Cardiac Myosin Inhibitor, CK-586, Minimally Reduces Systolic Function and Ameliorates Obstruction in Feline Hypertrophic Cardiomyopathy

Victor N. Rivas, MS[a,b]; Amanda E. Crofton, DVM[b]; Carina E. Jauregui, RVT, RLAT[b]; Jalena R. Wouters[b]; Betty S. Yang, BS[b]; Luke A. Wittenburg, DVM, PhD[c]; Joanna L. Kaplan, DVM[b]; Darren T. Hwee, PhD[d]; Anne N. Murphy, PhD[d]; Bradley P. Morgan, PhD[d]; Fady I. Malik, MD, PhD[d]; Samantha P. Harris, PhD[e]; **Joshua A. Stern, DVM, PhD**[a,b*]

[a]Department of Clinical Sciences, College of Veterinary Medicine, North Carolina State University, Raleigh, NC, United States of America; [b]Department of Medicine and Epidemiology, School of Veterinary Medicine, University of California-Davis, Davis, CA, United States of America; [c]Department of Surgical and Radiological Sciences, School of Veterinary Medicine, University of California-Davis, Davis, CA, United States of America; [d]Research and Non-clinical Development, Cytokinetics, Inc., South San Francisco, CA, United States of America; [e]Department of Physiology, University of Arizona, Tucson, AZ, United States of America.

Background

- Hypertrophic cardiomyopathy (HCM) affects 1 in 7 cats and is characterized by increased left ventricular (LV) wall thickness[1-4].
- In some cases, hyperdynamic LV contractility or morphologic changes causes systolic anterior motion (SAM) of the anterior mitral valve (MV) resulting in increased LV pressure overload and obstruction (oHCM)[4].
- Left ventricular outflow track obstruction (LVOTO) in humans is associated with[5-10]:
  - ↑ disease morbidity (exercise intolerance, syncope, angina).
  - ↑ severe disease sequalae (congestive heart failure, thrombosis, sudden death).
- Small-molecule inhibitors that modulate the sarcomere are promising novel therapeutics for LVOTO management in oHCM patients.

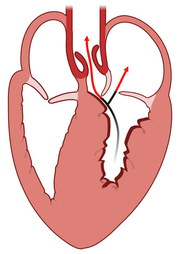


Fig 1. LVOTO in an HCM-affected heart. Increased hypercontractility or structural changes to the LV result in increased LVOT flow velocities and/or SAM (red arrows).

- We previously demonstrated successful acute, dose-related reductions in LV systolic function, left ventricular outflow tract maximum pressure gradient (LVOTmaxPG), and isovolumetric relaxation times (IVRT) after a single oral gavage dose of aficamten (CK-274) in cats with asymptomatic oHCM[11,12].

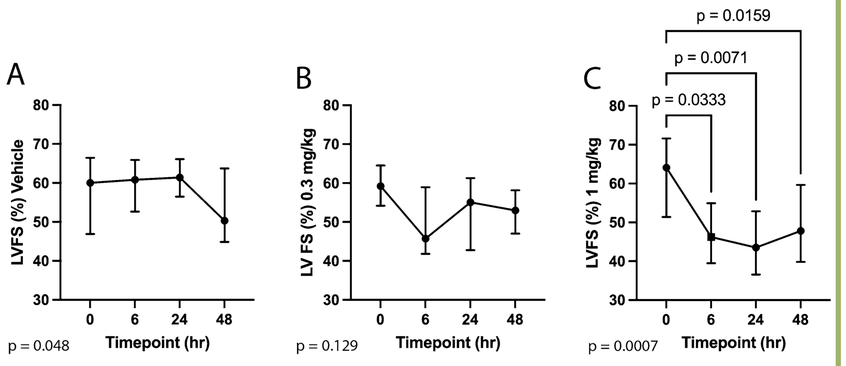
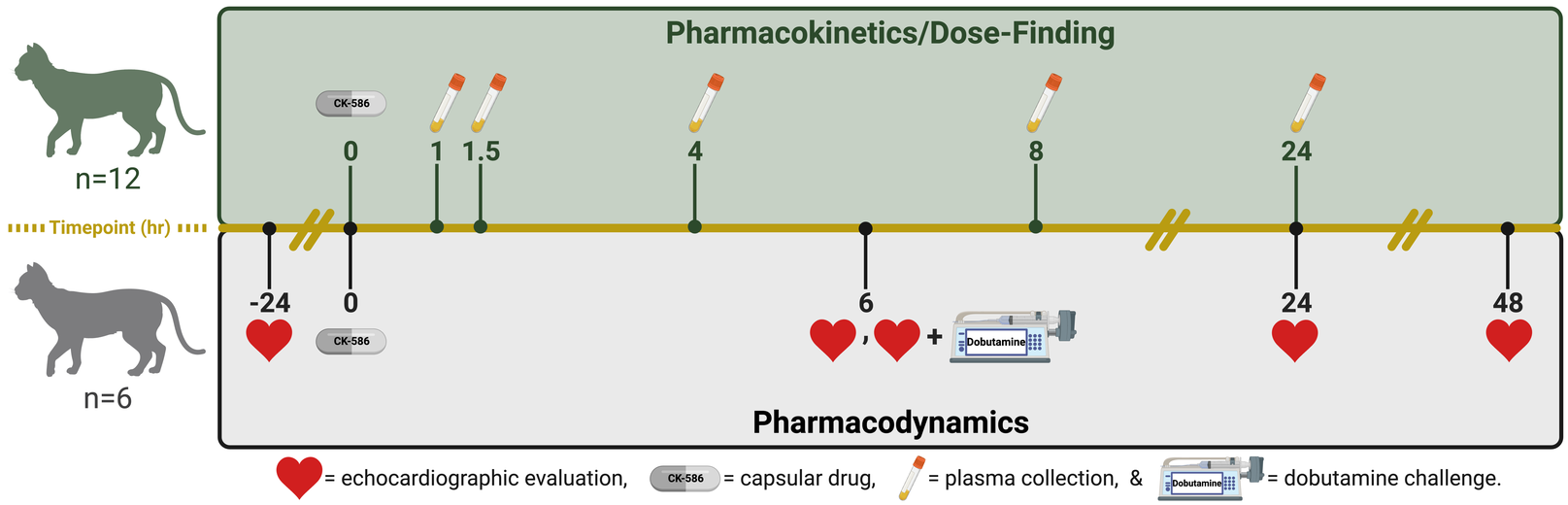


