Cytokinetics

EMPOWERING

MUSCLE

EMPOWERING

LIVES

Forward Looking Statements

This Presentation contains forward-looking statements for purposes of the Private Securities Litigation Reform Act of 1995 (the "Act"). Cytokinetics disclaims any intent or obligation to update these forward-looking statements, and claims the protection of the Act's Safe Harbor for forward-looking statements. Examples of such statements include, but are not limited to, statements relating to Cytokinetics' and its partners' research and development activities; the design, timing, results, significance and utility of preclinical study results, including Cytokinetics' expectations regarding the timing or results from its clinical trials of *reldesemtiv*, enrollment of patients in GALACTIC-HF and pipeline expansion in 2018; and the properties and potential benefits of *reldesemtiv* and Cytokinetics' other drug candidates. Such statements are based on management's current expectations; but actual results may differ materially due to various risks and uncertainties, including, but not limited to, potential difficulties or delays in the development, testing, regulatory approvals for trial commencement, progression or product sale or manufacturing, or production of Cytokinetics' drug candidates that could slow or prevent clinical development or product approval, including risks that current and past results of clinical trials or preclinical studies may not be indicative of future clinical trial results, patient enrollment for or conduct of clinical trials may be difficult or delayed, Cytokinetics' drug candidates may have adverse side effects or inadequate therapeutic efficacy, the FDA or foreign regulatory agencies may delay or limit Cytokinetics' or its partners' ability to conduct clinical trials, and Cytokinetics may be unable to obtain or maintain patent or trade secret protection for its intellectual property; Astellas' or Amgen's decisions with respect to the design, initiation, conduct, timing and continuation of development activities for *reldesemtiv* or *omecamtiv mecarbil*, respectively; Cytokinetics may incur unanticipated research, development and other costs or be unable to obtain financing necessary to conduct development of its products; standards of care may change, rendering Cytokinetics' drug candidates obsolete; competitive products or alternative therapies may be developed by others for the treatment of indications Cytokinetics' drug candidates and potential drug candidates may target; and risks and uncertainties relating to the timing and receipt of payments from its partners, including milestones and royalties on future potential product sales under Cytokinetics' collaboration agreements with such partners. For further information regarding these and other risks related to Cytokinetics' business, investors should consult Cytokinetics' filings with the Securities and Exchange Commission.

Our Mission

We are developing muscle biology-directed potential medicines to improve the healthspan of people with devastating diseases of impaired muscle function and conditions of muscle weakness associated with aging

Agenda & Speakers

Muscle Forward: Cytokinetics R&D Day		
8:30 – 8:45	**Opening Remarks**	Robert Blum
8:45 – 9:00	**From Concept to Clinic**	Fady Malik, MD, PhD
Skeletal Muscle Program		
9:00 – 9:30	**Program Overview**	Andrew Wolff, M.D.
9:30 – 10:00	**The Promise of FSTAs in Neuromuscular Disease** *Panel Discussion*	John Day, M.D. (via video) Jinsy Andrews, MD, MSc Jackie Montes, PT, EdD, NCS
10:00 – 10:15	*Break*	
Cardiac Muscle Program		
10:15 – 10:45	**Program Overview**	Fady Malik, MD, PhD
10:45 – 11:05	**AMG 594: Cardiac Troponin Activator**	Brad Morgan, PhD Whit Tingley, MD, PhD
11:05 – 11:45	**CK-274: Cardiac Myosin Inhibitor**	Brad Morgan, PhD Whit Tingley, MD, PhD
11:45 – 12:15	**A New Generation of Cardiovascular Therapies** *Panel Discussion*	John Teerlink, MD Greg Lewis, MD
12:15 – 12:30	**Summary & The Look Ahead**	Robert Blum
12:30 – 1:30	*Meet & Greet*	

Cytokinetics Leadership Team

ROBERT BLUM

President and Chief Executive Officer

FADY MALIK, MD, PHD

Executive Vice President, Research and Development

ANDREW WOLFF, MD

Senior Vice President, Chief Medical Officer

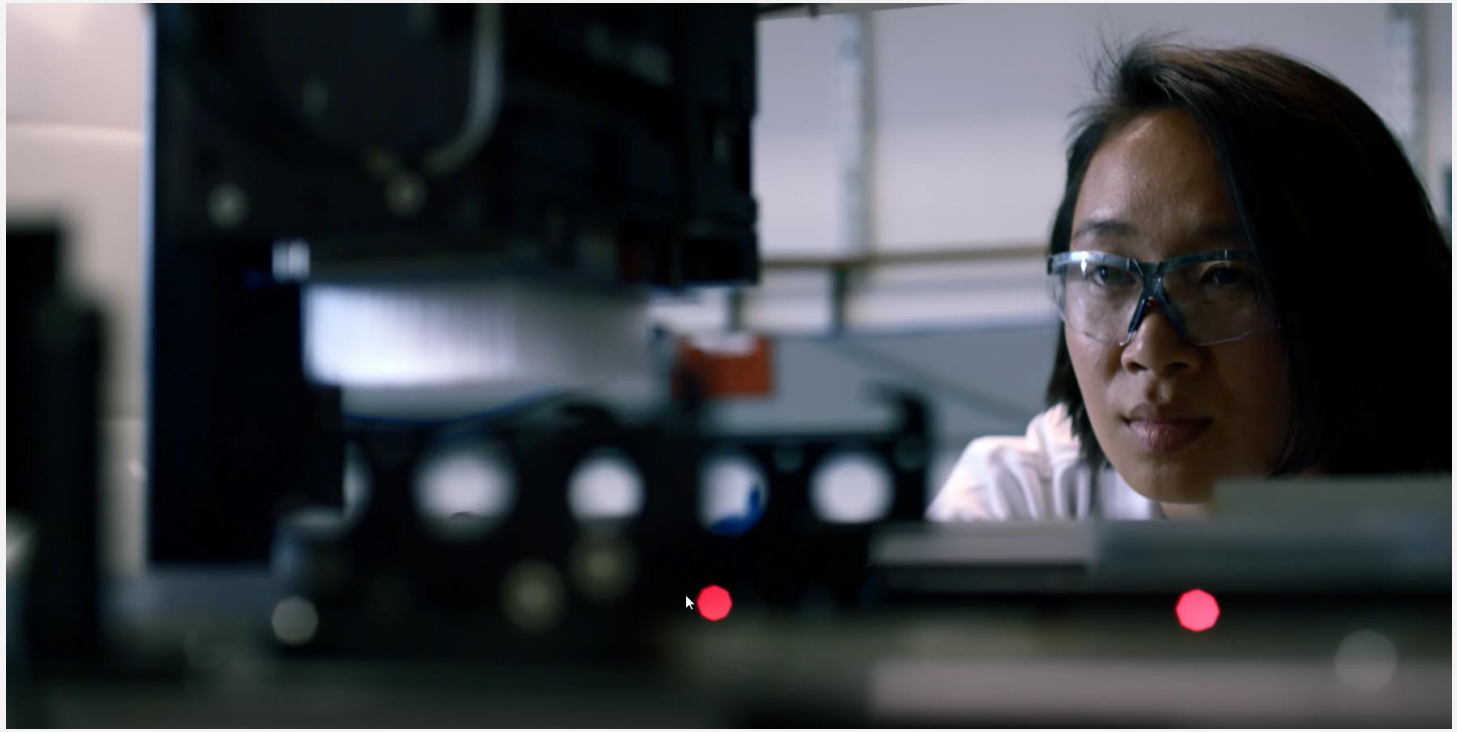
BRADLEY MORGAN, PHD

Senior Vice President, Research and Non-Clinical Development

WHITTEMORE TINGLEY, MD, PHD

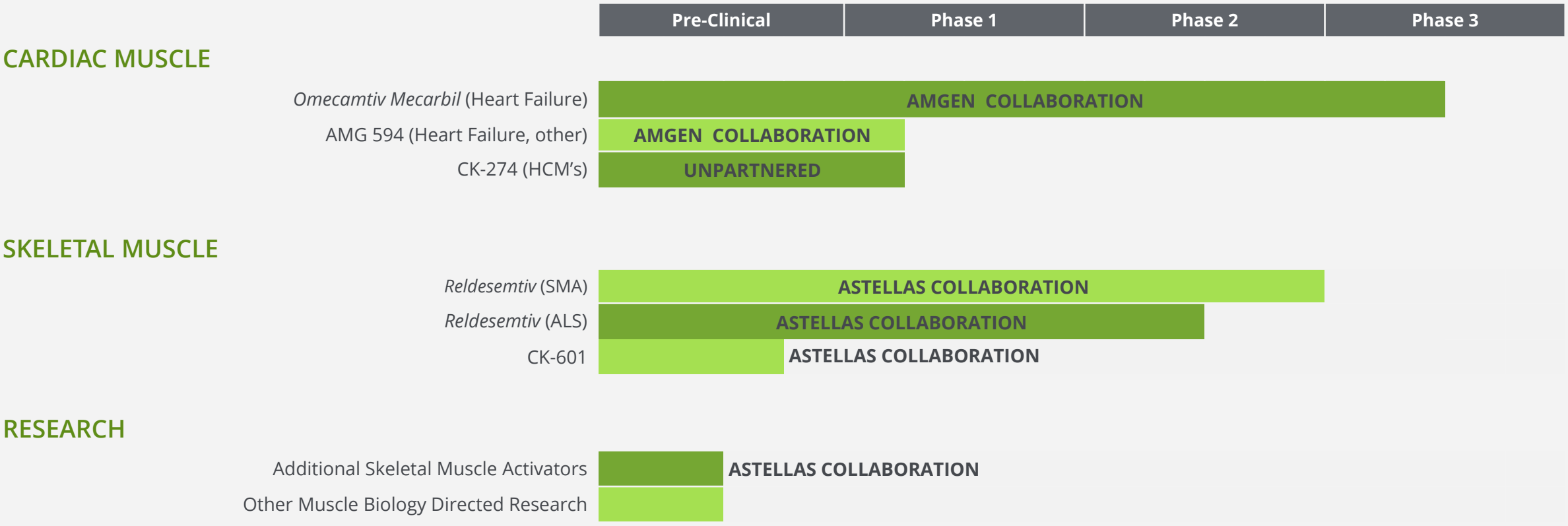
Vice President, Clinical Research, Cardiology

Why We Do What We Do



See the video online at www.cytokinetics.com

Pipeline of Novel Muscle Biology Compounds



Investigational products – not approved as safe or effective for any indication.

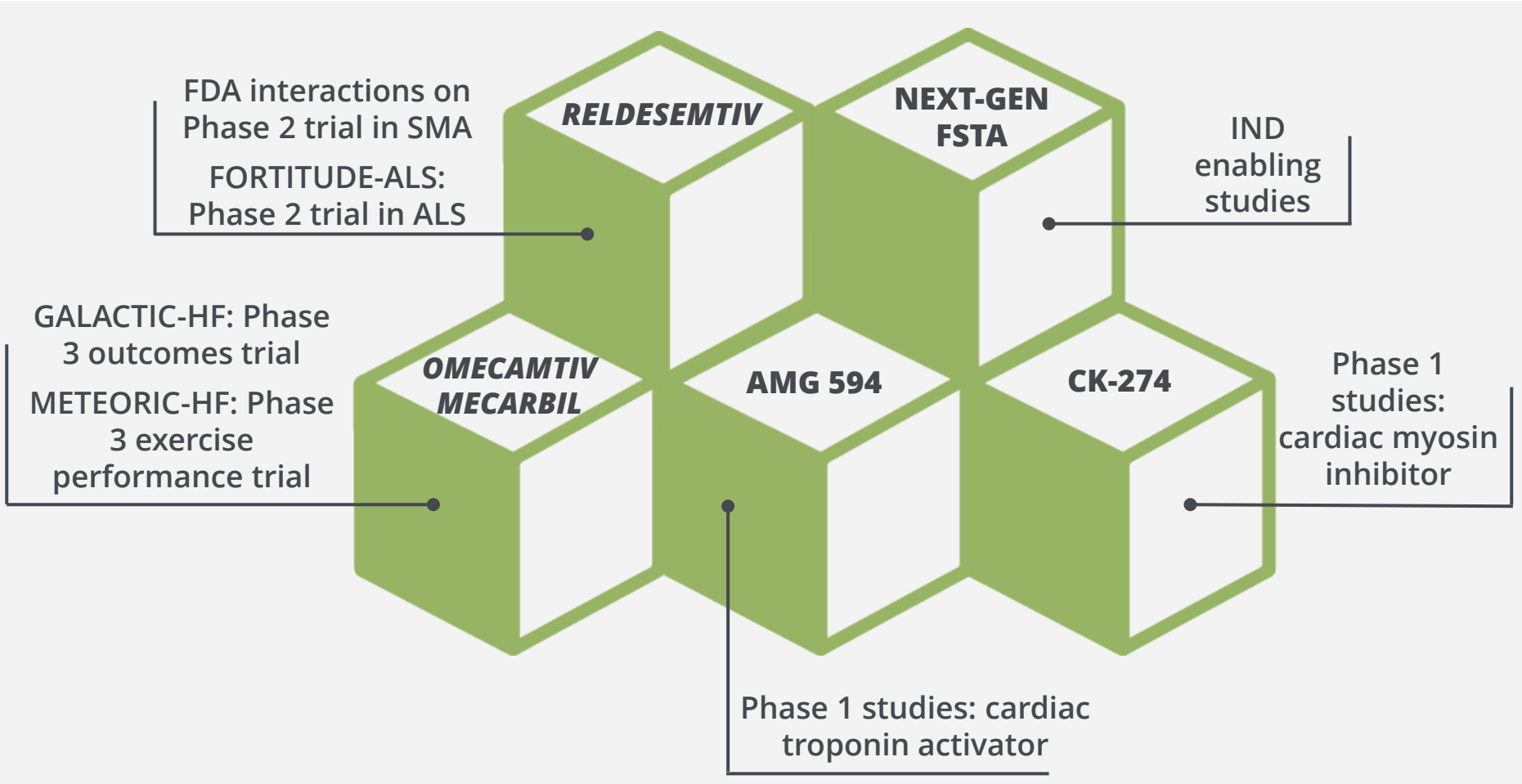
Investing in Muscle Biology Leadership

Leader in Muscle Biology, with Core Foundation in Diseases of Cardiac Muscle Dysfunction

Leveraging Expertise to Expand Pipeline to Diseases of Skeletal Muscle Weakness

Eligible for >500M in pre-commercial milestone payments & >500M in sales-based milestone payments & royalties that can exceed >20% under deals with Amgen & Astellas

>24 months cash



FROM

CONCEPT

TO

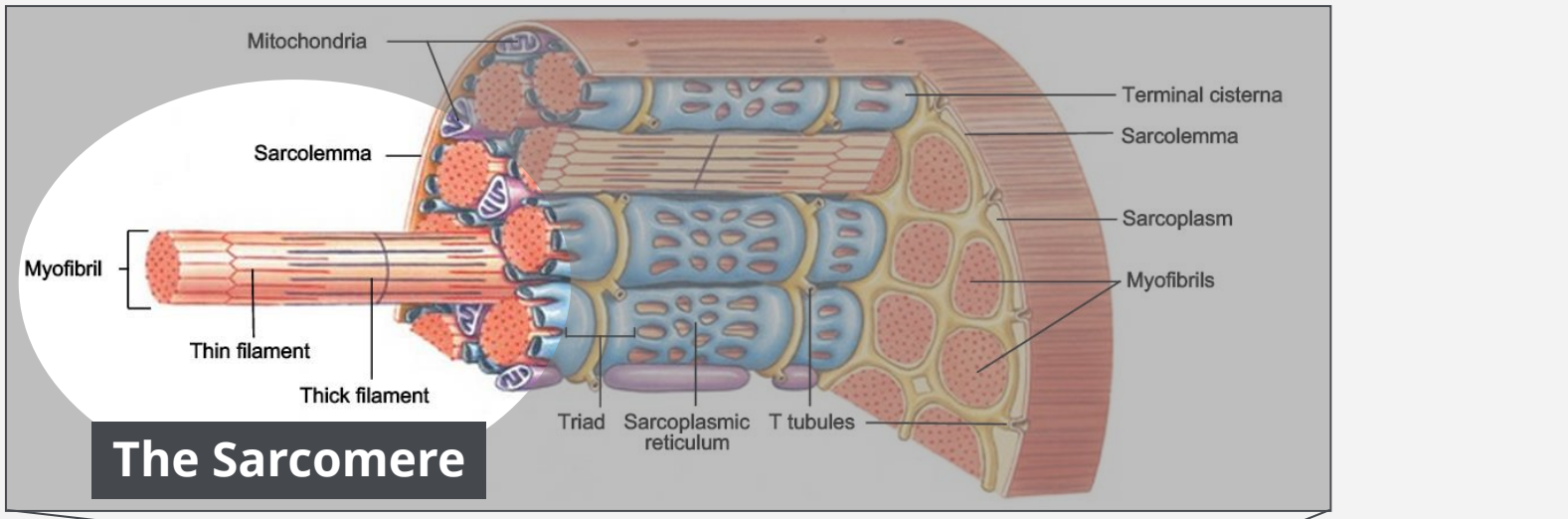
CLINIC

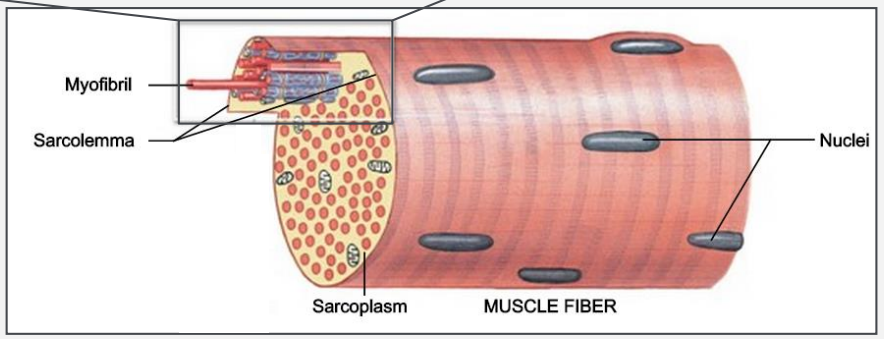
Fady Malik, MD, PhD
EVP, Research & Development

Targeting Muscle Contractility

	Cardiac Muscle	Skeletal Muscle	Smooth Muscle
Diversity of **Contractile Function**	Ventricular ejection Ventricular filling	Mobility Strength	Bronchial tone Pulmonary vascular tone Systemic vascular tone
Diversity of **Therapeutic Application**	Systolic heart failure Diastolic heart failure	Neuromuscular diseases Conditions of muscle weakness/wasting	Asthma/COPD Pulmonary hypertension Systemic hypertension

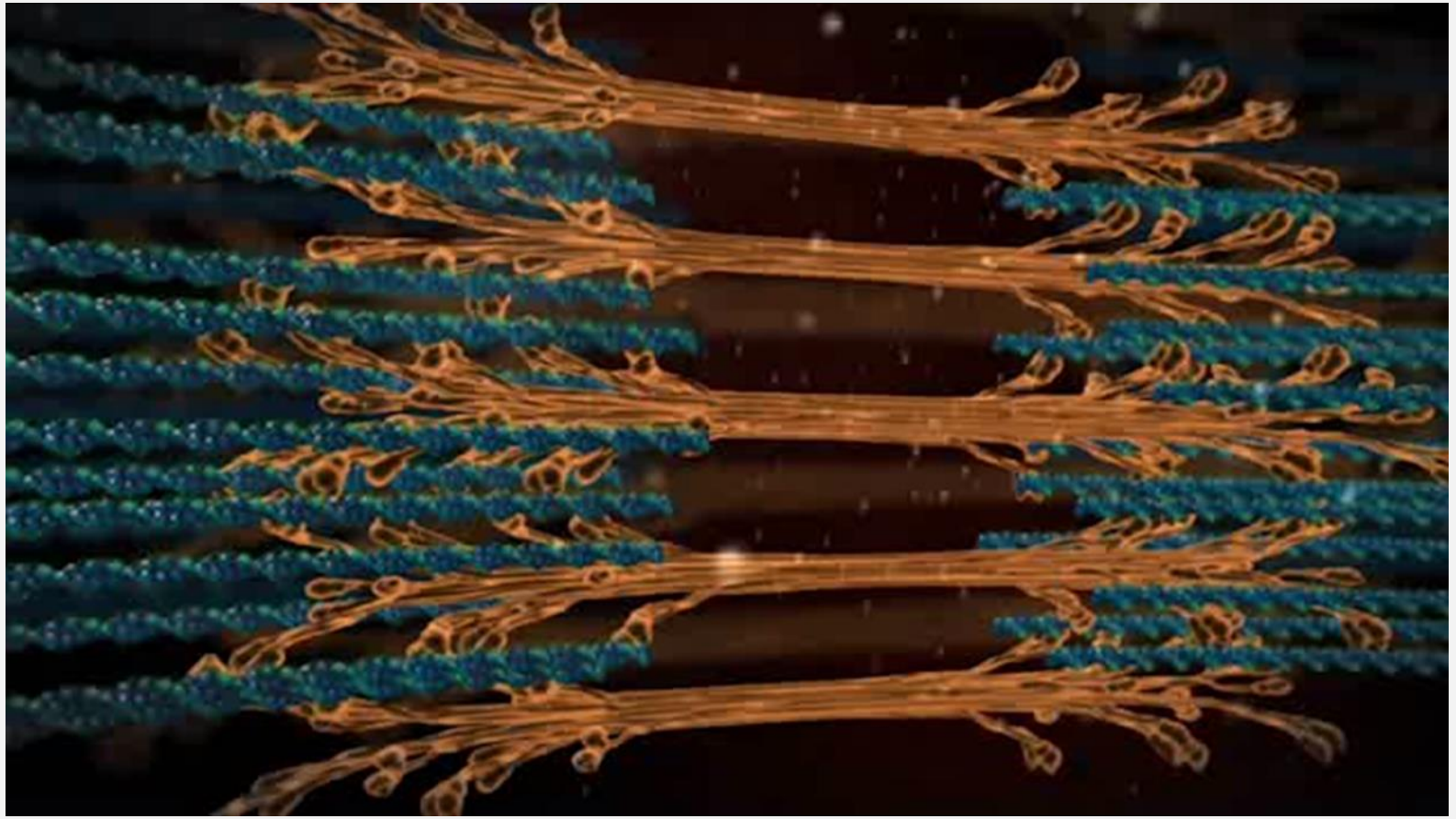
Muscle is a Challenging Therapeutic Target





Cytokinetics has pioneered a pipeline of sarcomere based potential therapeutics

Sarcomere: Fundamental Unit of Muscle Contractility



Pioneers in the Pharmacology of Muscle Contractility

Muscle Contractility

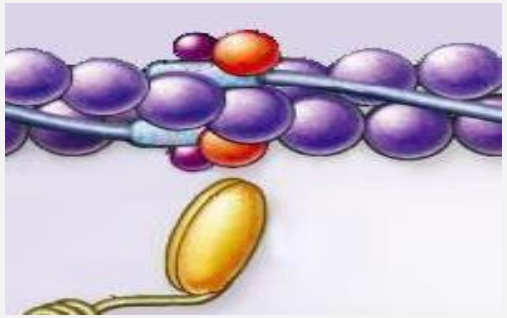
Novel molecular targets require novel assays

Faithful representation of biological function from in vitro to in vivo setting

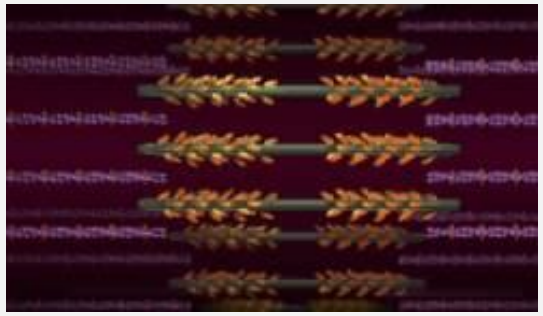
Correlation of molecular findings with functional effects

Purpose-built measurement technologies

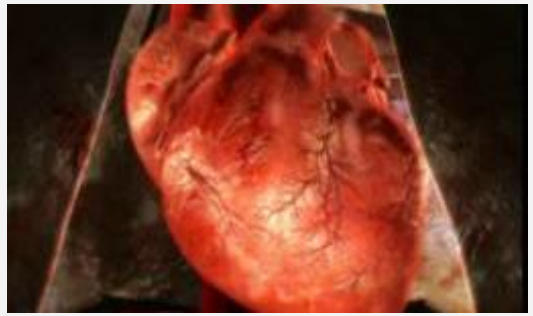
Reconstituted Sarcomere
Flexible Biochemical Assay



Muscle Fiber
Assay in Native Context



Organ and *In Vivo*
Functional Outcome

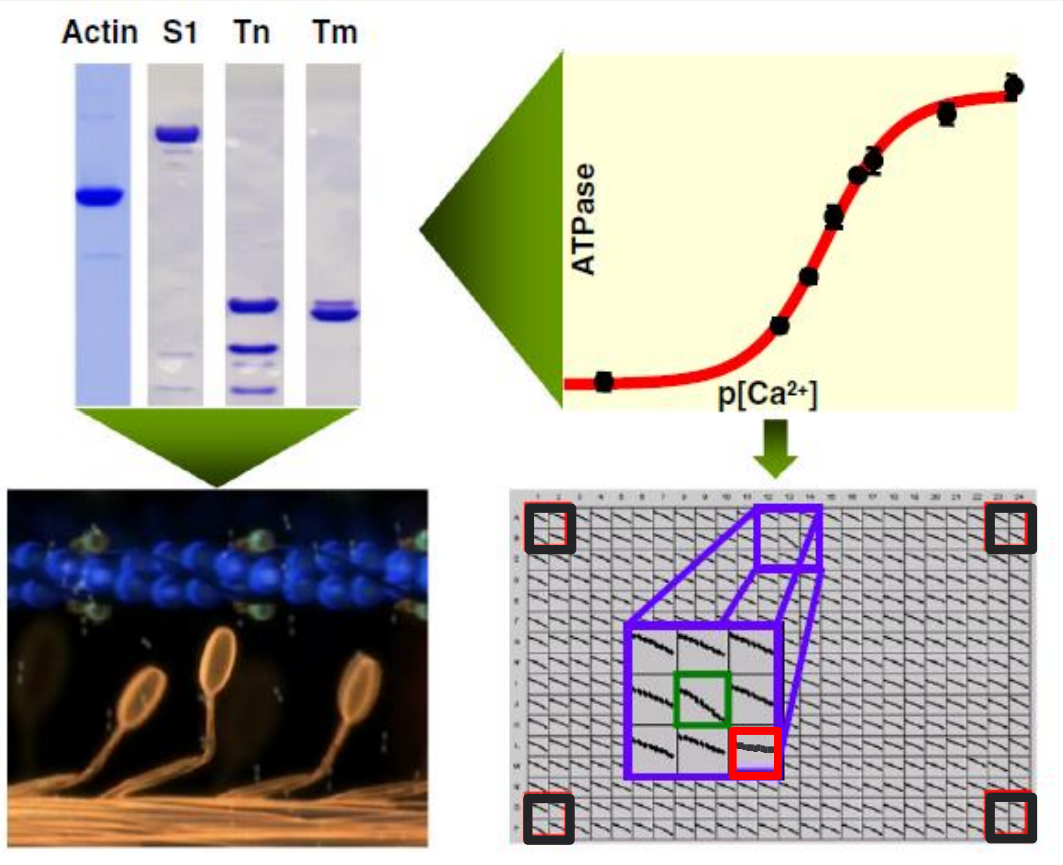


Low complexity → High complexity

High Throughput → Low Throughput

Coherence

High Throughput Screening of a Functional Sarcomere



Malik and Morgan, JMCC 2011

Unique, Robust, Multi-Target High Throughput Assay

Developed at Cytokinetics

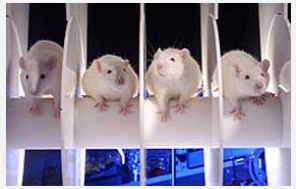
Sensitive to Activators and Inhibitors of Sarcomere Function

Number of compounds screened:

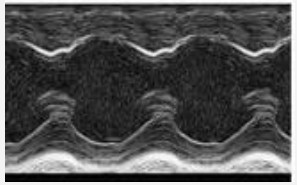
> 17 Million

Extensive Capabilities Support Muscle-Targeted Therapies

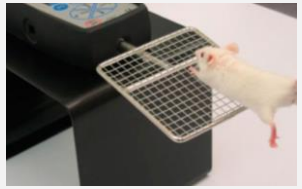
Rotarod running to assess motor co-ordination



Echocardiography to assess cardiac function



Grip test to assess muscle strength

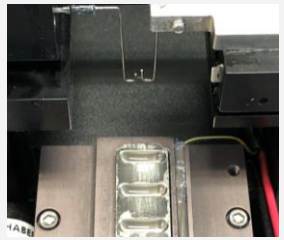


Open field activity to assess spontaneous motor behavior

Rodent treadmill to assess endurance

Running wheels to assess endurance

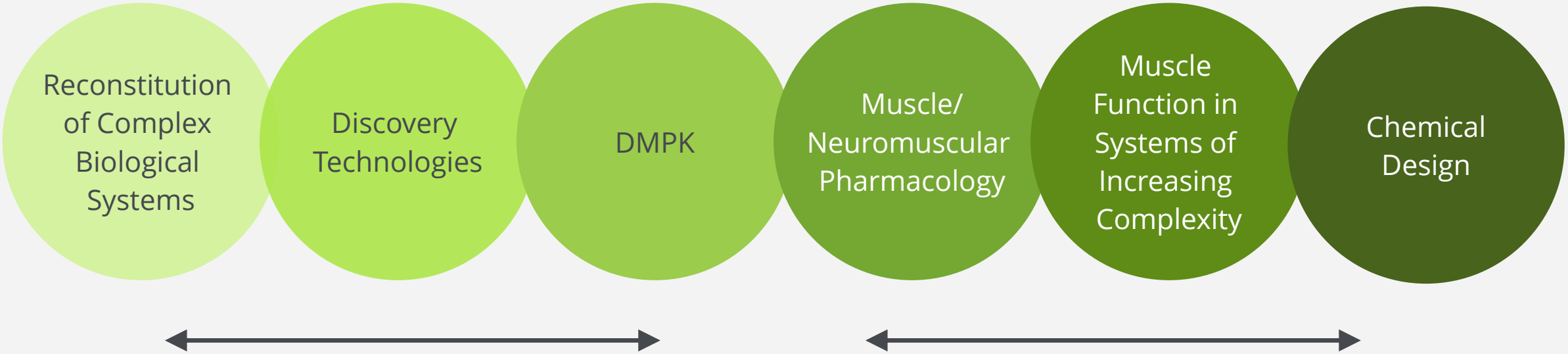
Skinned fiber rig



Mouse grid hang time to assess motor function

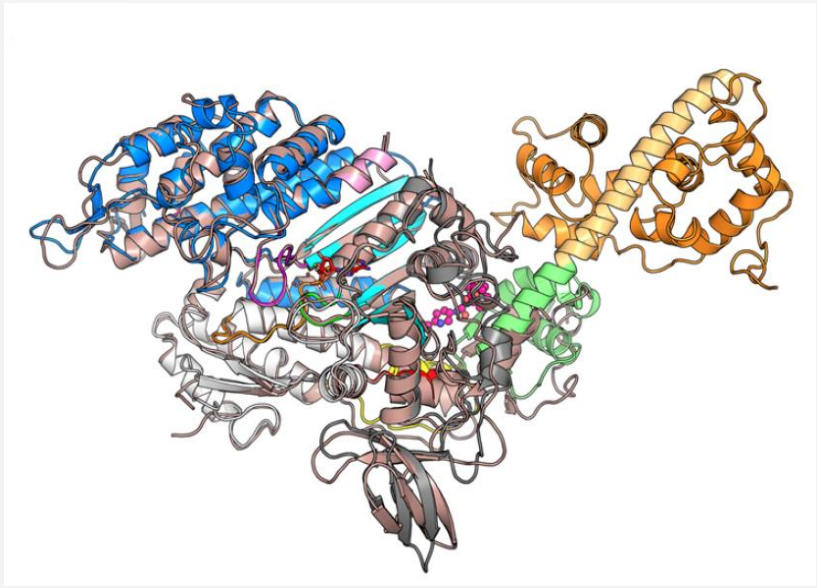
Pharmacology studies focus on assessments of contractility, motor co-ordination and endurance

