Discovery of CK-274: A novel, small molecule, cardiac myosin inhibitor for the treatment of hypertrophic cardiomyopathies (HCM)

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Heart Failure: Many Phenotypes with Unmet Need

Inability to pump an adequate supply of blood to the body

Decreased Cardiac Contractility

Heart Failure with Reduced Ejection Fraction (HFrEF)

Activate *Omecamtiv Mecarbil* (Cardiac)

Genetic Dilated Cardiomyopathy

Pulmonary Hypertension with Right Ventricular Heart Failure

Increased / Preserved Cardiac Contractility

Non-obstructive Hypertrophic Cardiomyopathy (nHCM)

Inhibit CK-274 (Cardiac)

Obstructive Hypertrophic Cardiomyopathy (oHCM)

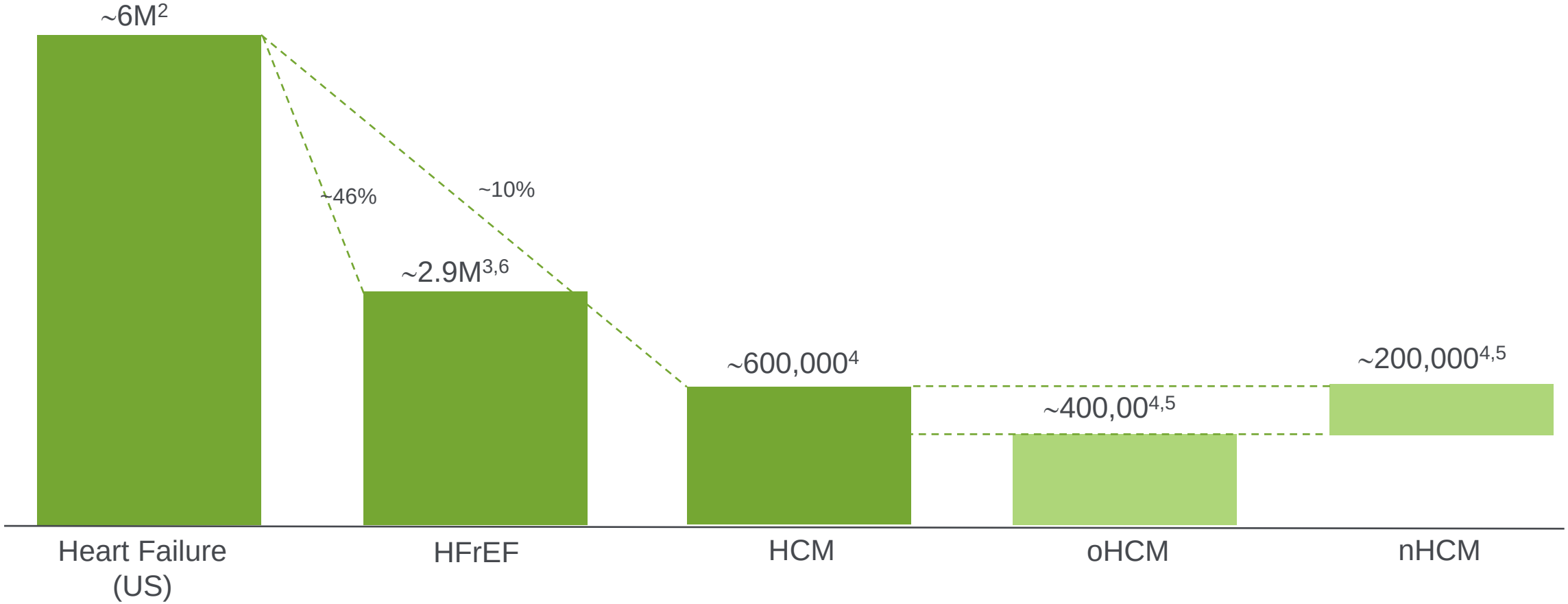
Heart Failure with Preserved Ejection Fraction (certain HFpEF subsets)

CK-274 is an investigational product and has not been approved as safe or effective for any indication

>64 Million People Worldwide[1] and >6 Million Americans With HF[2]

~50% of patients with HF have HFrEF[3]; ~10% of patients have HCM[4]

Prevalence of HFrEF and HCM in the US



HF= heart failure; HFrEF= heart failure with reduced ejection fraction HCM = hypertrophic cardiomyopathy; nHCM = nonobstructive HCM; oHCM = obstructive HCM.

1. James SL, et al. *Lancet*. 2018;392:1789-1858. 2. Benjamin EJ, et al. *Circulation*. 2018;137:e67-e492. 3. Benjamin EJ, et al. *Circulation*. 2019;139:e56-e528. 4. Gersh BJ, et al. *J Am Coll Cardiol*. 2011;58:2703-2738. 5. Hebl VB, et al. *Mayo Clin Proc*. 2016:9:279-287. 6. Shah KS, et al. *J Am Coll Cardiol*. 2017;70:2476-2486.

Significant Unmet Need in HCM

Current therapies do not target underlying disease

HCM is an inherited cardiovascular disease

1 in 500 have genetic mutation[1]

1 in 3200 have HCM[2,3,4]

Subset of patients have progressive symptoms, atrial fibrillation, stroke, sudden death

Surgical intervention not permanent solution

Invasive therapy to reduce septal thickness is effective

Surgical myectomy or percutaneous ablation

Current medical therapy does not target underlying disease

Indirect mechanisms of action with systemic side effects

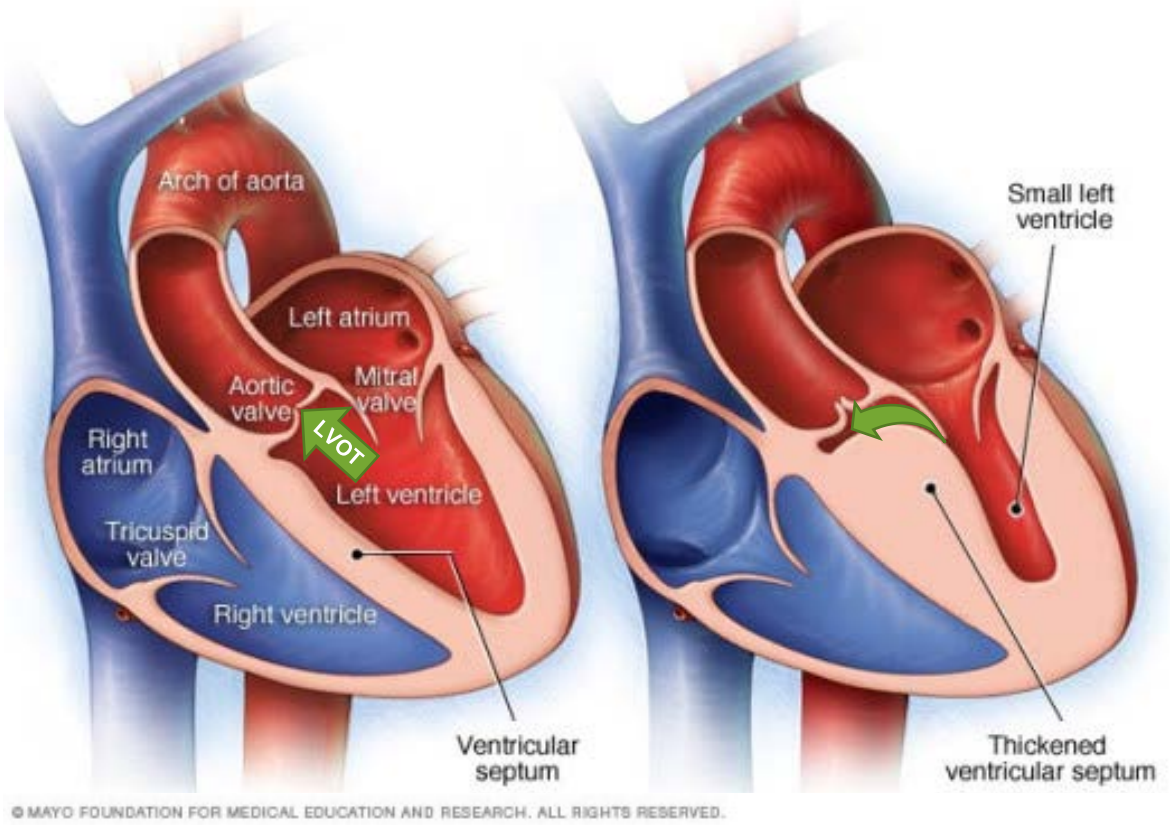
Variable efficacy, often inadequate

1. Maron BJ, et al. *Circulation* 1995;92:785-789.
2. Husser, et al. *PloS one*, 2018; 13:e0196612.
3. Magnusson, et al. *Clinical epidemiology*, 2017; 9, 403-410.
4. Pujades-Rodriguez. el al. *PloS one*, 2018; 13:e0191214.

