Date of Approval: March 14, 2025

CORRECTED FREEDOM OF INFORMATION SUMMARY (FOI)

APPLICATION FOR CONDITIONAL APPROVAL

Application number 141-604

felycin®-CA1

(sirolimus delayed-release tablets)

Cats

For the management of ventricular hypertrophy in cats with subclinical hypertrophic cardiomyopathy (HCM).

Subclinical HCM refers to cats with left ventricular (LV) hypertrophy (LV wall thickness of ≥6 mm at end diastole by 2D or M-mode assessment) in the absence of systemic hypertension, other causes of compensatory myocardial hypertrophy, current or historic symptoms of congestive heart failure, arterial thromboembolism, and severe LV outflow tract obstruction.

Sponsored by:

TriviumVet

Executive Summary

felycin®-CA1 (sirolimus delayed-release tablets) is conditionally approved for the management of ventricular hypertrophy in cats with subclinical hypertrophic cardiomyopathy (HCM). Subclinical HCM refers to cats with LV hypertrophy (LV wall thickness of ≥6 mm at end diastole by 2D or M-mode assessment) in the absence of systemic hypertension, other causes of compensatory myocardial hypertrophy, current or historic symptoms of congestive heart failure, arterial thromboembolism, and severe LV outflow tract obstruction.

Sirolimus (also known as rapamycin), the active ingredient in felycin®-CA1, is a macrocyclic lactone produced by the bacterium *Streptomyces hygroscopicus*. At higher doses, sirolimus is used as an immunosuppressant in humans receiving organ transplants.[1] felycin®-CA1 is given to cats at a target dose of 0.3 mg/kg orally once weekly.

An animal drug that addresses a serious or life-threatening disease, or addresses an unmet animal or human health need, for which demonstrating effectiveness would require a complex or particularly difficult study or studies is eligible for conditional approval. Subclinical HCM often progresses to clinical HCM, which has a mortality and morbidity that substantially impact day-to-day functioning in cats. Therefore, the conditionally approved use of felycin®-CA1 addresses a serious or life-threatening disease or condition. The management of ventricular hypertrophy in cats with subclinical HCM is an unmet animal health need because there is no approved animal drug currently marketed in the United States for this use in cats. Finally, demonstrating effectiveness would require a complex or particularly difficult study or studies because the nature of subclinical HCM makes it unusually time-consuming and difficult to enroll sufficient numbers of eligible cats and requires the use of advanced diagnostic tests. Therefore, the Food and Drug Administration (FDA) determined that felycin®-CA1 met the eligibility criteria for conditional approval.

Safety and Reasonable Expectation of Effectiveness

Reasonable expectation of effectiveness for felycin®-CA1 was based on a review of published scientific literature and the results from a pilot field study. The studies described in the literature review demonstrated that sirolimus reduced ventricular size without compromising cardiac function in mice with induced cardiac hypertrophy and in human cardiac transplant recipients.

The sponsor conducted a pilot field study to evaluate the safety and effectiveness of felycin®-CA1 in client-owned cats with subclinical HCM. Enrolled cats were mainly male, ranged in age from 1 to 12 years, and were a variety of weights and breeds. Diagnosis of subclinical HCM was based on echocardiography findings of LV hypertrophy with no evidence of congestive heart failure, arterial thromboembolism, or arrhythmias that required specific anti-arrhythmic therapy. LV hypertrophy was defined as a maximum wall thickness (MWT) of ≥6 mm. Cats were administered felycin®-CA1 at 1X the label

[1] National Institutes of Health National Cancer Institute Drug Dictionary. Available at https://www.cancer.gov/publications/dictionaries/cancer-drug/def/sirolimus. Accessed Dec 26, 2024.

dose (0.3 mg/kg), felycin®-CA1 at 2X the label dose (0.6 mg/kg), or a placebo control tablet orally once weekly for 6 months (180 ± 10 days).

The sponsor did not select the effectiveness criteria before the study began. After conducting exploratory analyses, the sponsor selected MWT of the LV on Day 180 as the effectiveness endpoint. LV wall thickness was comparable between the three study groups at baseline (Day 0). On Day 180, the MWT of the LV in cats in the 1X group decreased by a mean value of 0.17 mm compared to baseline. In contrast, the MWT increased by a mean value of 0.94 mm and 0.50 mm in the placebo group and the 2X group, respectively.

The most common adverse reactions seen in the pilot field study were cardiac in nature, with most relating to the variable disease progression of HCM. Arrhythmia, congestive heart failure, syncope, and pericardial effusion were noted in cats treated with felycin®-CA1. Three of the 15 cats in the 2X group progressed to congestive heart failure or sudden death (presumed to be cardiac related). These cats all had risk factors associated with progression of HCM at enrollment. Because of the small sample size and the variable disease progression of HCM, it is unknown if the heart failure and sudden death were associated with treatment with felycin®-CA1. Other non-cardiac adverse reactions included lethargy, vomiting, diarrhea, and inappetence. One cat in the 1X group developed diabetes mellitus which went untreated, and the cat presented in diabetic ketoacidosis and died of acute cardiac arrest. Based on this finding, felycin®-CA1 should not be used in cats with pre-existing diabetes mellitus.

The sponsor conducted a laboratory margin of safety study in healthy, young adult, intact male and female cats. Cats were administered felycin®-CA1 at 0X, 1.3X, 3.8X, or 6.3X the label dose of 0.3 mg/kg (0, 0.38, 1.13, or 1.88 mg/kg, respectively) orally once weekly for 24 weeks. Several cats in the 1.3X, 3.8X, and 6.3X groups had elevated transaminase liver enzymes, including alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST), that was not dose dependent. No cats in the 0X group had elevated transaminase liver enzymes. All affected cats remained clinically normal, and there was no evidence of liver pathology on postmortem examination.