Core Scientific Capabilities of Cytokinetics



Omecamtiv Mecarbil: A Cardiac Myosin Activator

Crystal Structure of *Omecamtiv Mecarbil* Bound to Cardiac Myosin

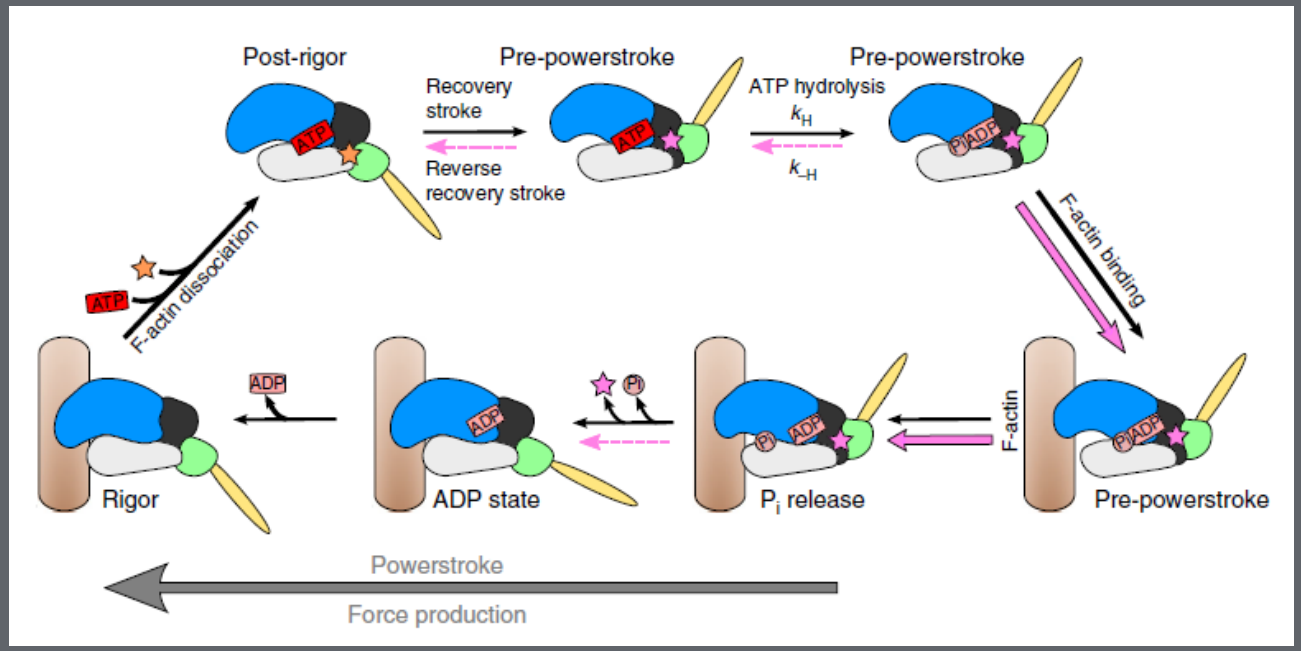


Planelles-Herrero, et al, Nature Comm 2017b

Binding of *Omecamtiv Mecarbil* Stabilizes the Pre-Powerstroke State

Omecamtiv mecarbil increases the number of independent force generators (myosin heads) interacting with the actin filament

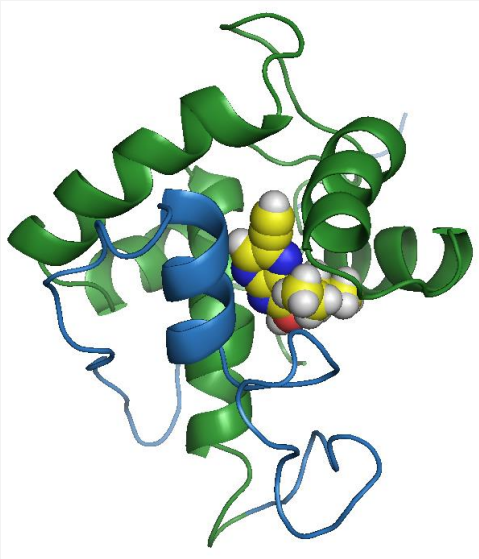
"More hands pulling on the rope"



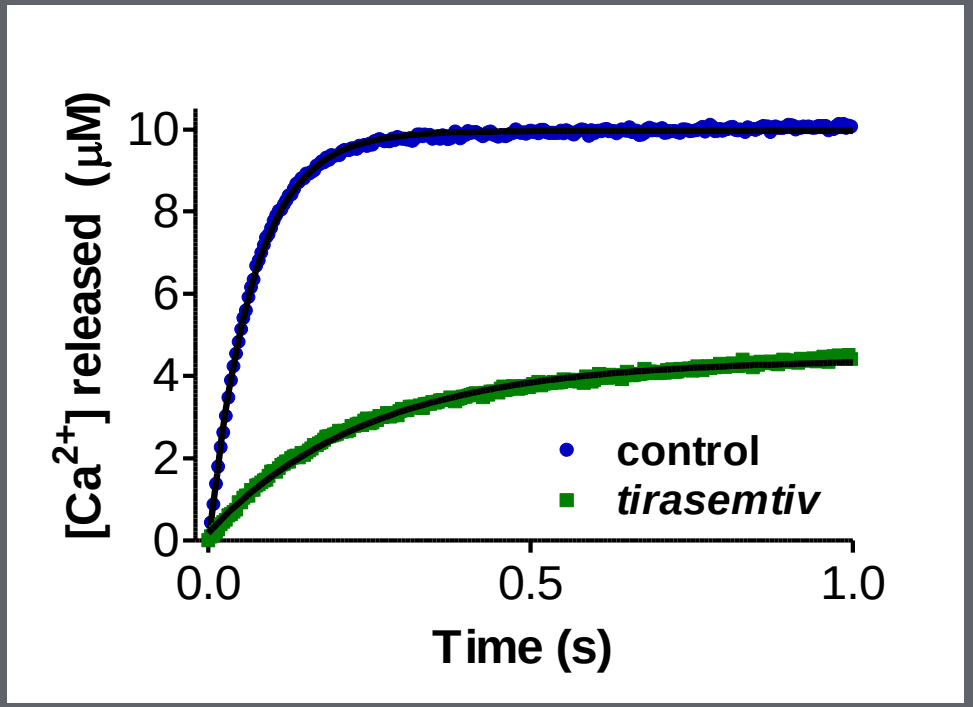
Planelles-Herrero, et al, Nature Comm 2017

Tirasemtiv: Fast Skeletal Muscle Troponin Activator (FSTA)

Crystal Structure of
Tirasemtiv Bound to
Fast Skeletal Muscle Troponin



FSTAs Slow Calcium Release from Troponin
Increasing Its Affinity for Calcium



Russell et al, Nature Medicine, 2012

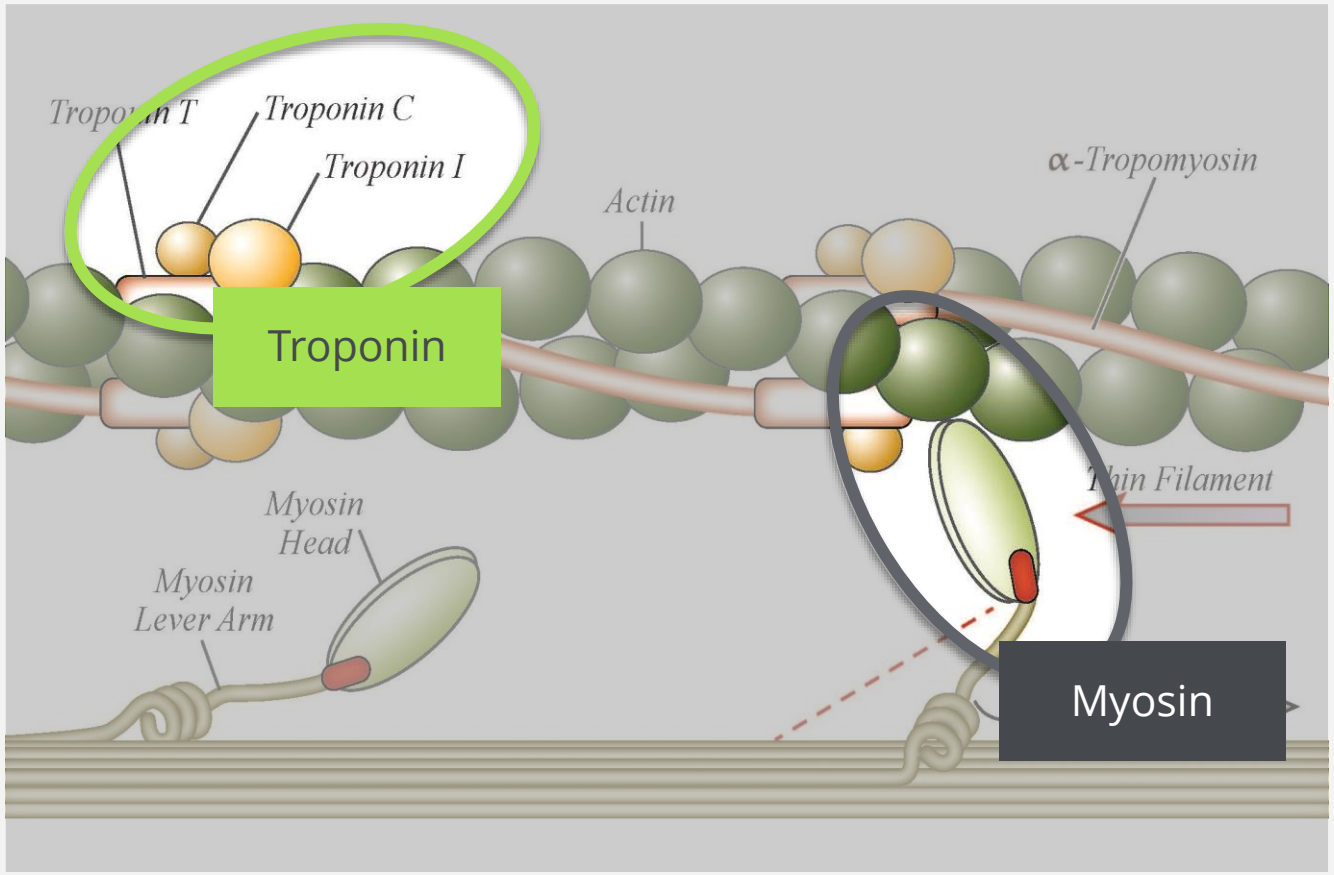
A Deep and Long-Standing Expertise in Muscle Biology

Mean Tenure of Senior Scientific Leadership

> 10 Years

Pioneers in the discovery and optimization of sarcomere based therapeutics

Development Stage Sarcomere-Based Therapeutics



Cardiac Sarcomere

- ***Omecamtiv Mecarbil*** — *TARGET: MYOSIN*
- **CK-274** — *TARGET: MYOSIN*
- **AMG 594** — *TARGET: TROPONIN*

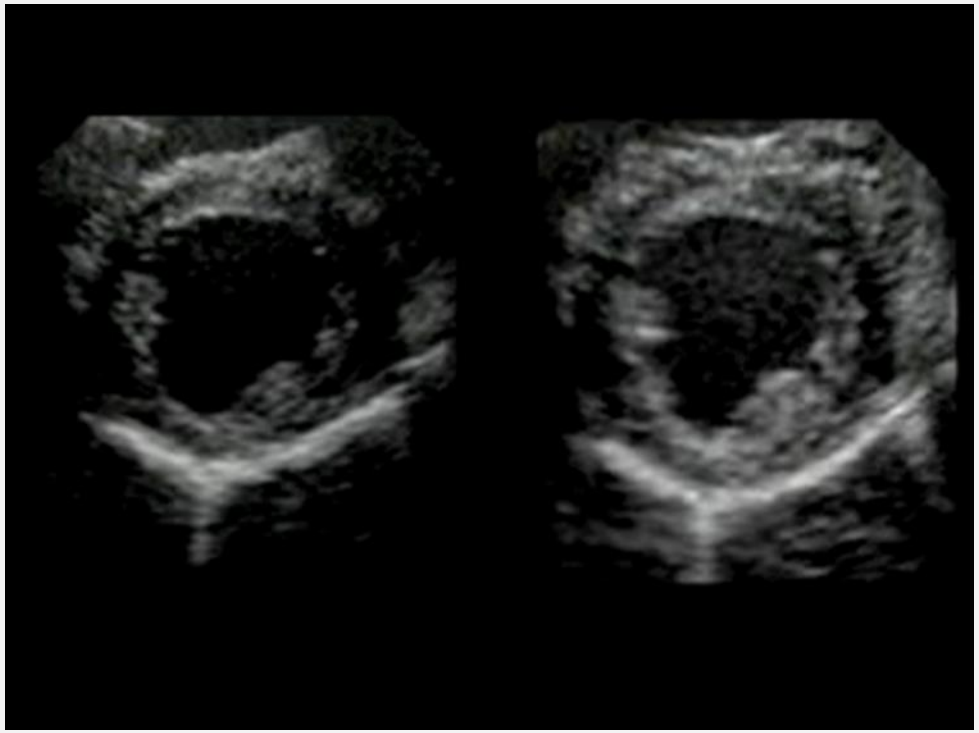
Fast Skeletal Sarcomere

- ***Reldesemtiv*** — *TARGET: TROPONIN*
- **CK-601** — *TARGET: TROPONIN*


PRE-CLINICAL
TRANSLATIONAL RESEARCH & PHARMACODYNAMICS
CLINICAL OUTCOMES

Omecamtiv Mecarbil: Effect on Cardiac Function

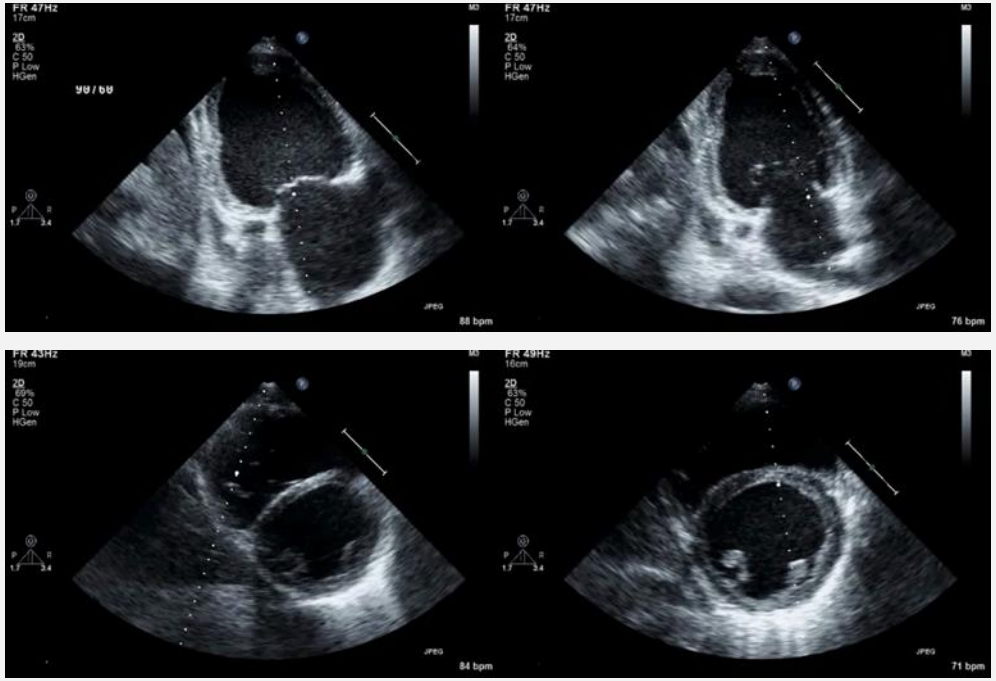
Preclinical Model



Prior to Dosing – left image
During Dosing – right image

Human Translation

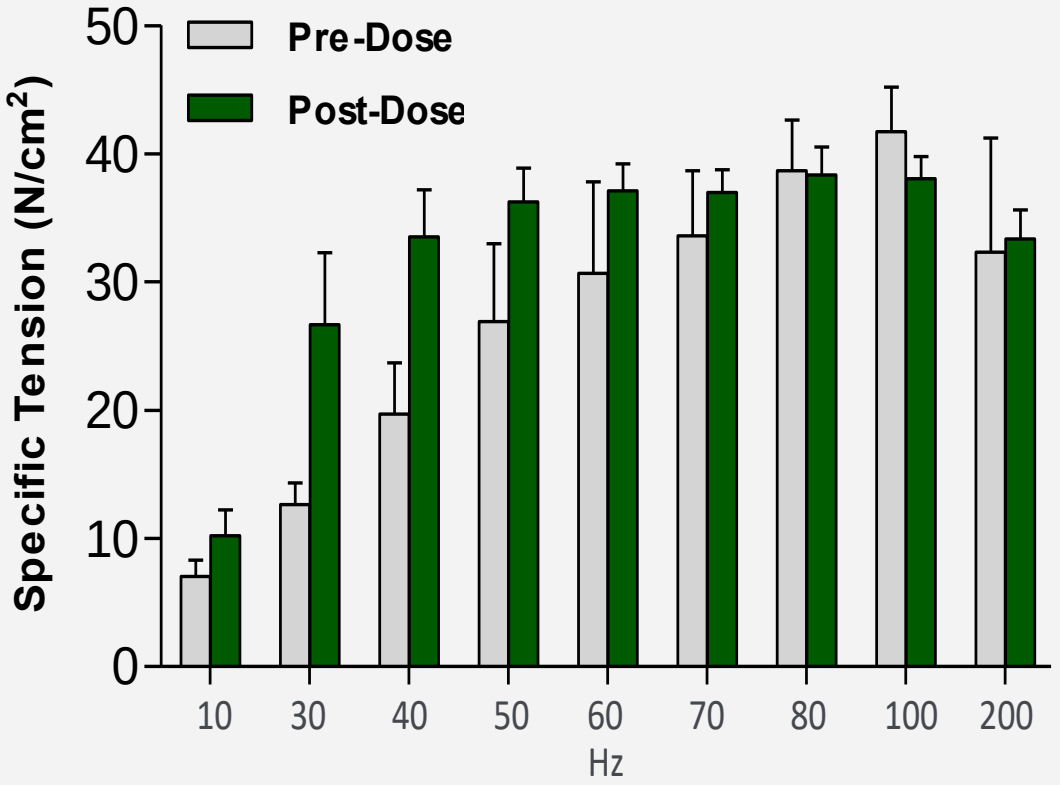
Short Axis & 2 Chamber Views



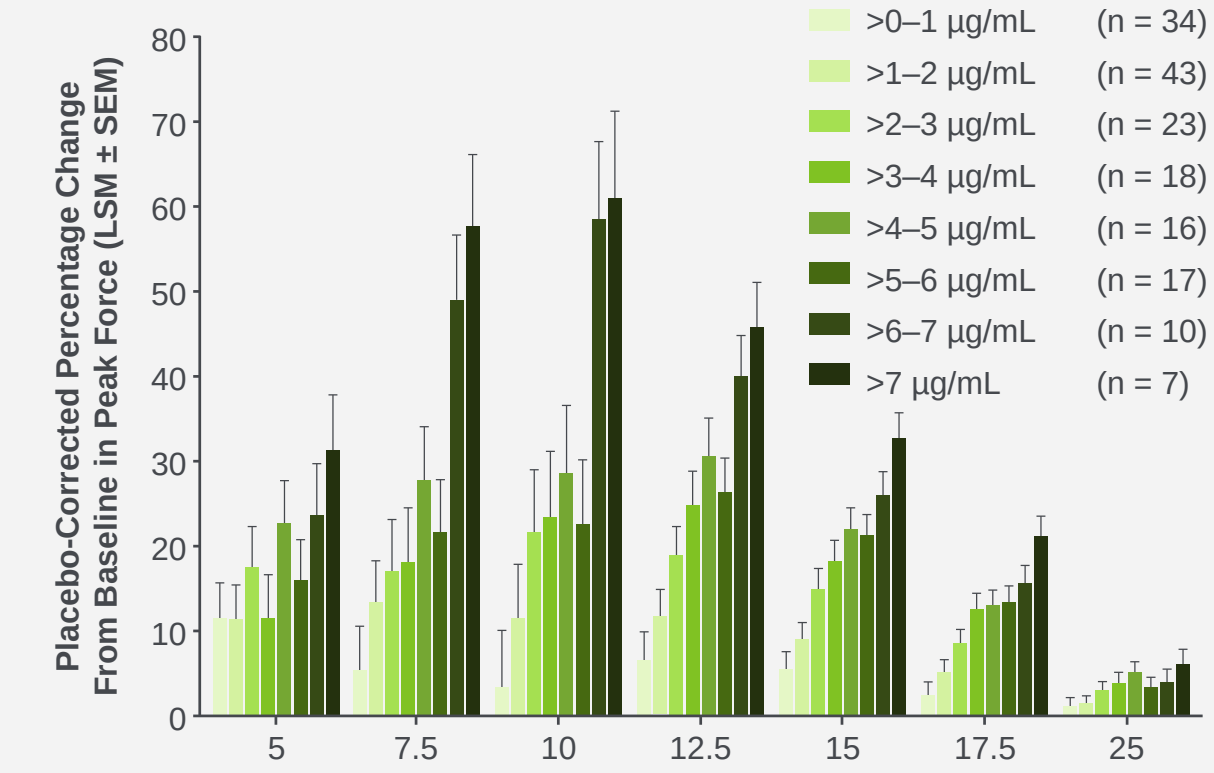
Images and data from patient enrolled in CY 1121

Reldesemtiv: Amplifies Muscle Response to Nerve Input

Preclinical Model



Human Translation



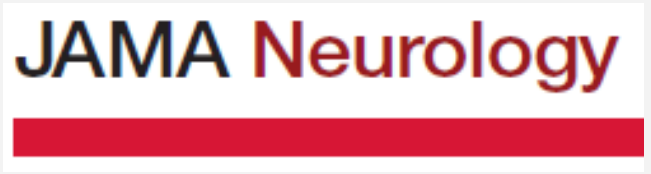
Andrews et al, Muscle Nerve, 2017

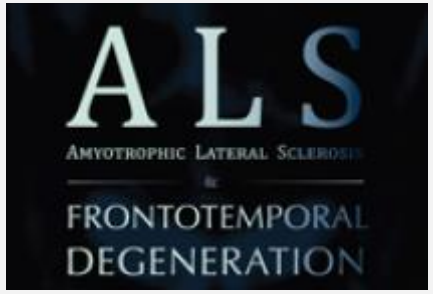
Experience Conducting Multi-National Clinical Trials

Tirasemtiv	*Reldesemtiv*	*Omecamtiv Mecarbil*
>2000 subjects in completed trials; 4 Phase 1 Trials 7 Phase 2 Trials 2 Phase 3 Trials 13 Overall	**>200 subjects in completed trials;** 6 Phase 1 Trials 3 Phase 2 Trials 9 Overall	**>1500 subjects in completed trials;** 11 Phase 1 Trials 4 Phase 2 Trials 2 Phase 3 Trials 17 Overall

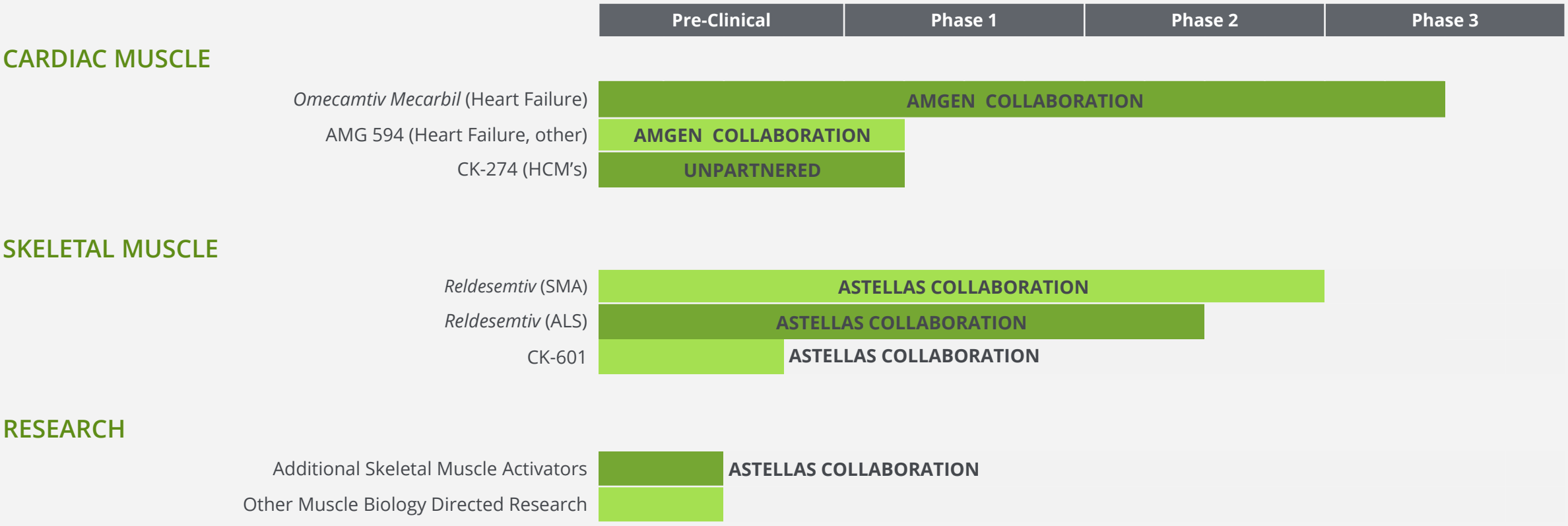
Cytokinetics has conducted clinical trials in North America, Western Europe, Eastern Europe, Russia, & Australia

Extensive Publication History in High Impact Journals





Pipeline of Novel Muscle Biology Compounds



Investigational products – not approved as safe or effective for any indication.

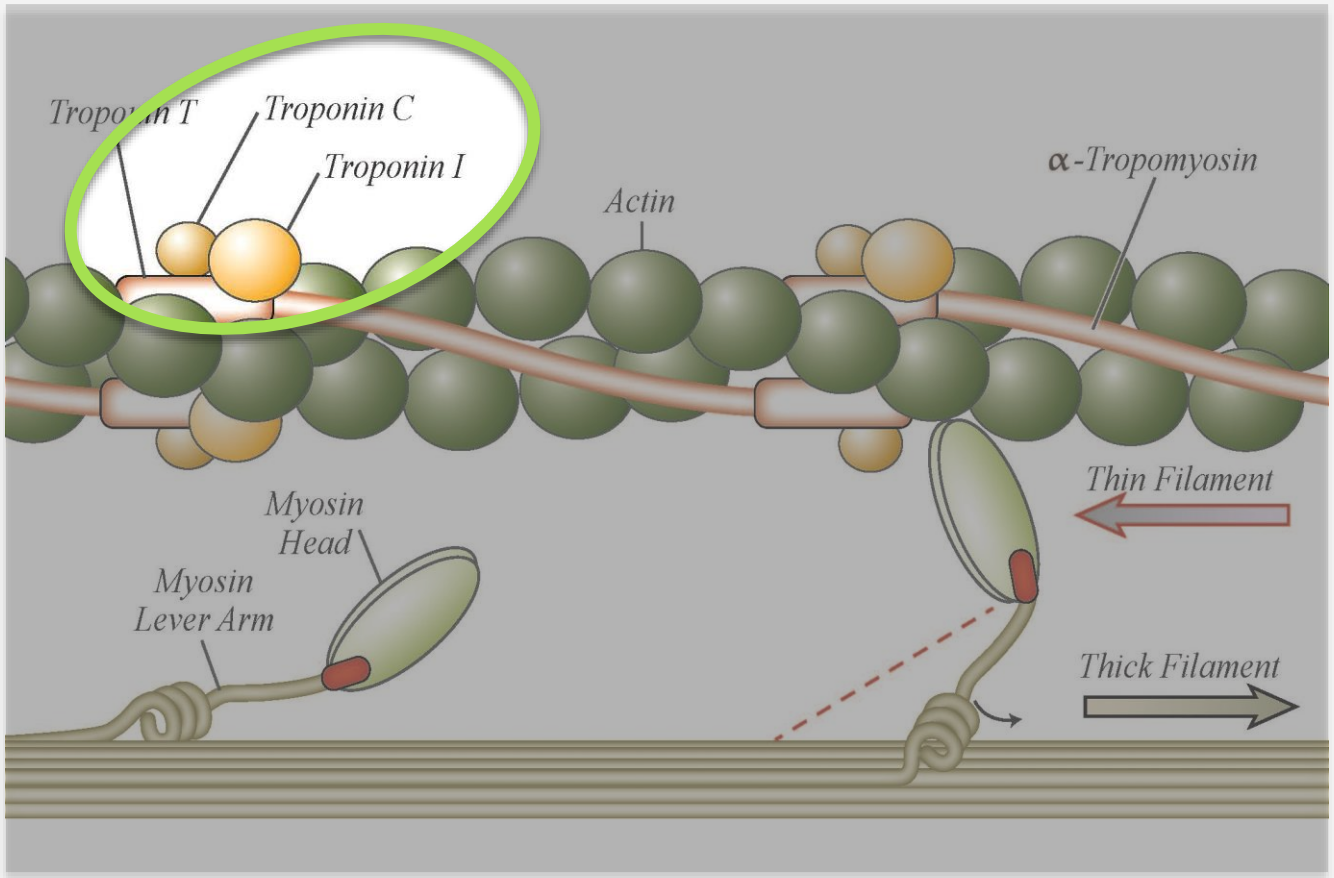
SKELETAL MUSCLE

SKELETAL MUSCLE

PROGRAM OVERVIEW

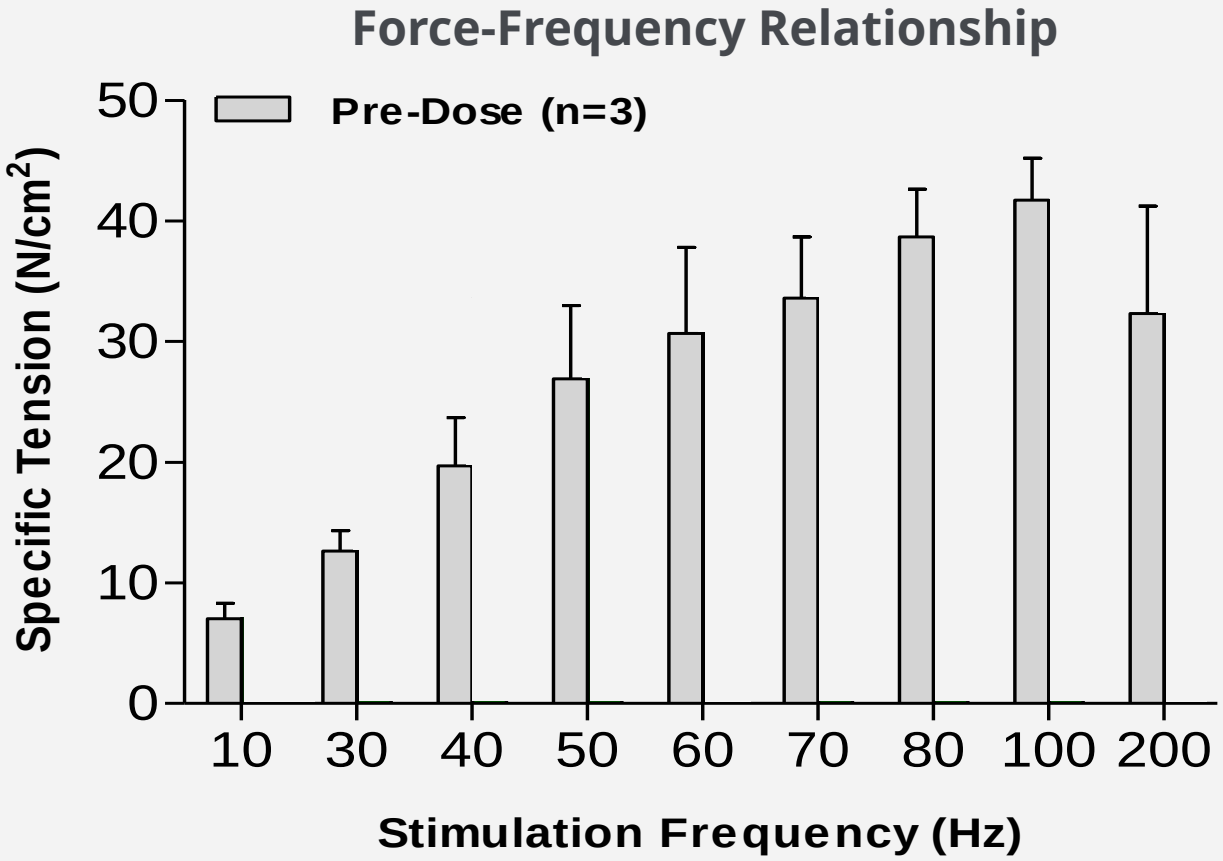
Andrew Wolff, MD, FACC
SVP, Chief Medical Officer

FSTAs Increase Muscle Force During Nerve Stimulation



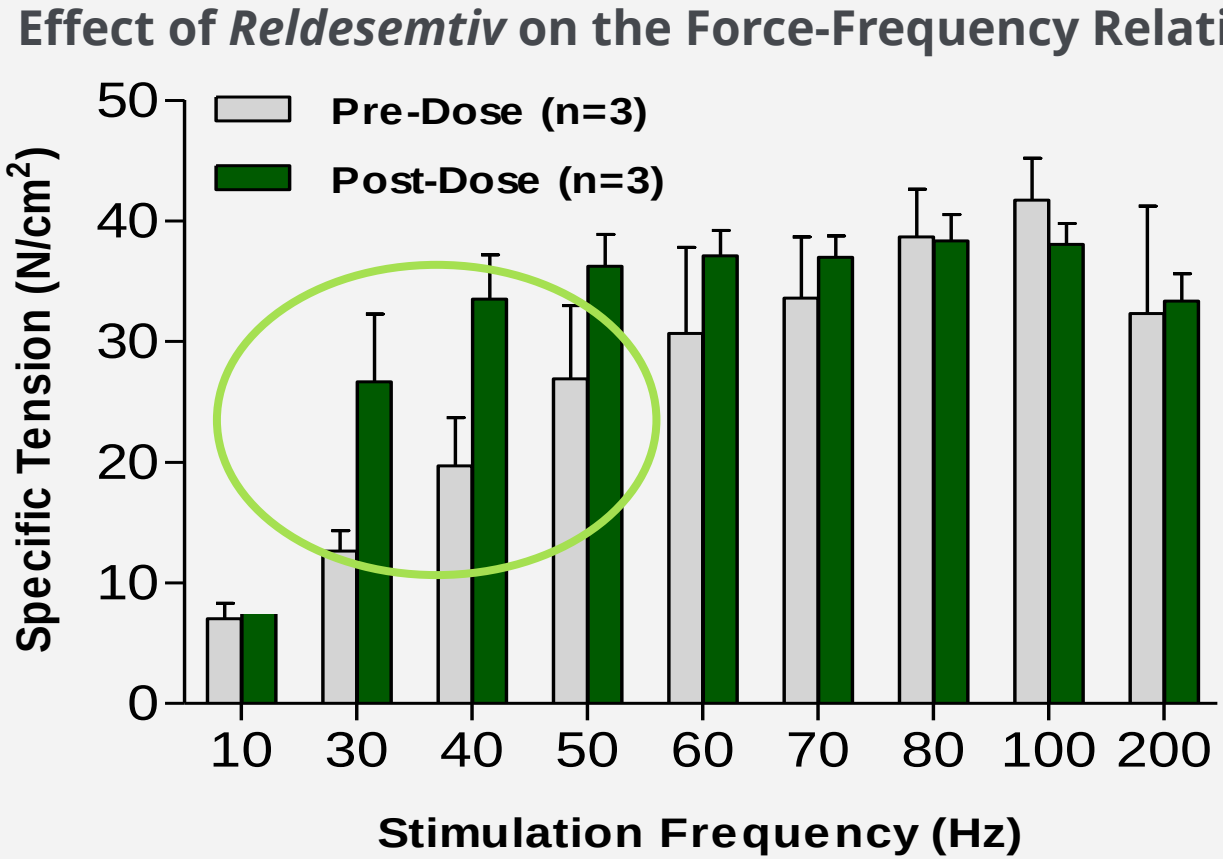
Tirasemtiv and *reldesemtiv* are selective small-molecule fast skeletal muscle troponin activators (FSTAs) that sensitize the sarcomere to Ca^{2+} by increasing the affinity of troponin C for Ca^{2+}