Obstructive HCM (oHCM):
Left ventricular outflow tract (LVOT) obstruction

Normal heart

oHCM heart



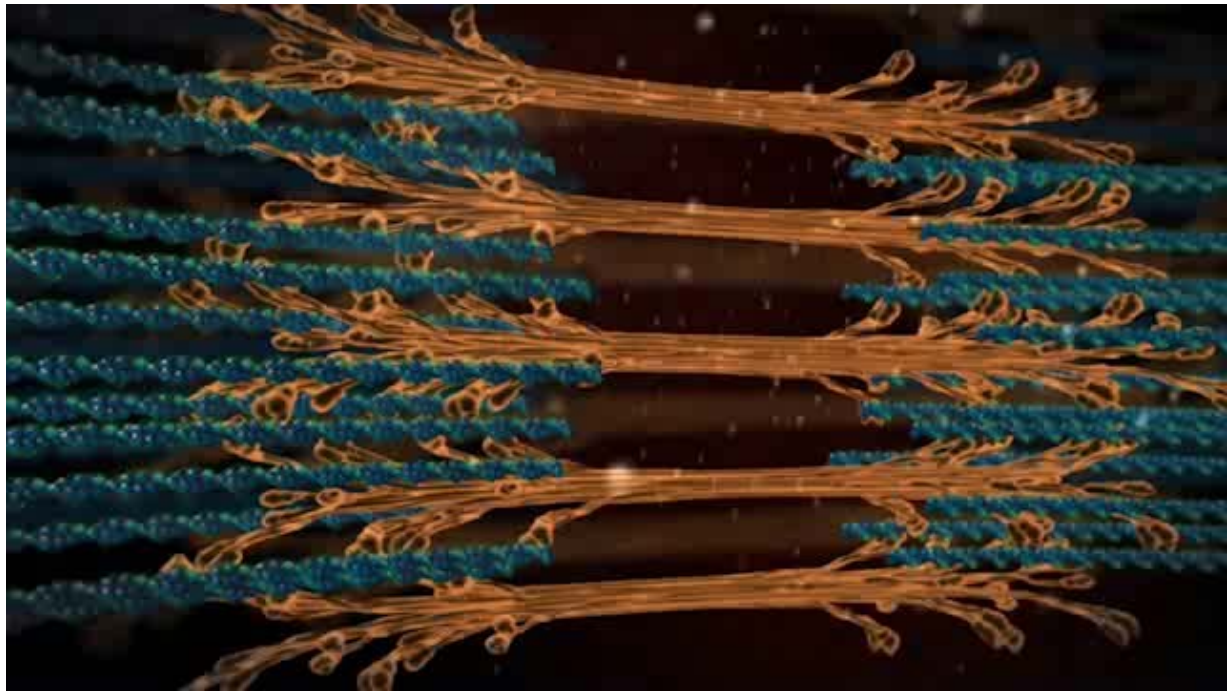
Phenotype of oHCM

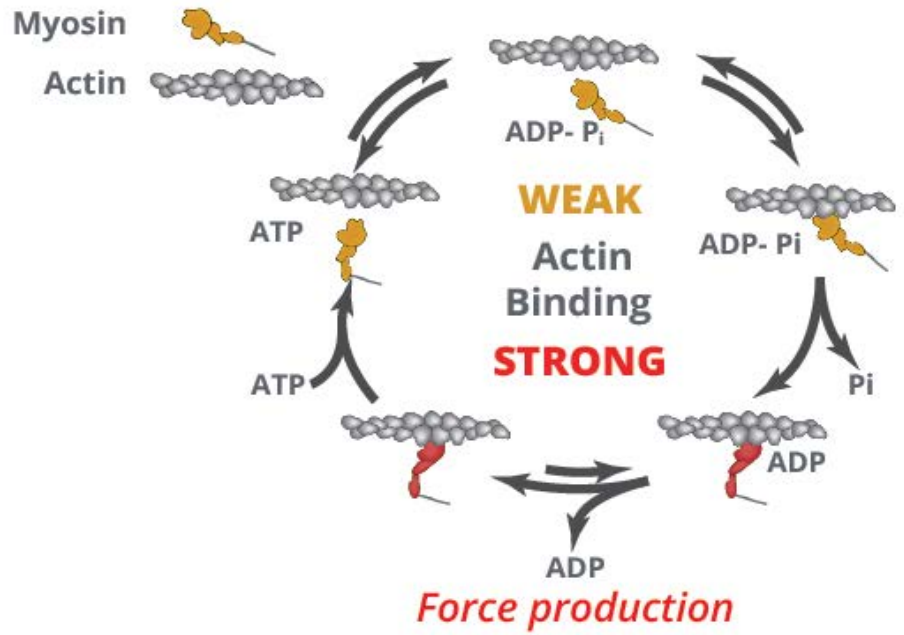
- Thickening of the left ventricular septum
- Narrowing the LV outflow tract
- Creating resistance to blood flow
  - ↑resting LVOT pressure gradient ≥50 mmHg

Diagnosis by echocardiography

Focus on the Sarcomere: Key to Muscle Contractility

Cardiac myosin inhibition may be a viable approach to address hypercontractility





HCM

- Mutation in sarcomere
- Excess myosin heads engage with actin
- Hypercontractility may result in cardiac hypertrophy

Therapeutic Hypothesis

- Reduce myosin head engagement with actin
- Allow the heart muscle to properly relax
- Reduced contractility may reverse hypertrophy

Assay Systems for Muscle Contractility Lead Optimization

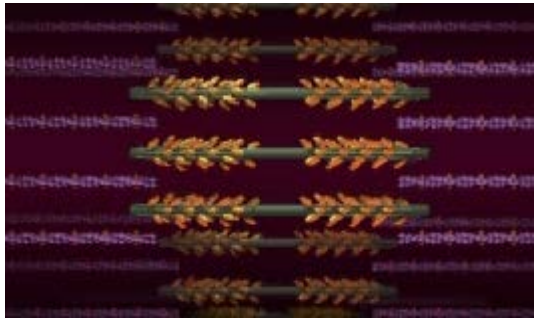
Muscle Contractility

Complexity

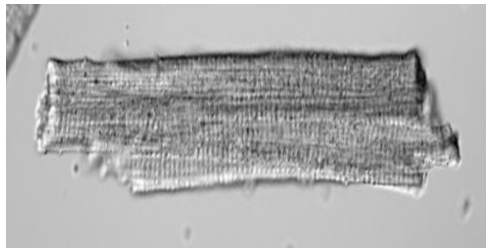
Throughput

Coherence

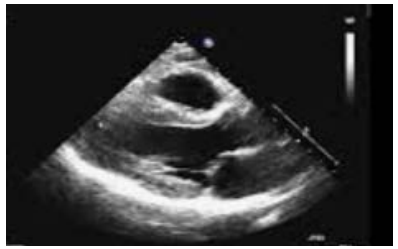
Myofibril suspension
Intact Sarcomere

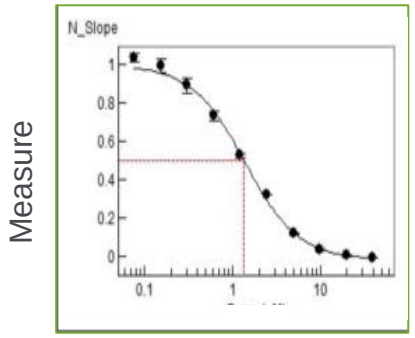


Cardiac Myocyte
Assay in Native Context



Organ and *in vivo*
Functional Outcome





Compound Conc.