The margin of safety study had no recovery period following the last weekly administration of felycin®-CA1. However, the sponsor conducted an earlier pilot tolerance safety study that included a recovery period where cats were further monitored after felycin®-CA1 was discontinued. In that study, healthy, adult, intact male and female cats were administered felycin®-CA1 at 0X, 1.5X, 4.5X, or 7.5X the label dose (0, 0.15, 0.45, or 0.75 mg/kg, respectively) orally three times weekly for 4 weeks (a total of 12 doses), followed by a 4-week recovery period during which no treatment was given. During the dosing period, 8 of the 24 cats in the felycin®-CA1 treatment groups had mild elevations in transaminase liver enzymes but no clinical signs of liver disease. By the end of the recovery period, all elevated ALT values returned to normal and the elevated AST values either returned to normal or showed a downward trend after felycin®-CA1 was discontinued.

In addition to the two safety studies mentioned above, the sponsor conducted two pilot field studies using felycin®-CA1 dosed at either 0.3 mg/kg given once weekly (the label dose) or 0.6 mg/kg once weekly in client-owned cats with subclinical HCM or chronic

kidney disease (CKD). Only one cat in these two studies had elevated liver enzymes. This cat had pre-existing liver disease, and after several months of treatment with felycin®-CA1, experienced a progressive decline in appetite, elevated liver enzymes compared to pre-treatment, and icterus, and the cat was euthanized approximately 4 months after exiting the study. Based on these findings, cats should be screened for pre-existing liver disease before starting felycin®-CA1.

Due to the potential immunosuppressive effects of felycin®-CA1, the sponsor conducted a vaccine response study to determine the drug's effect on the immune response following Rabies vaccination in vaccine naïve cats. Healthy, adult, intact male and female cats were administered felycin®-CA1 at 3X the label dose (0.9 to 1.14 mg/kg) orally once weekly for 56 days (8 weeks). On Day 29, all cats received a United States Department of Agriculture (USDA)-licensed killed Rabies virus vaccine. All cats achieved an adequate immune response to Rabies vaccination, as quantified by a Rabies viral titer level >0.5 IU/mL on Day 57. In addition, no cats in this study had elevated transaminase liver enzymes.

User Safety
The labeling for felycin®-CA1 includes instructions for drug handling and administration and recommends that people avoid direct contact with a treated cat's vomit and saliva and with any tablet remnants. During normal handling of felycin®-CA1, the coating on the tablets will prevent contact with the active ingredient, sirolimus. However, if the coating breaks down after accidental ingestion by a person or if a cat vomits a tablet after treatment, then exposure to sirolimus can occur and cause a range of symptoms in people, including fever, hypertension, headache, and gastrointestinal effects. Pregnant and breastfeeding women should avoid contact with felycin®-CA1.

Conclusions
Based on the data submitted by the sponsor for the conditional approval of felycin®-CA1, FDA determined that the drug is safe and has a reasonable expectation of effectiveness when used according to the labeling.

Table of Contents

I. GENERAL INFORMATION

A. File Number

Application number 141-604

B. Sponsor

TriviumVet
Unit 1N, Block1A, Cleaboy Business Park
Old Kilmeaden Road
Waterford, Waterford, X91 DEC4, IRELAND

Drug Labeler Code: 86169

U.S. Agent Name and Address:

Bill Zollers, PhD
Argenta
2029 Becker Drive
Suite 222
Lawrence, KS 66047

C. Proprietary Name

felycin®-CA1

D. Drug Product Established Name

sirolimus delayed-release tablets

E. Pharmacological Category

Macrocyclic lactone

F. Dosage Form

Delayed-release tablets

G. Amount of Active Ingredient

Three tablet strengths: 0.4 mg, 1.2 mg, 2.4 mg

H. How Supplied

12 tablets per carton

I. Dispensing Status

Prescription (Rx)

J. Dosage Regimen

Administer felycin®-CA1 at a target dosage of 0.3 mg/kg once weekly.

K. Route of Administration

Oral

L. Species/Class

Cats

M. Indication

For the management of ventricular hypertrophy in cats with subclinical hypertrophic cardiomyopathy (HCM).

Subclinical HCM refers to cats with left ventricular (LV) hypertrophy (LV wall thickness of ≥6 mm at end diastole by 2D or M-mode assessment) in the absence of systemic hypertension, other causes of compensatory myocardial hypertrophy, current or historic symptoms of congestive heart failure, arterial thromboembolism, and severe LV outflow tract obstruction.

II. EFFECTIVENESS

Conditional Dose: The conditional dose for the indication "for the management of ventricular hypertrophy in cats with subclinical hypertrophic cardiomyopathy" is 0.3 mg/kg administered orally once weekly. The safety data and the data to demonstrate reasonable expectation of effectiveness provide support for this conditional dose.

A. Dosage Characterization

A dose of sirolimus administered orally at 0.3 mg/kg once weekly is supported by a United States (U.S.) field study conducted at two referral veterinary cardiology centers in which 43 cats were randomized to one of three groups: placebo control, or 0.3 mg/kg of felycin®-CA1, or 0.6 mg/kg of felycin®-CA1 administered once weekly for 6 months. Effectiveness was evaluated by measuring effects on ventricular hypertrophy, assessed using echocardiography. After a 180-day treatment period, mean maximum wall thickness (MWT) was lower in the sirolimus treated groups compared to the control group. The lowest mean MWT was observed in the group treated with felycin®-CA1 at the dose 0.3 mg/kg once weekly. This study is further described below under Reasonable Expectation of Effectiveness.

B. Reasonable Expectation of Effectiveness

Reasonable expectation of effectiveness for felycin®-CA1 is based on published scientific literature and the results from a pilot field study, titled "Blinded, randomized, placebo-controlled clinical trial of a novel veterinary rapamycin product in cats with subclinical hypertrophic cardiomyopathy (HCM)".

1. Published Literature

   a. Shioi, T., McMullen J.R., Tarnavski, O., Converso, K. Sherwood, M.C., Manning, W.J., & Izumo, S. (2003). Rapamycin Attenuates Load-Induced Cardiac Hypertrophy in Mice. *Circulation, 107*(12), 1664–70.