Force Increases with Nerve Stimulation Frequency



Nerve to Rat Extensor Digitorum Longus Stimulated *In Situ*

Reldesemtiv Increases Force with Nerve Stimulation



Nerve to Rat Extensor Digitorum Longus Stimulated *In Situ*

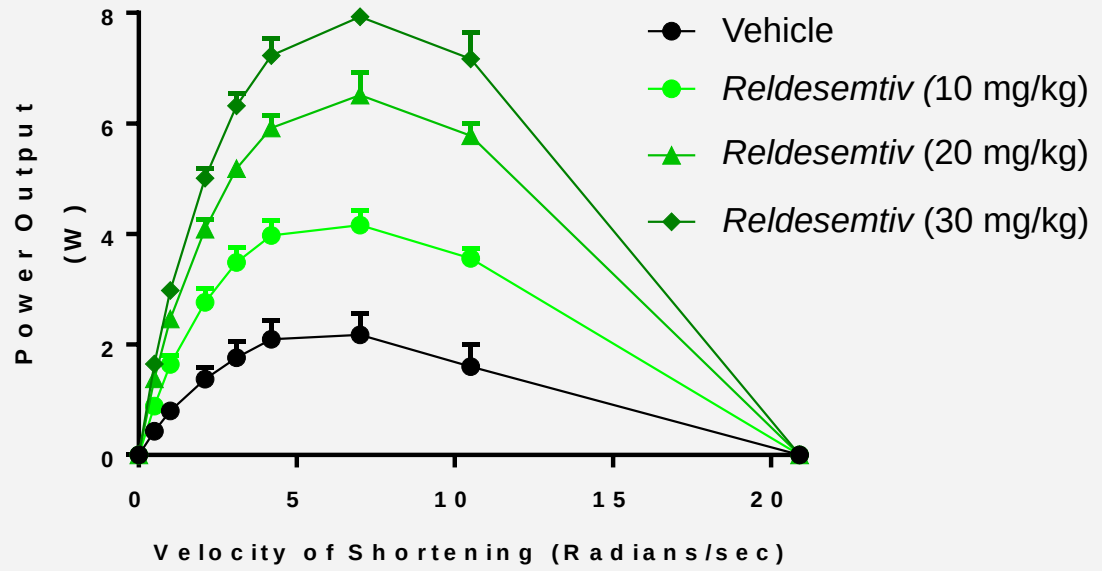
Effects of Fast Skeletal Troponin Activation on Skeletal Muscle Function

Skeletal Troponin Activators Amplify Response to Motor Neuron Input

Skeletal Troponin Activators Increase Muscle Power

Skeletal Troponin Activators Improve Muscle Fatigability

Reldesemtiv Increases Power Output



Power (force x velocity) of muscle is increased

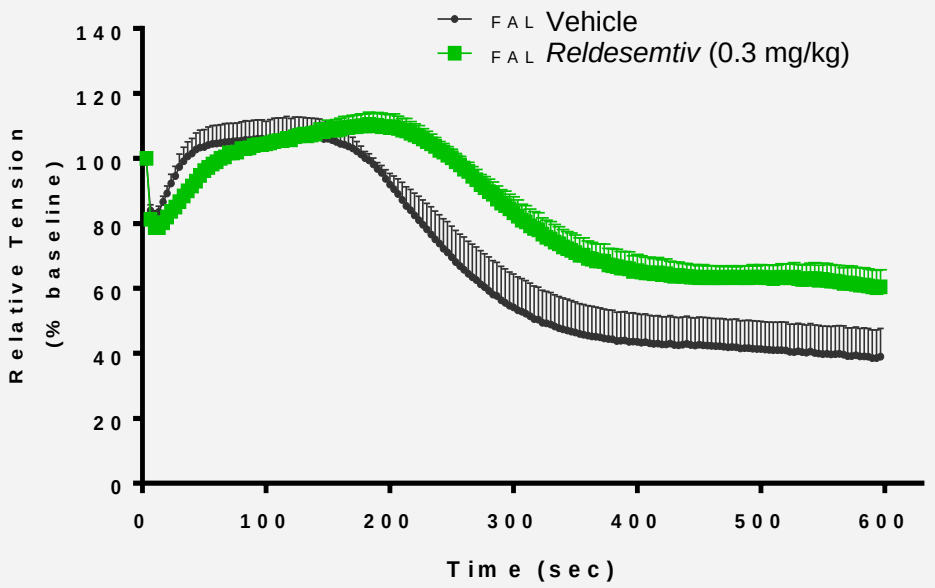
Effects of Fast Skeletal Troponin Activation on Skeletal Muscle Function

Skeletal Troponin Activators Amplify Response to Motor Neuron Input

Skeletal Troponin Activators Increase Muscle Power

Skeletal Troponin Activators Improve Muscle Fatigability

Femoral Artery Ligation (Extensor Digitorum Longus *in situ)*



Troponin activators slow the development of muscle fatigue in a model of vascular insufficiency

Effects of Fast Skeletal Troponin Activation on Skeletal Muscle Function

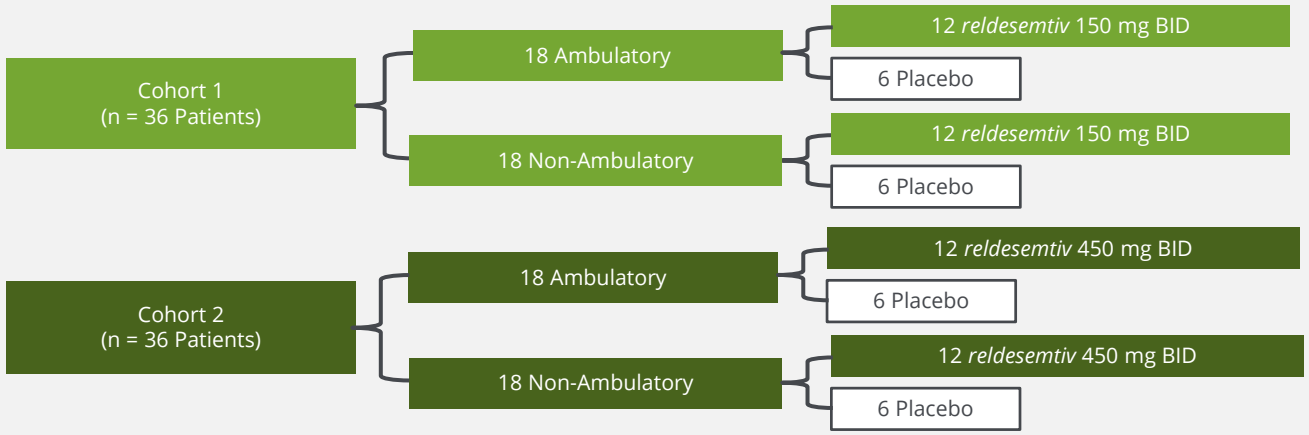
Skeletal Troponin Activators Amplify Response to Motor Neuron Input	Sensitizes muscle to nerve stimulation to increase force at submaximal forces ***Potential utility for ALS, SMA and myasthenia gravis***
Skeletal Troponin Activators Increase Muscle Power	Increases sub-maximal shortening velocity and power ***Potential utility for multiple conditions that result in weakness and frailty***
Skeletal Troponin Activators Improve Muscle Fatigability	Reduces fatigue in normal, atrophied, and hypoxic muscle ***Potential utility for neuromuscular diseases, COPD, CHF, etc.***

Preclinical models provide a translational framework for clinical development

Reldesemtiv Neuromuscular Program

SMA

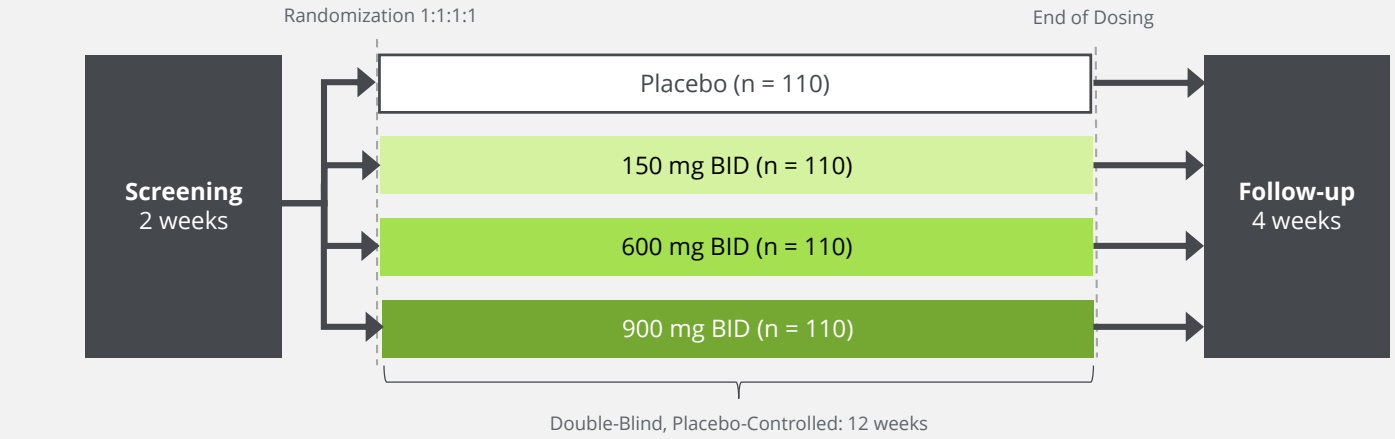
A severe, genetic, neuromuscular disease that manifests in various degrees of severity as progressive muscle weakness resulting in respiratory and mobility impairment



Phase 2 – CY 5021
Hypothesis generating study enrolled 70 people with Type II-IV SMA over 8 weeks. Study included two dose cohorts, stratified by ambulatory versus non-ambulatory status, randomized 2:1 to receive *reldesemtiv* or placebo 2 times daily.

ALS

Progressive, degenerative neuromuscular disease that affects the nerve cells in the brain and spinal cord



Phase 2 – FORTITUDE-ALS
Parallel group, dose ranging study enrolling 450 patients with ALS in the US and Canada, evaluating change from baseline in the percent predicted slow vital capacity (SVC) at 12 weeks of treatment with *reldesemtiv* or placebo

Cytokinetics' Deep Experience with Clinical Trials in ALS

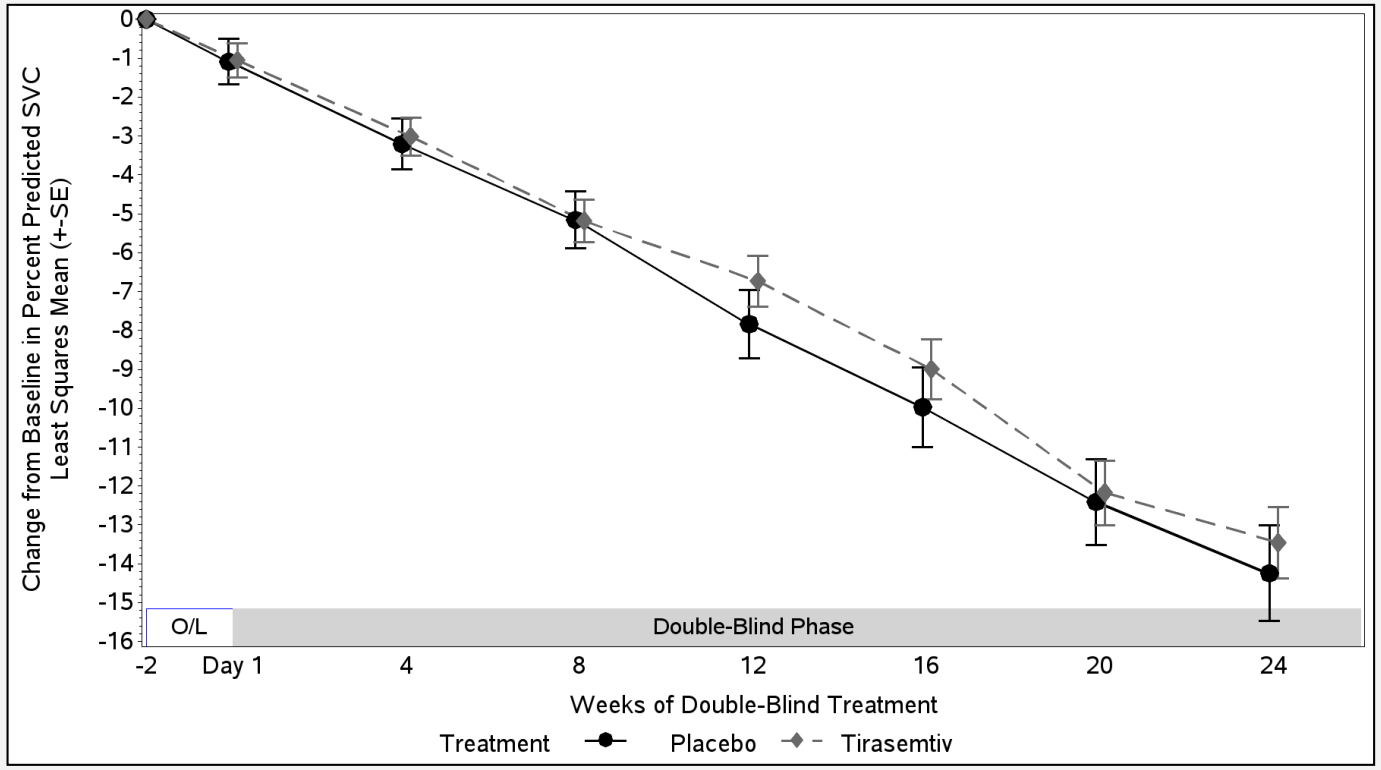
STUDY # (NAME)	DRUG	PHASE	N	SITES	COUNTRIES
CY 4021	*Tirasemtiv*	2a	67	14	USA
CY 4024	*Tirasemtiv*	2a	49	9	USA
CY 4025	*Tirasemtiv*	2a	28	11	USA
CY 4026 (BENEFIT-ALS)	*Tirasemtiv*	2b	711	75	USA, Canada, France, Germany, United Kingdom, Spain, Ireland, Netherlands
CY 4031 (VITALITY-ALS)	*Tirasemtiv*	3	744	79	USA, Canada, Italy, Germany, Spain, France, Belgium, Ireland, Netherlands, United Kingdom, Portugal
CY 5022 (FORTITUDE-ALS)	*Reldesemtiv*	2b	>370	65	USA, Canada, Spain, Ireland, Netherlands, Australia

Well-understood pharmacodynamics, pharmacokinetics, safety & tolerability assessed in 6 randomized, double-blind, placebo-controlled trials

Almost 2000 patients enrolled from over 80 sites across 12 countries

Phase 3 Trial of *Tirasemtiv* in ALS

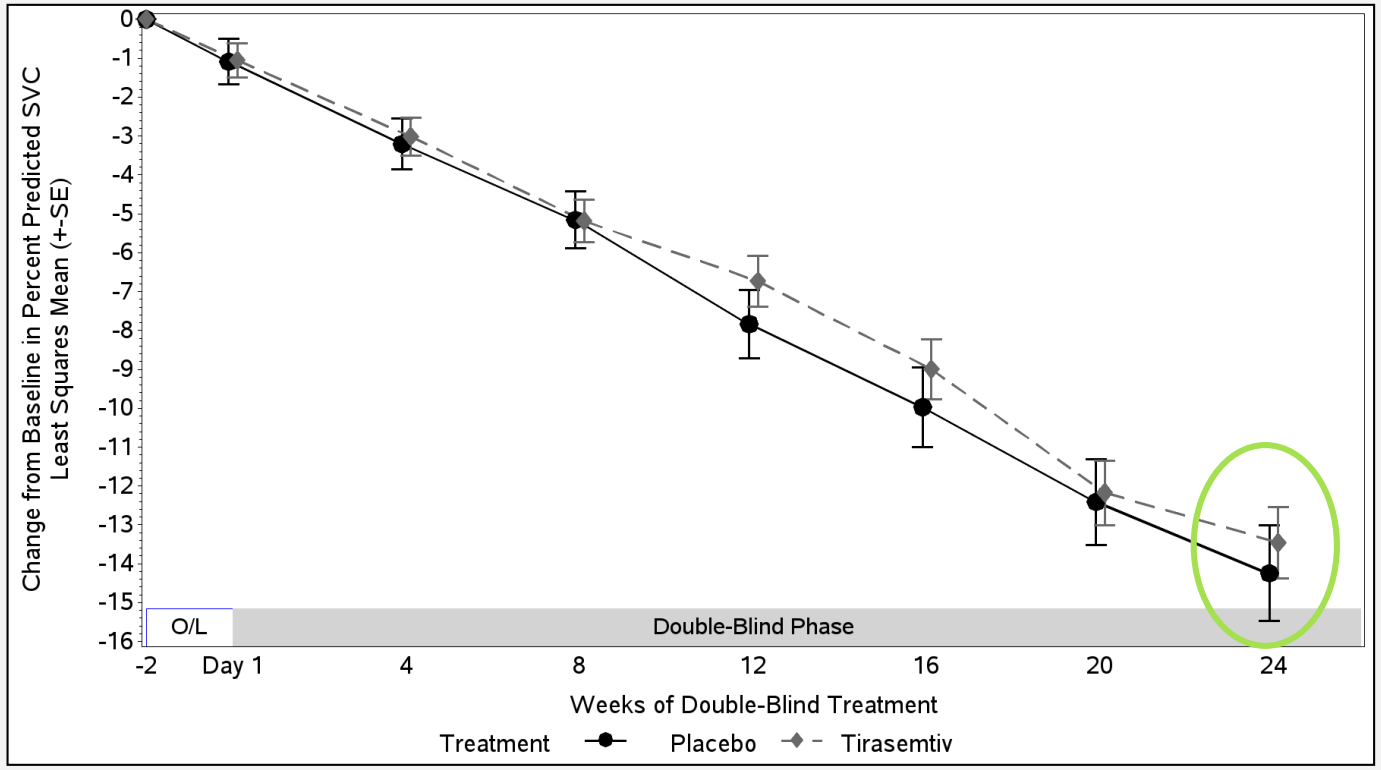
Primary Endpoint: Change from Baseline in Percent Predicted SVC at 24 Weeks



A Phase 3 Trial of *Tirasemtiv* in Patients with ALS Change from Baseline in Percent Predicted SVC (As Randomized)

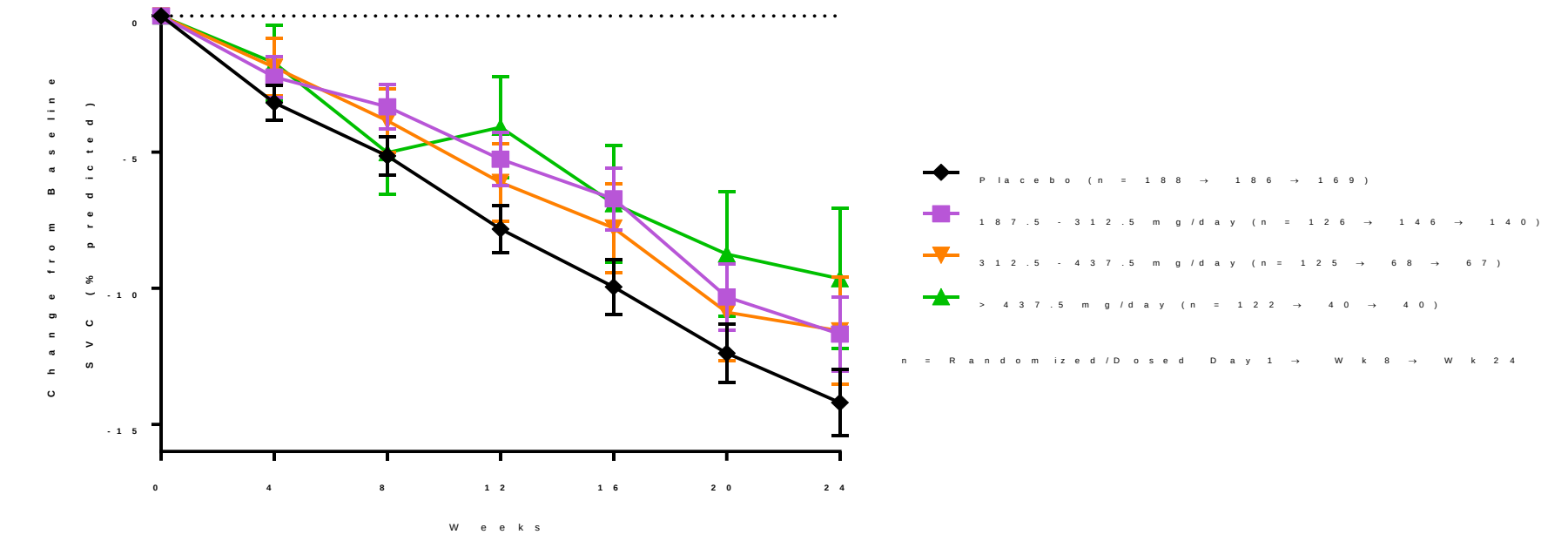
Phase 3 Trial of *Tirasemtiv* in ALS

Primary Endpoint: Change from Baseline in Percent Predicted SVC at 24 Weeks



A Phase 3 Trial of *Tirasemtiv* in Patients with ALS Change from Baseline in Percent Predicted SVC (As Randomized)

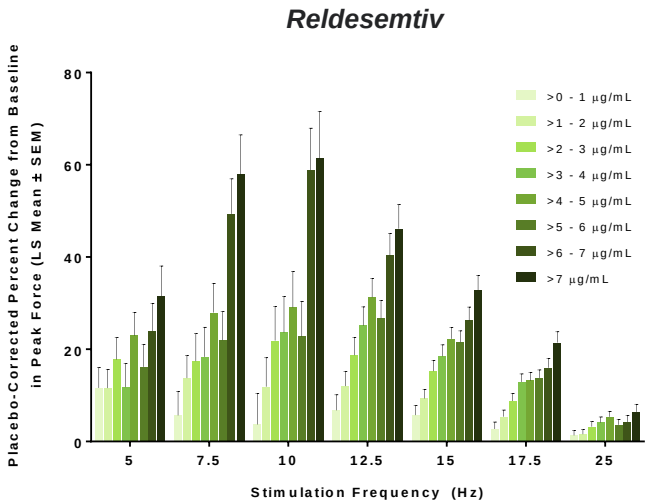
Change from Baseline in Percent Predicted SVC by Average Maintenance Dose

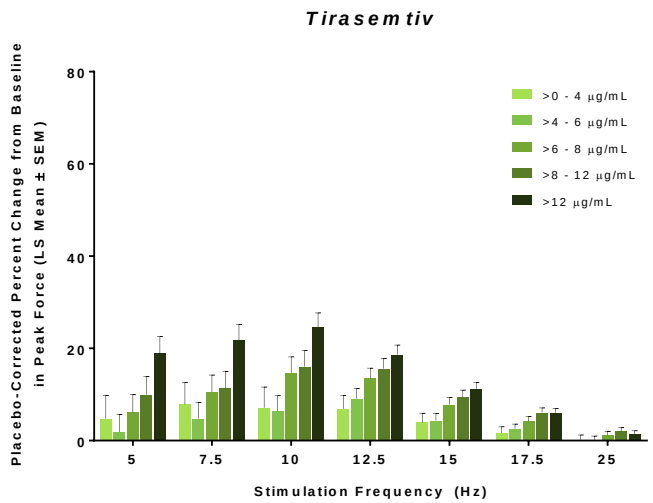


	mg/day	Placebo	187.5 – 312.5	312.5 – 437.5	> 437.5
LS mean change from baseline to 24 weeks		-14.23	-11.68	-11.56	-9.65
LS mean difference from placebo			2.55	2.67	4.57
p-value			0.160	0.247	0.107

Reldesemtiv: Potentially More Potent, Well Tolerated

- *Reldesemtiv* increased the force generated by the tibialis anterior muscle versus placebo in response to nerve stimulation in a dose, plasma concentration, and frequency-dependent manner
- The overall largest increase from baseline in peak force, compared to placebo, was **58.7** (10.2)% (least-squares mean [SE]) at a stimulation frequency of 10 Hz.
- The largest response *tirasemtiv* produced in a comparable study was a **24.5** (3.1)% increase in peak force at 10 Hz
- Single doses of *reldesemtiv* were well-tolerated in healthy volunteers at doses up to 4000 mg. No SAEs were reported, AEs were mild or moderate

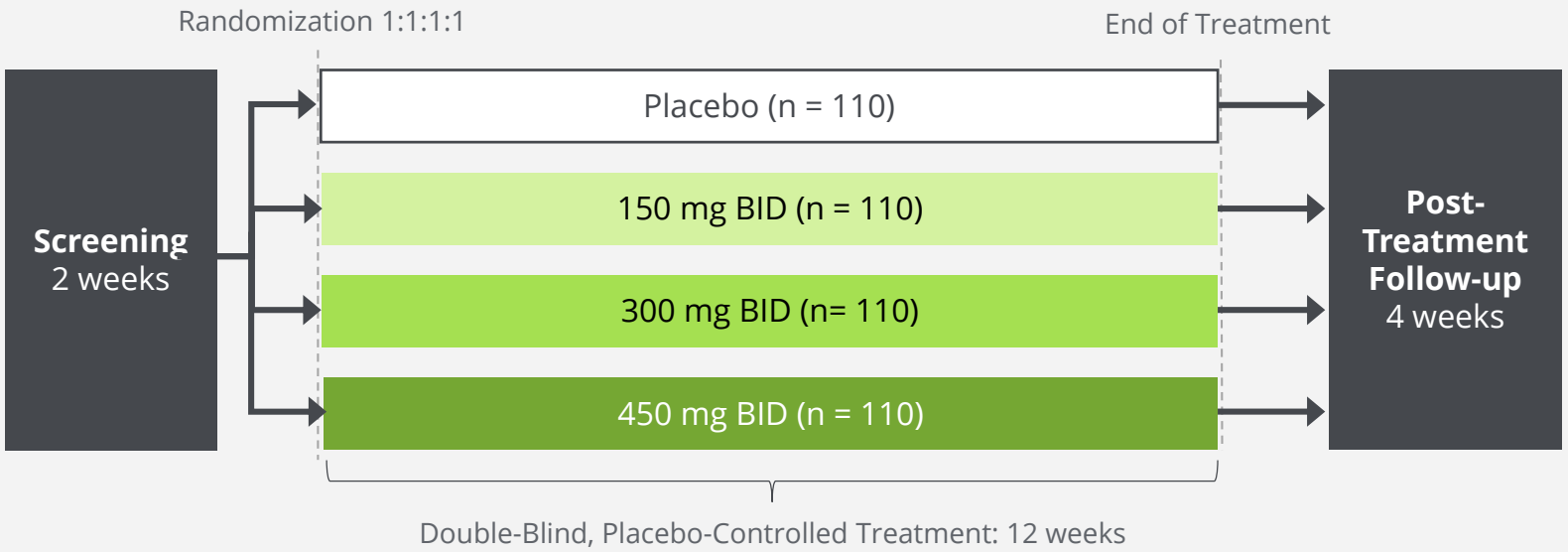




Results from Three Phase 1 Studies of *Reldesemtiv* Published in *Muscle & Nerve*

Andrews JA, Miller TM, Vijayakumar V, Stoltz R, James JK, Meng L, Wolff AA, Malik FI. CK-2127107 amplifies skeletal muscle response to nerve activation in humans. *Muscle & Nerve*. 2017 Nov 18.

Reldesemtiv in Patients with ALS



- **Primary Endpoint:**
  - Change from baseline to Week 12 in percent predicted SVC
- **Secondary Endpoints:**
  - Slope of the change from baseline in the mega-score of muscle strength measured by hand held dynamometry and handgrip dynamometry from baseline to Visit Week 12
  - Change from baseline to Visit Week 12 in the ALS Functional Rating Scale – Revised
  - The incidence and severity of treatment-emergent adverse events
  - Plasma concentrations of *reldesemtiv*

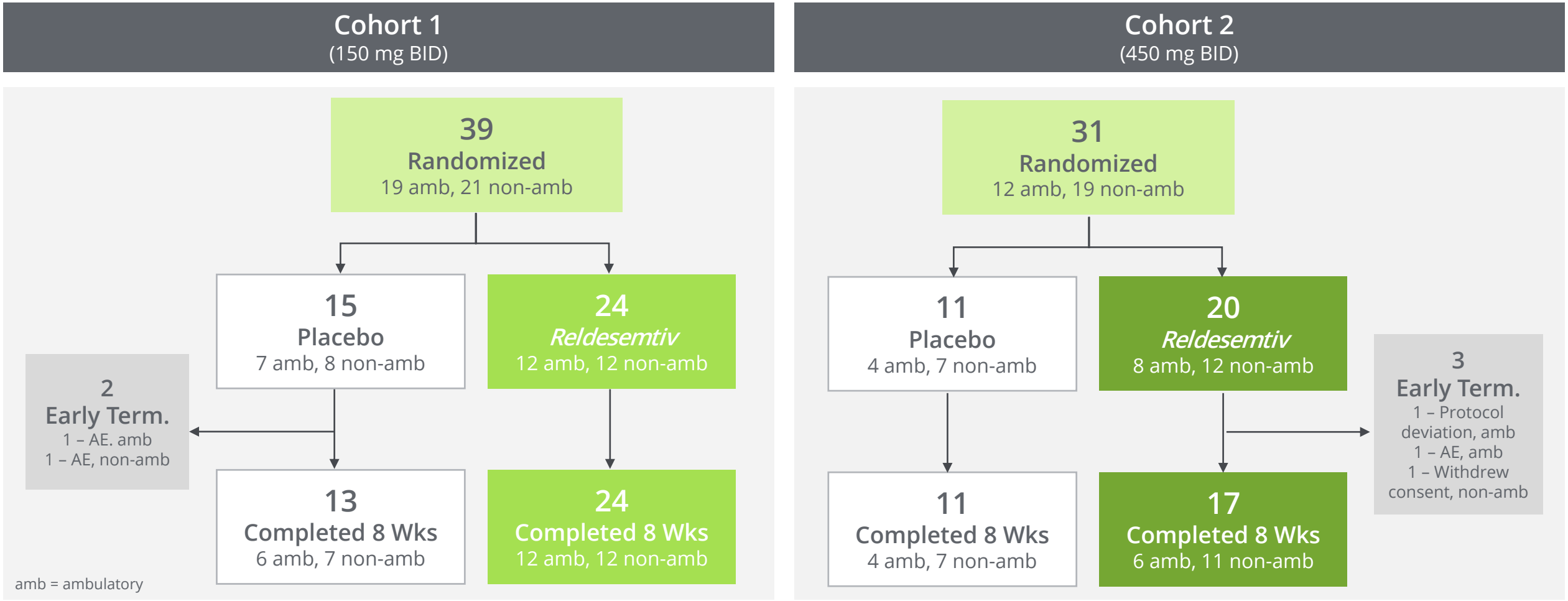
Reldesemtiv in Patients with ALS

FORTITUDE ALS

North America	Australia	Europe
57 Sites	5 sites	3 sites

375 Patients Enrolled

CY 5021: Phase 2 Trial in SMA; Patient Disposition



CY 5021: Demographics & Baseline Characteristics

Demographics

	Placebo (N=27)	150 mg BID (N=26)	450 mg BID (N=17)
Age, years, mean (SD)	28.5 (16.03)	27.8 (11.96)	32.6 (17.92)
Age < 18 years, n (%)	8 (30.8%)	7 (29.2%)	5 (25.0%)
Male, n (%)	15 (57.7%)	14 (58.3%)	12 (60.0%)
Caucasian, n (%)	22 (84.6%)	23 (95.8%)	18 (90.0%)
BMI, mean (SD)	24.3 (7.39)	25.4 (9.24)	25.1 (5.52)
SMA Type II, n (%)	2 (7.7%)	3 (12.5%)	1 (5.0%)
SMA Type III, n (%)	24 (92.3%)	21 (87.5%)	19 (95.0%)
Ambulatory, n (%)	11 (42.3%)	12 (50.0%)	8 (40.0%)

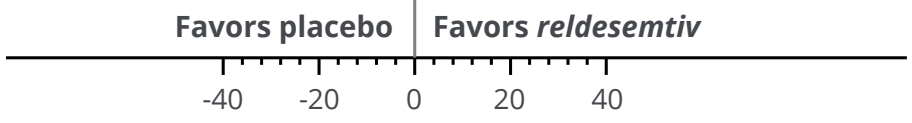
Baseline Characteristics

mean (SD)	Placebo (N=27)	150 mg BID (N=26)	450 mg BID (N=17)
% Predicted FVC	84.4 (22.39)	83.1 (22.05)	85.9 (21.21)
MEP (cm H2O)	86.5 (36.87)	94.0 (43.44)	88.9 (47.68)
MIP (cm H2O)	-106 (38.45)	-109 (44.18)	-101 (43.15)
HFMS-E Score	30.6 (16.60)	36.0 (17.17)	30.4 (16.25)
RULM Total Score	31.0 (8.74)	34.8 (7.90)	33.7 (8.00)
Timed Up and Go (sec)	21.5 (11.00)	15.7 (6.52)	22.8 (16.05)
Six Minute Walk (m)	240.1 (111.8)	316.6 (68.96)	311.0 (107.3)
SMA-HI Total Score	33.1 (19.91)	NA	39.7 (17.11)