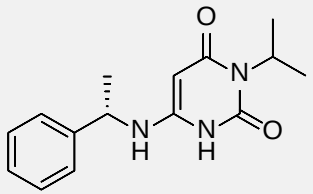
- Potency measures
  - Myofibrils: ATPase inhibition = IC_{50}
  - Cardiac Myocyte: %FS @ conc.
  - Cardiac Myocyte Ca^{2+} transient
  - *In vivo*: Rat echocardiogram = window assessment IC_{50}/IC_{10}*

*IC_{50}/ IC_{10}= conc for 50% reduction in fractional shortening (FS) / conc for 10% reduction in fractional shortening (FS)

A Next-in-Class Cardiac Sarcomere Inhibitor (CSI)

Finding a next-in-class compound to expand the utility of this MOA

First-in-Class CSI inhibitor, *mavacamten*, has a long human $t_{1/2}$



Mavacamten

- Demonstrated clinical benefit in oHCM patients
- Observe CYP3A4 induction (human hepatocytes)[1]
- Exhibits $t_{1/2}$ of 7-9 days in humans[2,3]
  - Reach steady-state around 6 weeks

Origin of Initial Hit

CK compound libraries: 1-7

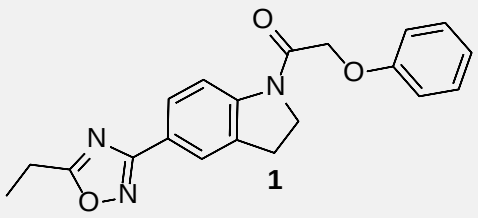
Primary Optimization Objectives

- ✓ Predicted human $t_{1/2}$ for *qd* dosing and reach steady state within 2 weeks
- ✓ No substantial CYP induction or inhibition (human hepatocytes / microsomes)
- ✓ Large therapeutic index *in vivo* with clear PK/PD relationship
  - ✓ Echocardiography to assess the relationship of conc. vs fractional shortening (FS)
  - ✓ Shallow dose response curve *in vivo* with larger PD window (IC_{50}/IC_{10})[4]

CK compound libraries: 8 and beyond

1. MP Grillo, *et.al. Xenobiotica,* 2019; *49*, 718-733; . 2. Myokardia S-1 SEC filling September 28, 2015. 3. SB Heitner, *et.al*. *Ann. Intern. Med.* 2019, Jun4; *170 (11*), 741-748.
4. IC_{50}/ IC_{10}= conc. 50% reduction in fractional shortening (FS) / conc. 10% reduction in fractional shortening (FS) measured in rat models

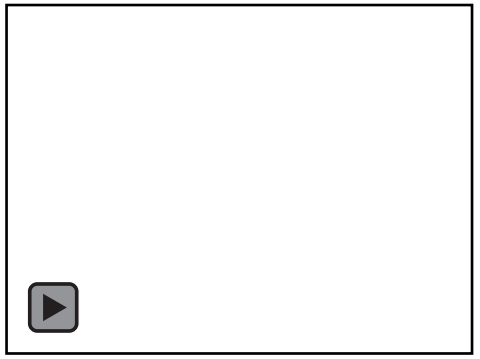
Screening Hit 1: Properties and Direct Inhibition of Cardiomyocyte Contractility

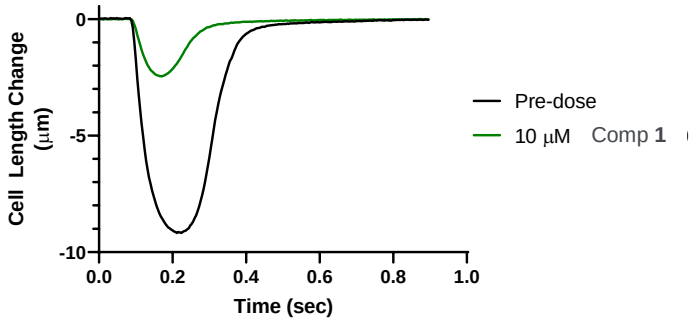


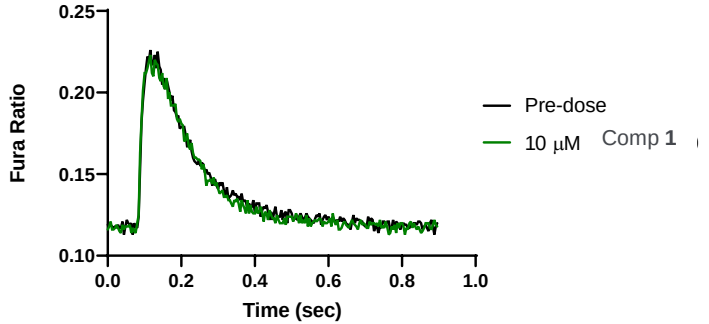
HTS hit	
CDMF[1] Ca75 IC_{50}	2.7 µM
SMM[2] IC_{50}	> 39 uM
LE[3]	0.28
cLogP[4]	3.5
ER[5] (r); ER (h)	>0.69; >0.76
MW	349

- Singleton hit
  - Reasonable potency and ligand efficiency
  - "Drug-Like" cLogP and MW
  - No SMM inhibition observed
- Metabolic hot spots to address
  - Phenyl rings and the glycolic linker
  - Indoline

Adult Rat Ventricular Cardiomyocyte





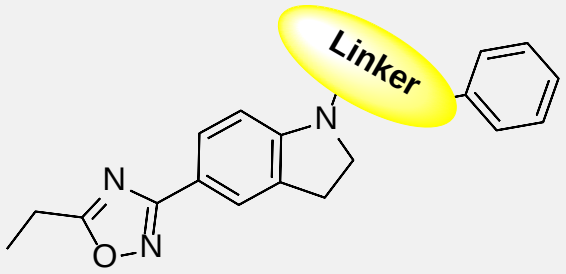


❖ Strong contractility reduction observed without affecting the Ca^{2+} concentration

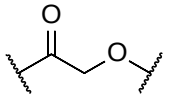
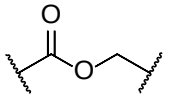
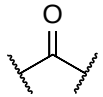
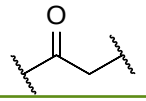
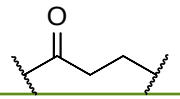
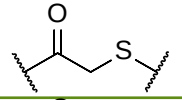
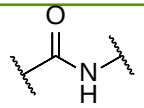
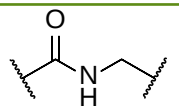
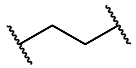
1. CDMF Ca75: cardiac myofibril ATPase assay with Ca concentration @ 75% of the maximum contraction
2. SMM: smooth muscle myosin
3. LE: ligand efficiency based on number of heavy atoms
4. cLogP: determined using ACD calculator
5. ER microsomal extraction ratio (ER = (Clint)/(Clint + hepatic blood flow), h=human r=rat

Linker Optimization Challenging

Hints of potentially alternative linker



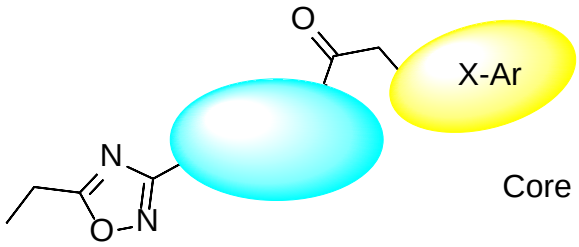
- Glycol linker replacement exercise:
  - Used IC_{15} to better assess SAR
  - Failed to retain potency in most cases
- Only phenyl acetamide linker (**4**) retained some potency and solubility

Cmpd	Linker	CDMF IC_{50} (µM)	CDMF IC_{15} (µM)	cLogP
1		2.7	0.9	3.5
2		>39*	1.3	4.7
3		>39	>39	3.2
4		19.1	3.5	4.1
5		>39	>39	4.6
6		>39	>39	4.6
7		>39	>39	3.2
8		>39	>39	3.2
9		>39*	3.4	4.9

