of this product with other mAbs has not been evaluated.

**ADVERSE REACTIONS**
The safety of SOLENSIA was evaluated in a masked, controlled 112-day field study to evaluate the effectiveness of SOLENSIA for the control of pain associated with osteoarthritis in cats. Enrollment included 275 cats weighing 2.5-to 11.4 kg and 1.6-to 22.4 years old; 182 cats were treated with SOLENSIA and 93 cats were administered a vehicle control. Cats were dosed at 28-day intervals and received up to three injections. The most common adverse reactions reported during the field study are presented below.

**Table 2. Adverse Reactions Reported in the Field Study[1]**

| Adverse Reaction | Solensia N=182 (%) | Vehicle Control N=93 (%) |
|---|---|---|
| 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 a 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

The safety of SOLENSIA was also evaluated in a masked, controlled 56-day exploratory field study to evaluate the effectiveness of SOLENSIA for the control of pain associated with osteoarthritis in cats. Enrollment included 126 cats; 85 cats were treated with frunevetmab injection manufactured similar to SOLENSIA and 41 cats were administered a vehicle control. Cats were dosed at 28-day intervals and received up to two injections. The most frequently reported adverse reactions were digestive tract disorders, including vomiting and diarrhea, and skin disorders, including dermatitis/eczema and alopecia that were mostly attributed to irritation by an activity monitor collar required for the study.

**Immunogenicity**
All therapeutic proteins, including monoclonal antibodies, 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 termed anti-drug antibodies (ADA). SOLENSIA, therefore has 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 controlled field effectiveness studies in cats with osteoarthritis (see **EFFECTIVENESS**), four out of 259 cats that received SOLENSIA once monthly developed anti-drug antibodies (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 clinical significance. No assessment for neutralizing antibodies was performed.

The observed incidence of antibody positivity in an assay is highly dependent on several factors including assay sensitivity and specificity, assay methodology, sample handling, timing of sample collection, concomitant medications, and underlying disease. For these reasons, comparison of the incidence of antibodies to SOLENSIA with the incidence of antibodies to other products may not be appropriate.

**CONTACT INFORMATION**
To report suspected adverse drug events, for technical assistance or to obtain a copy of the Safety Data Sheet (SDS), contact Zoetis Inc. at 1-888-963-8471.

For additional information about reporting adverse drug experiences for animal drugs, contact FDA at 1-888-FDA-VETS or http://www.fda.gov/reportanimalae.

**CLINICAL PHARMACOLOGY**
**Mechanism of Action**
Frunevetmab is a felinized monoclonal antibody that binds to nerve growth factor (NGF), reduces NGF binding to the tropomyosin receptor kinase A (TrkA) and $p75^{NTR}$ receptors, and decreases signal transduction in cell types involved in pain. *In vitro* binding studies suggest that frunevetmab binds with high affinity to NGF, but does not bind to other neurotrophins, including human neurotrophin-3 (NT-3), feline and human neurotrophin-4 (NT-4), and human brain-derived neurotrophic factor (BDNF).

NGF has been found to be elevated in osteoarthritic joints of multiple species. Following a noxious stimulus, inflammatory cytokines and NGF are released by tissues of the joint. NGF binds to TrkA/$p75^{NTR}$ receptors found on peripheral nerves, immune cells, endothelial cells, synoviocytes, and chondrocytes to induce peripheral sensitization, neurogenic inflammation, and increased pain perception.

Frunevetmab binds to NGF and prevents NGF/TrkA/$p75^{NTR}$ cellular signaling. In *in vitro* studies, frunevetmab potently inhibits NGF-mediated signaling as measured by reducing proliferation of TF-1 cells, a human erythroleukemia cell line, and functionally blocks NGF-induced neurite outgrowth in rat PC-12 neuronal cells.

NGF binds to TrkA receptors located on immune cells to elicit the release of additional proinflammatory mediators, including NGF itself. These inflammatory mediators lead to further peripheral sensitization involved in pain perception. Frunevetmab reduces the expression of these inflammatory mediators in rat PC-12 neuronal cells.

**Pharmacokinetics**
In a laboratory safety study in healthy cats administered SOLENSIA (frunevetmab injection) subcutaneously once every twenty-eight days for six consecutive doses (2.8 mg/kg), area under the plasma concentration time curve from time zero to the end of the dose interval (AUC) and maximum plasma concentration ($C_{max}$) increased in a less than dose proportional manner. Dosing every 28 days resulted in minimal accumulation over the course of five consecutive SOLENSIA doses of 2.8 mg/kg.