CY 5021: Change from Baseline at Week 8

150 mg BID vs. Placebo

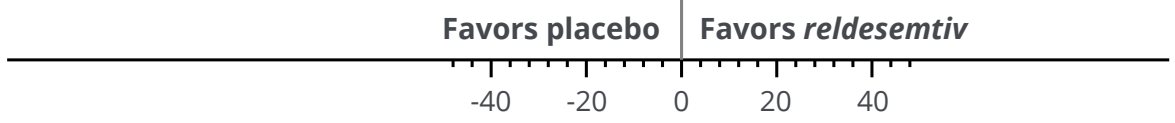
	No. of Patients (pbo / *reldesemtiv*)	Estimate	*P* value
% Predicted FVC	26/24	-1.14	0.4411
MIP	26/24	-2.94	0.5382
MEP	26/24	**11.69**	**0.0378**
Muscle Mega-Score	26/24	-4.59	0.5461
HFMS-E	26/24	-0.38	0.6849
RULM	26/24	0.61	0.2878
6MWD	11/12	7.72	0.4684
TUG*	9/10	0.78	0.7612



*Difference between placebo vs. *reldesemtiv* pbo, placebo; LSM, least squares mean

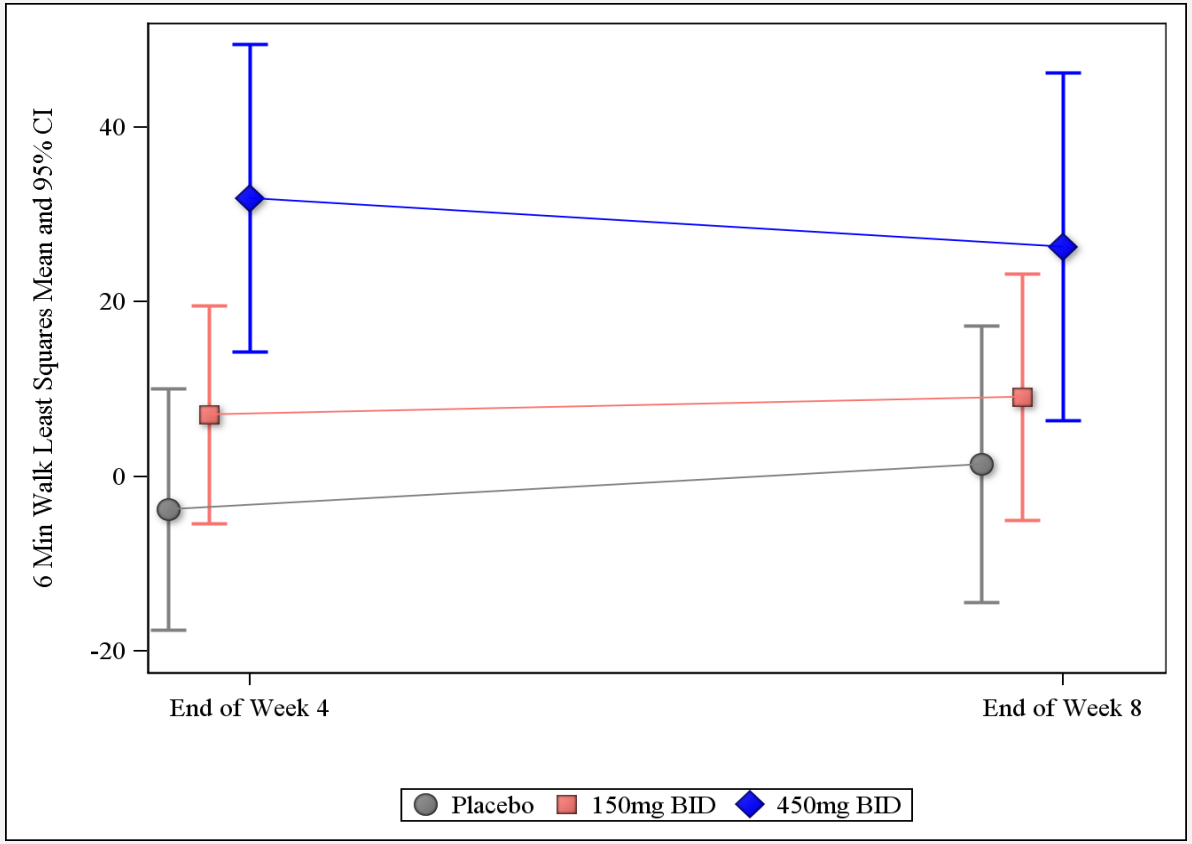
450 mg BID vs. Placebo

	No. of Patients (pbo / *reldesemtiv*)	Estimate	*P* value
% Predicted FVC	26/19	-2.04	0.1980
MIP	26/19	0.99	0.8464
MEP	26/19	**13.15**	**0.0298**
Muscle Mega-Score	26/19	-15.2	0.0672
HFMS-E	26/19	-1.00	0.3091
RULM	26/19	-0.12	0.8512
6MWD	11/7	**24.89**	**0.0584**
TUG*	9/4	3.10	0.3502
SMA-HI*	10/19	0.93	0.8281

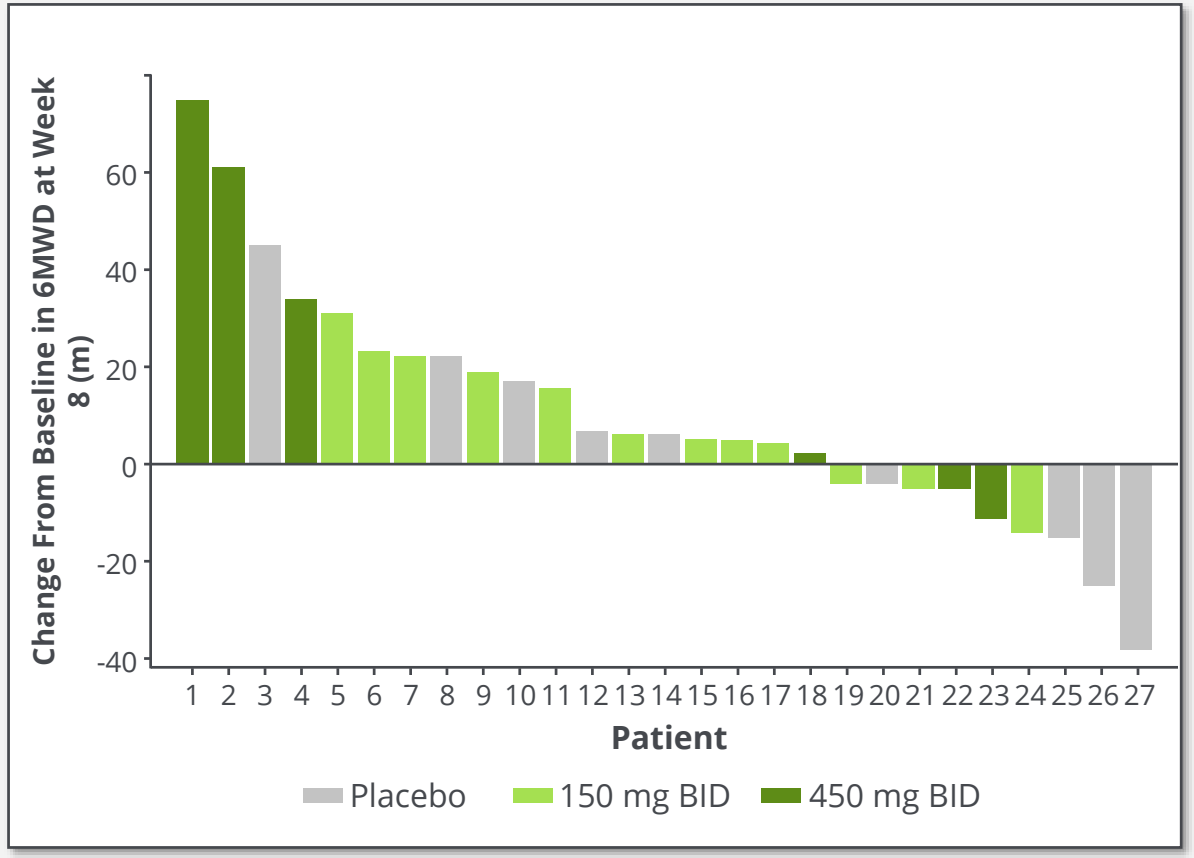


CY 5021: Dose-Dependent Increase in 6MWD

Change from Baseline Over Time

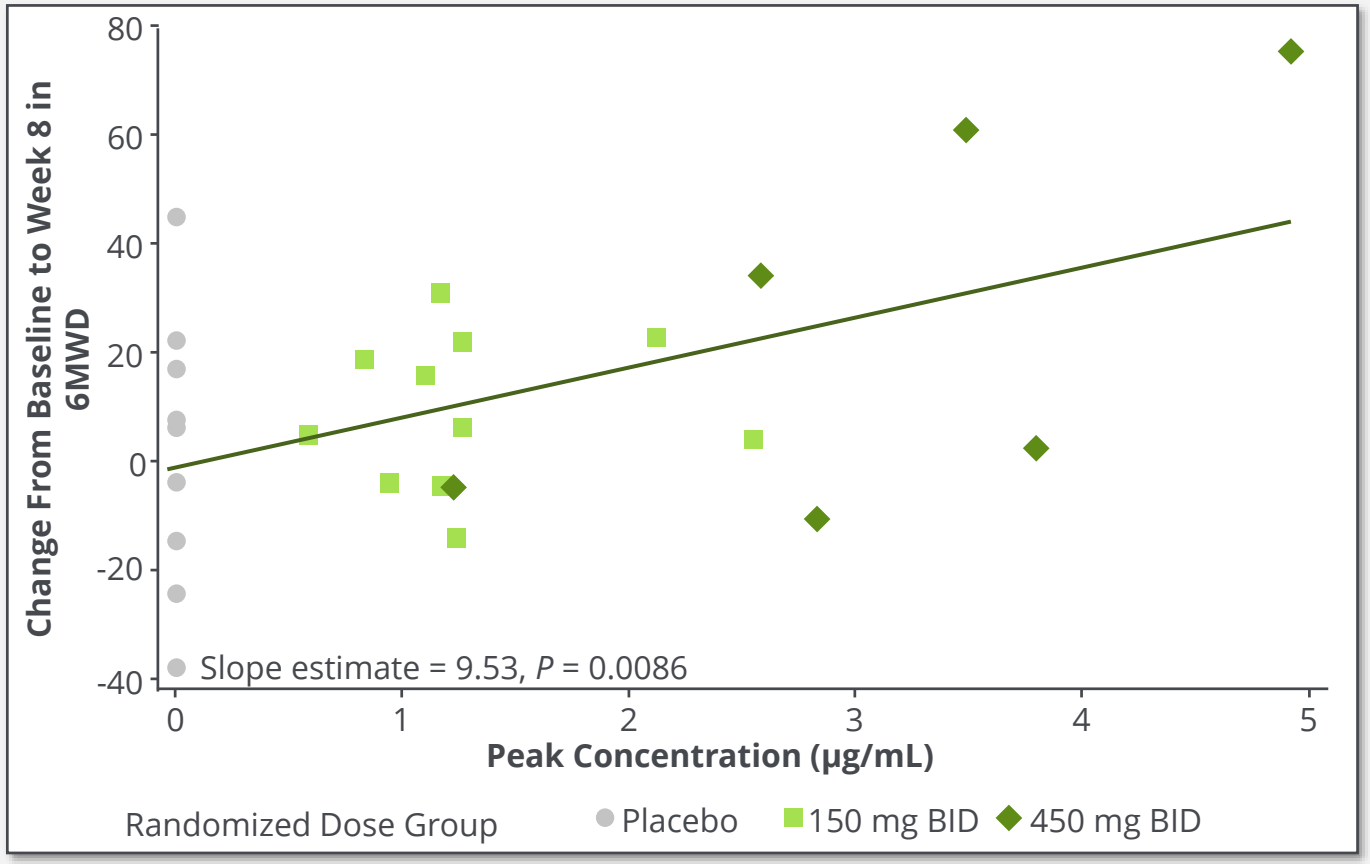


Change from Baseline at Week 8



CY 5021: Concentration-Dependent Increase in 6MWD

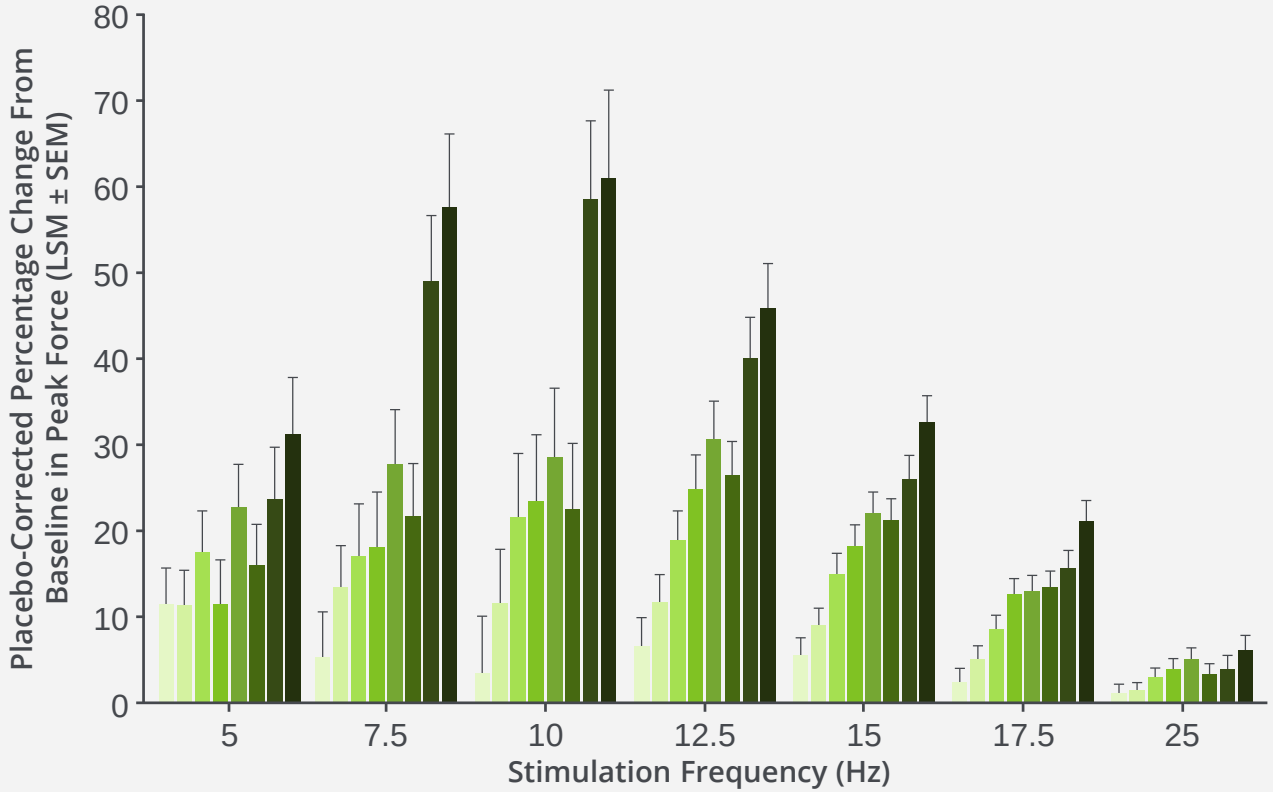
6 Minute Walk Change from Baseline at Week 8 versus C_{max}



C_{max}, maximum concentration
Data Transfer on 24MAY18

Force-Frequency Response in Healthy Subjects after Treatment with *Reldesemtiv*

Data From CY 5013: A Phase 1, Double-Blind, Randomized, Placebo-Controlled, Single-Dose, 4-Period Crossover Study of *Reldesemtiv* in Healthy Male Volunteers

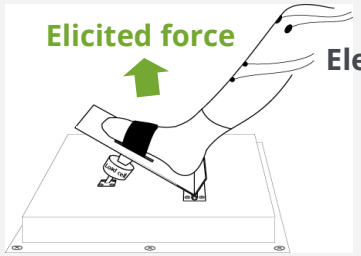


BID, twice daily; LSM, least squares mean; SEM, standard error of the mean

>0–1 µg/mL	(n = 34)
>1–2 µg/mL	(n = 43)
>2–3 µg/mL	(n = 23)
>3–4 µg/mL	(n = 18)
>4–5 µg/mL	(n = 16)
>5–6 µg/mL	(n = 17)
>6–7 µg/mL	(n = 10)
>7 µg/mL	(n = 7)

Expected concentrations on 150 mg BID in CY 5021

Expected concentrations on 450 mg BID in CY 5021



Electrical stimulus

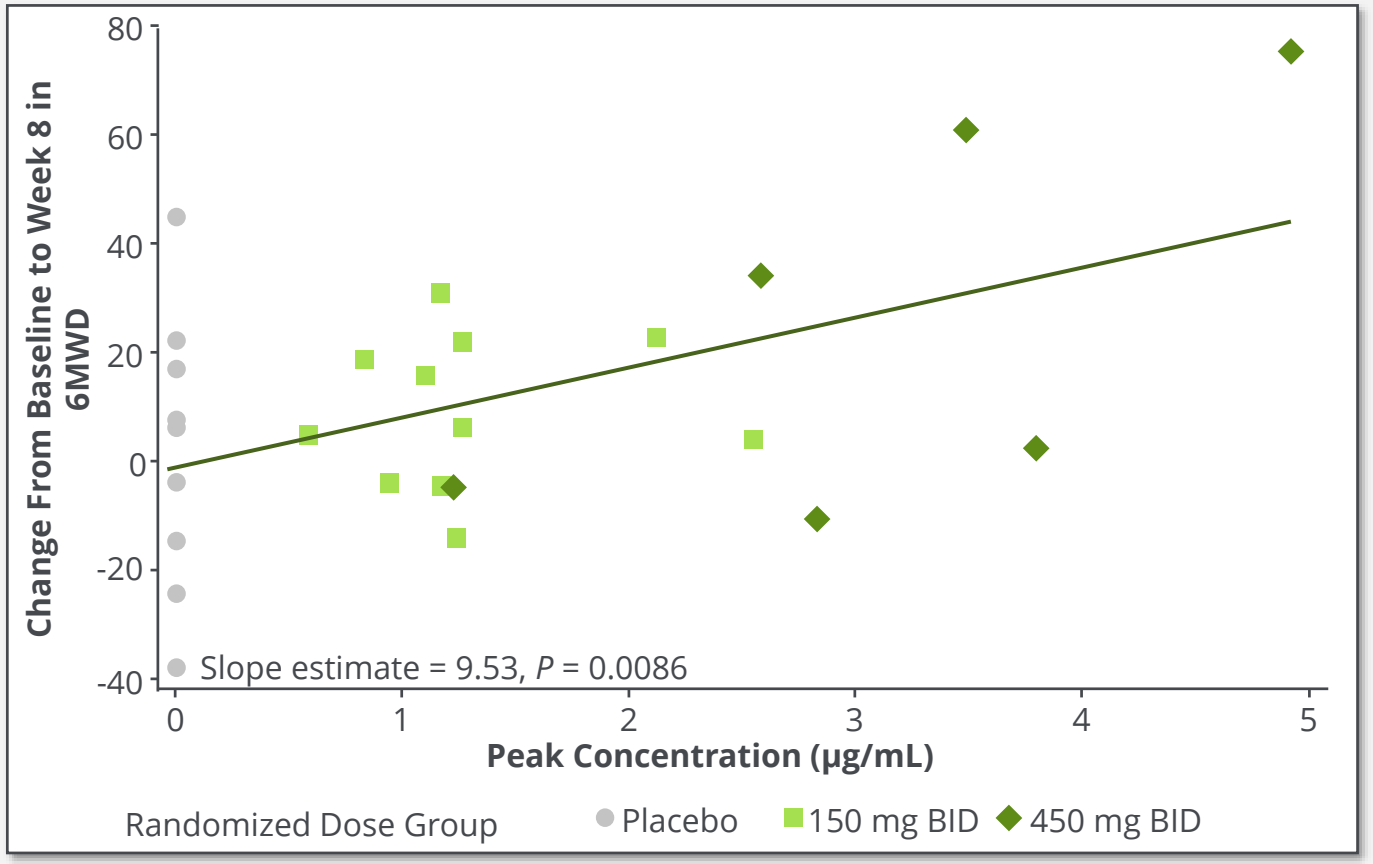
Electromyography recording

Increase in Muscle Force in Response to Nerve Stimulation Confirms

Translation of MOA into Humans

CY 5021: Concentration-Dependent Increase in 6MWD

6 Minute Walk Change from Baseline at Week 8 versus C_{max}



C_{max}, maximum concentration
Data Transfer on 24MAY18

CY 5021: Adverse Events

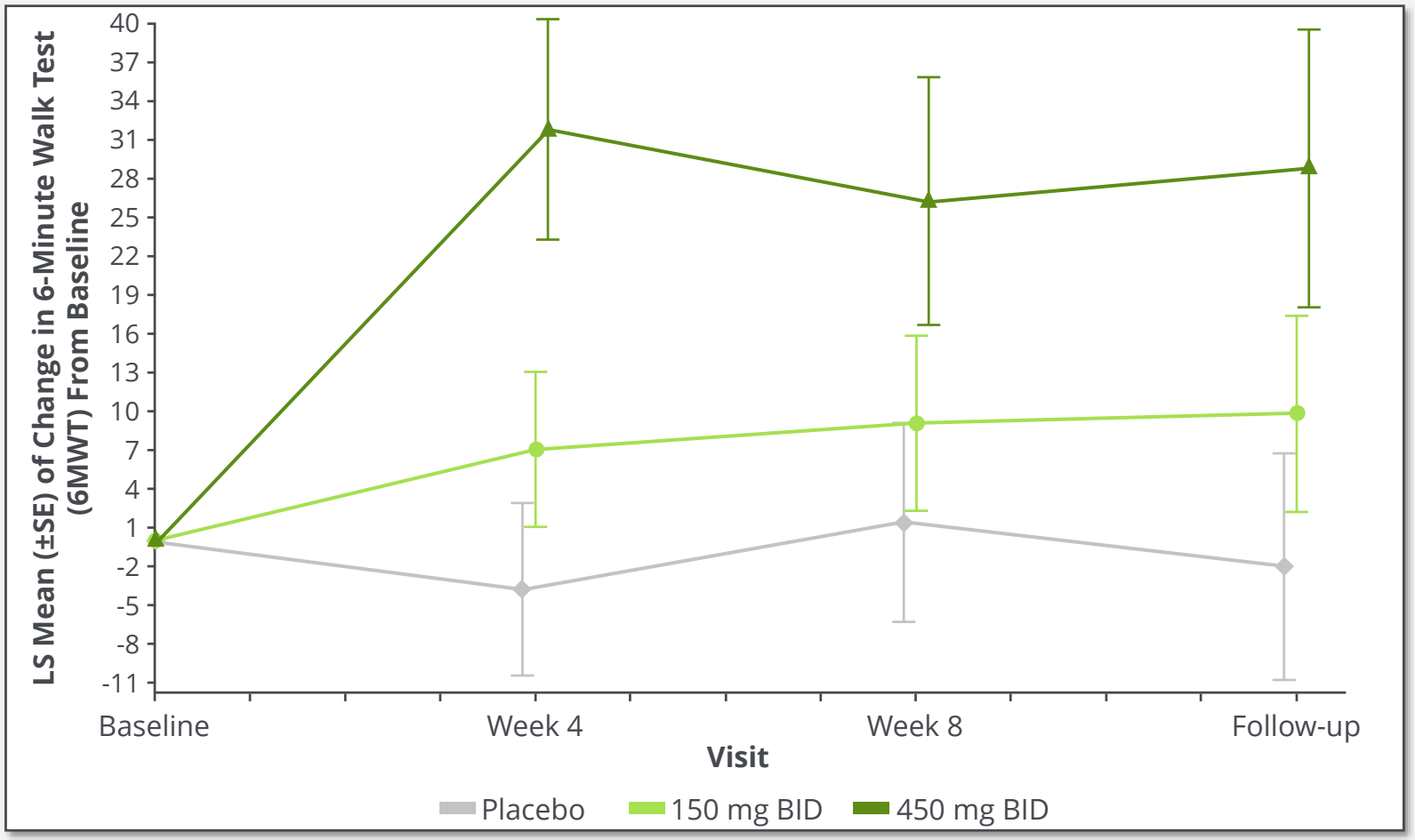
Treatment-Emergent Adverse Events (≥ 2 Patients on *Reldesemtiv*)

Preferred Term, n (%)	Placebo (N=26)	150 mg BID (N=24)	450 mg BID (N=20)	All Active Doses (N=44)	Overall (N=70)
Patients with AEs	24 (92.3%)	20 (83.3%)	17 (85.0%)	37 (84.1%)	61 (87.1%)
Headache	5 (19.2%)	6 (25.0%)	5 (25.0%)	11 (25.0%)	16 (22.9%)
Constipation	0	3 (12.5%)	2 (10.0%)	5 (11.4%)	5 (7.14%)
Nausea	5 (19.2%)	3 (12.5%)	2 (10.0%)	5 (11.4%)	10 (14.3%)
Fatigue	4 (15.4%)	2 (8.33%)	2 (10.0%)	4 (9.09%)	8 (11.4%)
Diarrhoea	2 (7.69%)	2 (8.33%)	1 (5.00%)	3 (6.82%)	5 (7.14%)
Dyspepsia	0	2 (8.33%)	1 (5.00%)	3 (6.82%)	3 (4.29%)
Nasopharyngitis	3 (11.5%)	3 (12.5%)	0	3 (6.82%)	6 (8.57%)
Abdominal pain upper	1 (3.85%)	2 (8.33%)	0	2 (4.55%)	3 (4.29%)
Blood creatine phosphokinase increased	0	0	2 (10.0%)	2 (4.55%)	2 (2.86%)
Contusion	0	2 (8.33%)	0	2 (4.55%)	2 (2.86%)
Decreased appetite	1 (3.85%)	1 (4.17%)	1 (5.00%)	2 (4.55%)	3 (4.29%)
Fall	3 (11.5%)	1 (4.17%)	1 (5.00%)	2 (4.55%)	5 (7.14%)
Hypoaesthesia	0	1 (4.17%)	1 (5.00%)	2 (4.55%)	2 (2.86%)
Respiratory tract congestion	0	2 (8.33%)	0	2 (4.55%)	2 (2.86%)
Respiratory tract infection	0	1 (4.17%)	1 (5.00%)	2 (4.55%)	2 (2.86%)
Skin abrasion	0	0	2 (10.0%)	2 (4.55%)	2 (2.86%)
Upper respiratory tract infection	4 (15.4%)	0	2 (10.0%)	2 (4.55%)	6 (8.57%)

Adverse Events Resulting in Early Treatment Termination

Preferred Term, n (%)	Placebo (N=26)	150 mg BID (N=24)	450 mg BID (N=20)
Patients with AEs	2(7.69%)	0	1(5.00%)
Blood creatine phosphokinase increased	0	0	1(5.00%)
Asthenia	1(3.85%)	0	0
Gait disturbance	1(3.85%)	0	0
Muscular weakness	1(3.85%)	0	0

CY 5021: 6MWD Changes From Baseline to Follow-Up



Persistence of Effect Four Weeks after the Last Dose

CY 5021: Disease Burden Assessed by the SMA-Health Index Decreases as 6MWD Increases

- The SMA Health Index (SMA-HI) is a patient reported outcome measure
  - Assesses SMA disease burden across a variety of functional domains
  - Higher scores indicate greater disease burden
- The correlations between the change from baseline to Week 8 in the Six Minute Walk Distance with the changes in the SMA-HI total score and the 9 functional domain scores were calculated
  - All 10 correlations were negative, indicating that disease burden assessed by the SMA-HI tended to decrease as the Six Minute Walk Distance increased
  - 6 correlations were nominally (or borderline; i.e., $p \leq 0.1$) statistically significant

SMA-HI Domain	Pearson's Correlation Coefficient	p-value
SMA-HI Total Score	**-0.853**	**0.028**
Back, Chest, & Abdominal Function	-0.746	0.095
Fatigue	-0.897	0.012
Activity Participation	-0.820	0.045
Hand and Finger Strength	-0.738	0.101

CY 5021: Potential Clinical Benefit of *Reldesemtiv* in SMA

- Treatment with *reldesemtiv* in CY 5021 showed potentially clinically beneficial effects in adolescent and adult patients with SMA as evidenced primarily by increases vs. placebo in:
  - Six Minute Walk Distance
  - Maximal Expiratory Pressure
- Data from CY 5021 support the evaluation of higher doses of *reldesemtiv* in future clinical trials in SMA given:
  - No efficacy plateau was demonstrated
  - No dose-limiting safety or tolerability issues were observed
  - Exposures were below those that were well tolerated and associated with increased pharmacodynamic activity in Phase 1

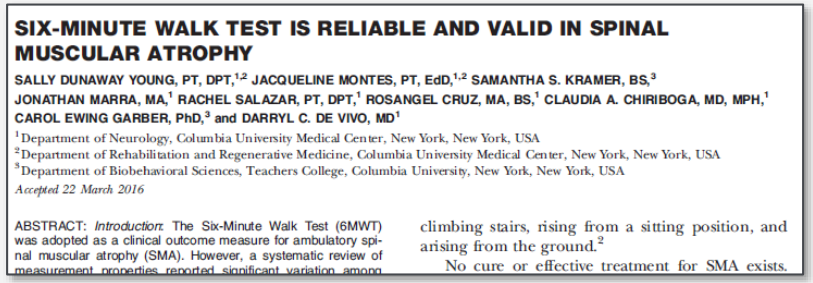
This hypothesis-generating study provides the first data indicating that a **muscle-directed therapy,** namely the FSTA, *reldesemtiv*, may be clinically beneficial in patients with SMA

6MWD is Validated, Approvable Endpoint

Drug Name	Disease	Duration of Treatment (weeks)	Study Size	Improvement in 6MWD compared to placebo (meters)	Indication	6MWD in Label
ALDURAZYME (laronidase)	MPS I Hurler/Hurler-Scheie	26	45	38 (p = 0.07)	Increase walking capacity	Yes
ELAPRASE (idursulfase)	MPS II Hunter syndrome	53	64	35 (p = 0.01)	Increase walking capacity	Yes
VIMIZIM (elosulfase)	MPS IVA Morquio A syndrome	24	176	22.5 (p = 0.017)	Treat MPS IVA	Yes
LUMIZYME (alglucosidase alpha)	GAA deficiency Pompe Disease	78	90	28 (p=0.06)	Pompe Disease	Yes
TRACLEER (bosentan)	Pulmonary Hypertension	213	16	35 (low dose), 54 (high dose) (p = 0.01, 0.0001)	Increase exercise ability	Yes
LETAIRIS (ambrisentan)	Pulmonary Hypertension	201	12	27 (low dose), 39 (high dose) (p = 0.008, <0.001)	Increase exercise ability	Yes

6 Minute Walk Distance Used as Endpoint in Clinical Trials Outside of SMA and Included in Labels

6MWD is Reliable, Valid Outcome Measure in SMA



SIX-MINUTE WALK TEST IS RELIABLE AND VALID IN SPINAL MUSCULAR ATROPHY

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[3]Department of Biobehavioral Sciences, Teachers College, Columbia University, New York, New York, USA

Accepted 22 March 2016

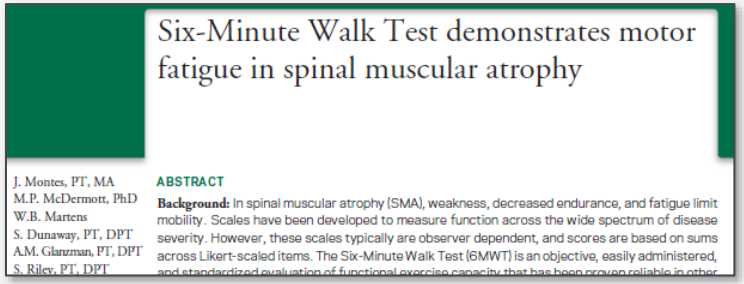
ABSTRACT: *Introduction:* The Six-Minute Walk Test (6MWT) was adopted as a clinical outcome measure for ambulatory spinal muscular atrophy (SMA). However, a systematic review of measurement properties reported significant variation among

climbing stairs, rising from a sitting position, and arising from the ground.[2]

No cure or effective treatment for SMA exists.

- Outcome measure in ambulatory SMA **captures disease severity, demonstrates the required measurement properties,** confirms **reliability and validity** of the 6MWT in ambulatory SMA patients
- Supports acceptance of the 6MWT as **a valuable outcome measure for ambulatory SMA** and the **primary endpoint of choice**

Dunaway Young, S., Montes, J., Kramer, S.S., Marra, J., Salazar, R., Cruz, R., Chiriboga, C.A., Garber, C.E. and De Vivo, D.C.. Six-minute walk test is reliable and valid in spinal muscular atrophy. *Muscle & nerve.* 2016 May 13.