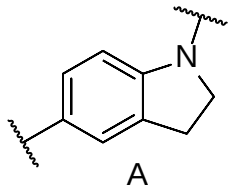
*Potential issue with solubility

Indoline and Aryl Substituent Preferences

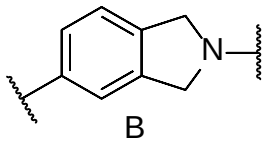
Hints for achieving metabolic stability



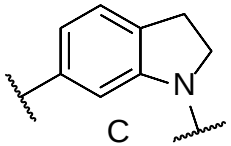
Core



A



B



C

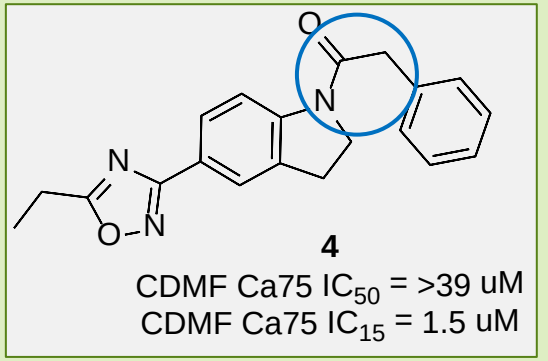
Cmpd	Core	X-Ar	CDMF IC_{50} (μM)	CDMF IC_{15} (μM)	ER[2] (r)	ER[2] (h)	cLogP	fb[1] (r,%)
1	A	O-Ph	2.7	0.9	>0.69	>0.76	3.5	99
4	A	-Ph	19.1	3.5			4.1	98
10	B	-Ph	>39	15.9			4.1	--
11	C	-Ph	>39	>39			4.1	--
12	A	-2-Py	>39	>39	>0.69	<0.34	2.6	88
13	A	-3-Py	>39	>39	>0.69	0.37	2.6	89
14	A	-4-Py	>39	7.2	>0.69	0.36	2.6	84

- Other indoline orientations
  - – Potency attenuation
- Pyridine acetamide
  - ✓ Lower cLogP
  - ✓ Reduced microsomal turnover
  - ✓ Improved plasma free fraction
  - – Some potency preservation with 4-pyridine

1. fb: Plasma protein fraction bound as measured by equilibrium dialysis, r = rat
2. ER: microsomal extraction ratio (ER = (Clint)/(Clint + hepatic blood flow), h=human r=rat

From misfit to the right fit

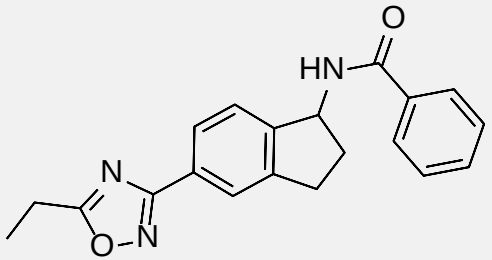
Reframe Presentation of Phenyl Acetic Acid moiety



4

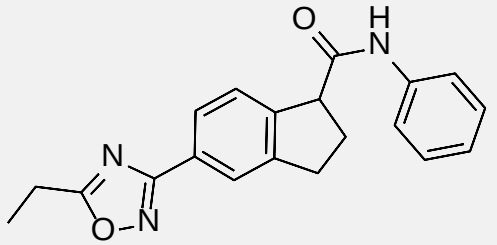
CDMF Ca75 IC_{50} = >39 uM

CDMF Ca75 IC_{15} = 1.5 uM



15

CDMF CA75 IC_{50} 1.0 uM



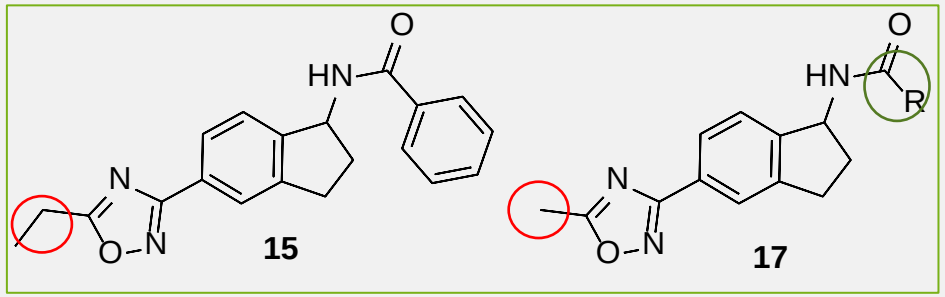
16

CDMF CA75 IC_{50} 6.1 uM

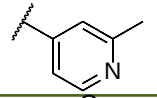
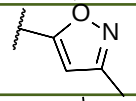
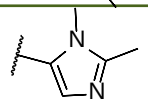
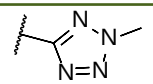
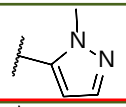
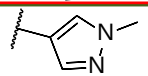
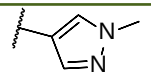
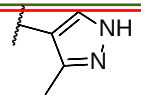
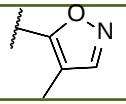
- Selected compound **15** to follow up
  - ✓ Greater potency improvement
  - ✓ Removal of aniline moiety
  - ✓ Chiral amino indane obtainable

Promising Direction in Replacing Phenyl

Good calculated properties and liver microsomal stability with heterocyclic amides



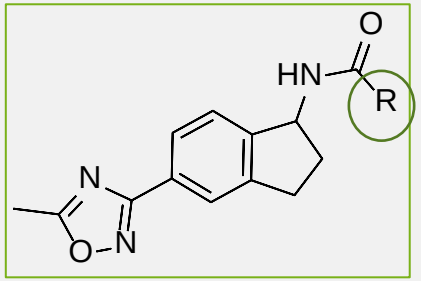
- RHS phenyl replacement:
  - ↑ plasma fraction unbound
  - ↓ microsomal turnover
  - ↓ cLogP
  - ↔ potency in desired range
- 10X Eudysmic ratio observed

Cmpd	R	CDMF IC_{50} (μM)	ER^2 (r)	ER^2 (h)	cLogP	fb^1 (r,%)
15	Ph	1.0	>0.69	>0.76	3.7	98
17	Ph	1.9	>0.69	0.55	3.2	96
18		7.1	<0.27	<0.34	2.4	90
19		8.1	0.47	<0.34	1.3	93
20		7.6	<0.27	<0.34	1.7	92
21		5.1	<0.27	<0.34	0.9	81
22		3.0	>0.69	0.39	1.5	91
23[3]		4.4	<0.27	<0.34	1.5	94
24[4]		>39	<0.27	<0.34	1.5	85
25		4.8	0.65	<0.34	2.1	91
26		2.5	0.46	<0.34	1.3	94

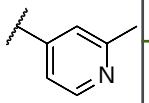
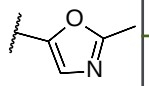
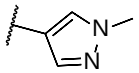
1. fb: Plasma protein fraction bound as measured by equilibrium dialysis, r = rat
2. ER: microsomal extraction ratio (ER = (Clint)/(Clint +hepatic blood flow), h=human r=rat
3. Compound **23** prepared as a single isomer as *R*-configuration.
4. Compound **24** prepared as a single isomer as *S*-configuration.

Subtle Differences in ADME Properties Linked to Stereochemistry

Better microsomal stability with preferred isomer



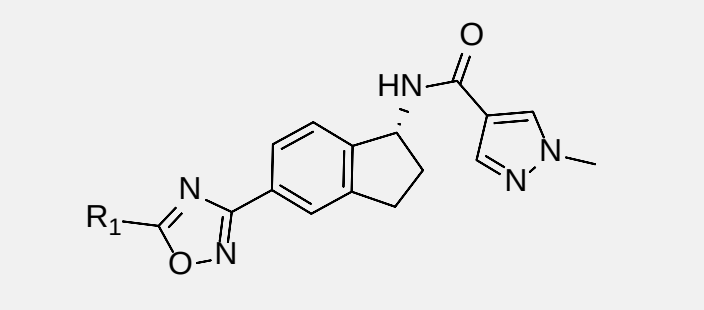
- Stereochemical preference
  - Preferred *R*-isomer confirmed through synthesis
  - *S*-isomer inactive up to top concentration (40 uM)
  - Eudysmic ratio is >40x
  - Generally greater microsomal stability *in vitro* with *R* isomer

Cmpd	Chirality	R	CDMF IC_{50} (µM)	CDMF IC_{15} (µM)	ER^2 (r)	ER^2 (h)	cLogP	fb^1 (r,%)
27	*R*		3.5	1.0	<0.27	0.37	2.4	92
28	*S*		>39	>39	0.31	0.55	2.4	90
29	*R*		4.9	1.4	<0.27	<0.34	0.7	75
30	*S*		>39	>39	0.42	<0.34	0.7	79
23	*R*		4.4	1.2	<0.27	<0.34	1.5	94
24	*S*		>39	>39	<0.27	<0.34	1.5	85