      This study examined the role of mammalian target of rapamycin (mTOR) in load-induced cardiac hypertrophy and the effect of administration of sirolimus in an aortic banding mouse model, a model eliciting concentric hypertrophy of the left ventricle and diastolic dysfunction. Mice were treated with sirolimus or vehicle control prior to aortic banding. Pre-treatment with sirolimus significantly decreased the left ventricular diastolic and systolic diameters, and suppressed load-induced increase in heart weight/tibial length ratio following the banding procedure. Cardiac contractility, assessed by fractional shortening, was not different between vehicle control and sirolimus-treated animals. Thus, sirolimus treatment was associated with a decrease in chamber size and normal systolic function in normal mice. Pre-treatment with sirolimus effectively attenuated load-induced ventricular hypertrophy, and this was associated with attenuation of the increase in myocyte cell size. This study demonstrated that sirolimus can reduce heart size without disturbing cardiac function in a model of load induced cardiac hypertrophy.

   b. McMullen, J.R., Sherwood, M.C., Tarnavski, O., Zhang, L., Dorfman, A.L., Shioi, T., & Izumo, S. (2004). Inhibition of mTOR Signaling with Rapamycin Regresses Established Cardiac Hypertrophy Induced by Pressure Overload. *Circulation, 109*(24), 3050–55.

      This study evaluated the administration of sirolimus after the aortic banding of mice and development of ventricular hypertrophy. The study demonstrated that sirolimus could regress established hypertrophy in mice with both compensated hypertrophy (increase in left ventricular wall thickness, normal function: fractional shortening ≥45%) and decompensated cardiac hypertrophy (increase in left ventricular thickness and dilation, depressed function: fractional shortening <45%). In mice with compensated cardiac hypertrophy, the heart weight to body weight ratio of aortic-banded mice receiving sirolimus for 1 week was significantly lower than that of control mice. In mice with decompensated hypertrophy, sirolimus regressed cardiac hypertrophy to a lesser extent. In this model, sirolimus significantly regressed ventricular hypertrophy induced by pressure overload, in the absence of deleterious effects on cardiac function or mortality.

   c. Raichlin, E, Chandrasekaran, K., Kremers, W.K., Frantz, R.P., Clavell, A.L., Pereira, N.L., Rodeheffer, R.J., Daly, R.C., McGregor C.G., Edwards B.S., & Kushwaha S.S. (2008). Sirolimus as Primary Immunosuppressant Reduces Left Ventricular Mass and Improves Diastolic Function of the Cardiac Allograft. *Transplantation, 86*(10), 1395–1400.

      In this study, 70 human cardiac transplant recipients were either transitioned from a calcineurin inhibitor (CNI, e.g., cyclosporine) to sirolimus or remained

on the CNI. Three consecutive echocardiographic studies were conducted at 1-year intervals and demonstrated that the sirolimus group had significant decreases in interventricular septal thickness, left ventricular mass, and left ventricular mass index; and a significant improvement in the left atrial volume index. These differences were not associated with changes in blood pressure. In this study, replacement of a CNI with sirolimus in human cardiac transplant recipients resulted in a decrease in left ventricular mass and improvement in diastolic function.

2. Pilot Field Study

Title: Blinded, Randomized, Placebo-Controlled Clinical Trial of a Novel Veterinary Rapamycin Product in Cats with Subclinical Hypertrophic Cardiomyopathy (HCM). (Study No. TRIV-5)

Study Dates: January 2021 to December 2022

Study Locations: Davis, CA and Raleigh, NC

Study Design:

Objective: The objectives of this study were to evaluate the safety of chronic sirolimus treatment in client-owned cats with subclinical HCM and to evaluate the effectiveness of sirolimus in reversing or slowing the progression of myocardial hypertrophy and consequent cardiac dysfunction in client-owned cats with subclinical HCM.

Study Animals: A total of 43 cats of various breeds received either felycin®-CA1 at the oral dose of 0.3 mg/kg once weekly (n=15) or 0.6 mg/kg once weekly (n=15), or placebo control tablets once weekly (n=13).

Cats ranged between 1 and 12 years of age and weighed between 3.3 and 14 kg at study enrollment; 37 of the 43 cats were male. To be eligible for enrollment, cats were confirmed to have evidence of subclinical HCM based on echocardiographic findings of LV MWT ≥6 mm, with no evidence of congestive heart failure (CHF), arterial thromboembolism, or arrhythmias requiring specific anti-arrhythmic therapy. Cats were ineligible if they were found to have evidence of cardiogenic pulmonary edema, severe LV outflow tract obstruction, clinically significant tachyarrhythmias, cardiac disease other than HCM, systemic hypertension, significant systemic disease, or were receiving long-term corticosteroid treatment.

Experimental Design: This study was conducted in accordance with Good Clinical Practice (GCP) guidelines. Client-owned cats diagnosed with subclinical HCM were enrolled and randomized to one of three groups (0, 0.3, or 0.6 mg/kg of felycin®-CA1; the placebo, low-, and high-dose groups, respectively).

Table II.1: Treatment Groups.

Treatment Group	Dose and frequency of felycin®-CA1 administration	Number of Cats (Male, Female)
High-dose	0.6 mg/kg once weekly	15 (11M, 4F)
Low-dose	0.3 mg/kg once weekly	15 (14M, 1F)
Placebo	0 mg/kg once weekly	13 (12M, 1F)

Drug Administration: Of the 43 cats enrolled in the study, 15 received felycin®-CA1 orally once weekly at a dose of 0.3 mg/kg (label dose), 15 received felycin®-CA1 once weekly at a dose of 0.6 mg/kg, and 13 received a placebo control tablet. Of the evaluable cases in the two felycin®-CA1 groups, the low-dose and high-dose groups were dosed within ranges of 0.25 to 0.38 mg/kg and 0.52 to 0.73 mg/kg, respectively. Cats were dosed according to Table II.2.

Table II.2: Dosing Chart.