Six-Minute Walk Test demonstrates motor fatigue in spinal muscular atrophy

J. Montes, PT, MA
M.P. McDermott, PhD
W.B. Martens
S. Dunaway, PT, DPT
A.M. Glanzman, PT, DPT
S. Riley, PT, DPT

ABSTRACT

Background: In spinal muscular atrophy (SMA), weakness, decreased endurance, and fatigue limit mobility. Scales have been developed to measure function across the wide spectrum of disease severity. However, these scales typically are observer dependent, and scores are based on sums across Likert-scaled items. The Six-Minute Walk Test (6MWT) is an objective, easily administered, and standardized evaluation of functional exercise capacity that has been proven reliable in other

Cross-sectional study of 18 ambulatory participants showed:

- 6MWT **correlates with established outcome measures** and is sensitive to fatigue-related changes
- Assessments of walking ability and endurance are direct measures of functional mobility and considered **inherently clinically meaningful**

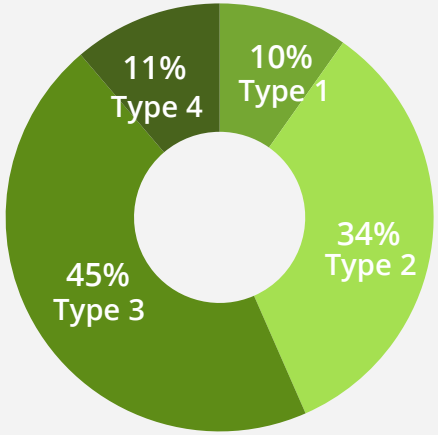
Montes J, McDermott MP, Martens WB, Dunaway S, Glanzman AM, Riley S, Quigley J, Montgomery MJ, Sproule D, Tawil R, Chung WK. Six-Minute Walk Test demonstrates motor fatigue in spinal muscular atrophy. *Neurology*. 2010, Mar 9.

Growing Population of Ambulatory Patients

Clinical Manifestation:

- **Type 1** patients treated with *nusinersen* survive but with significant disability
- **Type 2** patients have delayed motor milestones; Most advanced milestone achieved is sitting unsupported. These children suffer from general weakness
- **Type 3** patients can usually stand and walk but have increasingly limited mobility. They have difficulties running, climbing steps or rising from a chair, depending the severity of the disease
- **Type 4** patients have symptoms similar to Type 3s. Patients are typically able to walk but can no longer run

SMA Prevalence (US)



~10,000 living SMA patients

Life Expectancy

Type 1	4 Years
Type 2	30 Years
Type 3	78 Years
Type 4	78 Years

2018: ~3,500-5,000 ambulatory SMA patients

2023: Potentially up to 10,000 ambulatory SMA patients*

*Assuming advent of genetically directed therapies alter Type 1 and Type 2 phenotype

Source: Proprietary market research and company estimates

Perspectives on CY 5021 in Spinal Muscular Atrophy

PANEL DISCUSSION

The Promise of FSTAs in Neuromuscular Disease

MODERATOR

Andrew Wolff, MD, FACC

SVP, Chief Medical Officer
Cytokinetics

Jacqueline Montes, PT, EdD, NCS

Assistant Professor of Clinical Rehabilitation and Regenerative Medicine, Columbia University Irving Medical Center

Jinsy Andrews, MD, MSc, FAAN

Assistant Professor of Neurology, Director of Neuromuscular Clinical Trials, Columbia University

CARDIAC MUSCLE

CARDIAC MUSCLE

PROGRAM OVERVIEW

Fady Malik, MD, PhD
EVP, Research & Development

Heart Failure: Many Phenotypes with Unmet Need

Decreased Cardiac Contractility

Heart Failure with Reduced Ejection Fraction (HFrEF)

Genetic Dilated Cardiomyopathy

Pulmonary Hypertension with Right Ventricular Heart Failure

Increased / Preserved Cardiac Contractility

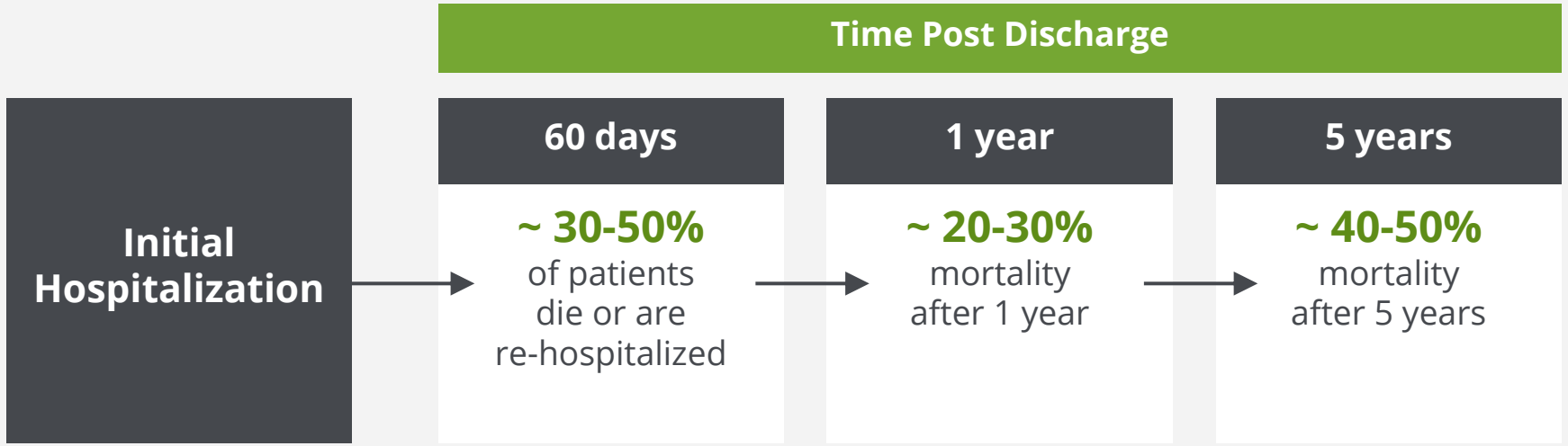
Non-obstructive Hypertrophic Cardiomyopathy (nHCM)

Obstructive Hypertrophic Cardiomyopathy (oHCM)

Heart Failure with Preserved Ejection Fraction (certain HFpEF subsets)

HFrEF: High Mortality and Hospital Readmission Rates

High Mortality and Hospital Readmission Rates



Acute heart failure is the most frequent cause of hospitalization in people > 65

> 1 million hospitalizations with primary diagnosis of heart failure annually in US

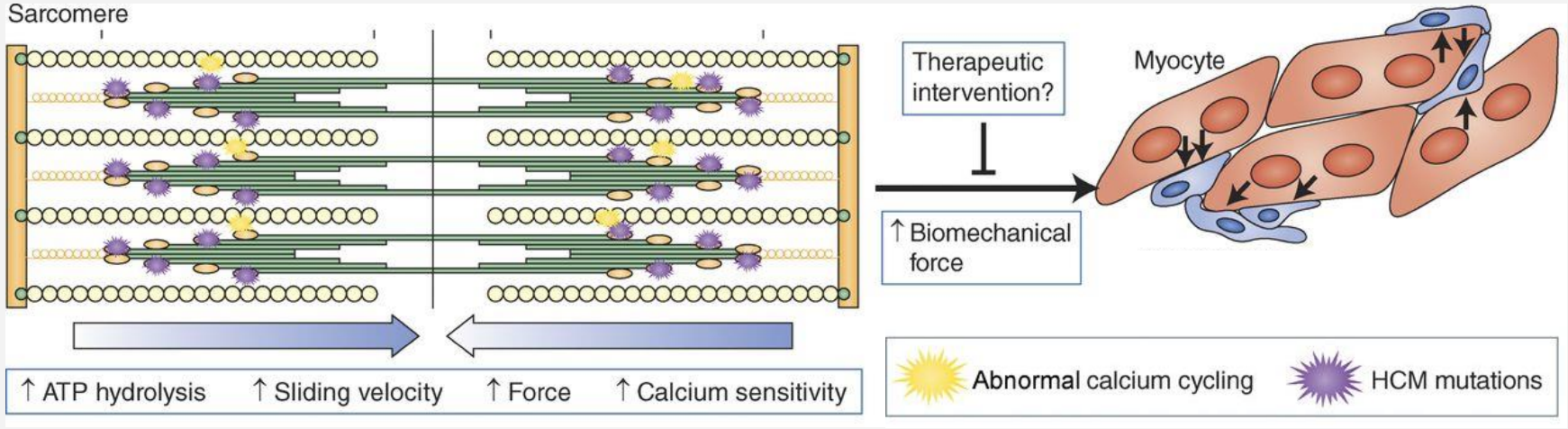
Adams et al. Am Heart J 2006; 149:209-16
Dickstein et al. Eur Heart J 2008;29:2388-442
Chen et al. JAMA 2011;306:1669-78

Loehr et al. Am J Cardiol 2008;101:1016-22
Roer et al. Circulation 2012;125:32-220

Significant Unmet Need Exists To Address Mortality And Hospital Readmission

HCM: Lack of Therapy Targeting Underlying Disease Biology

HCM is a Disease of the Sarcomere

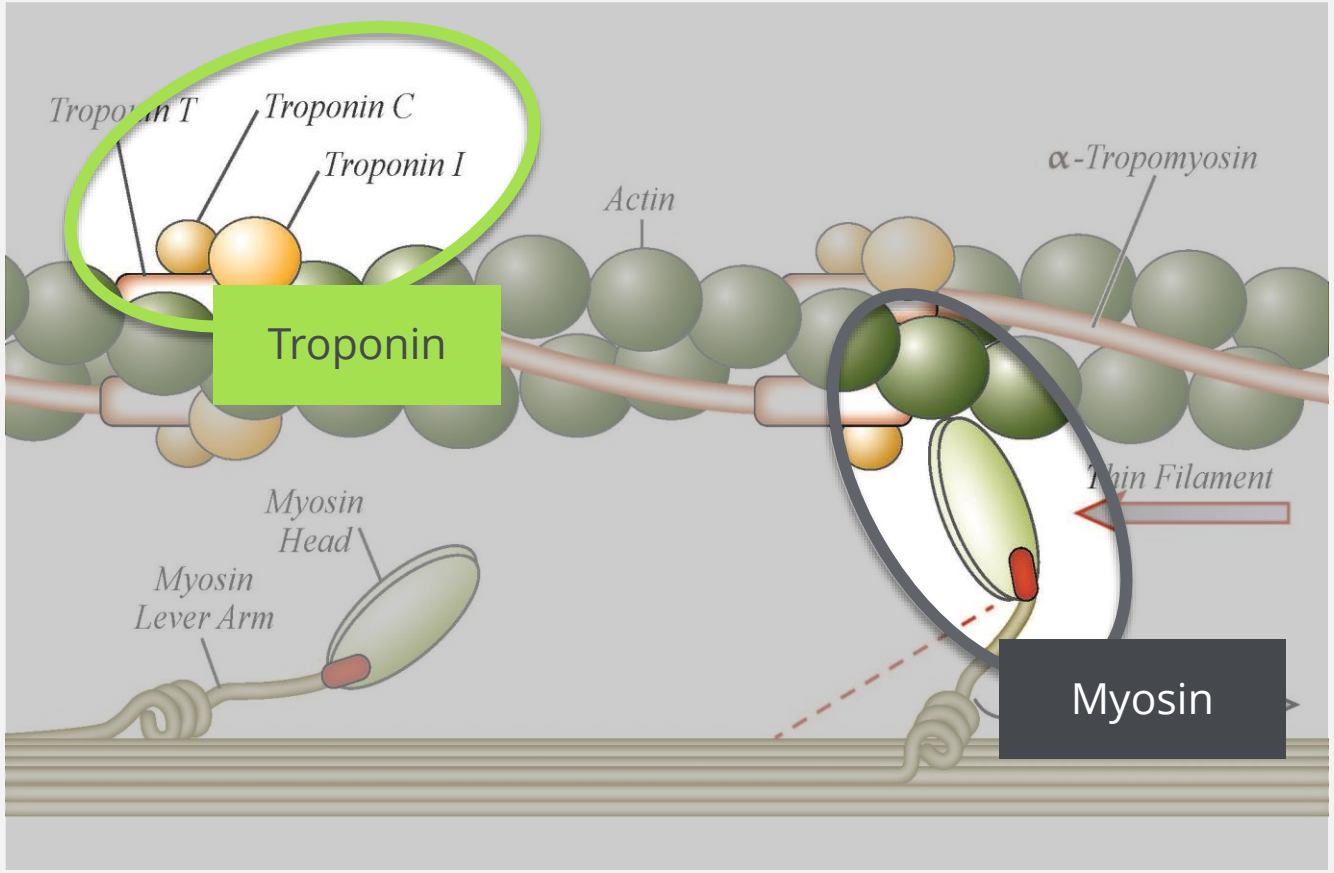


Teekakirikul et al., JCB 2012

Current Medical Therapy:
Indirect mechanisms of action with systemic side effects
Variable efficacy, often inadequate
Treatment failure means resorting to surgical myomectomy or percutaneous ablation

Targeted Oral Therapy Addressing Disease Etiology May Improve Symptoms, Exercise Capacity, and Slow Disease Progression

The Cardiac Sarcomere and Therapeutic Intervention



Cardiac Sarcomere Activators

Omecamtiv Mecarbil

TARGET: MYOSIN

AMG 594

TARGET: TROPONIN

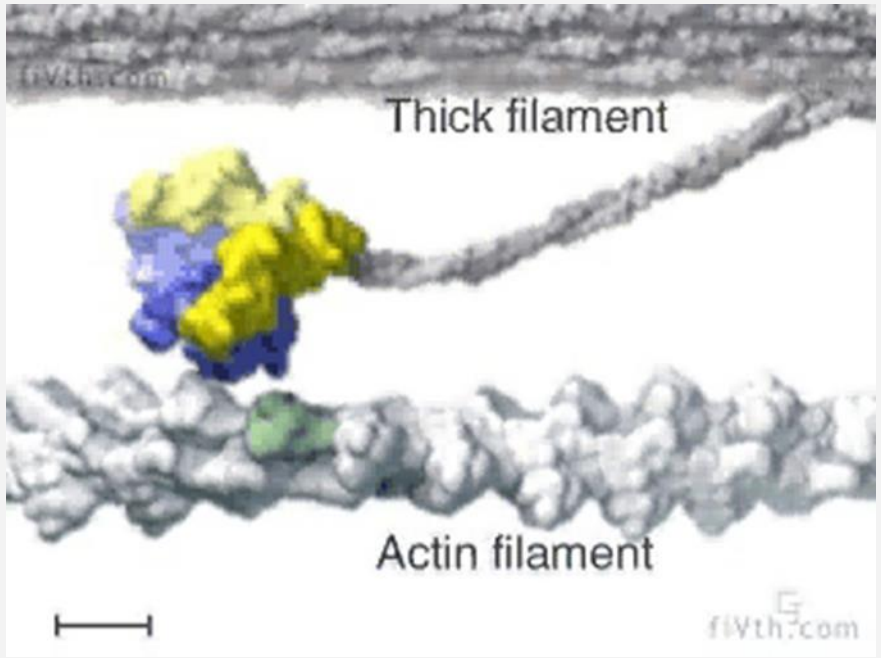
Cardiac Sarcomere Inhibitor

CK-274

TARGET: MYOSIN

Omecamtiv Mecarbil: Key Takeaways

Omecamtiv mecarbil **increases entry rate of myosin into tightly-bound, force-producing state with actin**
"More hands on the rope"



Vale & Milligan, Science 2000, Malik, et al Science 2011 Shen, et al, Circ HF, 2011

- No increase in myocyte calcium
- Increases duration of systole
- Increases stroke volume
- No change in blood pressure
- Decrease in heart rate
- No change in rate of contraction
- No increase in MVO_2

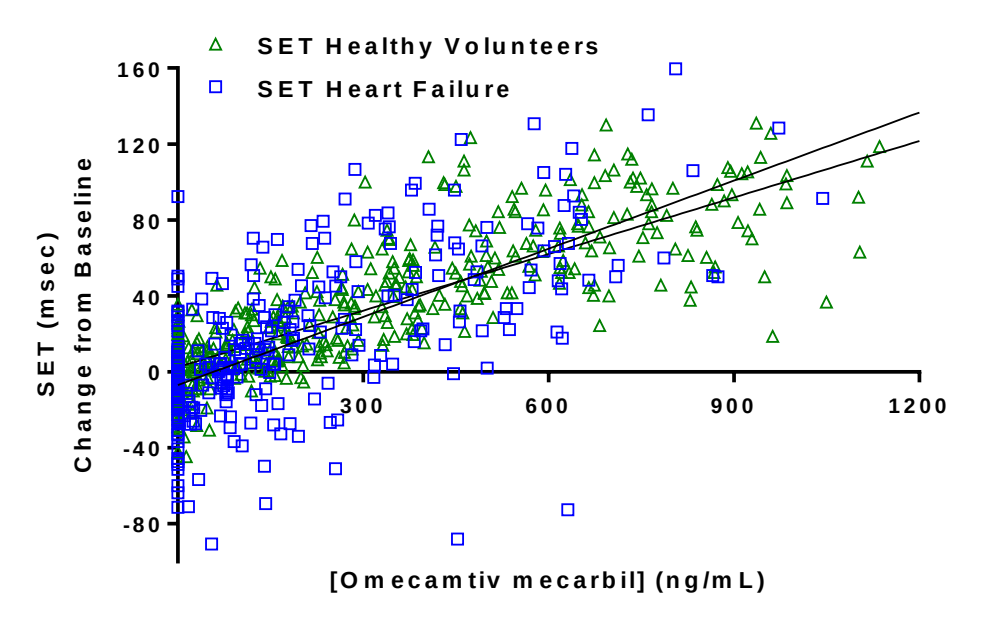
Omecamtiv Mecarbil: Development Program

Phase 1-2a	**Phase 1-2a IV** PK/PD, tolerability Healthy Volunteers Stable HF Patients: EF < 40%, stable therapy	**Phase 1-2a Oral** PK, tolerability Healthy Volunteers Stable HF Patients: EF ≤ 35%, stable therapy
Phase 2	**ATOMIC-AHF** (N = 613) IV formulation in Acute HFrEF (EF ≤ 40%) Evaluate safety, tolerability, echo PD, & clinical efficacy	**COSMIC-HF** (N = 448) Oral formulations in Chronic HFrEF (EF ≤ 40%) Evaluate PK, safety, tolerability, echo PD
Phase 3	**GALACTIC-HF** (N = 8000) Oral dosing Evaluate clinical efficacy Establish safety and tolerability	

Evaluation across a range of heart failure patient populations
17 Phase 1 & 2 Studies completed; >3000 subjects dosed; >1000 subject years of exposure

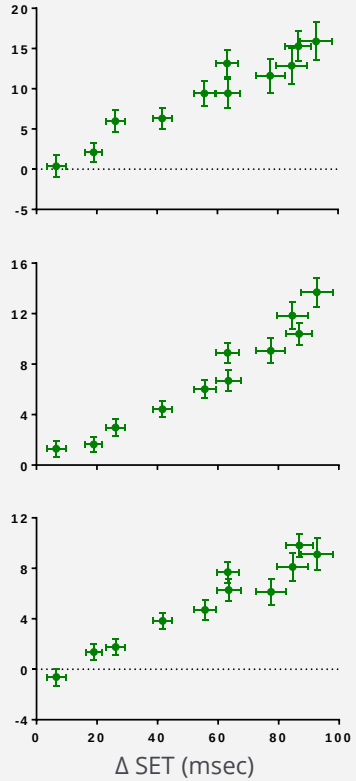
Omecamtiv Mecarbil: Increases in Systolic Ejection Time (SET) Underlie the Improvements in Cardiac Function

Healthy Volunteers vs. Stable HF Patients



Teerlink JR, *et al. Lancet* 2011; 378: 667–75.
Cleland JGF, *et al. Lancet* 2011; 378: 676–83
SEM, standard error of the mean

Healthy Volunteers



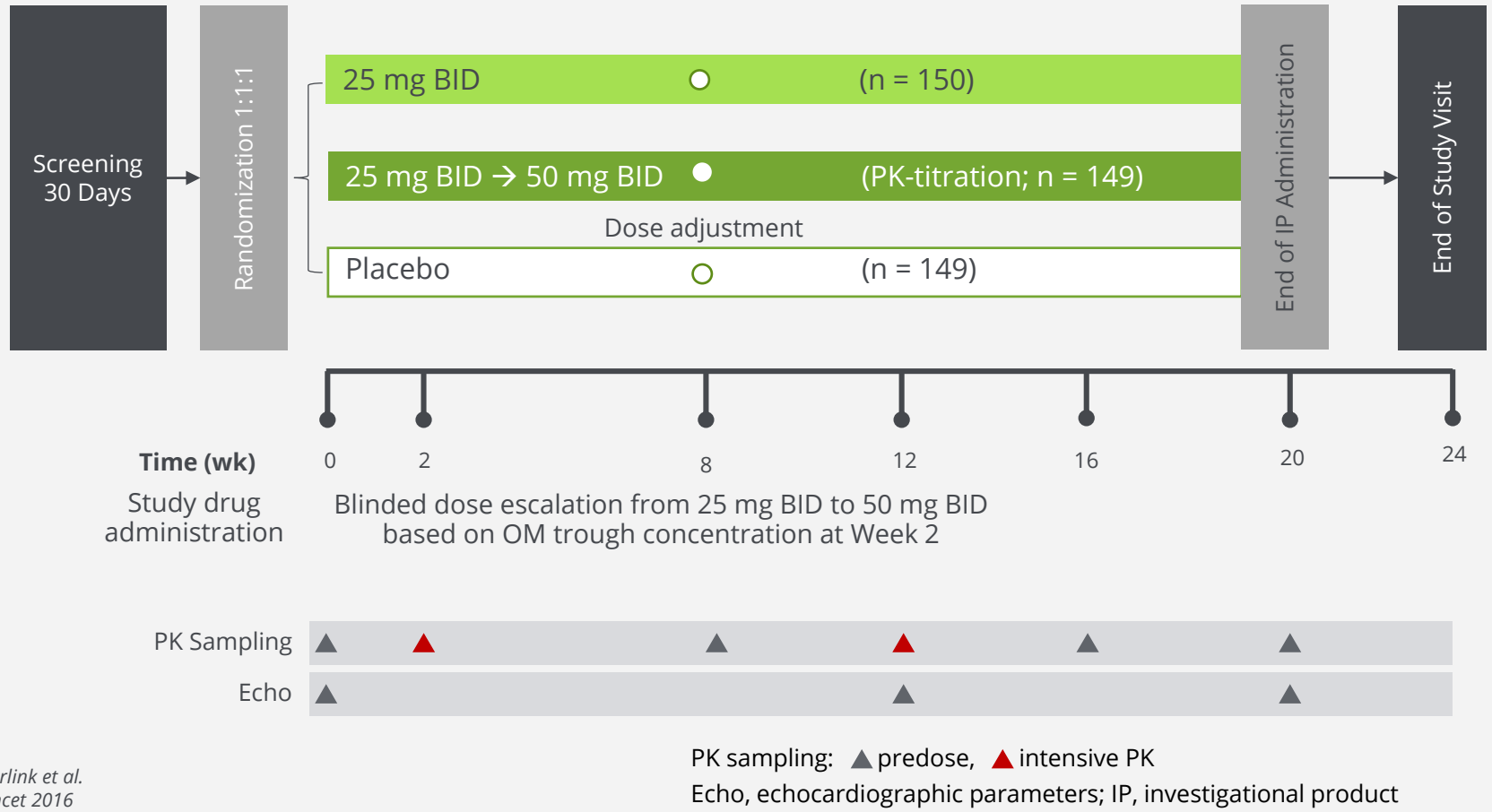
Δ Stroke Volume (mL)

Δ Fractional Shortening (% points)

Δ Ejection Fraction (% points)

Δ = placebo corrected change from baseline; Mean ± SEM

Study Design



PK sampling: ▲predose, ▲intensive PK

Echo, echocardiographic parameters; IP, investigational product

Teerlink et al. Lancet 2016

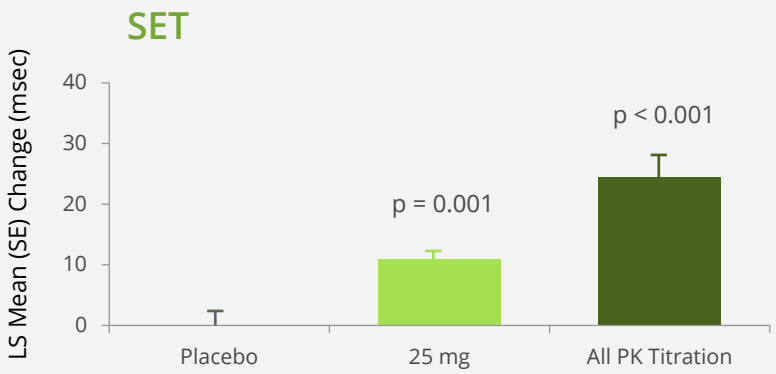
PK-based dose adjustment

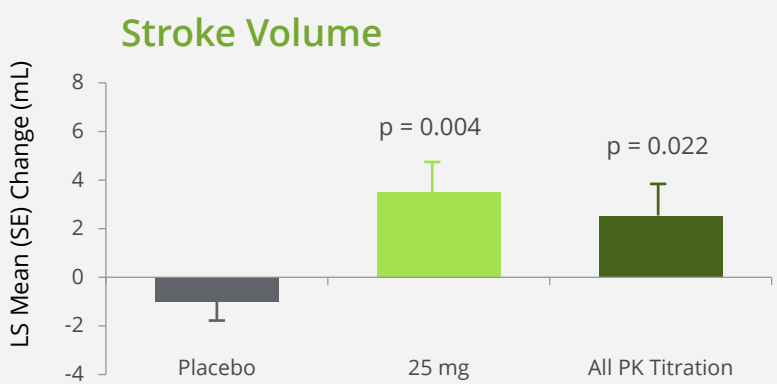
All subjects started at 25mg BID

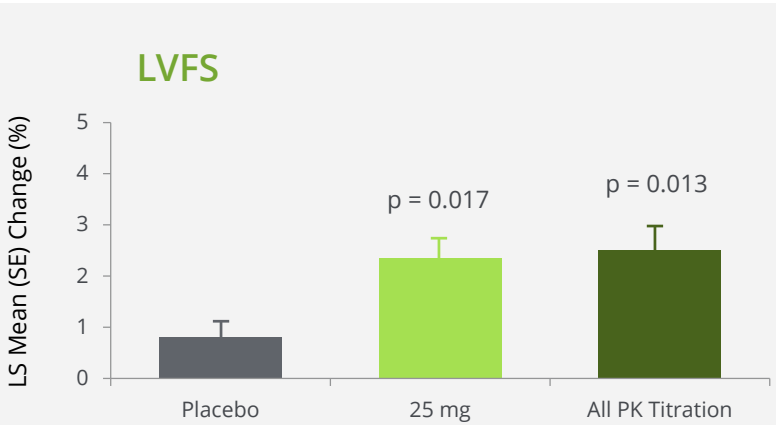
- At 2 weeks, C_{trough} was assessed
- If the value was < 200 ng/mL, the subject was uptitrated to 50mg BID
- If the value was ≥ 200 ng/mL, the subject was maintained on 25 mg BID

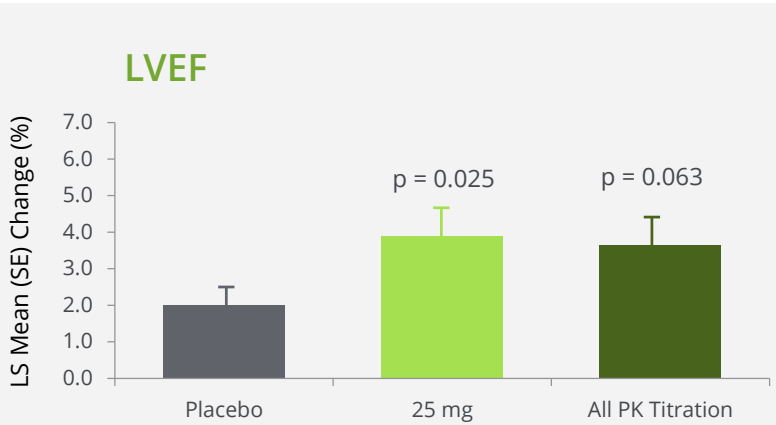
Pharmacodynamic Effects

Dose-dependent Increases in Cardiac Performance







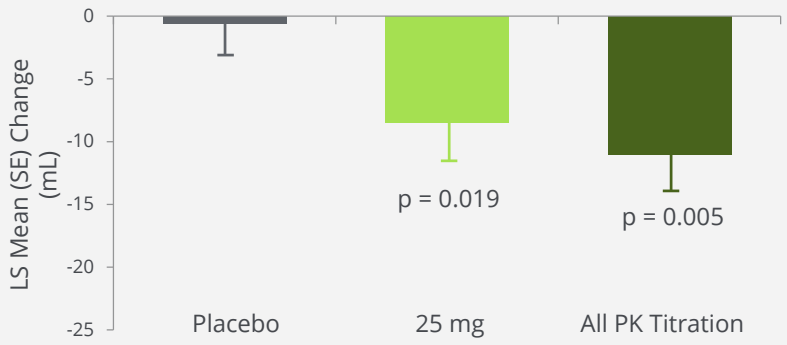


LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening;
SE, standard error; SET, systolic ejection time ; all p values are nominal without multiplicity adjustment.

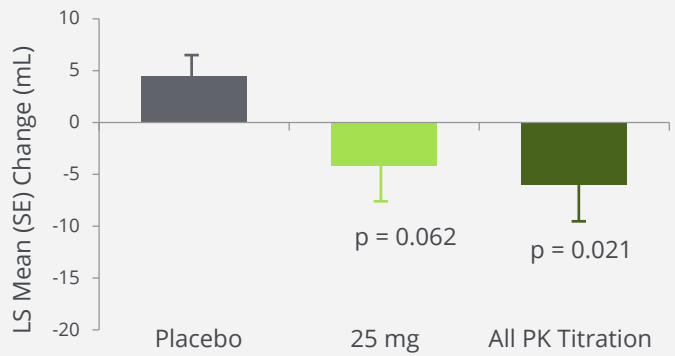
Pharmacodynamic Effects

LVESD left ventricular end systolic diameter
LVEDD left ventricular end diastolic diameter
LVESV left ventricular end systolic volume
LVEDV left ventricular end diastolic volume
All p values are nominal without multiplicity adjustment

LVESV

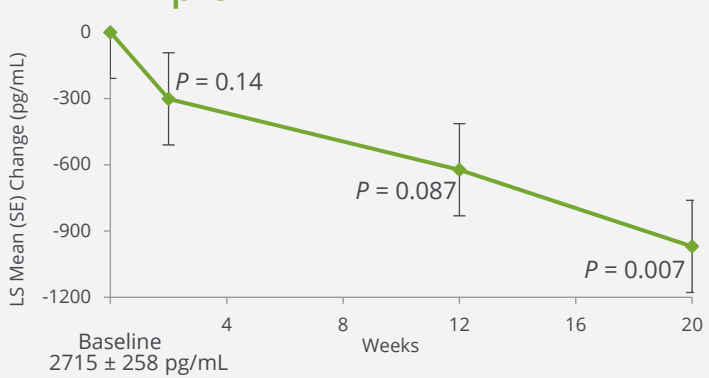


LVEDV



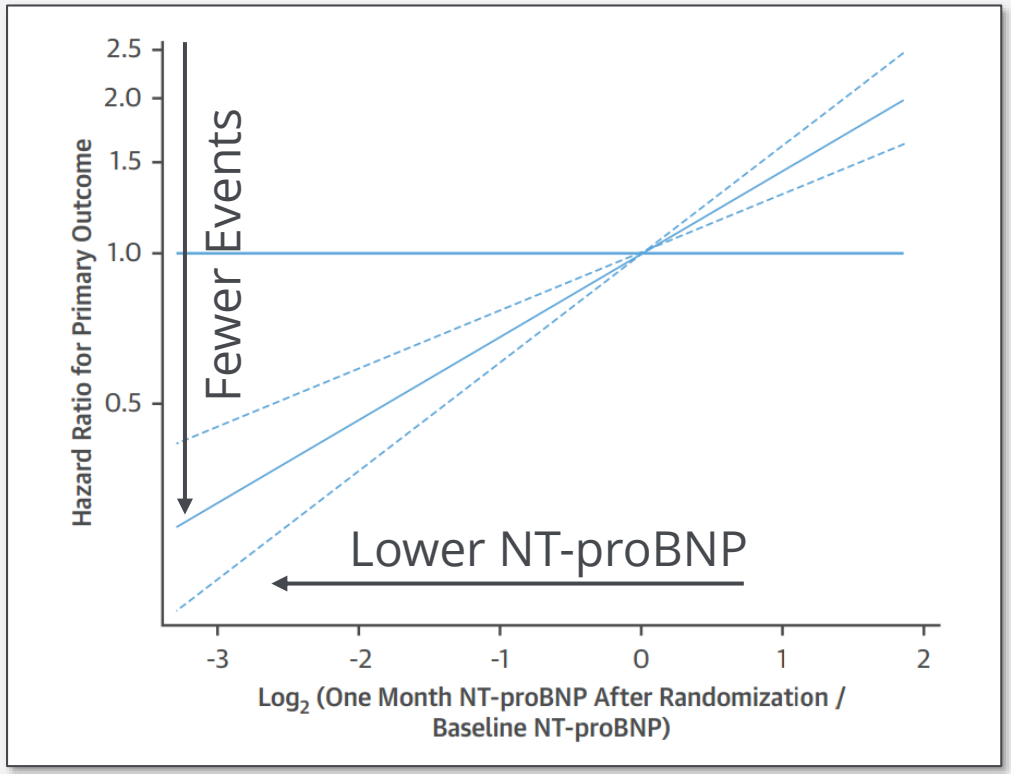
Heart Rate

NT-proBNP



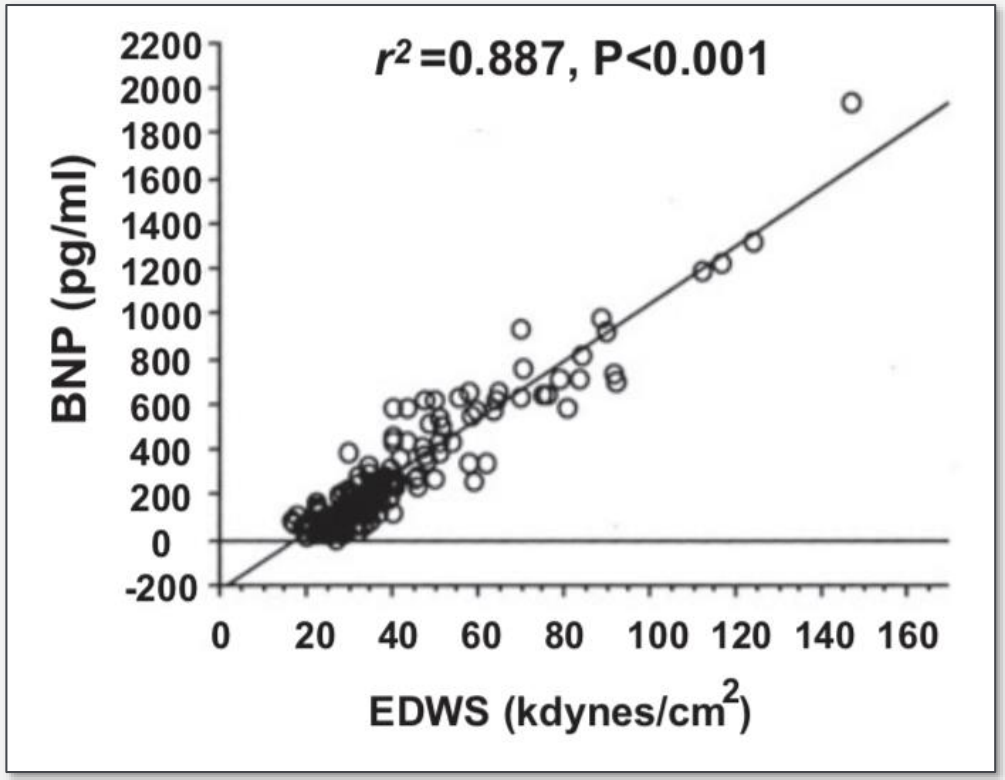
Lower NT-proBNP/BNP Correlates with Decrease in Diastolic Wall Stress, HF Hospitalization & CV Mortality