1. fb: Plasma protein fraction bound as measured by equilibrium dialysis, r = rat
2. ER: microsomal extraction ratio (ER = (Clint)/(Clint + hepatic blood flow), h=human r=rat

Oxadiazole Substituent SAR

Et-oxadiazole the best balance in potency, P-chem and ADME properties



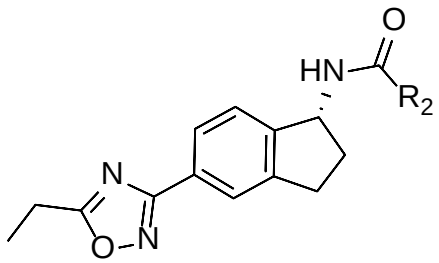
- R1 preference:
  - Most small substituents tolerated
    - Et>cPr=diFMe>iPr=Me>>H
  - Polar groups attenuate potency
  - Metabolic soft spot α position of oxadiazole ring
  - diFMe and cPr confer most metabolic stability (hepatocyte data not shown)
  - Et substitution best balance in potency, P-chem and ADME properties

Cmpd	R1	CDMF IC_{50} (μM)	ER[2] (r)	ER[2] (h)	cLogP	fb[1] (r / h %)	Sol pH 6.8 (uM)
31	H	>39	-	-	1.0	-/-	-
29	Me	4.4	<0.27	<0.34	1.5	93/86	86
32	CD_3	5.4	<0.27	<0.34	1.5	90/-	100
33	Et	1.4	<0.27	<0.34	2.1	96/91	97
34	cPr	2.7	-	-	1.9	96/94	33
35	iPr	4.1	-	-	2.4	98/90	-
36	diFMe	2.4	<0.27	<0.34	2.0	98/94	37
37	cBu	3.2	-	-	2.5	-/-	14
38	$MeOCH_2$	6.8	<0.27	<0.34	1.4	91/88	63
39	$MeOCH_2CH_2$	>39	-	-	1.5	-/-	-
40	$HOCH_2CH_2$	>39	-	-	0.9	-/-	-

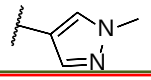
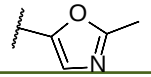
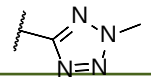
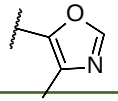
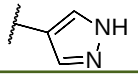
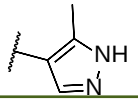
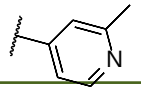
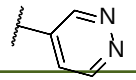
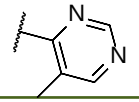
1. fb: Plasma protein fraction bound as measured by equilibrium dialysis, r = rat
2. ER: microsomal extraction ratio (ER = (Clint)/(Clint + hepatic blood flow), h=human r=rat

Fine Tuning Pharmacokinetic Properties and Potency

Pyrazole stands out with balance of in vitro and in vivo PK properties



- R2 modification:
  - Tolerance for wide range of 5-and 6-membered heterocycles
  - Various Cl, $t_{1/2}$, and %F observed
  - Cmpd **33** has the best overall balance in PK profile

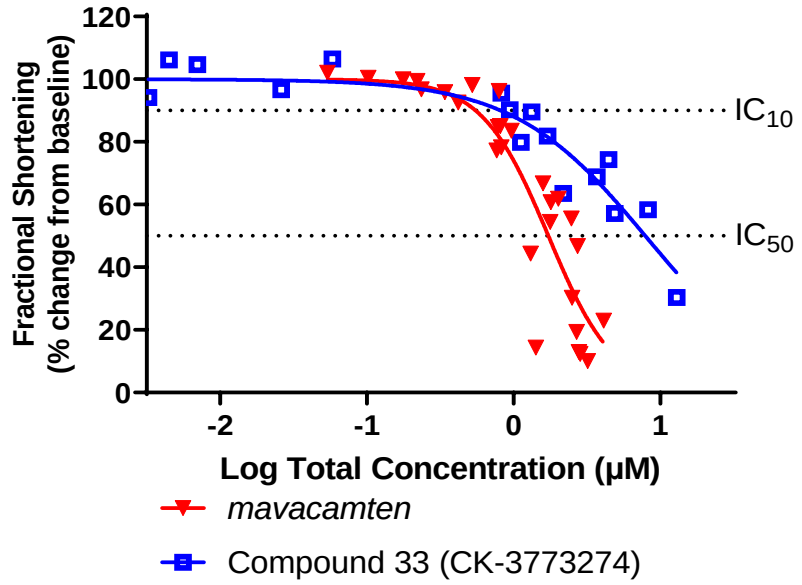
Cmpd	R2	CDMF IC_{50} (μM)	Rat, Cl (mL/min/kg)	Rat, $t_{1/2}$ (hour)	Rat, %F	ER[2] (r)	ER[2] (h)	fb[1] (r / h%)
33		1.4	3.1	2.5	65	<0.27	<0.34	98 / 90
41		1.7	21.4	4.1	13	<0.27	<0.34	95 / 82
42		0.9	19.5	5.9	60	<0.27	<0.34	89 / 71
43		0.8	39.7	14.7	0	0.69	<0.34	98 / 90
44		1.1	62.5	1.4	9.5	0.54	<0.34	80 / 80
45		1.2	120.5	8.4	3.7	0.69	<0.34	- / 15
46		1.2	13.0	3.5	32	0.3	<0.34	98 / 92
47		1.2	43.8	6.5	16	-	<0.34	- / 69
48		1.8	20.2	5.9	26	0.3	<0.34	95 / 91

1. fb: Plasma protein fraction bound as measured by equilibrium dialysis, r=rat h=human
2. ER: microsomal extraction ratio (ER = (Clint)/(Clint + hepatic blood flow), r=rat h=human

Efficacy Demonstrated with *in vivo* Echocardiography Measurement

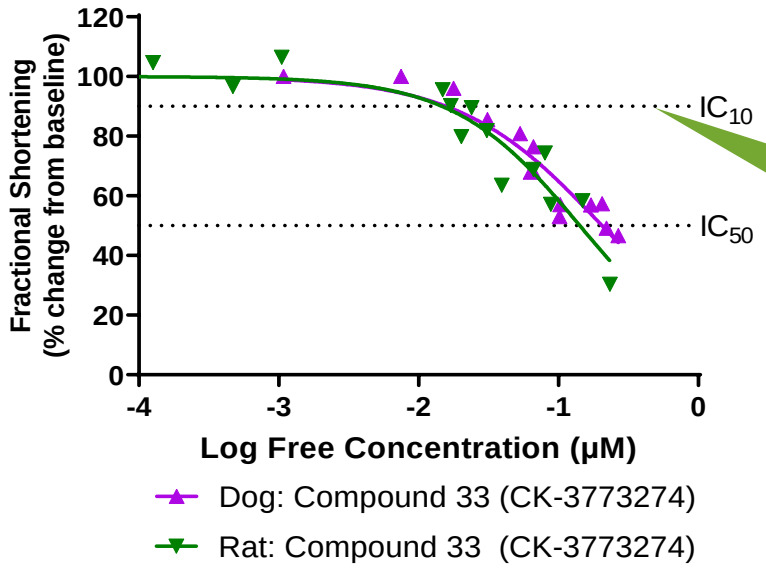
Wide PD Window in Healthy Rat and Dog Models with Compound 33 (CK-3773274)

Rat Model: Conc. vs. FS



	IC_{10} (µM)$_{total}$ *	IC_{50} (µM) $_{total}$*	IC_{50}/IC_{10}*
mavacamten	0.55	1.73	3.1
Cmpd 33	0.83	7.98	9.6

Rat vs Dog Model: Conc. vs. FS



	IC_{10} (µM) $_{unbound}$*	IC_{50} (µM) $_{unbound}$*	IC_{50}/IC_{10}*
Dog	0.016	0.205	12.8
Rat	0.015	0.142	9.5

* IC_{50}/ IC_{10}: Pooled concentration for 50%/10% reduction of FS (fractional shortening) in normal Sprague Dawley rat or Beagle Dog

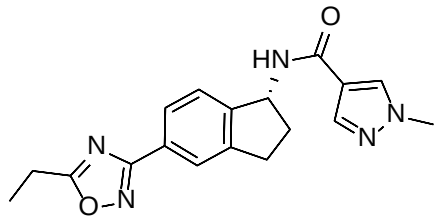
Shallow exposure-response relationship of **CK-274** in rats and dogs