**Table 3. Mean ± Standard Deviation frunevetmab pharmacokinetic parameters following subcutaneous dosing to laboratory and osteoarthritic cats.**

| Parameter | Laboratory Cats | Osteoarthritic Cats |
|---|---|---|
| Dose (mg/kg) | 2.8 | 3.0 |
| $C_{max}$ (µg/mL) | 42.8 ± 10.4 | 30.2 ± 5.5 |
| $T_{max}$ # (day) | 3.5 (1-7) | 7.0 (3-7) |
| AUC (day*µg/mL) | 596 ± 245 | 653.0 ± 132 |
| $t_{1/2}$ (day) | 9.8 ± 3.1 | 11.0 ± 2.5 |
| Bioavailability (%) | Not determined | 73.2 ± 14.8 |

#Median and range

In a cross-study comparison of the pharmacokinetics in healthy laboratory cats and cats with naturally occurring osteoarthritis, the median time to maximum concentration ($T_{max}$) was approximately 3.5 days longer in cats with osteoarthritis compared to healthy cats. $C_{max}$ was greater in healthy cats compared to cats with osteoarthritis. Overall drug exposure (AUC) and half-life were similar between healthy cats and cats with osteoarthritis. Compared to an intravenous dose, subcutaneously-administered frunevetmab had a bioavailability of approximately 73% in cats with osteoarthritis.

In a field effectiveness study at the label dose in cats with osteoarthritis, steady-state was achieved after approximately 2 doses.

**EFFECTIVENESS**

Because of the limitations currently inherent in studies designed to assess chronic pain and the response to 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 SOLENSIA was effective for the control of pain associated with osteoarthritis in cats. Based on current thinking, the endpoints used to evaluate the effectiveness of SOLENSIA for the control of osteoarthritic pain in cats are observer-reported measures conducted by either owners or veterinarians. When taken together, the results of the two studies described below demonstrate the effectiveness of SOLENSIA for the control of pain associated with osteoarthritis in cats. Additional information related to the evaluation of these studies, including the study endpoints, is available in the Freedom of Information Summary available at https://animaldrugsatfda.fda.gov.

**Field Effectiveness Study #1**

A 56-day, masked, randomized, controlled field study was conducted at 14 U.S. veterinary clinics. The study enrolled 126 client-owned cats with clinical signs of osteoarthritis (OA) confirmed by radiography and orthopedic examination; enrolled cats weighed 3.3 to 10.5 kg and were over 6 months old. The enrolled cats were randomized to treatment with frunevetmab injection (n=85) manufactured similar to SOLENSIA or vehicle control (n=41), administered subcutaneously on Days 0 and 28 or intravenously on Day 0 and subcutaneously on Day 28. Cats were dosed with frunevetmab injection or vehicle control based on body weight (2.5-7 kg cats received 1 mL, 7.1-14 kg cats received 2 mL).

Outcome measures for the control of pain associated with OA included comparison of the owner's evaluation of Client Specific Outcomes Measures (CSOM) at Days 14, 28, 42, and 56 compared to baseline (Day 0, before treatment); Owner Global Assessments on Days 28 and 56; and total orthopedic pain score completed by the veterinarian at screening and on Days 28 and 56. For the CSOM, treatment success was defined as a reduction of at least 2 in the total CSOM score compared with the score at baseline. Cats that had an increase in any individual CSOM activity score (regardless of the total CSOM score) were considered treatment failures. For the Owner Global Assessment, success was defined as an owner's impression of the response to treatment as Good or Excellent (versus Fair or Poor). Success was not defined for the veterinarian-assessed total orthopedic pain score. The proportion of cats considered treatment successes based on the owner CSOM assessment and the Owner Global Assessment was greater in the frunevetmab injection group compared to the control group for all assessments. The mean total orthopedic pain score was lower in the frunevetmab injection group compared to the control group at all post-dosing assessments.

**Table 4. Percent CSOM Success by Assessment Day**

| Study Day | Frunevetmab Injection (%) | Vehicle Control (%) |
|---|---|---|
| 14 | 61.8 | 60.6 |
| 28 | 68.6 | 55.9 |
| 42 | 73.5 | 55.9 |
| 56 | 80.0 | 47.1 |

**Table 5. Percent Owner Global Assessment Success by Assessment Day**

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

**Table 6. Mean Veterinarian-Assessed Total Orthopedic Pain Score by Assessment Day**

| Study Day | Frunevetmab Injection (change from baseline) | Vehicle Control (change from baseline) |
|---|---|---|
| Screening | 31.88 | 32.25 |
| 28 | 27.08 (-4.8) | 28.03 (-4.22) |
| 56 | 25.69 (-6.19) | 27.75 (-4.5) |

**Field Effectiveness Study #2**

A 112-day, masked, randomized, controlled field study was conducted at 21 U.S. veterinary clinics. The study enrolled 275 client-owned cats with clinical signs of osteoarthritis (OA) confirmed by radiography and orthopedic examination; enrolled cats weighed 2.5 to 11.4 kg and were 1.6 to 22.4 years old. The enrolled cats were randomized to treatment with SOLENSIA (n=182) or vehicle control (n=93), administered subcutaneously on Days 0, 28, and 56. Cats were dosed with SOLENSIA (frunevetmab injection) or vehicle control based on body weight (2.5-7 kg cats received 1 mL, 7.1-14 kg cats received 2 mL).