Decrease in Heart Failure Hospitalization or CV Death



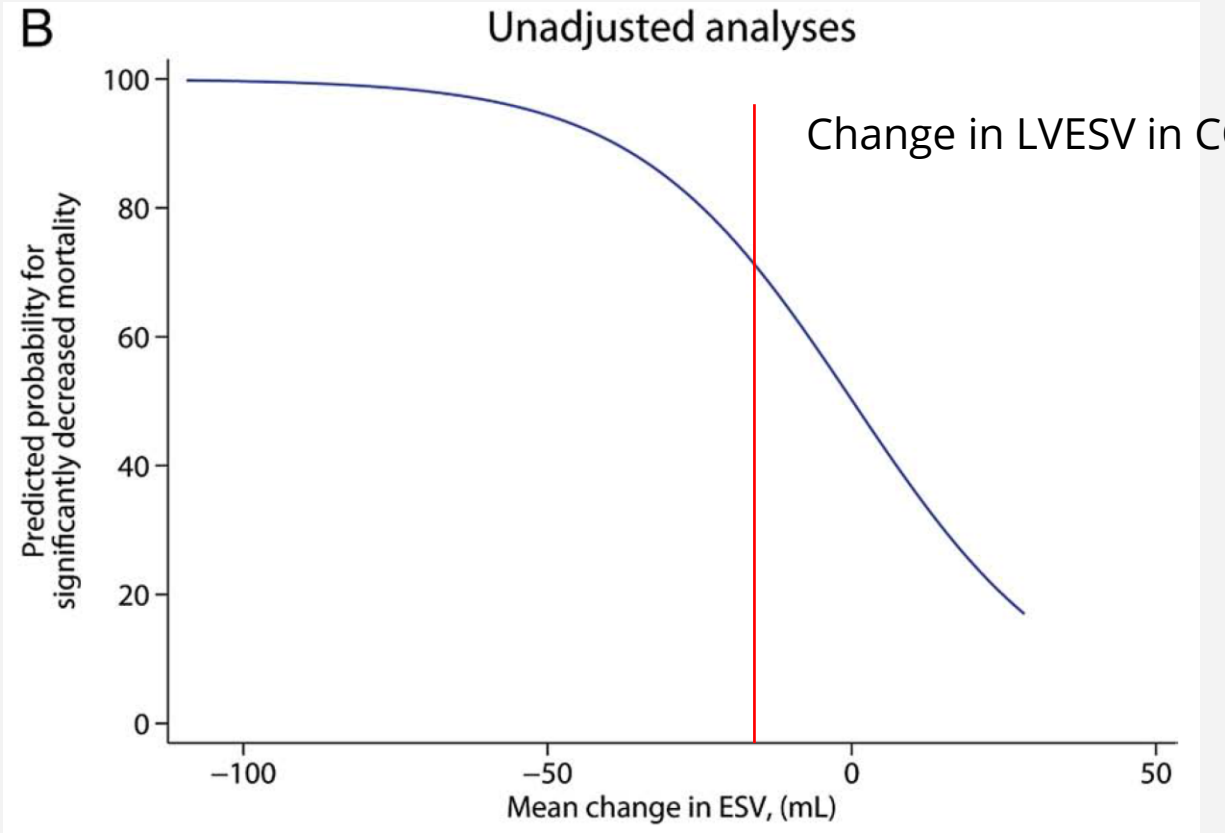
Data from PARADIGM-HF: Zile, et al JACC 2016

Decrease in End Diastolic Wall Stress (EDWS)



Iwanaga, et al JACC 2006

Decreases in Ventricular Size Predict Improved Survival



* Kramer DG, *et al. J Am Coll Cardiol* 2010;56:392–406.

Meta-Analysis of Intervention Studies in HFrEF* Showed Decreases in Ventricular Size Predict Improved Survival

* *Omecamtiv mecarbil* has not been shown to improve survival which is currently being studied in the CV outcomes clinical trial, GALACTIC-HF

Cardiac Serious Adverse Events

n (%)	Placebo (n = 149)	25 mg (n = 150)	PK-guided titration arm			Pooled OM (n = 296)
			25 mg (n = 58)	50 mg (n = 78)	All PK Titration (n = 146)[a]	
Cardiac SAEs	19 (13)	18 (12)	7 (12)	7 (9)	17 (12)	35 (12)
Cardiac failure	4 (3)	3 (2)	1 (2)	3 (4)	5 (3)	8 (3)
Cardiac failure acute	1 (1)	3 (2)	1 (2)	2 (3)	3 (2)	6 (2)
Cardiac failure congestive	3 (2)	3 (2)	2 (3)	-	3 (2)	6 (2)
Angina pectoris	-	3 (2)	1 (2)	-	1 (1)	4 (1)
Ventricular tachycardia	1 (1)	2 (1)	1 (2)	-	1 (1)	3 (1)

Teerlink et al., Lancet 2016

[a] Excludes 3 patients that were not dosed

Cardiac Troponin I

Troponin I (ng/mL)	Placebo (n = 149)	Pooled OM (n = 296)
	Baseline	
Median	0.025	0.022
Q1, Q3	0.016, 0.041	0.016, 0.040
	Change to Week 20	
Median	0.000	0.004
Q1, Q3	-0.007, 0.004	0.000, 0.019
	Change to Week 24	
Median	0.000	0.000
Q1, Q3	-0.006, 0.008	-0.003, 0.009

Teerlink et al., Lancet 2016

Number of increased troponin events adjudicated by CEC for MI = 0/278

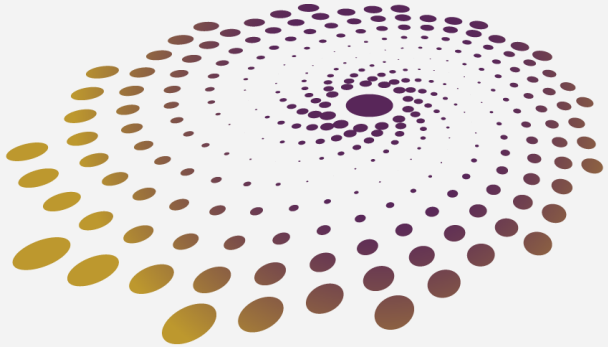
- cTnI > 0.04 ng/mL (99%URL) when prior undetectable OR
- cTnI > 0.03 ng/mL (10%CoV) greater than prior when prior detectable

Conclusions

- **Pharmacokinetics**
  - The pharmacokinetic-based dose titration reliably controlled patient exposure to *omecamtiv mecarbil* in the PK-titration group
- **Efficacy Measures**
  - Improvements in SET, stroke volume, and LVEF
  - Decreases in cardiac dimensions and volumes
  - Decreases in HR and NT-proBNP
- **Safety Measures**
  - Small increase in troponin I without imbalance in cardiac adverse events
  - Overall AE/SAE profile and tolerability similar to placebo

The results from this study led to the conduct of the ongoing, Phase 3, cardiovascular outcomes trial, GALACTIC-HF

GALACTIC-HF



Global **A**pproach to **L**owering **A**dverse **C**ardiac Outcomes **T**hrough **I**mproving **C**ontractility in **H**eart **F**ailure

GALACTIC-HF Executive Committee:

Chair:

John R. Teerlink, Director, Heart Failure Program, SFVAMC, School of Medicine, University of California San Francisco, CA, USA

Members:

Rafael Diaz, Executive Director, ECLA Estudios Clinicos Latino America, Rosario, Argentina

Michael Felker, Chief Heart Failure Section, Duke University School of Medicine, Durham, NC, USA

John J V McMurray, Professor of Medicinal Cardiology, University of Glasgow, Scotland, UK

Marco Metra, Professor of Medical Cardiology, University of Brescia, Brescia, Italy

Scott Solomon, Professor of Medicine, Harvard Medical School, Boston, MA, USA

Phase 3 Trial Has Enrolled >5000 Patients

GALACTIC-HF

Study Overview

- Enrolling 8,000 patients at ~1,000 sites in 35 countries

Primary endpoint

- Composite of time to CV death or first HF event*, whichever occurs first

Secondary endpoints

- Time to CV death
- Change in Kansas City Cardiomyopathy Questionnaire Total Symptoms Score (KCCQ TSS) from baseline to Week 24
- Time to first HF hospitalization
- Time to all-cause death

*An HF event defined as the presentation of the subject for an urgent, unscheduled clinic/office/ED visit, or hospital admission, with a primary diagnosis of HF, where the patient exhibits new or worsening symptoms of HF on presentation, has objective evidence of new or worsening HF, and receives initiation or intensification of treatment specifically for HF (Hicks et al, 2015). Changes to oral diuretic therapy do not qualify as initiation or intensification of treatment.

Key Design Points

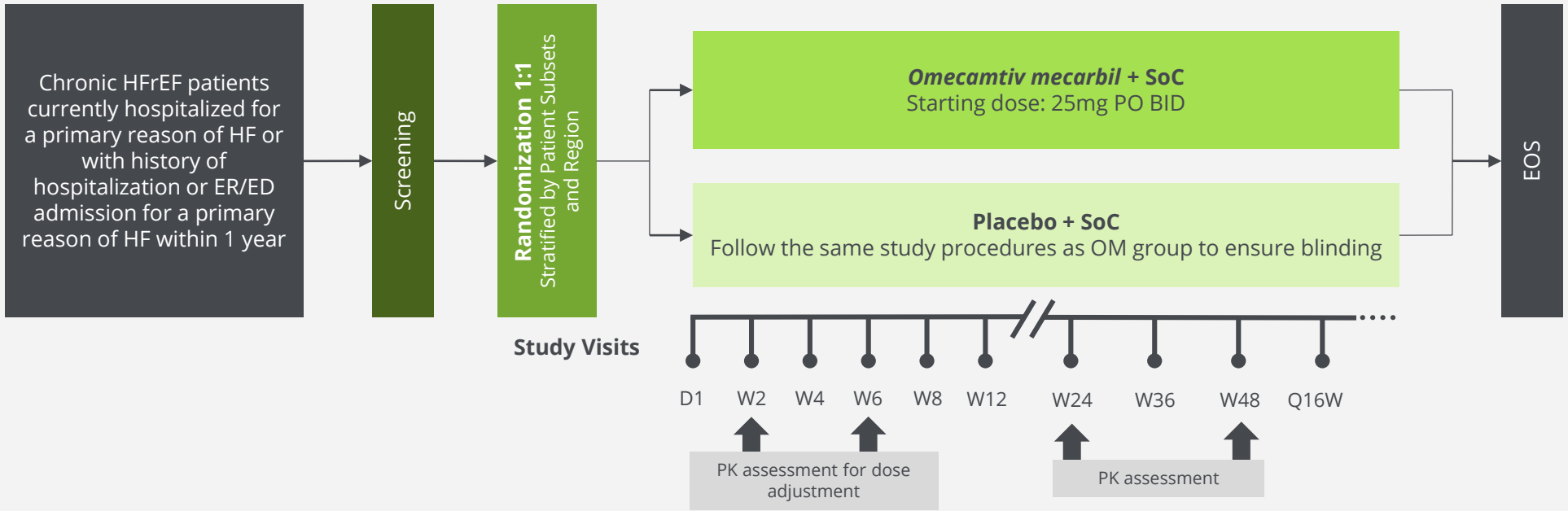
- Dose optimization based on trough concentration of *omecamtiv mecarbil* at 2 weeks and 6 weeks
  - Starting Dose = 25 mg BID
  - Escalation (or not) at Week 4 to 37.5 mg or 50 mg BID based on plasma concentration of *omecamtiv mecarbil* at Week 2
  - Recheck at Week 6, adjust dose downward if necessary
- Enroll patients from time of hospitalization to within 1 year of discharge
  - In-hospital enrollment target is approximately 25% of total enrollment
  - Stratify on randomization setting
- Event driven with 90% power based on secondary endpoint of CV Death

Global
Approach to
Lowering
Adverse **C**ardiac
Outcomes
Through
Improving
Contractility in
Heart **F**ailure

Trial Overview

GALACTIC-HF

2 years enrollment, approx. 4 years total follow-up/study period



- Approximately 25% or more of the total planned enrollment will include subjects who are hospitalized at randomization
- Safety monitoring by independent DMC
- Clinical events adjudication by CEC
- Study ends when ~1,590 subjects have experienced CV death, expected study duration 4 years

~8000 patients randomized 1:1 to *omecamtiv mecarbil* versus placebo, stratified by inpatient versus outpatient at randomization

Event-driven; patients will be followed indefinitely until CV death events have accumulated (90% powered for CV Mortality)

GALACTIC-HF

Enrolling Intended High-Risk Population

- >5000 patients enrolled, anticipate enrollment completed in 1H 2019
- High Risk population as intended, on average…
  - EF < 30%
  - Time from last hospitalization < 4 months
  - NT-proBNP > 2000 pg/mL
  - 25% enrolled from an inpatient setting
- DMC meeting quarterly – no change to study conduct
- Event rates consistent with baseline assumptions
- Futility analysis conducted by DMC expected in 1H 2019
- Efficacy analysis for overwhelming benefit conducted by DMC in 2020

METEORIC-HF

Multicenter **E**xercise **T**olerance **E**valuation of ***O****mecamtiv Mecarbil* **R**elated to **I**ncreased **C**ontractility in **H**eart **F**ailure

9 Countries Planned in North America & Europe

METEORIC-HF Steering Committee:

Greg Lewis (Co-lead, US)
Michael Felker (Co-lead, US)
John Teerlink (US)
David Whellan (US)
Justin Ezekowitz (Canada)
Adriaan Voors (Netherlands)
Alain Cohen-Solal (France)
Piotr Ponikowski (Poland)
Michael Böhm (Germany)
Marco Metra (Italy)

Trial Design

Primary endpoint

- Change in peak VO_2 on Cardiopulmonary Exercise Testing (CPET) from baseline to Week 20

Secondary endpoints

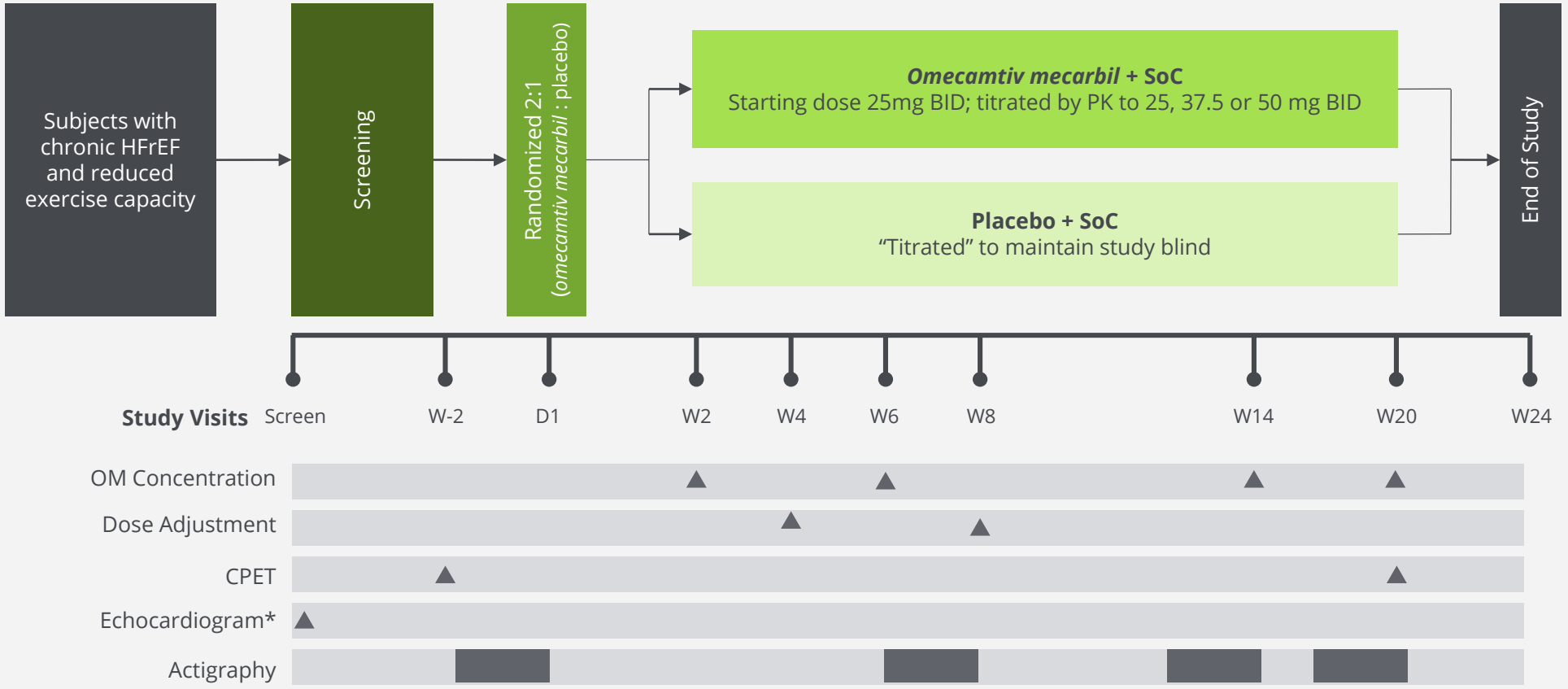
- Change in total workload during CPET from baseline to Week 20
- Change in ventilatory efficiency (V_E/VCO_2 slope) during CPET from baseline to Week 20
- Change in the average daily activity units measured over a 2 weeks from baseline to Week 18-20

Exploratory Endpoints

- Change from baseline to Week 20 in oxygen uptake efficiency slope ($VO_2/\log V_E$ slope), ventilatory threshold (by the V-slope method), VO_2 recovery kinetics, percent predicted pVO_2, and exercise duration
- Change from baseline in the average daily activity units at Week 6-8 and at Week 12-14
- Change from baseline in the KCCQ Total Symptom Score and its sub-domains from baseline to Week 20

VO_2 = Oxygen Uptake; CPET = Cardio-Pulmonary Exercise Testing; V_E = Ventilatory Efficiency

Trial Overview



* Screening echocardiogram is not required if an appropriate LVEF assessment has been performed within one year

~270 subjects

90% power

5 months of treatment (same as COSMIC-HF)

Dose titration of *omecamtiv mecarbil* same as GALACTIC-HF

Key Inclusion Criteria

Inclusion Criteria

Same or similar to GALACTIC-HF:

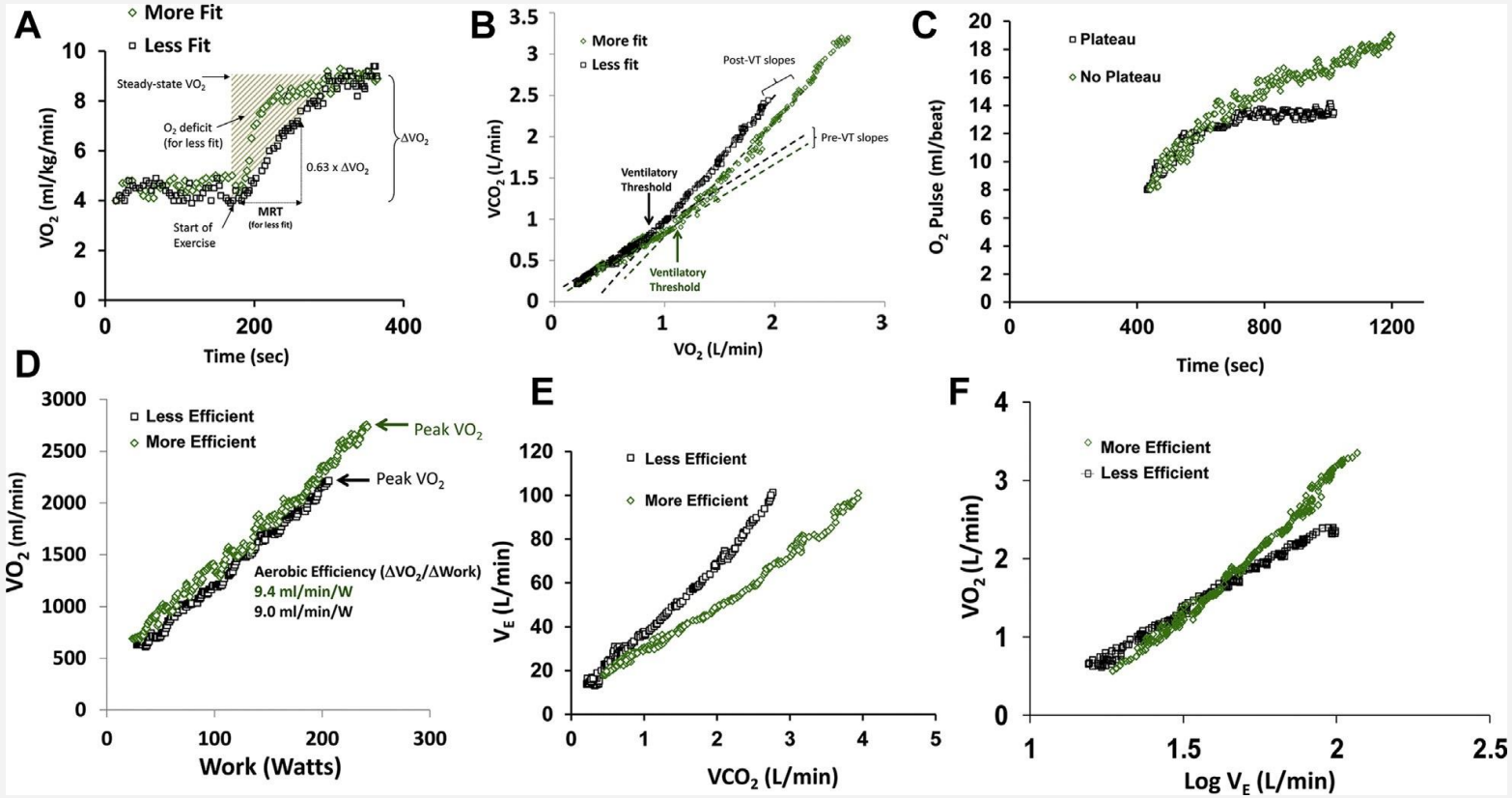
- ≥ 18 to ≤ 85 years of age
- Chronic HF (>3 months) managed with SoC therapies at stable doses
- LVEF ≤ 35% and NYHA class II to III
- NT-proBNP ≥ 200 pg/mL

Specific for METEORIC-HF:

- Ambulatory without assistance
- Able to perform CPET safely and achieve a respiratory exchange ratio ≥1.05 *
- Reduced exercise capacity, defined as peak VO2 ≤ 75% of the predicted normal value *
- No requirement for a prior HF hospitalization
- Outpatient only
  - Recent hospitalization (<3 months) is an exclusion

* Confirmed by CPET core laboratory

CPET: A Quantitative Assessment of Exercise Capacity



Malhotra et al, JACC-HF, 2016

- Peak VO_2 is gold standard measure of exercise capacity
- More precise, reproducible than other measures of physical function
- High reproducibility
- Lack of training effect
- Peak VO_2 is responsive to therapy (drug, device, exercise training)
- Assessment of volitional effort
- CPET outperforms 6MWT in predicting outcomes in HF[1,2]

1. Guazzi et al, Circulation HF 2009
2. O'Connor et al, Circulation HF 2014

AMG 594

CARDIAC TROPONIN ACTIVATOR

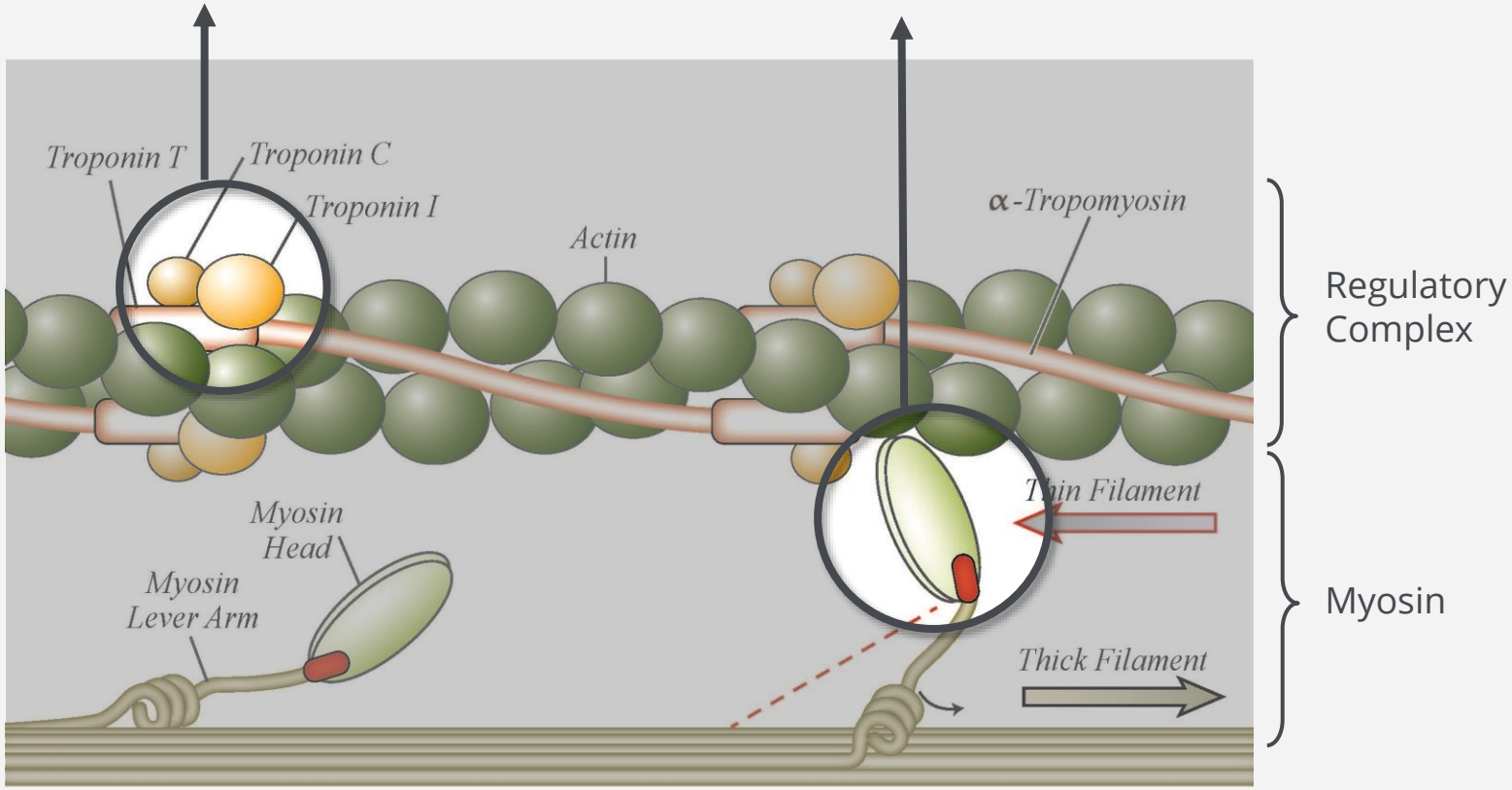
Brad Morgan, PhD
SVP, Research & Non-Clinical Development

Whit Tingley, MD, PhD
VP, Clinical Research, Cardiology

Modulation of Cardiac Muscle Contractility

AMG 594
Cardiac Troponin Activator

Omecamtiv Mecarbil
Cardiac Myosin Activator

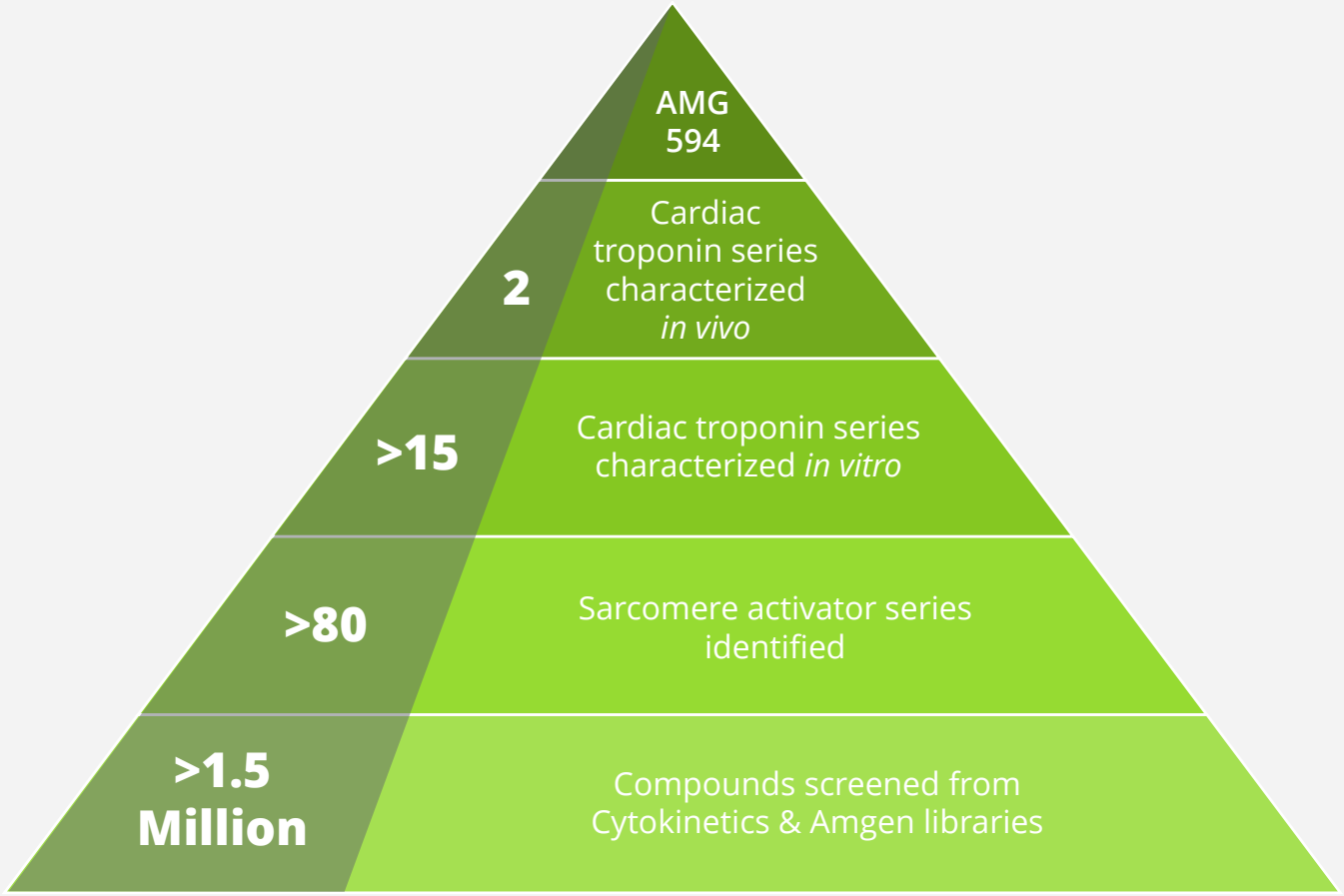


Next-Generation Cardiac Sarcomere Activator

AMG 594

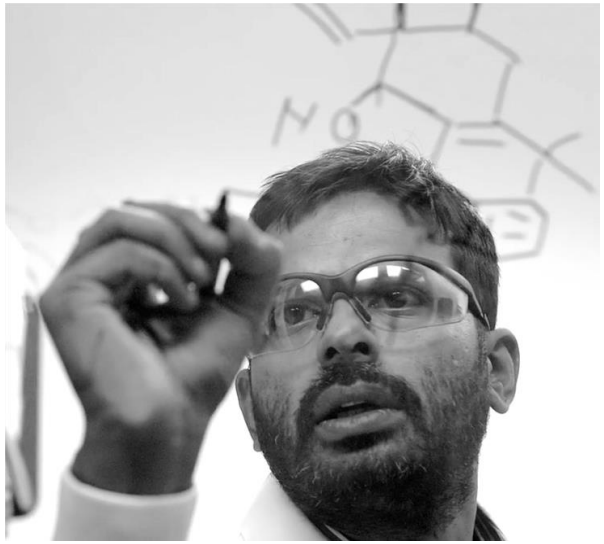
TARGET: TROPONIN

Extended Contractility Franchise to First, Selective Cardiac Troponin Activator (CTA)