CK-3773274 Accomplished Optimization Objectives

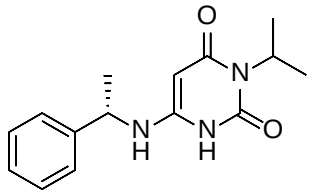
Objectives:

- ✓ Predicted human $t_{1/2}$ for *qd* dosing and reach steady state within 2 weeks
- ✓ No substantial CYP induction or inhibition (human hepatocytes / microsomes)
- ✓ Large therapeutic index across pre-clinical species with clear PK/PD relationship

	Assay	Parameters	
		Mavacamten	**CK-3773274**
***in vitro* pharmacology**	Bovine Cardiac Myofibril Ca75 IC_{50} (μM)	0.60 (0.54-0.67)[1]	1.26 (1.20-1.33)[1,2]
	Rat Cardiac Myocyte IC_{50} or (%FS @ (μM))	0.18 μM[3]	(33 ± 5.8 @ 5)[4]
***in vivo* pharmacology**	IC_{10} (μM)[5]	0.5	0.8
	IC_{50} / IC_{10}[5]	3.1	9.6
Human PK projection	Human $t_{1/2}$ projected (days) (Human $t_{1/2}$ actual)	9[8] (7-9)[6,7]	2.8[10] (3.4)[9]
CYP Profile	CYP450 IC_{50} (μM) (Time-dependent inhibition)	IC_{50} > 30[8,11]	IC_{50} > 30[11] (None)
	CYP450 Induction, EC_{50} (μM)[12]	2.2 ± 0.4 / CYP3A4[8] 5.1 ± 0.2 / CYP2B6[8]	No substantial induction up to 25 μM



CK-3773274

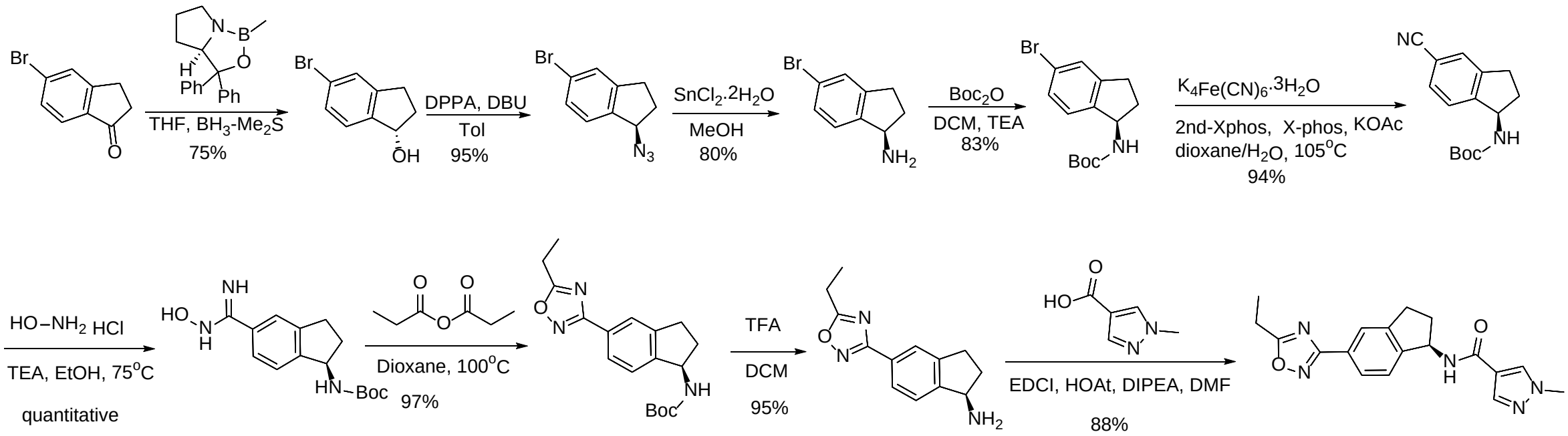


Mavacamten

1. Cytokinetics data on file. Bovine cardiac myofibrils assayed at 75% of max Ca-dependent activation. Mean values (95% confidence intervals). 2. JJ Hartman, *et al.* Poster# 2912 presented at 64th Biophysical Society Annual Meeting, February 19th, 2020. 3. EM Green, *et.al. Science*, 2016, *351 (6273),* 617-612. 4. WO 2019144041; ± equal to standard error of measurement. 5. Compounds were dosed orally to Sprague Dawley rats and compound effect assessed by echocardiography. A reduction in a measure of cardiac function (fractional shortening [FS]) was quantitated alongside plasma concentrations to calculate the inhibitory concentration at a 10% (IC_{10}) and 50% (IC_{50}) reduction in FS, IC_{50}/ IC_{10} 6. Myokardia S-1 SEC filling September 28, 2015. 7. SB Heitner, *et.al. Ann. Intern. Med.* 2019, Jun4; *170 (11*), 741-748. 8. MP Grillo, *et.al. Xenobiotica* 2019, *49,* 718-733. 9. LA Robertson, *et al.* Poster #210 presented at the 23rd HFSA Annual Scientific Meeting, September 13–16, 2019, Philadelphia, PA, USA. 10. P Cremin, *et al.* Poster # 887215 presented at AAPS annual meeting, Atlanta, Georgia, October 28-November 5, 2021. 11. *Mavacamten* include CYPs 1A2, 2B6, 2C9, 2C19, 2D6, 3A4 and 3A5; CK-274 include 1A2, 2B6, 2C8, 2C9, 2C19, 2D6, 3A4 12. The potential to induce CYP1A2, CYP2B6 and CYP3A4 was tested *in vitro* in cryopreserved palatable human primary hepatocytes from three separate donors using mRNA level as the end point.