Body Weight (kg)	0.3 mg/kg # tablets/ week			0.6 mg/kg # tablets/ week			Placebo # tablets/ week	
	0.4mg	1.2mg	2.4mg	0.4mg	1.2mg	2.4mg	1.2mg	2.4mg
3.5-4.7	0	1	0	0	0	1	0	1
>4.7-5.5	1	1	0	1	0	1	0	1
>5.5-6.3	1	1	0	0	1	1	1	1
>6.3-7.1	0	0	1	0	1	1	1	1
>7.1	0	0	1	0	0	2	1	1

Concomitant use of oral clopidogrel and/or angiotensin-converting enzyme (ACE) inhibitors was permitted. All concomitant medications were administered for at least 2 weeks prior to study enrollment. No new cardiac medications were permitted to be instituted during the course of the study.

Measurements and Observations: Screening included a physical examination, history, quality of life assessment, echocardiogram, 3-minute electrocardiogram, thoracic radiographs, and systolic blood pressure measurements. Routine 2D, M-mode, Color, and Spectral Doppler echocardiography were performed with or without sedation. Chamber size and wall thickness were assessed by both 2D and M-mode measurements obtained from the right parasternal imaging window. In addition to averaged values, the single end-diastolic MWT obtained via 2D assessment of the interventricular septum (IVSd) and Left Ventricular posterior wall (LVPWd) was recorded. Blood was collected for hematology, biochemistry, total thyroxine (T4), fructosamine, n-terminal pro-brain natriuretic peptide (NTproBNP), and cardiac troponin I, and urine was collected for urinalysis.

Eligible cats were enrolled on Day 0 with follow-up visits occurring on Days 60, 120, and 180 (all ± 10 days). Physical examination; quality of life assessment; systolic blood pressure measurement; blood collection for hematology, biochemistry, total T4, NTproBNP, and cardiac troponin I; urine collection for urinalysis; and study drug accountability were performed at all follow-up visits. Echocardiography was repeated at the Day 60 and 180 visits. Of the 43 cats enrolled in the study, 36 cats were considered evaluable following the Day 180 visit.

The effectiveness criteria were not selected *a priori.* Exploratory analyses were conducted evaluating measures of LV hypertrophy and left atrial dilation in addition to comparing the relationship between disease progression/response and baseline patient characteristics. The effectiveness endpoint selected was MWT of the LV; it was assessed by echocardiogram at three timepoints: at screening, Day 60, and Day 180.

Statistical Methods: The MWT of the LV was analyzed using the repeated measures analysis of covariance (RMANCOVA). The statistical model included treatment, time, and the treatment by time interaction as fixed effects. The screening value was used as the covariate. Where the treatment by time interaction was significant, within time, treatment effects were evaluated by comparing the two groups receiving felycin®-CA1 to the control group using linear contrasts and comparing the pooled felycin®-CA1 groups to the control group using a linear contrast. Where the interaction was not significant, the main effect of treatment was assessed, and where significant, the two felycin®-CA1 groups were compared to the control group using linear contrasts and comparing the pooled felycin®-CA1 groups to the control group using a linear contrast. All contrasts were evaluated using a two-sided alpha = 0.10 significance level. The percent of animals with a change from screening greater than 0.5 mm was calculated for both time points (Day 60 and Day 180) and statistically analyzed using Fisher's exact test at both time points.

Hematology and biochemistry data were analyzed using RMANCOVA with the pre-treatment value as a covariate. Treatment group, time, and the time by treatment group interaction were included in the statistical model as fixed effects, site, site by treatment, and the site by treatment by time interactions were included as random effects. Where the interaction was statistically significant, within-time, differences between treatment groups were evaluated using a two-sided alpha = 0.10 significance level. Where the interaction was not significant, the main effect of treatment was assessed. Safety outcomes were evaluated at two-sided alpha = 0.10.

Results: Of the 43 cats enrolled in the study, 37 cats were still enrolled at the final evaluation on Day 180. Six cats (five high-dose and one control) were excluded due to the progression of heart disease, death, or owner removal.

Echocardiographic values were comparable between the three study groups at baseline. Following 180 days of treatment, differences in LV wall thickness were evident. Cats treated with 0.3 mg/kg of felycin®-CA1 had a lower mean MWT and the difference between the felycin®-CA1 group and the control group was statistically significant on Day 60 and Day 180. No statistically significant treatment effects were detected for other echocardiographic values.

Sirolimus prevented significant increases in LV hypertrophy whereas a statistically significant change with increase compared to the baseline was observed in the placebo group. Within the 36 evaluable cases at Day 180, MWT decreased by a mean value of 0.17 mm in the low-dose group (n=14) compared to baseline. In contrast, MWT increased in the placebo group by a mean of 0.94 mm (n=12) and increased by a mean of 0.50 mm in the high-dose group (n=10).

Adverse Reactions: The most frequently observed adverse reactions noted in cats treated with felycin®-CA1 were cardiovascular in nature with most relating to the disease process or progression of HCM. Arrhythmia, congestive heart failure, syncope, and pericardial effusion were noted in cats treated with felycin®-CA1.

Three of the 12 cats in the high-dose group of felycin®-CA1 progressed to congestive heart failure or sudden death (presumed to be cardiac related). Two of these cats had severe pre-existing structural cardiac disease. The third cat did not have severe structural cardiac disease at enrollment but had a markedly elevated NTproBNP at enrollment (1344 pmol/L; normal <100 pmol/L), which can indicate an increased risk of disease progression. The relationship to treatment with felycin®-CA1 is unknown due to the small sample size of this study and the variable disease progression of HCM.

Other adverse reactions observed in cats treated with felycin®-CA1 included lethargy, vomiting, diarrhea, and inappetence.

One cat in the low-dose felycin®-CA1 group developed diabetes mellitus during the study, manifesting as hypercholesterolemia, hyperglycemia, and glucosuria with prior evidence of urinary tract infection at scheduled visits. Treatment for diabetes was not initiated, and the cat continued on the study. Subsequently, the cat presented in diabetic ketoacidosis, and despite intensive medical management, the cat died of acute cardiac arrest.