Fig 2. Effect of aficamten in oHCM cats. Changes in percent LV fractional shortening (LV FS%) between cats receiving (**A**) Vehicle, (**B**) 0.3 mg/kg, (**C**) and 1 mg/kg of CK-274. Median is denoted at each timepoint; whiskers represent the interquartile range. The overall *P*-values are denoted at the bottom of each panel. Significant pairwise comparisons are shown with their respective *P*-values.

Aims

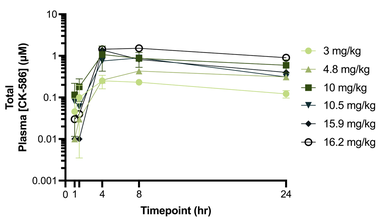
Examine the 24-hour pharmacokinetic and 6-, 24-, and 48-hour pharmacodynamic effects of a novel cardiac myosin inhibitor, CK-4021586 (CK-586), in purpose-bred cats with naturally occurring oHCM.

Methods

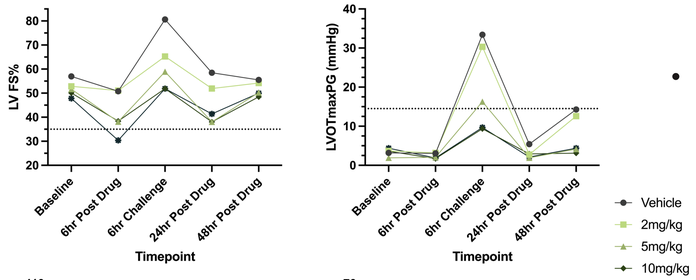


Results

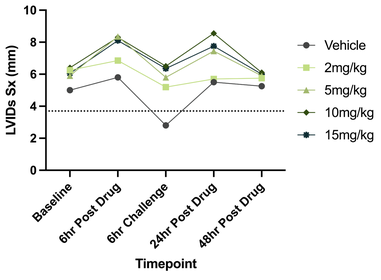
Pharmacokinetics



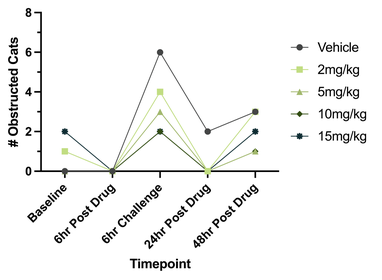
Indices of LV Function



Index of LV Chamber Size



Incidence of Obstruction



- No adverse events were observed in any cats receiving CK-586.
- Treatment with oral CK-586 ameliorated LVOTO in oHCM cats (data represented as medians).

Conclusions

- Single oral CK-586 doses resulted in improved or resolved LVOTO with well-tolerated, dose-dependent, reductions in LV systolic function.
- Peak drug effect was observed at the 6hr post-drug timepoint for the LV FS%, LV EF%, and LVOTmaxPG variables (10 & 15 mg/kg dose).

References

Funding

Cytokinetics® NIH

Conflicts of Interest

D.T.H., A.N.M., B.P.M., and F.I.M. are employees of Cytokinetics Inc. (San Francisco, CA, USA) which served as the Sponsor of this study and were compensated for their work.