Medicinal Chemistry Route for Synthesis of CK-3773274

Route enables scale up in medicinal chemistry lab

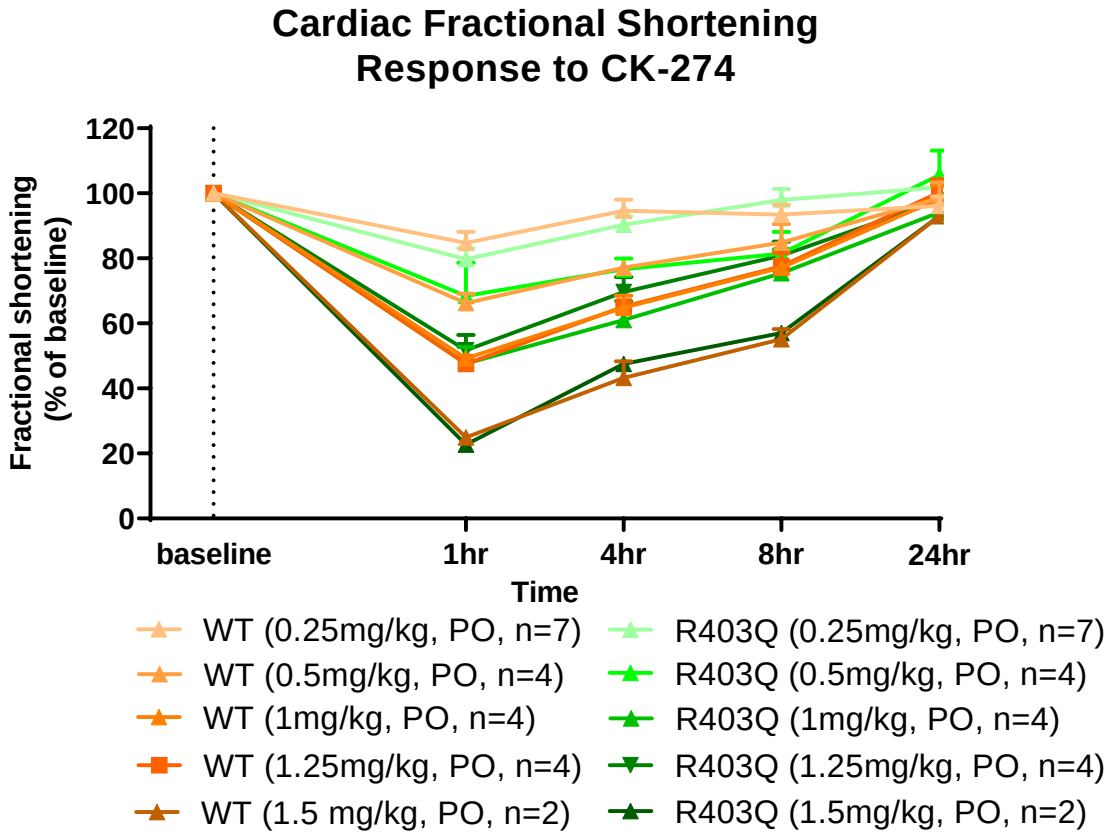


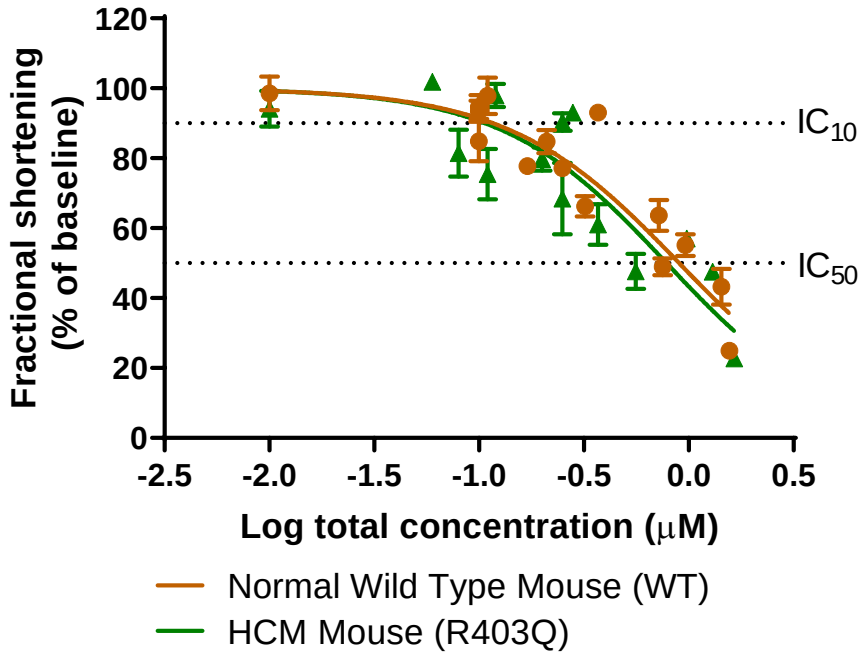
- 9 Steps with 36% overall yield; >500 g can be produced with this route
- (*1R*)-5-bromo-2,3-dihydro-1*H*-inden-1-amine is commercially available
- The chiral amine was produced from indanone through chiral CBS reduction and few transformation steps to obtain the amine in large scale (>500g)
- The de-Boc step with HCl (4N/dioxane) generated a solid HCl salt with quantitative yield

CK-3773274 Has a Similar PD Window in a Genetic HCM Mouse Model

CK-3773274 decreased fractional shortening in a dose-related fashion in WT and R403Q HCM mice

- *A dose of 0.25-1.5 mg/kg is sufficient to determine an IC_{50}/IC_{10} window*
- *The fractional shortening response to CK-274 is the same in WT and R403Q mice*

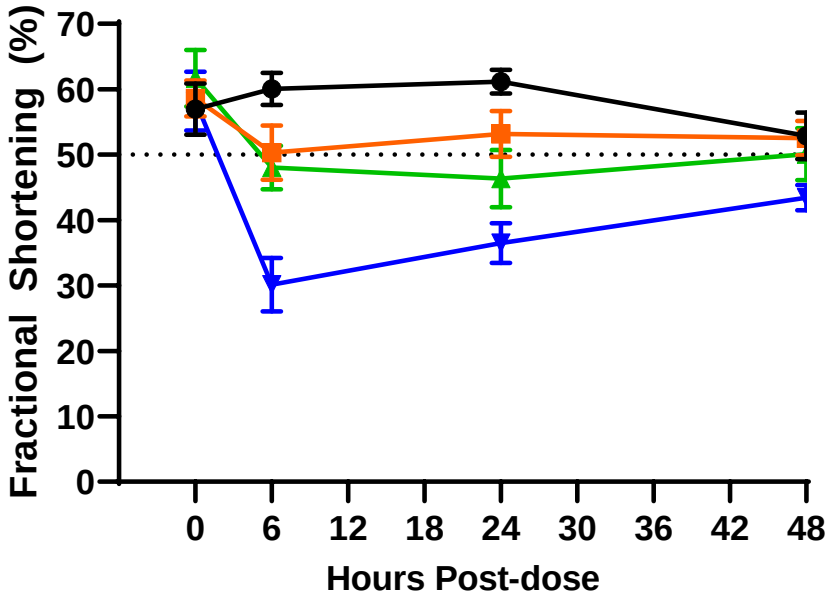


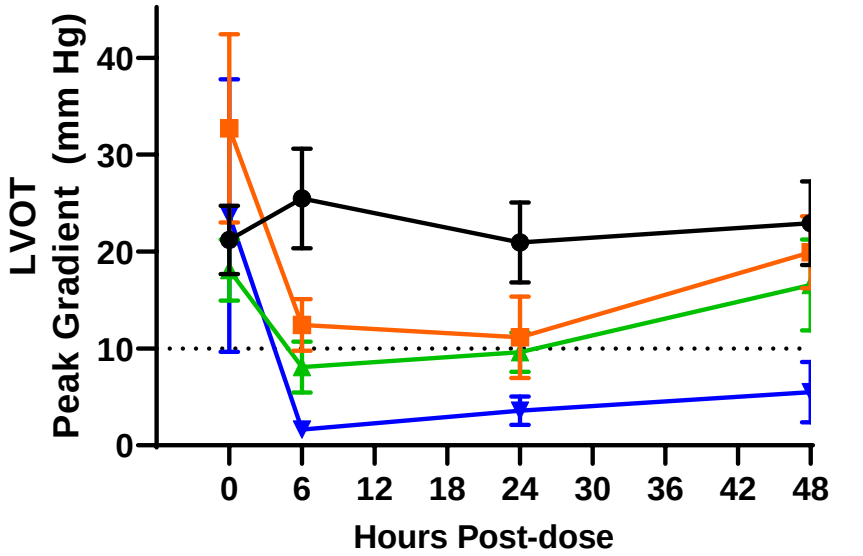


	IC_{10} (μM)	IC_{50} (μM)	IC_{50}/IC_{10}
WT	0.12	0.90	7.5
HCM (R403Q)	0.11	0.78	7.1

CK-3773274 Reduced FS* and LVOT* Obstruction in a Dose-dependent Manner in A31P HCM Maine Coon Cats[1]

- A31P HCM cats exhibit fractional shortening (> 50%) and LVOT peak gradient (>10 mm Hg) values that are above the normal range in cats





UC Davis / U Arizona

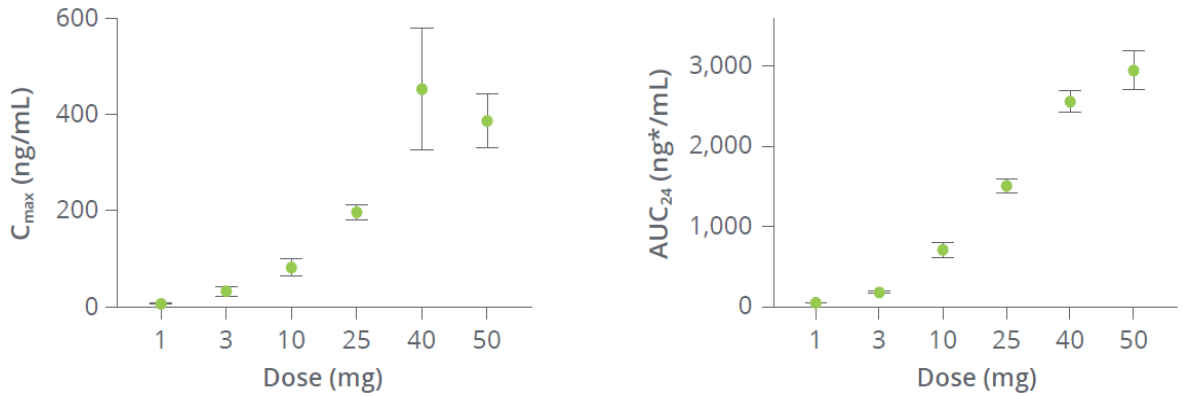
* FS= fractional shortening; LVOT left ventricular outflow tract