Conclusion: The study results demonstrate that felycin®-CA1 was well tolerated in cats with subclinical HCM and support a reasonable expectation of effectiveness of felycin®-CA1 for the management of ventricular hypertrophy in cats with subclinical hypertrophic cardiomyopathy when administered orally at the label dose of 0.3 mg/kg once weekly. felycin®-CA1 should not be used in cats with diabetes mellitus.

III. TARGET ANIMAL SAFETY

The safety of felycin®-CA1 was demonstrated in three well-controlled laboratory studies described below. The purpose of these studies was to provide information about the safety of felycin®-CA1 when administered at the conditional dose of 0.3 mg/kg administered orally once weekly in cats.

In a 24-week margin of safety study, several cats experienced elevations in their transaminase liver enzymes, including alanine aminotransferase (ALT) and/or aspartate aminotransferase (AST). These findings were not associated with any clinical or postmortem signs of liver toxicity. The cats in this study were administered felycin®-CA1 until the completion of the study with no recovery period. However, in an earlier pilot tolerance study, several cats also experienced mild transaminase elevations. The cats in this study also demonstrated no clinical signs of disease during the dosing period. This study included a 4-week recovery period following administration of felycin®-CA1 during which all elevated ALT values returned to within the reference range and AST values were either within the reference range or showing a downward trend following the discontinuation of felycin®-CA1 administration. Due to these findings, it is recommended

that cats are monitored for the development of transaminase elevations while being treated with felycin®-CA1.

Due to the potential immunosuppressive effects of felycin®-CA1, a vaccine response study was conducted to demonstrate that cats vaccinated with a commercially available killed Rabies vaccine could mount an adequate immune response to the vaccination while being administered felycin®-CA1. All cats in this study demonstrated an adequate immune response to vaccination with the killed Rabies vaccine and there were no cases of elevated transaminase values in this study.

In addition to these safety studies, felycin®-CA1 was administered in 42 client-owned cats with subclinical HCM or chronic kidney disease (CKD) in two pilot field studies. None of the cats in these studies experienced elevated transaminases except for one cat in the CKD field study that was enrolled with a history of pre-existing liver disease and elevated alkaline phosphatase (ALP). After treatment with felycin®-CA1, this cat experienced a progressive decline in appetite, elevation of liver enzymes (including ALP, ALT, and AST), and icterus, and was euthanized approximately 4 months after exiting the study. Due to these findings, pre-screening for existing liver disease should be conducted prior to starting treatment with felycin®-CA1.

A. Margin of Safety Study

Title: Target Animal Safety Study in Cats When Administered Sirolimus Delayed Release (DR) Tablets Once Weekly in Fed State for Twenty-Four Weeks. (Study No. IPD21016)

Study Dates: April 15, 2022 to April 20, 2023

Study Location: Ballina, Co Mayo, Ireland

Study Design:

Objective: To evaluate the safety of felycin®-CA1 at 1.3X, 3.8X, and 6.3X the label dose (0.3 mg/kg) when administered orally to cats once per week for 24 weeks.

Study Animals: A total of 32 cats (16 male and 16 female) that met the inclusion criteria were included in the study and randomized to treatment. Cats were 10 to 11 months old and weighed between 2.8 and 5.0 kg at the start of acclimation.

Experimental Design: This was a randomized, masked, nonclinical laboratory safety study, conducted in accordance with Good Laboratory Practice (GLP) regulations. A total of 32 cats were randomly allocated to 4 study groups (4 males and 4 females per group). Following randomization to groups, cats of the same sex within the same group were randomly allocated to rooms using paired housing, i.e., two cats stayed in a room.

Drug Administration: Cats were administered the final market formulation of felycin®-CA1 (0.4, 1.2, or 2.4 mg tablets) and were dosed orally once weekly for 24 weeks. Cats assigned to the control (Group 1) were untreated. Cats assigned to Groups 2, 3, and 4 were each dosed weekly with felycin®-CA1 at a dose of 0.38 mg/kg, 1.13 mg/kg, and 1.88 mg/kg (1.3X, 3.8X, and 6.3X the label dose), respectively. Cats

were dosed in a fed state. Doses were calculated based on the cat's last recorded scheduled body weight.

Table III.1: Treatment Groups.

Group Number	Number and Sex of Cats	Treatment	Dose (mg/kg/week)
1	4M, 4F	Untreated Control	0
2	4M, 4F	felycin®-CA1	0.38
3	4M, 4F	felycin®-CA1	1.13
4	4M, 4F	felycin®-CA1	1.88

Measurements and Observations: General health observations were performed daily except when clinical observations were performed, and on days of dosing, veterinary examinations, or necropsy. On each dosing day, clinical observations were performed prior to treatment and at 1 hour and 3 hour timepoints post-treatment. Veterinary examinations were performed three times during acclimatization and monthly during the dosing period. Systolic blood pressure was measured during acclimatization and monthly thereafter. Bodyweights were recorded three times during acclimatization and every two weeks during the dosing period. Diet consumption was recorded daily throughout the study.

Blood samples for clinical pathology analysis (hematology, clinical chemistry, coagulation, and symmetric dimethylarginine analysis (SDMA)) were collected once during acclimatization and monthly during the dosing period. Urine samples were collected during acclimation, mid-way through the dosing period, and at the end of the dosing period.

A complete macroscopic post-mortem examination was performed on Study Day 170. This examination included determination of selected organ weights and collection of tissues for histopathological examination.

Blood samples for measurement of sirolimus concentrations were collected prior to treatment on Study Days 0 and 147, and at the following timepoints after dosing: 0.5, 1, 2, 3, 4, 6, 8, 10, 12, 24, 48, 72, 120, and 168 hours. Blood samples were analyzed for sirolimus using a validated liquid chromatography with tandem mass spectrometry detection assay.