The primary outcome measure for success for the control of pain associated with OA was comparison of the owner's evaluation of CSOM at Day 56 compared to baseline (Day 0, before treatment). Treatment success was defined as a reduction of at least 2 in the total CSOM score at Day 56 compared with the score at baseline. Cats that had an increase in any individual CSOM activity score (regardless of the total CSOM score) or that received rescue analgesia prior to Day 56 were considered treatment failures. Secondary outcome measures included the total CSOM score on Days 28 and 84; Owner Global Assessments on Days 28, 56, and 84; and total orthopedic pain score completed by the veterinarian on Days 28, 56, and 84. For the Owner Global Assessment, success was defined as an owner's impression of the response to treatment as Good or Excellent (versus Fair or Poor). Success was not defined for the veterinary-assessed total orthopedic pain score. The proportion of cats considered treatment successes based on the owner CSOM assessment and the Owner Global Assessment was greater in the SOLENSIA group compared to the control group for all assessments. The mean total orthopedic pain score was lower in the SOLENSIA group compared to the control group at all post-dosing assessments.

**Table 7. Percent CSOM Success by Assessment Day**

| Study Day | Solensia (%) | Vehicle Control (%) |
|---|---|---|
| 28 | 66.9 | 51.6 |
| 56 | 75.1 | 64.8 |
| 84 | 76.5 | 67.3 |

**Table 8. Percent Owner Global Assessment Success by Assessment Day**

| Study Day | Solensia (%) | Vehicle Control (%) |
|---|---|---|
| 28 | 39.3 | 30.4 |
| 56 | 59.3 | 48.3 |
| 84 | 64.6 | 57.8 |

**Table 9. Mean Veterinarian-Assessed Total Orthopedic Pain Score by Assessment Day**

| Study Day | Solensia (change from baseline) | Vehicle Control (change from baseline) |
|---|---|---|
| Screening | 34.11 | 33.6 |
| 28 | 28.68 (-5.43) | 29.1 (-4.5) |
| 56 | 27.52 (-6.59) | 28.67 (-4.93) |
| 84 | 27.29 (-6.82) | 28.54 (-5.06) |

**TARGET ANIMAL SAFETY**

Frunevetmab injection was administered subcutaneously to healthy seven to eight-month-old cats (8 cats per group) at doses of 2.8 mg/kg (1X), 8.4 mg/kg (3X), and 14 mg/kg (5X) every 28 days for six consecutive doses. The control group (8 cats) received vehicle control injections. No clinically significant changes related to frunevetmab were observed among the cats for physical examination, lameness evaluation, and body weight.

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 including the placement of an e-collar for the remainder of the study.

Flinching was occasionally associated with injections, most frequently noted during the first dosing in all dosing groups. Occasionally, scabs, small abrasions, or spot of alopecia were observed at the injection sites in all dosing groups. A few cats had transient swelling at injection sites.

Body tremors and shivering were noted in one 3X cat on Day 28.

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

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.

One 1X cat had a small amount of bilirubinuria on Day 43. This cat had dark urine and hematuria on Days 43-45 with no evidence of UTI on urinalysis. The cat responded to a canned prescription urinary diet and recovered. This cat also vomited food, bile or hair on three days and had diarrhea or dark, tarry stools on two days. Another 3X cat had a small amount of bilirubinuria on Day 83 and orange colored urine. This cat also had elevated serum lactate dehydrogenase activity at three time points.

There was one 5X cat that had a small amount of bilirubinuria at the end of the study with lipid sediment. This cat also had focal hepatic lipidosis on histopathology.

**STORAGE CONDITIONS**

SOLENSIA should be stored upright in a refrigerator, between 35°– 46°F (2°– 8°C). Do not freeze. Protect from light. See in-use instructions provided in the **DOSAGE AND ADMINISTRATION** section.

**HOW SUPPLIED**

SOLENSIA is supplied as a sterile buffered solution of 7mg/mL of frunevetmab in single-use 4 mL glass vials containing an extractable volume of 1mL of clear solution with a butyl rubber stopper and aluminum overseal. Vials are available in cartons containing 2 or 6 vials.

Approved by FDA under NADA # 141-546

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