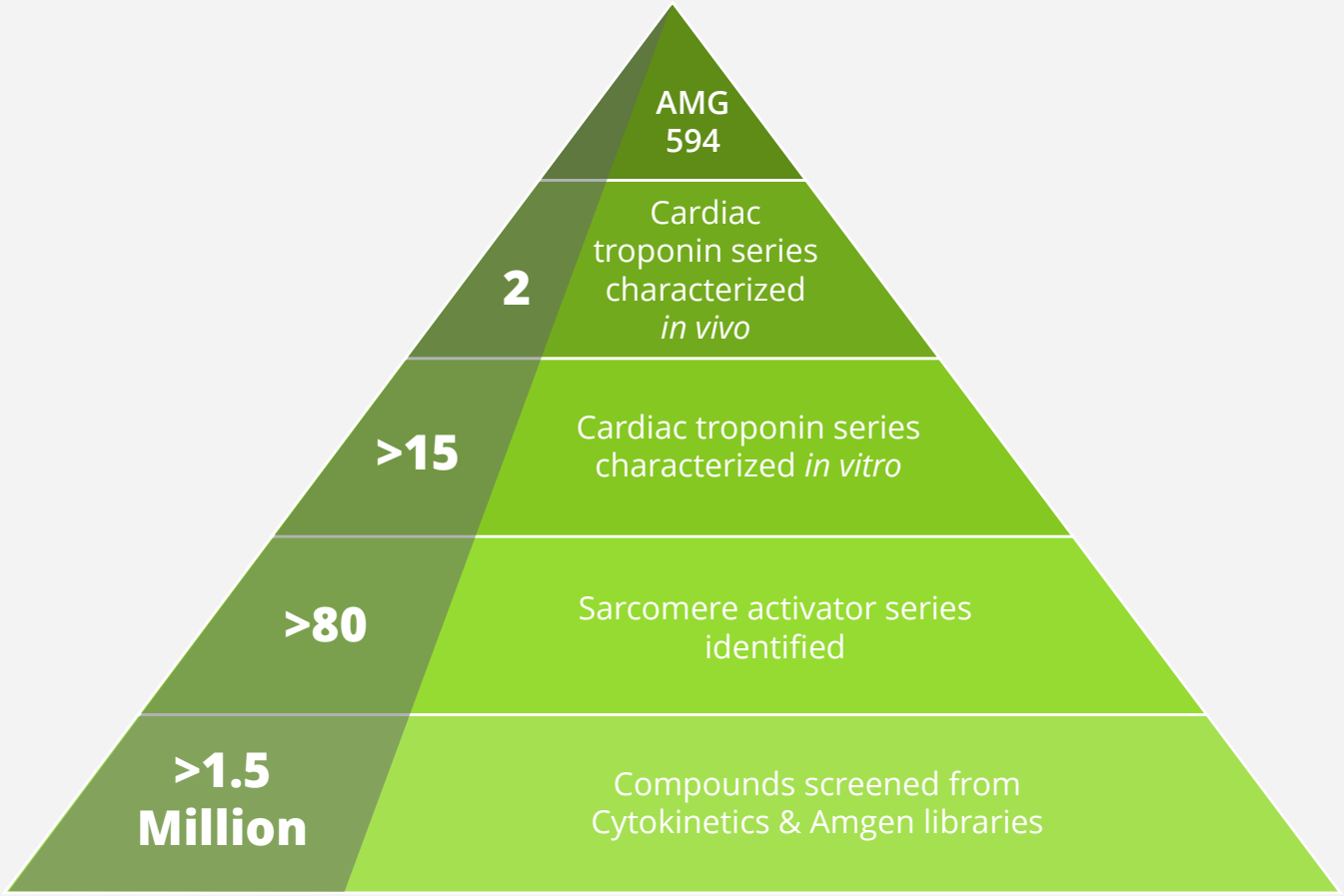


5-Year Research Collaboration with Amgen

Explored Multiple Mechanisms of Action with the Goal of Increasing Efficacy and Ease of Use



Extended Contractility Franchise to First, Selective Cardiac Troponin Activator (CTA)



5-Year Research Collaboration with Amgen

Explored diverse MOAs and chemotypes

Selected cardiac troponin activation given potential for improved efficacy and ease of use

Objectives of Cardiac Troponin Activator Program:

Selective for cardiac muscle

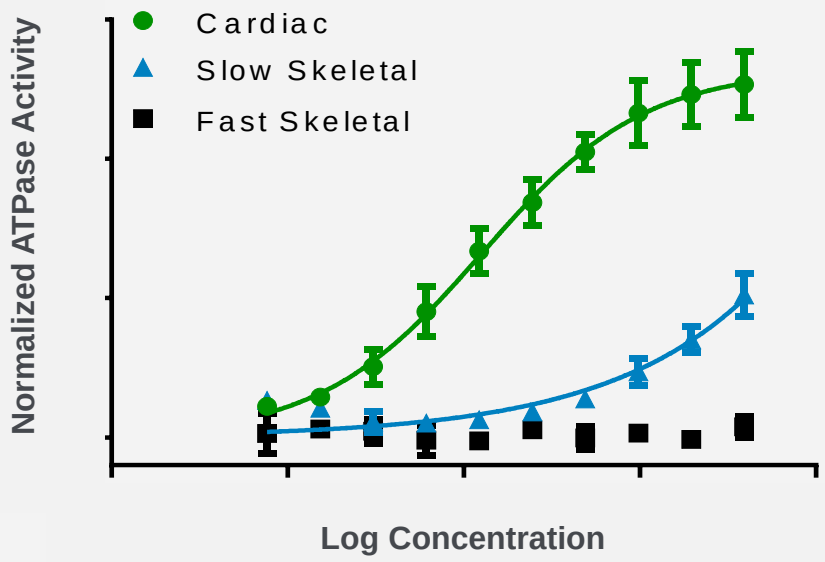
No PDE3 inhibition, no effect on calcium transients

Projected human PK adequate for once daily dosing

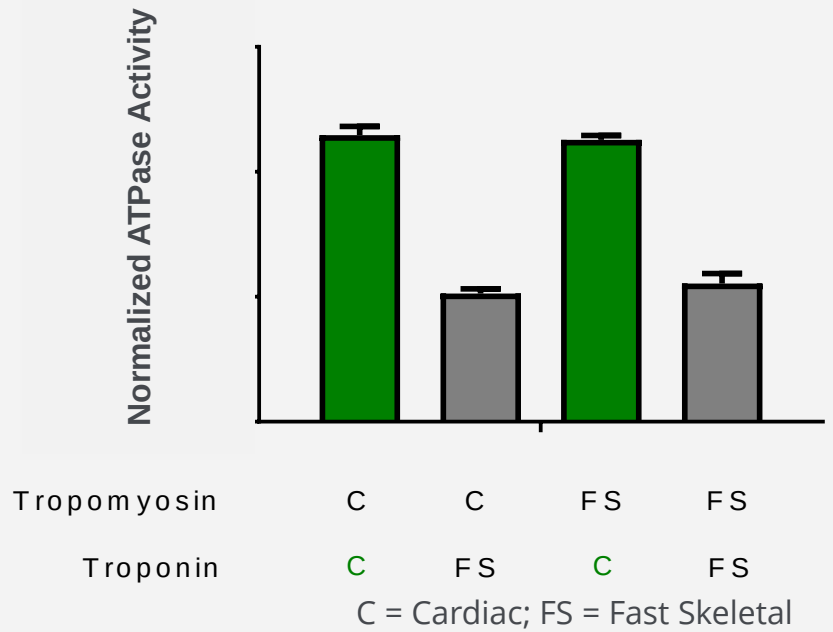
Wide Pharmacodynamic Window (preclinical)

Cardiac Troponin Activators Are Selective

CTA Selectively Activates the ATPase Activity of Cardiac Myofibrils



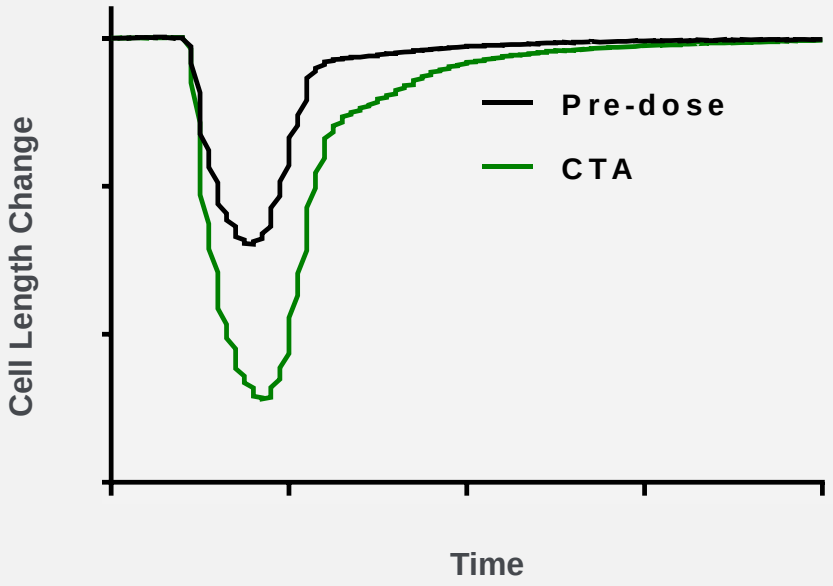
CTA Selectively Activates Hybrid Reconstituted Sarcomere Assays Containing Cardiac Troponin



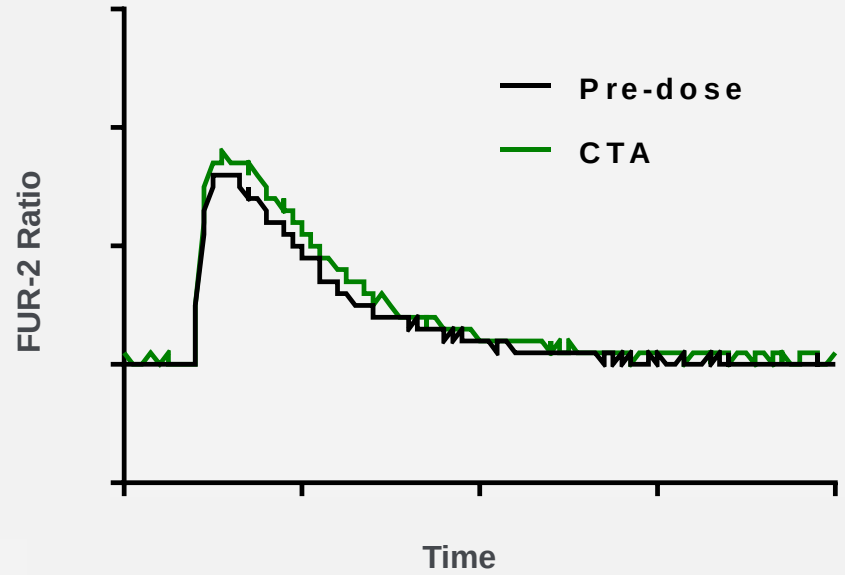
C = Cardiac; FS = Fast Skeletal

Cardiac Troponin Activator Increases Contractility in Cardiomyocytes Without Increasing Calcium Transients

Contractility strongly activated after treatment



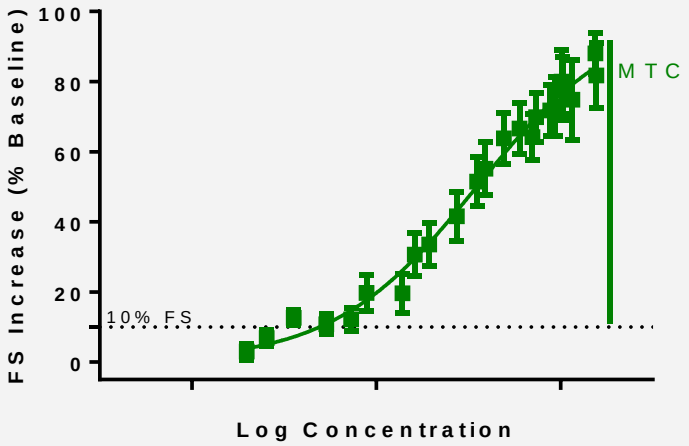
Calcium transients unchanged after treatment



Results consistent with direct activation of the sarcomere

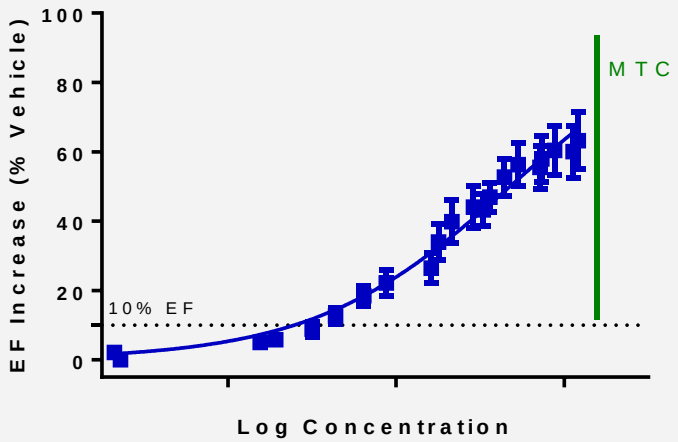
Cardiac Troponin Activator Has a Wide PD Window

Animal Models of Cardiac Function



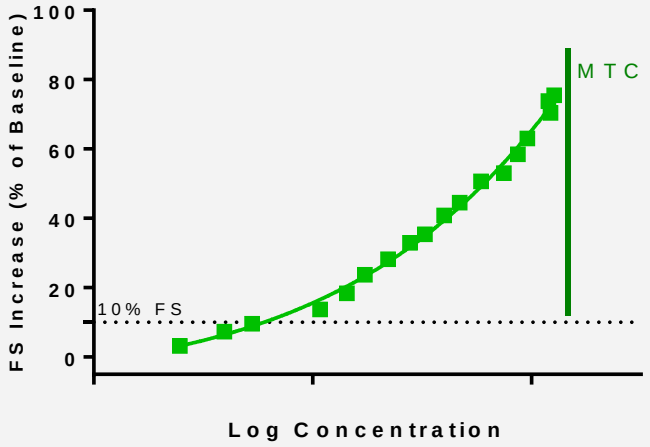
Healthy Rats PD Window[1]

≥ 15X



MI Rats PD Window[1]

≥ 15X

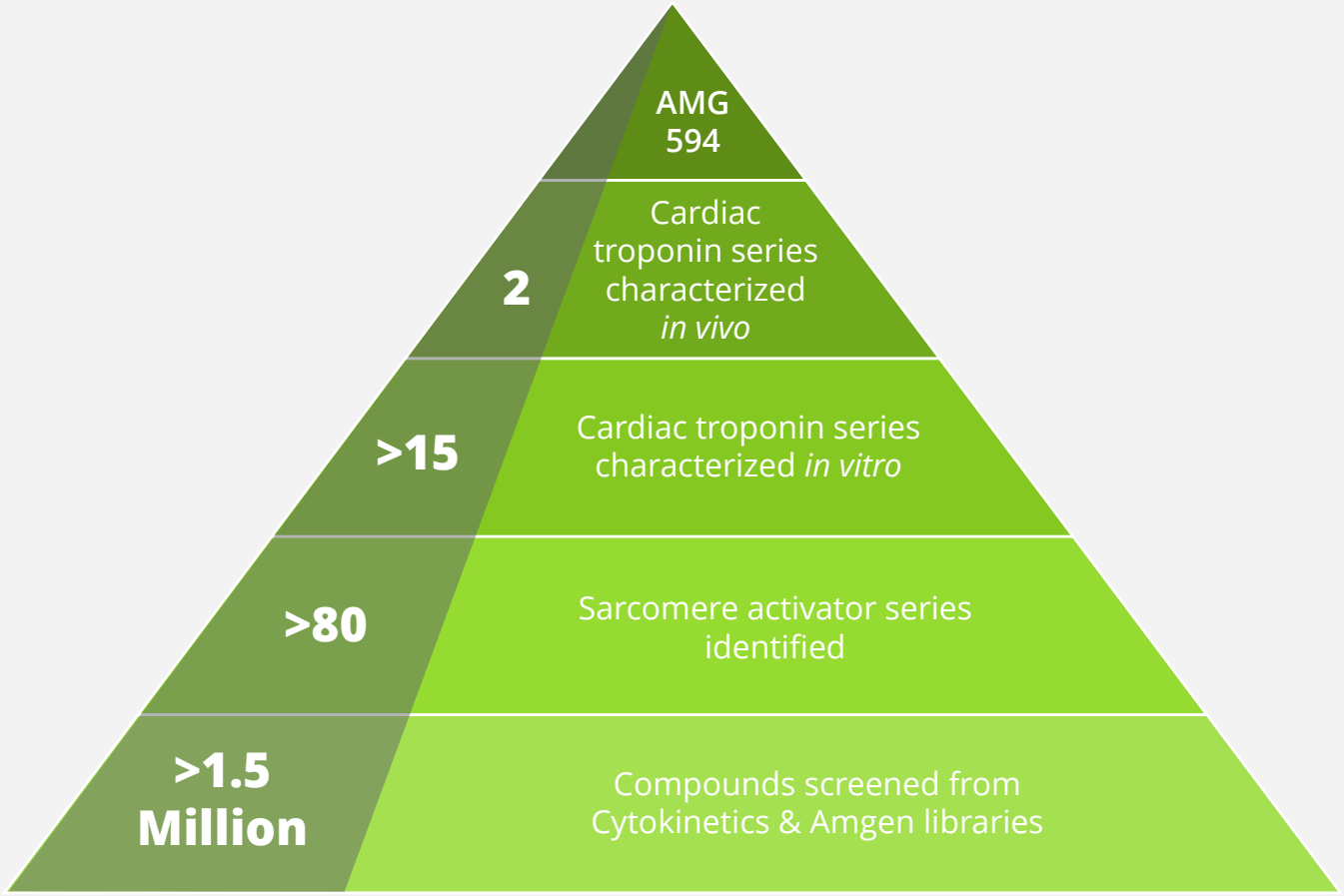


Healthy Dogs PD Window[1]

≥ 15X

[1]PD Window = Maximum Tolerated Concentration (MTC) / 10% increase in Fractional Shortening (FS) or Ejection Fraction (EF)

IND Filed, Initiating First in Human Clinical Studies in Q4



Explored diverse MOAs and chemotypes

Selected troponin activation for improved efficacy and ease of use

Properties of AMG 594:

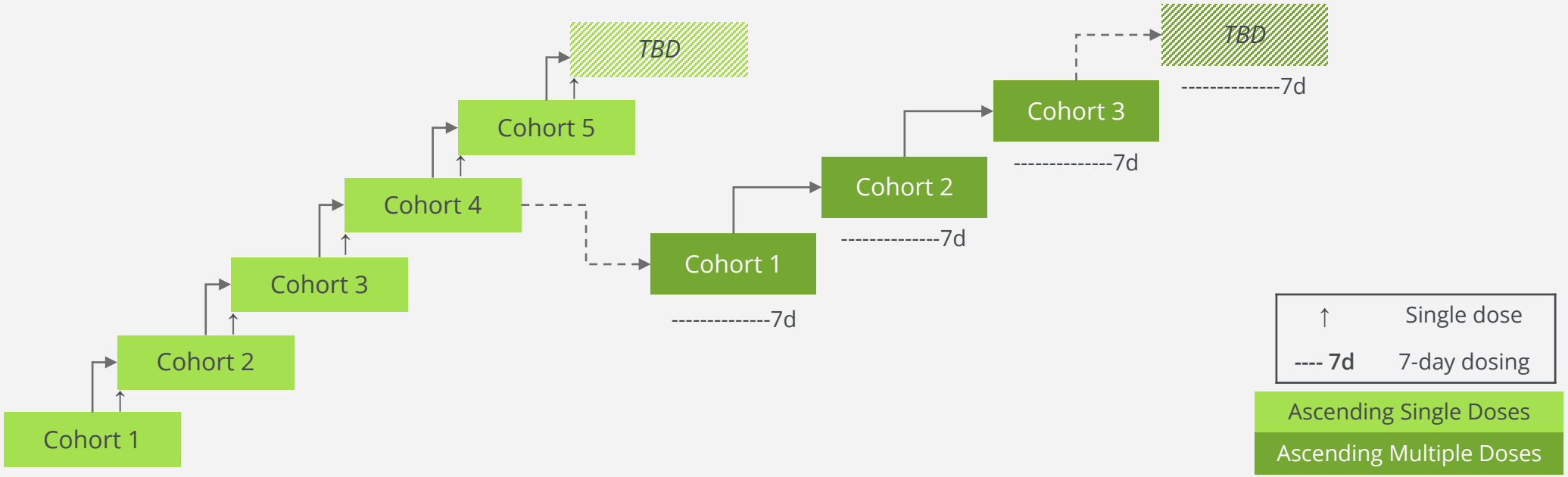
Selective for cardiac muscle

No PDE3 inhibition, no effect on calcium transients

Projected human PK adequate for once daily dosing

Wide Pharmacodynamic Window (preclinical)

AMG 594 Phase 1 Study Design: Nested SAD and MAD in Healthy Subjects



Randomized, placebo-controlled, double-blind, multi-part, single center study

- Part 1: 5 single ascending single oral doses (SAD)
- Part 2: 3 multiple ascending oral doses (MAD)
- ~64 healthy subjects overall

Objectives	Endpoints
Safety and tolerability	AEs, laboratories, cardiac markers, ECGs
Pharmacokinetics	C_{max}, T_{max}, AUC
Pharmacodynamics	LVEF, LVFS, LVOT-VTI, SET

Potential Path Forward

Decreased Cardiac Contractility

Heart Failure with Reduced Ejection Fraction (HFrEF)

Genetic Dilated Cardiomyopathy

Pulmonary Hypertension with Right Ventricular Heart Failure

Amgen & Cytokinetics are considering the Phase 2 clinical trials program

Potential Applications of AMG 594 for Patients with Distinct Types of Ventricular Dysfunction and Heart Failure are Under Discussion

Summary

- AMG 594 is an oral, small molecule cardiac troponin activator
  - Intended to improve ventricular systolic function in patients with heart failure
  - Selected from >1.5 million compounds in >80 distinct series
  - Preclinical results support the potential for optimized efficacy in HF
  - Projected once daily dosing
- Cytokinetics and Amgen are advancing AMG 594 into clinical development
  - IND filed
  - Early clinical trials will assess the safety and tolerability of AMG 594, as well as its potential to enhance ventricular contraction

AMG 594 is a Next Generation Cardiac Sarcomere Activator With Potential for Optimized Treatment of Patients with Heart Failure

CK-3773274

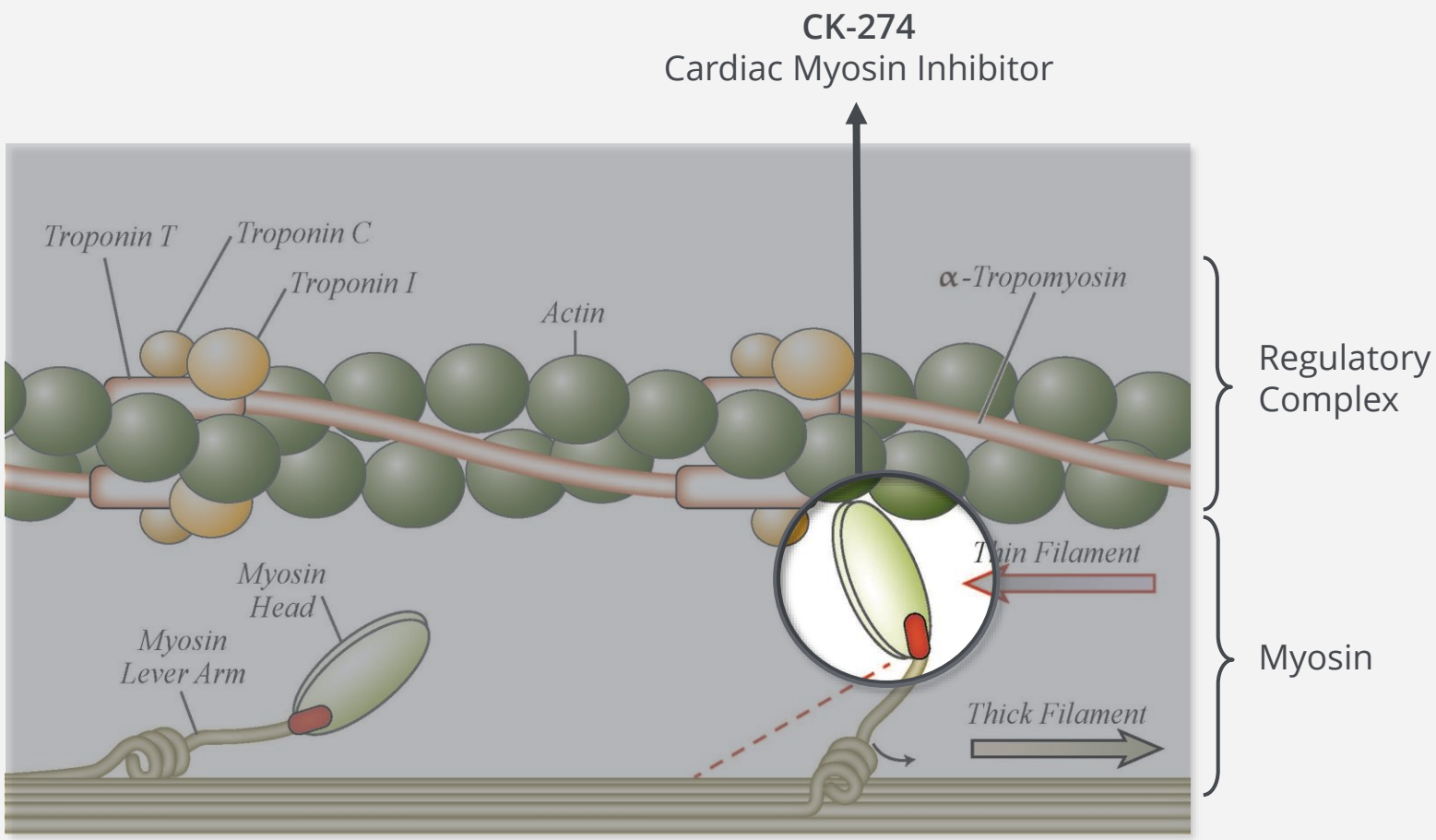
(CK-274)

CARDIAC MYOSIN INHIBITOR

Brad Morgan, PhD
SVP, Research & Non-Clinical Development

Whit Tingley, MD, PhD
VP, Clinical Research, Cardiology

Modulation of Cardiac Muscle Contractility



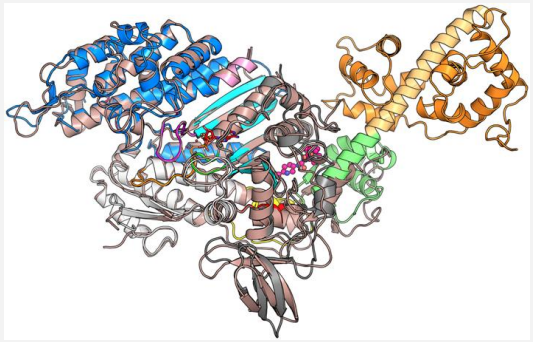
Targeting the Sarcomere

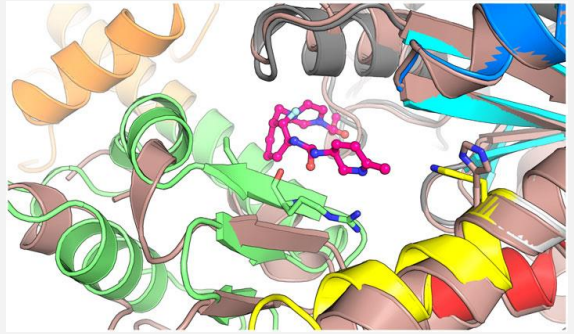
CK-274

TARGET: MYOSIN

Expertise in the Sarcomere: *Myosin Structure to Function*

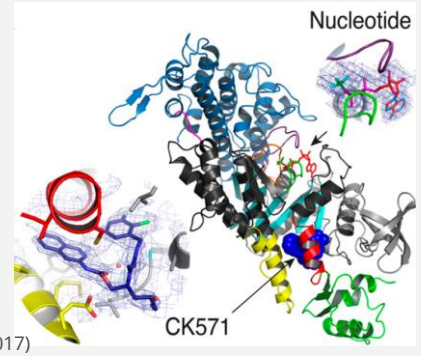
X-ray of cardiac myosin activator *omecamtiv mecarbil* bound to the pre-power stroke of cardiac myosin

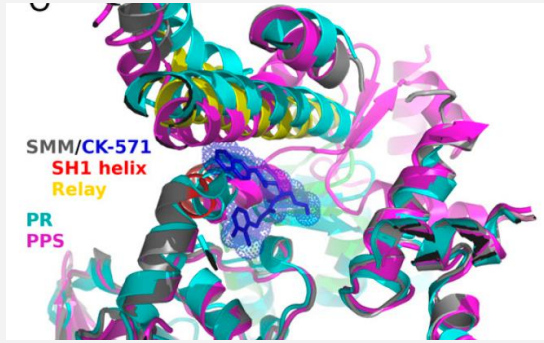




Planelles-Herrero *et al. Nature Communications* (4 Aug, 2017)

X-ray of smooth muscle myosin inhibitor bound to a novel allosteric pocket during the “recovery stroke” transition





Sirigu *et al. PNAS* (7 Oct, 2017)

Inhibition of myosin can be via an induced-fit mode of binding of small molecules

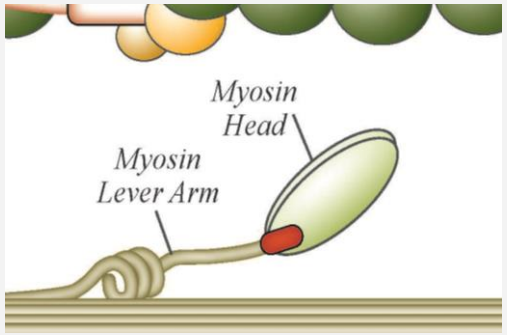
Mechanistic Characterization of Compounds

- Primary screen is agnostic to molecular mechanism of inhibition
- Hits classified based on performance in well-established panel of Cytokinetics assays

Target Myosin Motor

↓

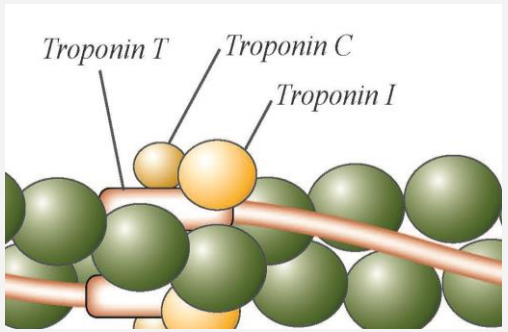
Interfere with force-generation



Target Regulatory Complex

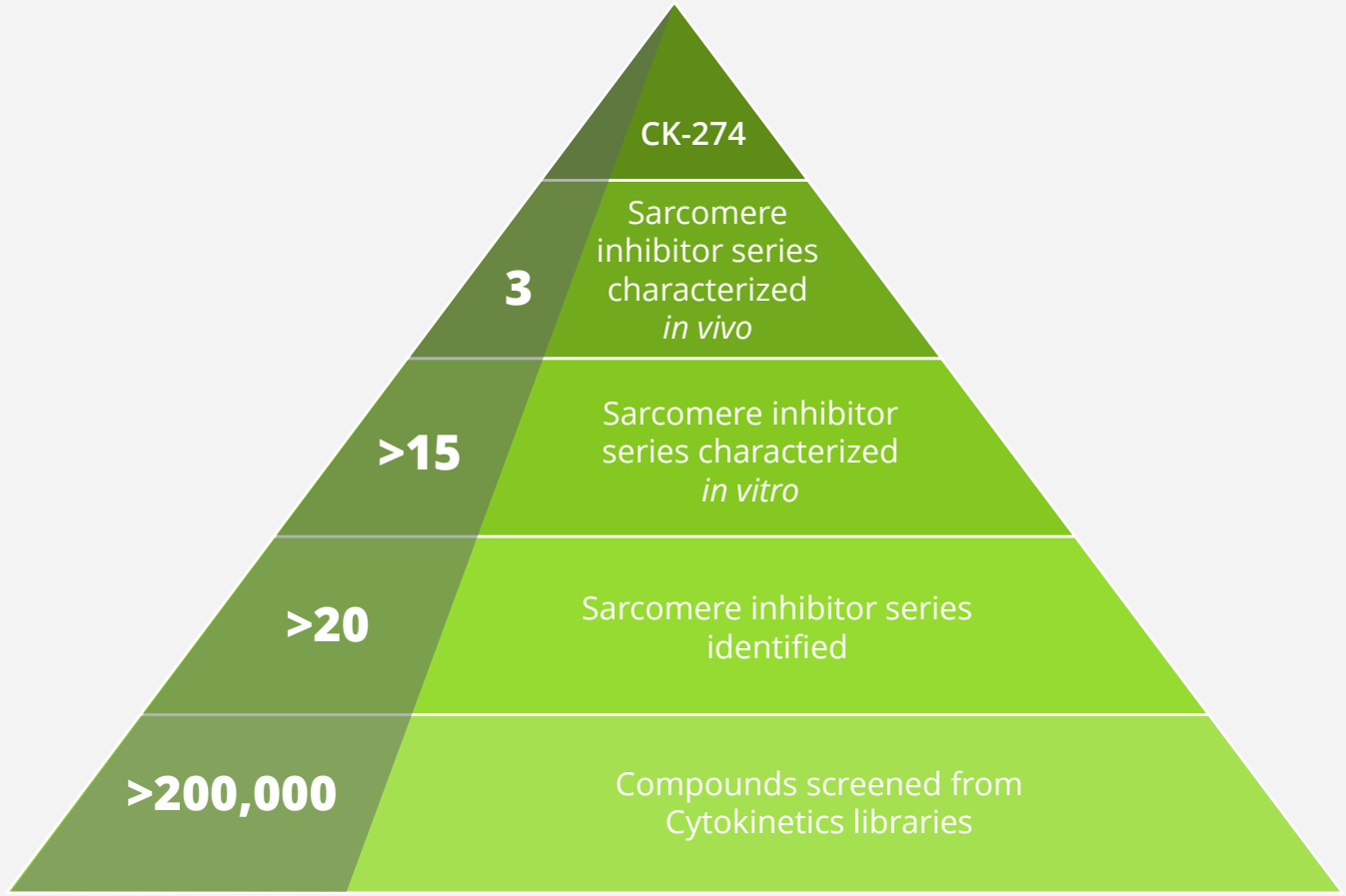
↓

Decrease calcium sensitivity



Cytokinetics has identified distinct classes of cardiac sarcomere inhibitors from multiple chemical series

