# Anti-nerve growth factor monoclonal antibodies for the control of pain in dogs and cats

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## Introduction

Nerve growth factor (NGF) was originally discovered as a neurotrophic factor essential for the survival of sensory and sympathetic neurons during development. However, in the adult, NGF and its interaction with tropomyosin receptor kinase A receptor (TrkA) has been found to play an important role in nociception and nervous system plasticity, especially osteoarthritis (OA) pain.

Given the role of NGF/TrkA signalling in chronic pain, various ways of disrupting this pathway have been investigated and monoclonal antibodies (mAbs) against NGF have shown particular promise, exhibiting very effective control of pain in clinical trials while appearing to maintain normal nociceptor function.

Recently, anti-NGF mAbs have been developed for the management of OA-associated pain in dogs and cats and the first clinical trials conducted.

This review explains the role of NGF in chronic pain, particularly OA; describes the current status of development of anti-NGF mAbs in human medicine; reviews the status of development of anti-NGF mAbs for canine and feline OA; and outlines the future potential of anti-NGF mAbs for other pain conditions.

## Approach

Relevant literature discussing the role of NGF in arthritic joints, efficacy of anti-NGF therapy based on murine OA models, and the current status of the development of anti-NGF mAbs in humans, was reviewed. The recent development of anti-NGF mAbs for the treatment of OA-associated pain in experimental and clinical studies in veterinary medicine was also appraised.

### KEY FINDINGS

- Anti-nerve growth factor monoclonal antibody therapy appears to have a positive analgesic effect and is well tolerated in dogs and cats suffering from osteoarthritis-associated pain.
- Given as a single injection, efficacy appears to last approximately four to six weeks and the magnitude of effect appears the same as, or greater than, that expected with NSAIDs.

## Results

Preclinical and clinical research over several decades has clearly demonstrated that NGF contributes to joint pathology as well as pain associated with arthritic joints, and anti-NGF mAb therapy looks very promising as an effective means of controlling OA pain. However, development programmes for anti-NGF mAbs were temporarily put on hold by the United States Food and Drug Administration (FDA) due to an increased incidence of rapidly progressing OA in some joints, especially following higher doses and concomitant use with NSAIDs. After reviewing the data, the FDA advisory committee concluded that these serious adverse events (AEs) were probably related to the anti-NGF treatment, but allowed clinical trials for the development of anti-NGF mAbs in humans to be restarted with the adoption of a risk mitigation strategy.

In veterinary medicine, two randomised, double-blind, placebo-controlled clinical trials evaluating the efficacy of a single intravenous injection of caninised anti-NGF mAb (ranevetmab) over at least a four-week period have been published. These studies showed that dogs that received ranevetmab had a significant improvement in subjective owners' assessment compared to baseline scores and significantly greater activity compared to a placebo group during the daytime over four weeks. Furthermore, the result of the owners' assessment was very similar to previous studies for the management of OA-associated pain using carprofen and grapiprant.

A single clinical trial has been published in cats with OA-associated pain to assess the efficacy of a single dose of felinised anti-NGF mAb (frunevetmab) over a nine-week period. In this randomised, double-blind, placebo-controlled pilot study, frunevetmab produced positive treatment effects in cats with OA-associated pain, with a duration of effect of up to six weeks. Increases in treated cat activity over the placebo group were greater than has been seen with NSAIDs.

No AEs associated with treatment were reported in either dogs and cats. Work is ongoing in the development of these, and likely other, anti-NGF mAbs.

## Interpretation

Overall, in both dogs and cats, significant improvement has been seen in subjective measures and objectively measured activity following administration of anti-NGF mAbs, suggesting a positive analgesic effect of the same magnitude or greater than that expected with NSAIDs. Although this is exciting, and while no anti-NGF therapy-related AEs in dogs and cats have been seen, the safety of long-term exposure over years, possibly starting early in life, needs to be determined. Additionally, the safety of concomitant use of NSAIDs with anti-NGF therapy has not been elucidated.

## Significance of findings

There are limited approved, or proven, therapies for the control of chronic OA-associated pain in dogs and cats, and there exists a critical need for other effective analgesic therapies to address chronic pain in these species, especially cats. Anti-NGF mAb therapy appears a very promising pharmacological pain management option, with a single injection potentially providing several weeks of pain relief.


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