

loyal

Product brief for veterinarians

**We're developing
the first longevity
drugs for dogs.**

Overview

Our aging thesis

Aging is the most significant modifiable risk factor for most degenerative and chronic diseases in adult dogs. Targeting the ways dogs age and decline over time may be one of the most effective and practical ways for veterinarians to increase the healthy lifespan of their canine patients.

At Loyal, our approach is to help dogs live longer and stay healthier as they age by targeting the underlying processes that lead to age-associated disease and disability. Our drugs aim to extend lifespan and quality of life by reducing the incidence and severity of age-related diseases.

Products in development

We have three lifespan extension drugs in development, targeting two molecular pathways.

LOY-002 is intended for dogs age 10 or older and weighing at least 14 lb. It aims to extend healthy lifespan by mitigating age-associated metabolic dysfunction.

LOY-001 and LOY-003 are intended for dogs age 7 and older and weighing 40 lb or more and target the overexpression of IGF-1, a hormone that we believe is associated with large dogs' shorter lifespan relative to small dogs.



For senior dogs



For large dogs

Purpose

Intended to extend lifespan and healthspan for older dogs of all but the smallest breeds

Intended to extend lifespan and healthspan for large and giant breed dogs

Description

As dogs age, their metabolic health declines, leading to disease and declining quality of life. LOY-002 is believed to improve metabolic health with the aim of reducing age-associated disease and extending healthy lifespan.

As a result of selective breeding, large dogs produce more of the hormone IGF-1 than required post-maturity. This is believed to reduce their lifespan relative to smaller dogs. LOY-001 and LOY-003 address this overexpression in adult dogs with the aim of reducing age-associated disease and extending healthy lifespan.

Target population

Dogs age 10 or older and weighing at least 14 lb

Dogs age 7 or older and weighing at least 40 lb

Dosage

Prescription flavored daily pill

LOY-001: Prescription injection
LOY-003: Prescription flavored daily pill

Planned launch

2025

2027

Milo
Age 10



Lifespan extension for dogs age 10 or older and weighing at least 14 lb

LOY-002

Mechanism of action

Disclaimer: Our products are still in development, so the drugs and exact mechanisms of action are currently confidential. We'll continue to publish our pre-clinical research data, and more detailed information will be made available to veterinarians if the drug is approved for use by the FDA.

LOY-002 is designed to be a daily flavored tablet given to dogs with the aim of extending lifespan and mitigating the decline in health and quality of life associated with aging. We believe it will accomplish this by addressing several aspects of the overall metabolic dysfunction that occurs with aging.

There is already some compelling evidence that targeting metabolic dysfunction can extend healthspan and lifespan. Caloric restriction is a commonly used research intervention to improve metabolic health and extend lifespan in mammals from mice to primates. A landmark study found that calorically restricted Labrador Retrievers lived almost two years longer on average than dogs fed to a normal body condition.¹ The calorie-restricted group also had significantly lower prevalence of common age-associated diseases, such as osteoarthritis and neoplasia.^{1,2}

While caloric restriction itself is not a practical way to extend lifespan in pet dogs, this study showed that improving metabolic health can have a direct and significant impact on lifespan in dogs. We believe drugs will be a more targeted and pragmatic approach to achieving similar benefits. Our aim with LOY-002 is to preserve metabolic health, which we believe will delay the onset of age-associated disease and help dogs maintain better function and quality of life.

The STAY study

We're actively enrolling in the STAY study — our double-blinded, placebo-controlled efficacy study intended to assess the effect of LOY-002 on lifespan and healthspan in treated dogs. The STAY study will be conducted over four years in partnership with 70 veterinary clinics across the country. Over 1,000 companion dogs 10 years and older and over 14 pounds will participate.

Over the span of STAY, we'll collect extensive data on health, quality of life, and lifespan in dogs receiving LOY-002 and those receiving a placebo. The results of the study will be part of our application for full FDA approval of the drug for lifespan extension and will also be shared with veterinarians.

Conditional approval

While conducting this unprecedented canine lifespan study, we're also pursuing conditional approval for LOY-002 based on existing efficacy, safety, and manufacturing data.

The FDA Center for Veterinary Medicine's expanded conditional approval pathway is meant for animal drugs that address an unmet medical need and require long or complex studies to complete the collection of the effectiveness data needed for full approval. Conditional approval has the same strict safety and manufacturing quality requirements as full approval, but it is a way to make needed drugs available to veterinarians more rapidly based on evidence showing a Reasonable Expectation of Effectiveness (RXE). RXE can be supported by evidence from various sources, including the scientific literature and pre-clinical or pilot studies, which are often smaller and shorter than trials like the STAY study.

Loyal is committed to following the rigorous scientific and manufacturing standards set by the FDA, and product timelines will depend on our ongoing work with the agency to meet those standards. However, if the FDA grants conditional approval for LOY-002, veterinarians may be able to prescribe the drug as soon as 2025 while the STAY study continues to gather the data required for full approval.

Safety

Because LOY-002 is part of a preventive medicine approach to aging and not a treatment for one specific disease, we consider safety to be of the utmost importance. While even serious side effects may be tolerable with a medication intended to treat a severe or life-threatening disease, preventive treatments such as LOY-002 should be as safe as possible.

We have extensive evidence from safety studies of the active ingredient in LOY-002. Over 400 dogs have been given the active ingredient in LOY-002 in multiple laboratory studies lasting from four weeks to a full year. This data has supported further development of the drug, and we've submitted it to the FDA. This includes studies at doses much higher than will be used in dogs treated with LOY-002. We have data from a 3-month pilot clinical trial with LOY-002 tablets where there were no clinically significant adverse effects. We are also running a 6-month study to assess the safety of LOY-002 tablets at up to five times the expected prescription dose.