1. MS Oldach, et al. Poster presented at AHA Scientific Sessions 2020, Virtual Congress November 13-17th, 2020.

SAD and MAD Pharmacokinetics of CK-3773274 in Healthy Volunteers

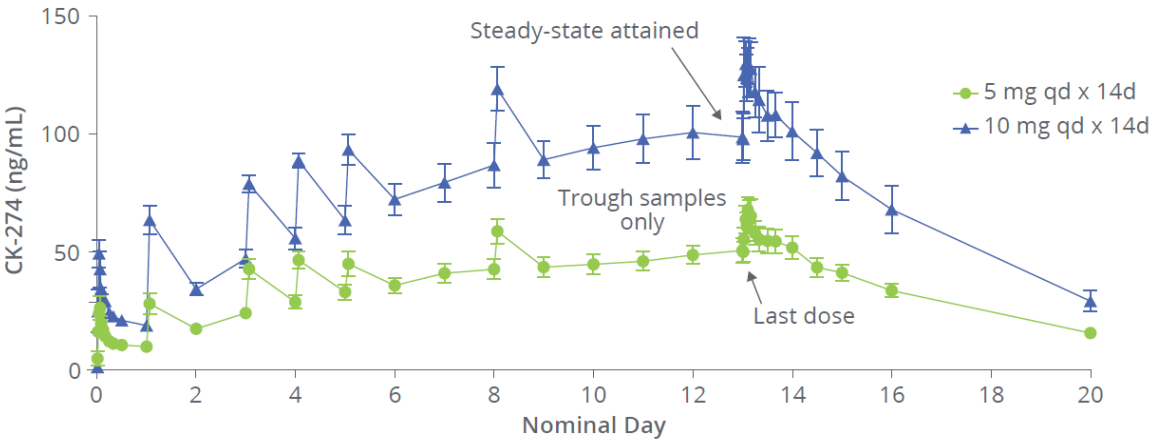
CK-274 demonstrated dose linearity and reached steady upon two weeks dosing[1]

SAD Pharmacokinetics Are Generally Dose Proportional



Data points represent mean ± standard error of the mean.
Cmax, maximum drug plasma concentration; AUC, area under the plasma concentration curve; SAD, single ascending dose.

Steady-state Appears Evident After 14 Days of Dosing



Data points represent mean ± standard error of the mean.
d, day; qd, once daily.

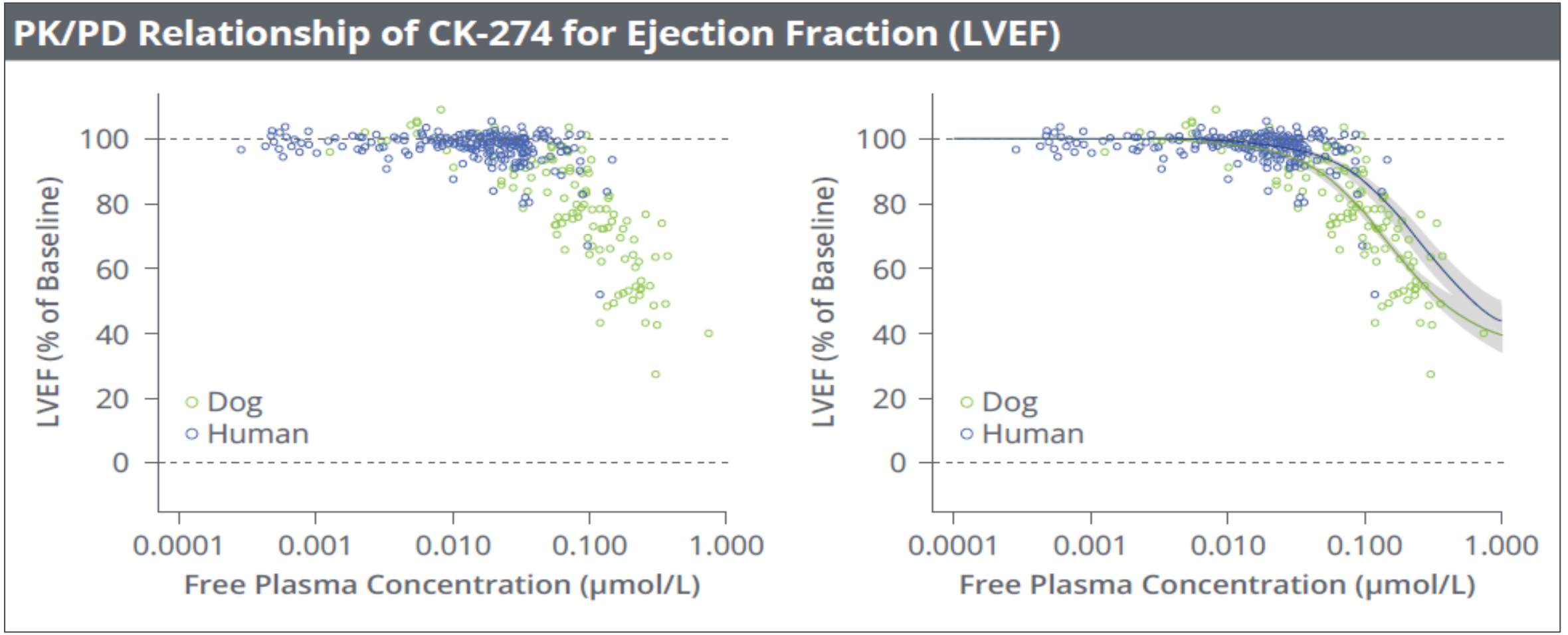
- ✓ CK-274 was safe and well tolerated in healthy participants
- ✓ No SAEs and no clinically meaningful changes in vital signs, ECGs, or laboratory tests
- ✓ Pharmacokinetics (C_{max} and AUC_{24}) were generally dose linear

- ✓ Steady-state reached after 14 days of daily dosing

1. LA Robertson, et al. Poster #210 presented at the 23rd HFSA Annual Scientific Meeting, September 13–16, 2019, Philadelphia, PA, USA.

PK-PD Relationship of CK-3773274 for LVEF in Healthy Volunteers

Shallow exposure-response relationship consistent with pre-clinical species[1]



The shallow exposure-response relationship observed preclinically appears to translate to humans and thereby may enable flexible dose optimization in humans

1. LA Robertson, et al. Poster #210 presented at the 23rd HFSA Annual Scientific Meeting, September 13–16, 2019, Philadelphia, PA, USA.

Conclusion and Summary

- Our goal to provide a next-in-class cardiac sarcomere inhibitor was met
  - *Optimized a unique chiral NCE from singleton hit*
  - *Observed shallow exposure-response relationship in pre-clinical species (rat and dog) and in humans*
  - *Presented favorable ADME properties with no CYP induction or inhibition*
  - *Presented no notable off targets effects with in vitro safety pharmacology screening*

- Human clinical trial on CK-3773274
  - *Results in First-in-Human study presented at HFSA 2019*
  - *These Phase 1 data support progression of CK-274 to a placebo-controlled, double-blind Phase 2*
  - *Phase 2 trial, REDWOOD-HCM, is fully enrolled and the result will be available in mid-2021*
    - *Interim analysis of cohort 1 reported in December 2020*
      - ✓ *substantial reduction in the average resting left ventricular outflow tract gradient (LVOT-G)*
      - ✓ *clinically relevant decreases in pressure gradients were achieved with only modest decreases in average left ventricular ejection fraction (LVEF)*
      - ✓ *no dose interruptions due to LVEF falling below 50%, the prespecified safety threshold*
      - ✓ *Pharmacokinetic data were similar to those observed in Phase 1*

Acknowledgements

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Grace Chuang
Kevin Lau
Mark VanderWal
Wenyue Wang

DMPK

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Jeanelle Zamora
Donghong Xu

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Khanha Taheri
Preeti Paliwal
Andre Derosier
Ken Lee

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Darren Hwee
Julie Ryans
Yangsong Wu
Jingying Wang
Xihui Xu
Eva Chin

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Clinical Team

Laura Robertson
Edward Robbie

Collaborators

UC Davis

Maureen Oldach
Eric Ontiveros
Samantha Fousse
Carina Gozalez
Joshua Stern

U Arizona

Samantha Harris

And patients inspire us to do what we do!