Statistical Methods: Analysis for descriptive statistics was performed on clinical observations, bodyweight, hematology parameters, clinical chemistry parameters (including SDMA), coagulation, urinalysis, all veterinary examinations, systolic blood pressure, organ weight, and diet consumption data. The experimental unit was the pair housed room.

An "on-study non-treatment" reference range was determined for hematology, clinical chemistry parameters, coagulation, urine parameters (numeric parameters only), rectal temperature, and heart rate. This consisted of all data collected from the control group throughout the study and all pre-treatment data collected from the treated groups. These reference ranges were used to assess the clinical significance.

For continuous variables (bodyweight, hematology parameters, clinical chemistry parameters, coagulation, numeric urinalysis parameters, glucose, numeric veterinary examination parameters, systolic blood pressure, organ weight, and diet consumption), each variable was averaged across the two animals in a room to obtain the room average.

The room averages were summarized using descriptive statistics (number of observations, median, mean, and standard deviation) for males and females by treatment group and by treatment group over time (where the variable was evaluated at multiple time points).

For binary and categorical variables (categorical clinical observations, categorical urinalysis parameters, categorical veterinary examination parameters) frequency distributions were prepared for males and females by treatment group and by treatment group over time (where the variable was evaluated at multiple time points).

For binary data, when the event occurred in one or both of the two animals in a room, it was counted as one event (event = "Yes") for that room. In order to be considered as event = "No" for a room, neither of the animals in the room should have had the event. For categorical data, the worst categorical level of the two animals in a room was determined for the room for each variable.

Frequency distributions of the numbers of rooms with abnormalities per group were presented.

Pharmacokinetic (PK) parameters for glucose and toxicokinetic parameters were calculated. Descriptive statistics and graphs of the plasma concentrations were prepared for individual groups and group mean concentration profiles.

Results: No clinically significant effects on physical examination, clinical observations, food consumption, bodyweight, or postmortem examination parameters were identified.

Administration of felycin®-CA1 was associated with changes in the following clinical pathology parameters; however, these findings were mild, generally within the reference, and were not considered clinically significant: elevated neutrophil and decreased eosinophil counts, elevated red cell distribution width (RDW), decreased hemoglobin concentration and mean corpuscular hemoglobin concentration (MCH), and elevated total bilirubin and cholesterol.

Administration of felycin®-CA1 was also associated with elevation in transaminase liver values (i.e., AST and ALT). Of the 24 cats that received felycin®-CA1, 15 cats experienced at least one transaminase value elevation during the course of the study. Affected cats were in all three felycin®-CA1 dosing groups and a dose-response was not present. Transaminase elevations were not observed in any of the control cats. Some of the elevations were transient and/or mild (i.e., less than 2X the upper limit of normal (ULN)). Four male littermates were found to have the most severe elevations, with maximum AST values of 110 to 515 U/L (reference range 16 to 34 U/L) and maximum ALT values of 255 to 4552 U/L (reference range 41 to 160 U/L). Transaminase elevations were observed at the first bloodwork collection

timepoint (Day 26/27) after the treatment initiation in 3 of the 4 littermates, and elevations were present throughout the 24-week dosing period. All affected cats remained clinically normal and there was no evidence of liver pathology on postmortem examination.

Plasma pharmacokinetic parameters calculated using a noncompartmental analysis after the first dose of felycin®-CA1 to cats at 0.38 mg/kg are presented in Table III.2. Mean dose normalized maximum plasma concentration (C_{max}) values decreased with increasing dose, suggesting the absorption of sirolimus may be saturated at higher doses in cats. The comparison between the area under the curve from dosing extrapolated to infinity (AUC_{inf}) at Day 0 and area under the curve from the time of dosing to the last quantifiable concentration (AUC_{last}) at Day 147 suggests that the pharmacokinetics are non-linear after multiple dosing. At 0.38 mg/kg, accumulation was observed between Days 0 and 147 with geometric mean accumulation ratios for the C_{max} and AUC_{last} of 1.33 and 1.62, respectively.

Table III.2: Mean (95% confidence interval) sirolimus pharmacokinetic parameters (0.38 mg/kg group, Day 0).

Parameter*	Estimate
AUC_{last} (h*ng/mL)	224 (127-395)
C_{max} (ng/mL)	17.5 (10.5-29.4)
$t_{1/2}$ (h)	58.3 (34.4-98.6)
T_{max} (h)	1.50 (1.00-12.0)

*Pharmacokinetic parameters are presented as geometric means (95% confidence interval) except for T_{max} which is presented as median (range)
AUC_{last} = area under the curve from dosing to 168 hours
C_{max} = maximum plasma concentration
$t_{1/2}$ = half-life
T_{max} = time to maximum plasma concentration

Conclusions: The results of this study demonstrate that felycin®-CA1 when administered orally to cats once per week for 24 weeks was well tolerated at doses up to 6.3X the label dose (0.3 mg/kg once weekly). Administration of felycin®-CA1 was associated with elevated transaminase levels, but these findings were not associated with clinical signs or evidence of liver toxicity on postmortem evaluation.

B. Dose Tolerance Study

Title: Pilot Tolerance of Rapamycin (felycin®-CA1) in Cats. (Study No. KFI-111-SF-1520)

Study Dates: June 2020 to April 2021

Study Location: Stouffville, Ontario, Canada

Study Design:

Objective: To evaluate the oral dose tolerance of a novel veterinary formulation of sirolimus (felycin®-CA1) when administered 3 times weekly for a total of 12 doses at 0, 0.15, 0.45, and 0.75 mg/kg to healthy, adult cats.

Study Animals: Thirty-five (35) cats were acclimated, with 32 cats (11 males and 21 females, aged 2 to 5 years) selected at the end of acclimatization phase for inclusion in the testing phase.

Experimental Design: This non-clinical laboratory study had a randomized, masked, controlled, parallel design. This study was conducted in accordance with GLP regulations.