Lifespan extension for dogs age 7 or older and weighing at least 40 lb

LOY-001

LOY-003

Mechanism of action

LOY-001 and LOY-003 both address the premature morbidity and mortality of large-breed dogs. LOY-001 will be an injectable administered by veterinarians every three to six months. LOY-003 will be a daily pill developed through our partnership with human biopharma company Crinetics Pharmaceuticals.

It is well-known that body size and lifespan are related in dogs and that larger dogs often have substantially shorter lifespans than smaller dogs. Larger body size is predominantly determined by the levels of certain hormones during development, including growth hormone (GH) and insulin-like growth factor 1 (IGF-1). However, these hormones have effects on metabolism other than stimulating growth.

There is extensive evidence in many species, including dogs, showing a correlation between high IGF-1 levels and shorter lifespan, and this is considered one of the core pathways of aging.³ We believe that sustained higher levels of GH and IGF-1 in larger dogs are partly responsible for shorter lifespan and the earlier development of age-associated disease and disability. If we are correct, then LOY-001 and LOY-003 will extend lifespan in part by reducing IGF-1 levels and delaying the onset of age-associated metabolic dysfunction and disease. These drugs will be administered only to skeletally mature dogs, not puppies, so they will not affect adult body size.

Working toward FDA approval

As with LOY-002, we are planning to seek full approval for LOY-001, which includes conducting a large, long-term efficacy trial similar to the STAY study.

We're also seeking conditional approval for these drugs to address the unmet need of early mortality in large dogs due to age-associated disease. In 2023, the FDA accepted the technical effectiveness portion of our conditional approval application, determining that LOY-001 had met the criteria for Reasonable Expectation of Effectiveness (RXE). We believe this to be the FDA's first-ever formal acceptance that a drug can be developed and approved to extend lifespan. This is only one of several elements in seeking conditional approval, but it is an important milestone.

If the FDA grants conditional approval for LOY-001, veterinarians may be able to prescribe the drug as soon as 2027. As always, these timelines will depend on our ongoing work to meet the rigorous scientific and manufacturing standards set by the FDA.

Safety

Both LOY-001 and LOY-003 are in early-stage development, and safety data is being gathered for both of these drugs. As with LOY-002, continued development of these products and potential FDA approval will require equally robust evidence ensuring safety as well as efficacy.

Akila

Age 7



Q&A

What are the potential benefits of your drugs?

The goal of all our programs is to develop FDA-approved drugs that extend healthy lifespan in dogs. By targeting specific pathways that lead to metabolic dysfunction, we believe we can delay age-associated disease and disability and give companion dogs substantially more time with good health, physical function, and quality of life. The STAY study and our other ambitious clinical trials will provide much more detail about the impacts of our drugs on health and lifespan.

What are the active pharmaceutical ingredients in your drugs?

Because our products are still in development, the drugs and their exact mechanisms of action necessarily remain confidential. We'll release these details — along with safety and efficacy data — as we get closer to launching each product.

Do your drugs treat specific cancers or other age-related diseases?

Our goal is to develop medications that preserve health and broadly delay or prevent age-associated disease rather than focusing on treating specific diseases after they have already developed.

Do dogs need to be healthy when taking your drugs?

We expect dogs with many pre-existing conditions will be able to take our drugs and benefit from them, but any specific guidelines will be based on the results of our clinical and safety studies.

What about younger or smaller dogs?

We expect to support the following populations with our drugs:

- For LOY-001 and LOY-003, dogs 7 years and older and weighing at least 40 pounds
- For LOY-002, dogs 10 years and older and weighing at least 14 pounds

Clinical studies are designed to measure effectiveness among a target population, and for our lifespan extension drugs, this means choosing a population that's most likely to benefit over the duration of our clinical studies. If approved, our drugs will be intended for use in the same populations studied in the clinical efficacy trials.

Our goal is to help as many dogs as possible, and we hope to pursue additional research to expand access to a broader population in the future.

Why develop both an injection and daily pill to treat overexpression of growth hormone in large dogs?

Our goal is to offer a range of options to suit the needs of veterinarians and dog owners.

An injectable formulation offers convenience and improved compliance, while a daily pill may be preferred by some owners.

What about cats?

We love them too, but don't currently have any plans to develop therapies for cats.

Sources

1 Lawler DF, Larson BT, Ballam JM, Smith GK, Biery DN, Evans RH, Greeley EH, Segre M, Stowe HD, Kealy RD. Diet restriction and ageing in the dog: major observations over two decades. *Br J Nutr.* 2008 Apr;99(4):793-805. doi: 10.1017/S0007114507871686. Epub 2007 Dec 6. Erratum in: *Br J Nutr.* 2009 Apr;101(7):1112. PMID: 18062831.

2 Kealy, R.D., Lawler, D.F., Ballam, J.M., Lust, G., Smith, G.K., Biery, D.N., & Olsson, S.E. (1997). Five-year longitudinal study on limited food consumption and development of osteoarthritis in coxofemoral joints of dogs. *Journal of the American Veterinary Medical Association*, 210(2), 222-225.

3 López-Otín C, Blasco MA, Partridge L, Serrano M, Kroemer G. Hallmarks of aging: An expanding universe. *Cell.* 2023 Jan 19;186(2):243-278. doi: 10.1016/j.cell.2022.11.001. Epub 2023 Jan 3. PMID: 36599349.

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