Drug Administration: Cats were allocated to four groups of eight cats. felycin®-CA1 was administered 3 times per week at doses of 0, 0.15, 0.45, or 0.75 mg/kg (0X, 1.5X, 4.5X, or 7.5X the label dose) for 4 weeks, followed by a 4-week recovery period. On each dosing day, cats administered felycin®-CA1 received a pre-calculated dose of test article tablets. Dosing occurred 3 times weekly for a total of 12 doses. Dosing was performed under fasted conditions. Cats in the control group were untreated.

Table III.3: Treatment Groups.

Group Number	Number of Cats	Treatment	Dose (mg/kg)	Total Dose per Week (mg/kg)
T0	8	Untreated Control	0	0
T1	8	felycin®-CA1	0.15	0.45
T3	8	felycin®-CA1	0.45	1.35
T5	8	felycin®-CA1	0.75	2.25

Measurements and Observations: The following parameters were evaluated in this study: clinical observations, physical examinations, body weights, food consumption, clinical pathology (including SDMA and fructosamine), urinalysis, systolic blood pressure, toxicokinetics (TK), and glucose tolerance testing.

Clinical observations were conducted once daily during acclimation, twice daily during the dosing phase, and then once daily during the recovery phase. Physical examinations were performed once during acclimation, three times during the dosing phase, and once in the recovery phase. Body weights were measured twice during acclimation and once weekly until the end of the study. Food consumption was measured daily throughout the study. Blood was collected for clinical pathology once during acclimation, twice during the dosing phase, and twice during the recovery phase. Urine was collected for urinalysis once during acclimation, twice during the dosing phase, and twice in the recovery phase. Systolic blood pressure was measured once during acclimation, twice in the dosing phase, and once in the recovery phase. Blood was collected for TK analysis a total of 24 times (12 time points on both Day 0 and Day 26) during the dosing phase (after doses 1 and 12). Blood was collected for determination of fructosamine once in the recovery phase. Glucose was administered for glucose tolerance testing twice in the recovery phase. Blood was collected, for blood glucose measurement, a total of 16 times (8 time points on both Day 28 and Day 55).

Statistical Methods: 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 continuous variables.

Results: Assessment of the clinical observations, physical examinations, body weight, and urinalysis outcomes did not reveal findings of clinical or toxicological significance during the study.

Comparison of mean values for individual parameters revealed minimal differences between dose groups with most values remaining within test facility reference ranges. Administration of felycin®-CA1 was associated with transient elevations in fibrinogen and mild reductions in mean corpuscular volume (MCV) and MCH, but these findings were not considered clinically significant.

Administration of felycin®-CA1 was also associated with mild transaminase elevations (up to 2X ULN), including ALT and/or AST in 8 of the 24 cats in the 3 felycin®-CA1 dosing groups. These elevations decreased following the final administration of felycin®-CA1. The elevated ALT vales in all cats administered felycin®-CA1 returned to within the reference range by Day 55. Five of eight cats with elevated AST values at the end of the dosing period had values return to within the reference range by Day 55 and the values in the remaining three cats were trending downwards at this point.

Conclusions: The results of this study demonstrate that felycin®-CA1 was well tolerated when administered orally 3 times weekly to cats at doses up to 7.5X the label dose (0.3 mg/kg once weekly). Administration of felycin®-CA1 was associated with mild transaminase elevations that were reversible once dosing with felycin®-CA1 was discontinued.

C. Vaccine Response Study

Title: Rabies Vaccine Response Study of Sirolimus in Cats. (Study No. TRIV-20)

Study Dates: October 18, 2022 to May 15, 2023

Study Location: Stouffville, Ontario, Canada

Study Design:

Objective: The objective of this vaccine response study was to determine the effect of felycin®-CA1 administration at 3X the label dose, once weekly for 56 days, on the immune response following Rabies vaccination in vaccine naïve cats.

Study Animals: The study was conducted in healthy, purpose-bred, specific pathogen free, vaccine naïve, domestic short hair intact male and female cats. Twenty (10 male and 10 female) cats, approximately 4 months of age (126 to 131 days old) and weighing between 2.3 to 3.6 kg, were selected for inclusion into the testing phase based on eligibility criteria.

Experimental Design: The study was a non-clinical laboratory study with a randomized, masked, controlled, parallel design. The animal phase was conducted at a single test facility site. The study included 20 animals randomly allocated to 1 of 2 sex-balanced groups consisting of 8 or 12 cats each. Following randomization to treatment group, cats were randomly assigned to cages by treatment and sex.

This study was conducted in accordance with GLP regulations under Animal Biosafety Level-2 conditions.

Drug Administration: Dosing was performed on individually housed cats. felycin®-CA1 was administered once weekly orally in the fed state.

Table III.4: Treatment Groups.

Dose Group	Number and Sex of Cats	Treatment	Dose (mg/kg/week)
T0	4M, 4F	Untreated Control	0
T1	6M, 6F	felycin®-CA1	0.9-1.14

Vaccine Administration: A USDA-licensed killed Rabies virus vaccine was administered on Day 29 to all cats in the study.

Measurements and Observations: Clinical observations were performed twice daily and dry food consumption was measured daily from the start of acclimation (Day -21) until the last day of the testing phase (Day 57). Fecal parasitological examination was performed during acclimation (Day -21). Body weight was measured during acclimation and weekly prior to dosing (Days 0, 7, 14, 21, 28, 35, 42, 49, and 56). Physical examinations were conducted weekly during the study period (Days -20 to 55). Post-dose monitoring was performed at 1 and 2 hours after each dose (Days 0, 7, 14, 21, 28, 35, 42, 49, and 56). Post-vaccination monitoring was performed at 0.5, 1, 2, 4, and 24 hours after Rabies vaccination (Day 29).

Blood for hematology, clinical chemistry, coagulation, and SDMA evaluations were collected 3 times during the study period (Days -5, 2, and 57). Urine was collected from each cat 4 times during the study period (Days -6 or -5, 1 or 2, 6, and 56 or 57). Blood for Rabies viral titer levels was collected from each cat 3 times: once during pre-acclimation, prior to vaccination (Day 29), and post-vaccination (Day 57).

Safety variables in this study included Rabies viral titer, body weight, physical examination, food consumption, clinical observations, clinical pathology, urinalyses, and SDMA.

Statistical Methods: The primary endpoint of interest was the vaccine response titer level to the Rabies virus while the cats were receiving test article (sirolimus). To conclude felycin®-CA1 did not interfere with the immune response to Rabies vaccine, all cats that received felycin®-CA1 (in Group T1, regardless of sex) needed to achieve an adequate immune response to vaccination with Rabies on Day 57. An adequate immune response was concluded if every cat in T1 had a Rabies viral titer level > 0.5 IU/mL (~1:50) post-vaccination.

For the primary endpoint, the experimental unit was the individual cat. For all additional analyses for descriptive statistics, the experimental unit was the cage (or pair housed animals).

For binary data, when the event occurred in one or both of the paired animals in each cage, one event was counted for the cage. The event was only noted as absent if it did not occur in either animal. For categorical variables, ordinal or otherwise, the

worst or otherwise most severe categorical level of the two animals in the same cage was counted for that cage. Frequency distributions were prepared for males and females by treatment group and by treatment group over time (where the variable was evaluated at multiple time points).

For continuous variables, each variable was averaged across the two animals in a room to obtain the room average. The room averages were summarized using descriptive statistics (number of observations, minimum, maximum, median, mean, and standard deviation) for males and females by treatment group and by treatment group over time (where the variable was evaluated at multiple time points).

Results: All cats in both groups achieved an adequate immune response to Rabies vaccination, as quantified by a Rabies viral titer level > 0.5 IU/mL on Day 57.

There were no drug-related changes in physical examination variables, including body condition score. There were no drug-related abnormalities in clinical observations, hematology, clinical chemistry, coagulation, SDMA, and urinalysis.

A decreased appetite in two female felycin®-CA1-dosed cats with a subsequent overall decrease in percentage weight gain may have been drug-related.

Conclusions: The results of this study demonstrate that felycin®-CA1 was well tolerated when administered orally at doses up to 3X the label dose (0.3 mg/kg once weekly). All cats achieved an adequate immune response to a commercially available killed Rabies vaccination while receiving felycin®-CA1 at 0.9 mg/kg (3x the target label dose) weekly for 56 days. Additionally, the study supports the safe administration of a Rabies vaccine with concurrent administration of felycin®-CA1 in cats 4 months of age and older.

IV. USER SAFETY

The product labeling contains the following information regarding safety to humans handling, administering, or exposed to felycin®-CA1:

Not for use in humans.
Keep out of reach of children.
Contact a physician in case of accidental ingestion by humans.

Accidental Ingestion of felycin®-CA1:
In case of accidental ingestion seek medical advice immediately and show the package insert or the label to the physician.

Sirolimus can cause a range of adverse effects including fever, hypertension, headache, and adverse gastrointestinal effects.

Drug Handling and Administration:
Pregnant and breastfeeding women should avoid contact with felycin®-CA1.

People with known hypersensitivity to sirolimus should administer felycin®-CA1 with caution.

Always store tablets in the original packaging and only remove the required number of tablets from the blister at the time of dosing.

Ensure that any tablets that are not swallowed by the cat are disposed of immediately.

Avoid direct contact with vomit, saliva, and tablet remnants. When cleaning up vomit, saliva, or tablet remnants, wear gloves and wash hands afterwards.

During normal handling of felycin®-CA1, the coating on the tablets will prevent contact with the active ingredient, sirolimus. However, if the coating is broken down through ingestion or vomiting by the cat, exposure to sirolimus can occur.

V. AGENCY CONCLUSIONS

The data submitted in support of this application satisfy the requirements of section 571(b) of the Federal Food, Drug, and Cosmetic Act (FD&C Act). The data demonstrate that felycin®-CA1, when used according to the label, is safe and has a reasonable expectation of effectiveness for the conditions of use in the General Information Section above.

A. Conditional Approval Eligibility

In 2018, the legislation reauthorizing FDA's animal drug user fee program (Animal Drug User Fee Program, or ADUFA, IV) expanded the conditional approval pathway to allow certain additional new animal drugs that are not Minor Use/Minor Species (MUMS) drugs to be eligible for conditional approval. As provided in section 571(a)(1)(A)(ii) of the FD&C Act, as amended by ADUFA IV, to qualify for conditional approval, the non-MUMS new animal drug must meet the following two criteria:

1. The new animal drug is intended to treat a serious or life-threatening disease or condition OR addresses an unmet animal or human health need; AND

2. A demonstration of effectiveness would require a complex or particularly difficult study or studies.

felycin®-CA1 was determined to be eligible for conditional approval under these provisions. Ventricular hypertrophy in cats with subclinical HCM is a serious or life-threatening disease or condition and management of this condition represents an unmet animal health need. In addition, the demonstration of effectiveness requires a complex or particularly difficult study or studies because the nature of the disease or condition makes it unusually time consuming or difficult to enroll sufficient numbers of eligible animals and requires the use of advanced diagnostic tests.

B. Marketing Status

felycin®-CA1 is conditionally approved for one year from the date of approval and is annually renewable for up to four additional one-year terms.

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 HCM.

C. Exclusive Marketing Rights

felycin®-CA1, as approved in our approval letter, does not qualify for exclusive marketing rights under section 573(c) of the FD&C Act because it is not a designated new animal drug under section 573(a) of the FD&C Act.

D. Patent Information

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

VI. Appendix

On May 7, 2025, the following corrections were made:

1. A typographical error was corrected in the “Statistical Methods” section of the study summary for Study No. TRIV-5 (section II.B.2).
2. All instances of the term “IVP” were replaced with “felycin®-CA1” in section II.B.2.
3. The maximum label dose multiplier was corrected in the “Conclusions” sections for studies IPD21016 (section III.A) and KFI-111-SF-1520 (section III.B).
4. The “Conclusions” text for study TRIV-20 (section III.C) was edited to align with the other target animal safety studies.