CK-274: Potentially Best-in-Class Cardiac Myosin Inhibitor



Extend and Expand the
Premier Contractility Platform to Discover the
Best-in-Class Cardiac Sarcomere Inhibitors

Exploring Diverse MOAs and Chemotypes

Objectives of Cardiac Sarcomere Inhibitor Program:

Selective for Cardiac Muscle Myosin

No effect on calcium transients

Projected human PK adequate for once daily dosing
(Rapidly reach steady state concentration)

Wide Pharmacodynamic window

Chemical Lead Optimization Overview

Series	# of Analogs	Comments
A	>850	Development candidate and potential back-ups Excellent PK and safety profile
B	~300	Robust SAR established DMPK optimization
C	>550	Many potent analogs Optimization of drug-like properties
D	~700	Compounds with good potency and DMPK found Safety characterization in progress
E	~250	Potency and DMPK optimization achieved *In vivo* activity observed
F	>100	Potency optimization achieved DMPK characterization in progress

Development Candidate:

CK-274

Several related Series A Compounds to explore and expand range of therapeutic application

Continuing to explore potential advantages of other chemical series

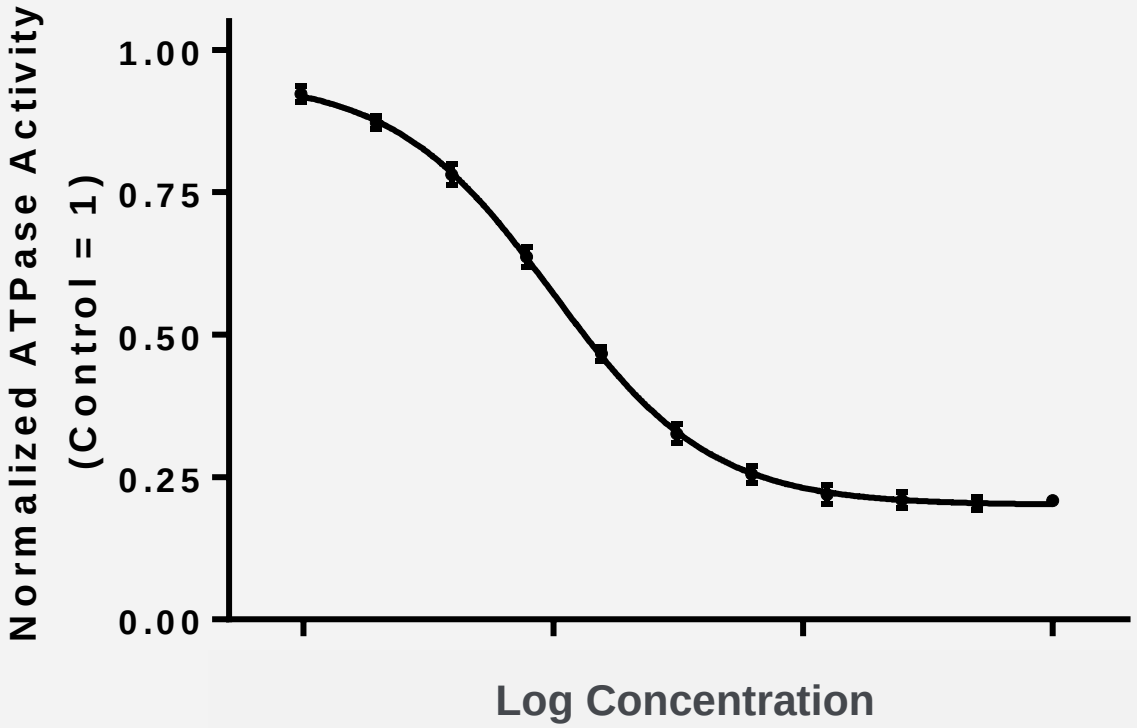
CK-274 Selected as First Development Candidate for HCM

- Favorable pharmacokinetic / pharmacodynamic properties and other candidate selection criteria
  - Selective allosteric inhibitor of cardiac myosin
  - No inhibition of smooth muscle myosin
  - *In vivo* pharmacodynamic advantages related to distinctive binding
  - Favorable ADME properties with no CYP inhibition or CYP induction
  - Good oral bioavailability across pre-clinical species
    - Excellent permeability without efflux
  - Clear pharmacokinetic/pharmacodynamic (PK/PD) relationship
  - **Projected once daily dosing to reach steady state rapidly in patients**
  - **Shallow dose response curve may translate to favorable therapeutic window in patients and broaden clinical utility**

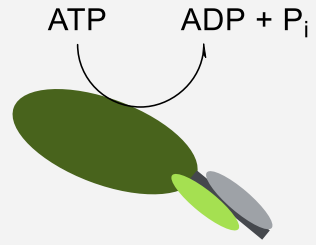
Selected from Multiple Potential Development Candidates (PDCs)

CK-274 Inhibits Cardiac Myosin S1 Basal ATPase Activity

Demonstrates compounds interact directly with myosin



Myosin S1 Fragment



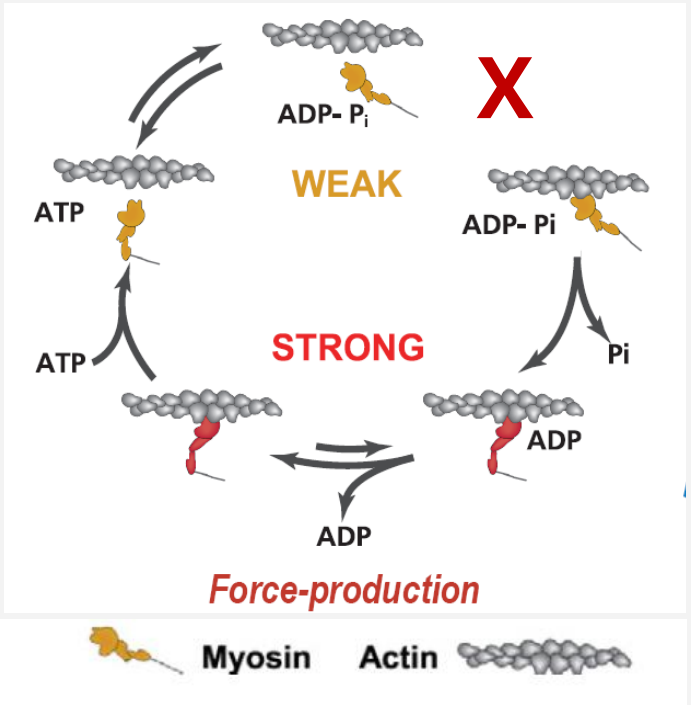
Simplest possible system to assess compound interaction with myosin

Only sensitive to compounds that interact directly with myosin

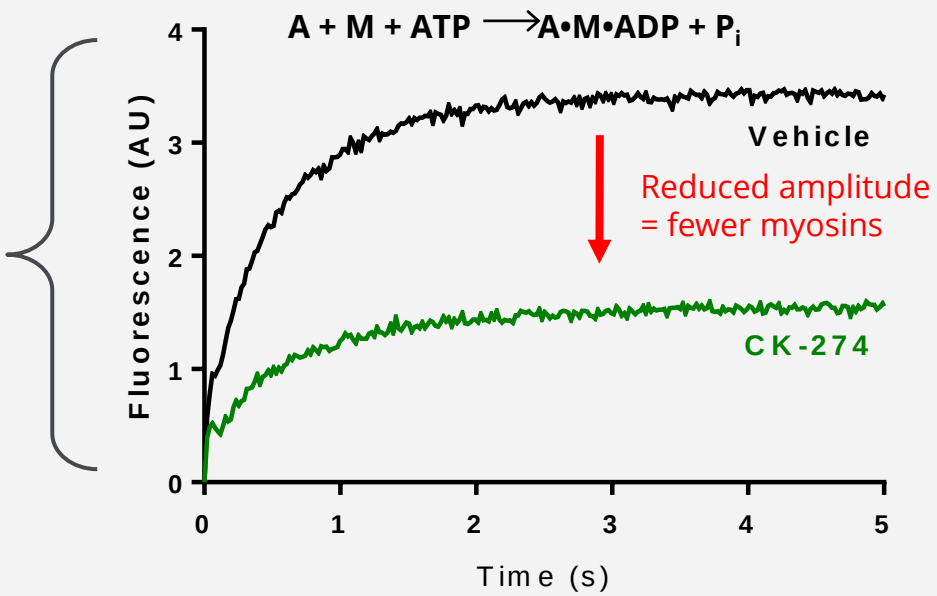
How Does a Cardiac Myosin Inhibitor Work?

The Chemical and Mechanical Cycles are Linked

The Actin–Myosin Cycle



CK-274 slows the transition rate from weak to strong binding states

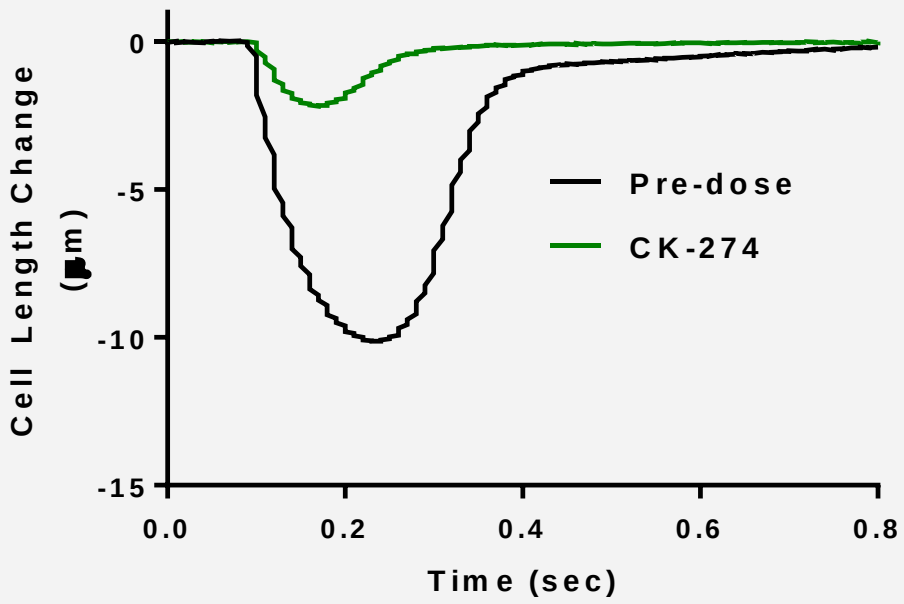


CK-274 decreases the number of independent force generators (myosin heads) interacting with the actin filament

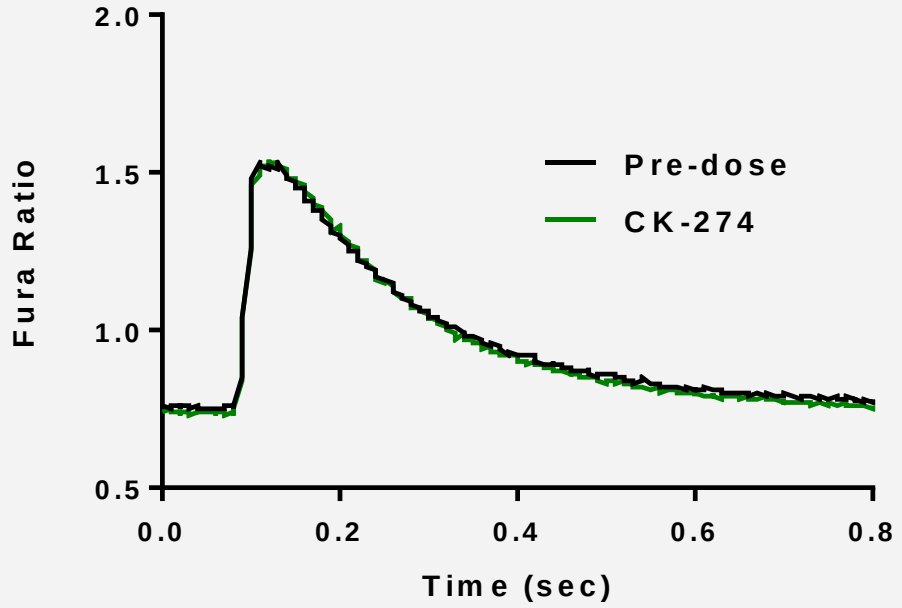
"Fewer hands pulling on the rope"

CK-274 Inhibits Contractility in Cardiomyocytes Without Changing Calcium Transients

Contractility decreased after treatment



Calcium transients unchanged after treatment

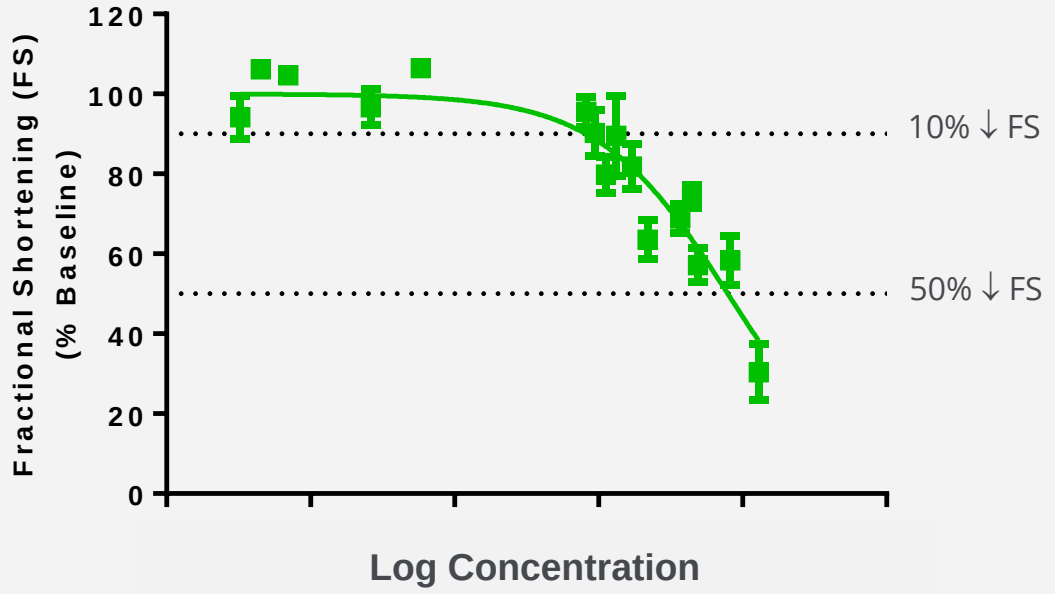


Results consistent with direct inhibition of the sarcomere

CK-274 Has a Wide PD Window in Rat and Dog Models

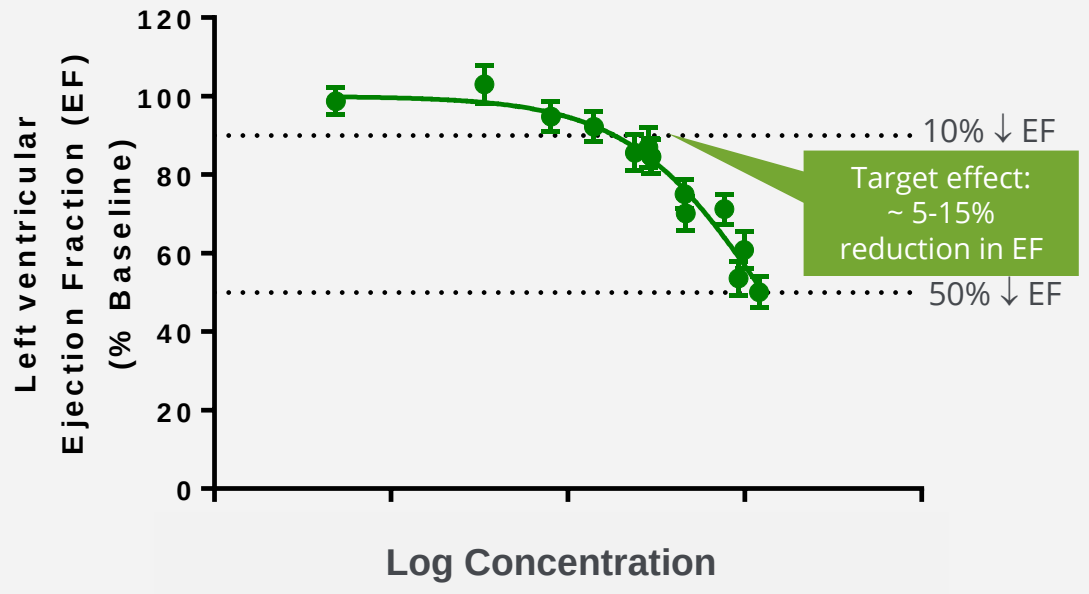
Shallow exposure-response relationship of CK-274 in rats and dogs

Rat Model: Concentration vs. Fractional Shortening



Rat PD Window (IC_{50}/IC_{10}) **> 7X**

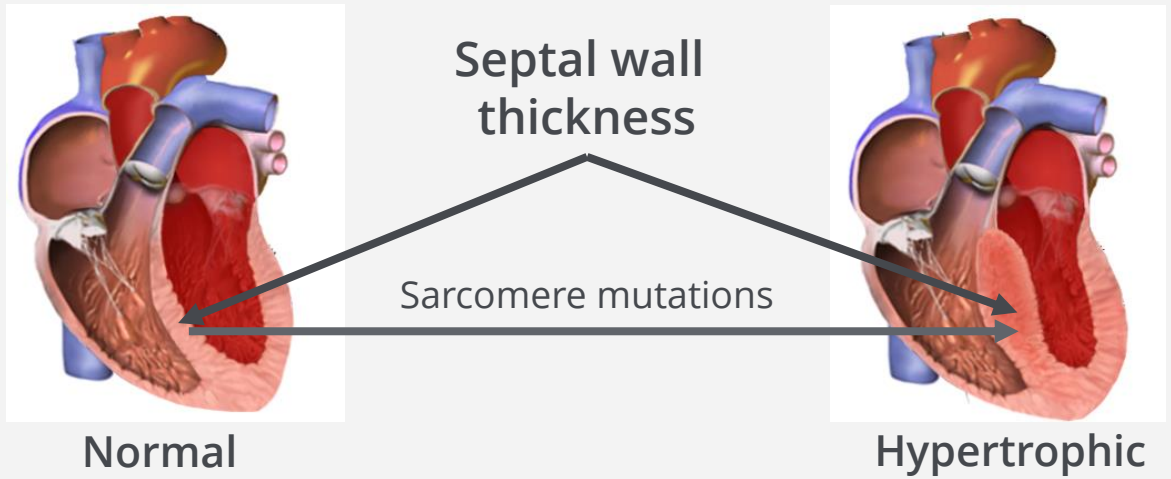
Dog Model: Concentration vs. Ejection Fraction



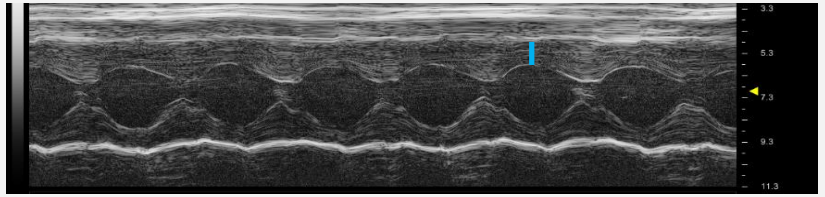
Dog PD Window (IC_{50}/IC_{10}) **> 7X**

Cardiac Myosin Inhibitor (CMI) is Efficacious in Model of HCM *Structurally and Pharmacologically Similar to CK-274*

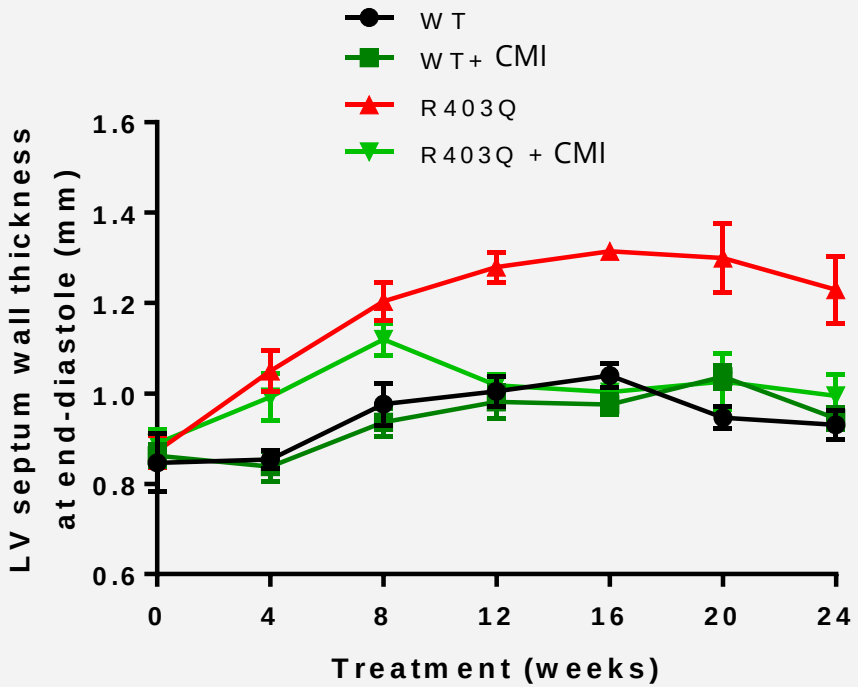
Decreased left ventricular septal wall thickness in R403Q transgenic mice after 24 weeks treatment



Representative M-mode image

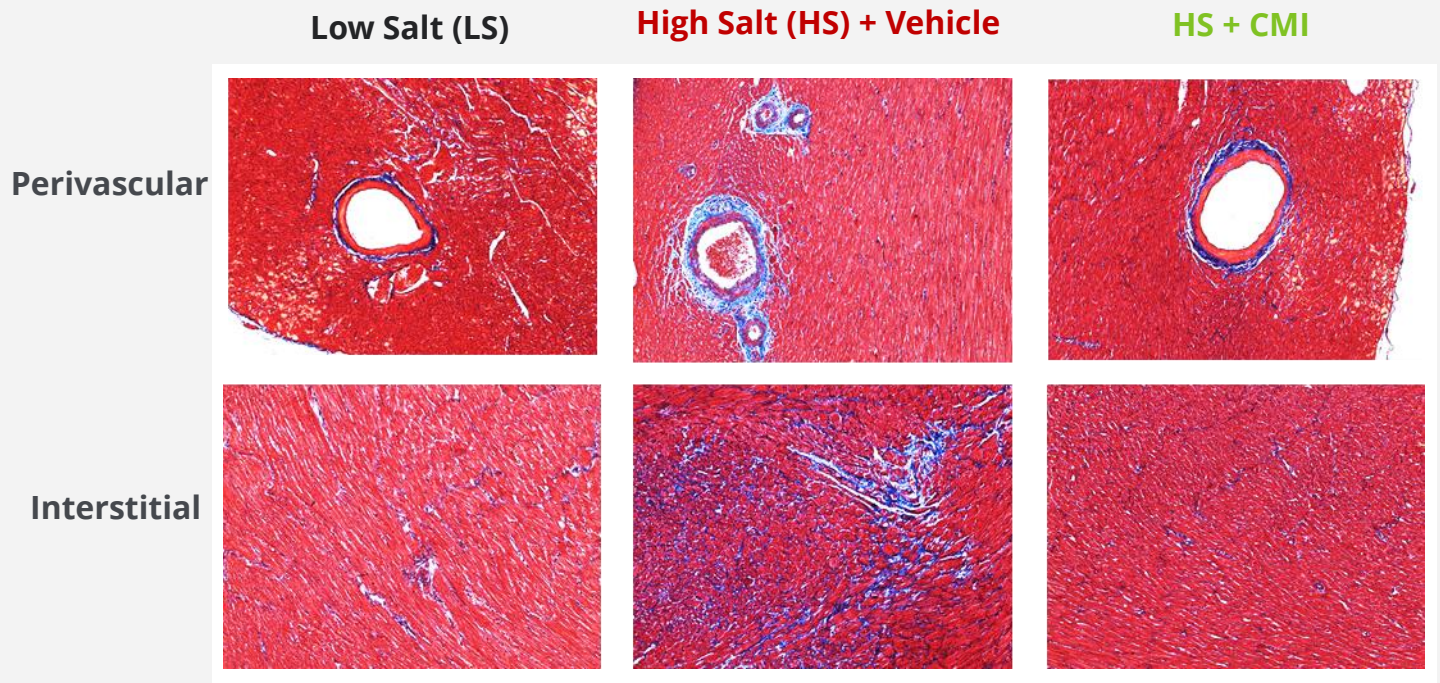


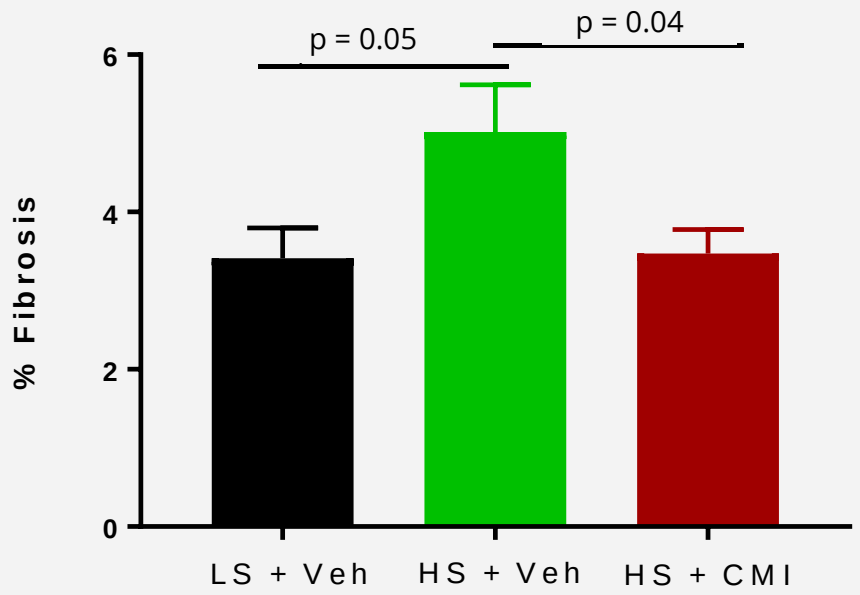
Septal wall (SW) thickness, diastole



Cardiac Myosin Inhibitor in Model of Cardiac Hypertrophy

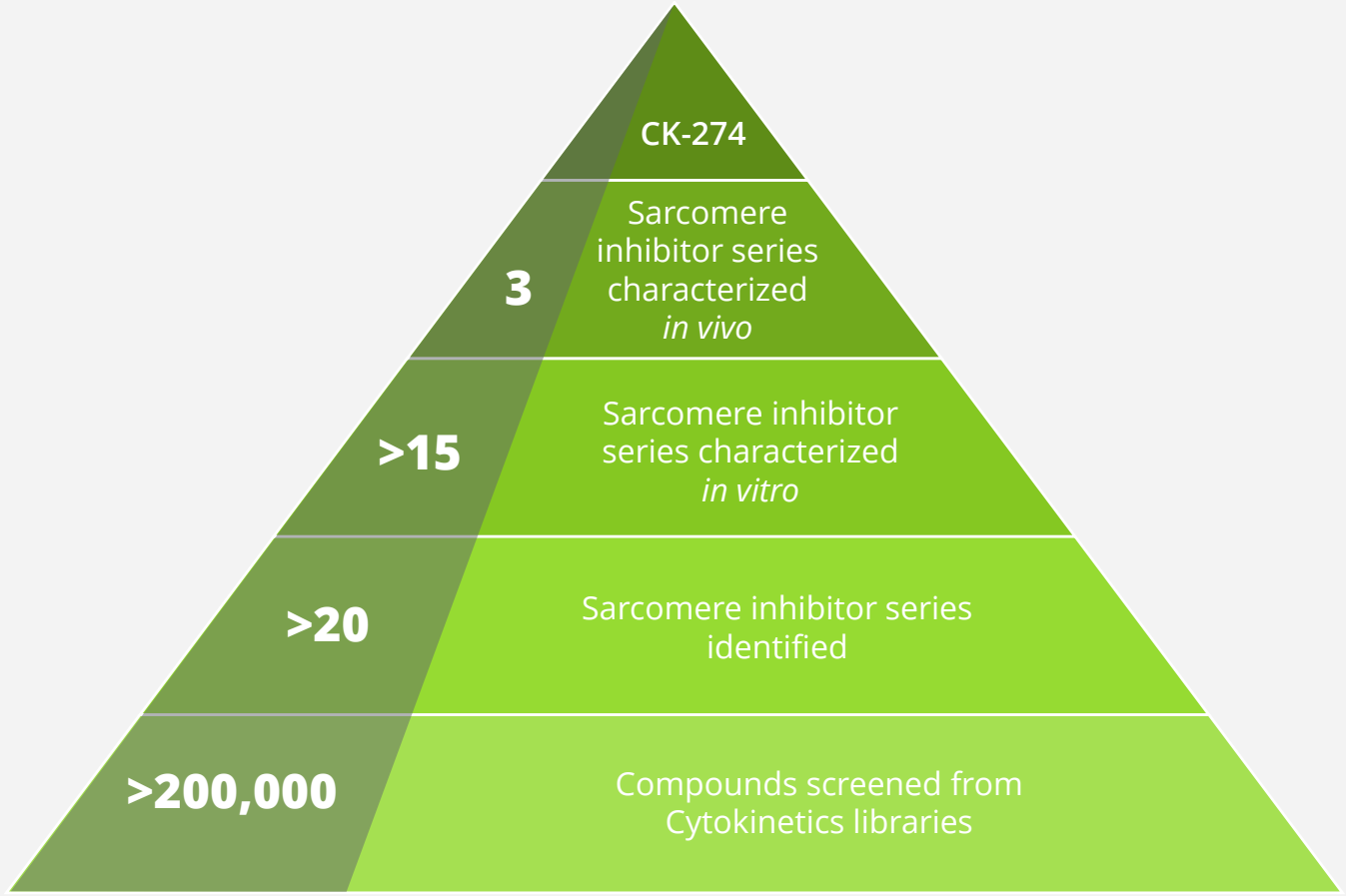
Dahl Salt Sensitive Rat Model of Cardiac Hypertrophy





Significant Decrease in Perivascular and Interstitial Fibrosis

IND Filed, Initiating First in Human Clinical Studies in Q4



Extend and Expand the
Premier Contractility Platform to Discover the
Best-in-Class Cardiac Sarcomere Inhibitors

Exploring Diverse MOAs and Chemotypes

Properties of CK-274:

Selective for Cardiac Muscle Myosin

No effect on calcium transients

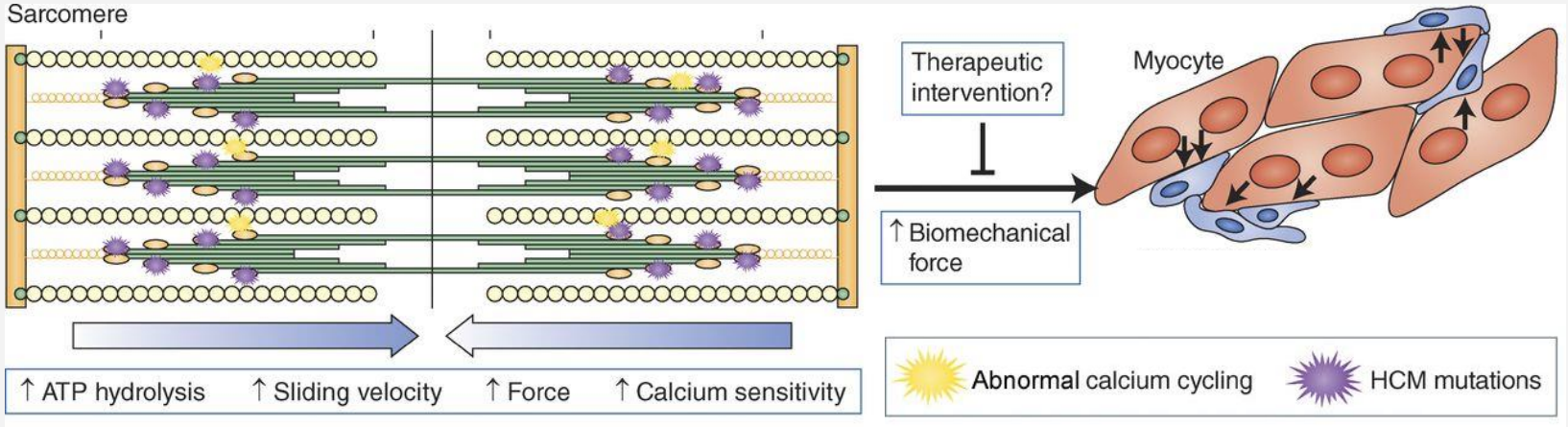
Projected human PK adequate for once daily dosing
(Rapidly reach steady state concentration)

Wide Pharmacodynamic Window

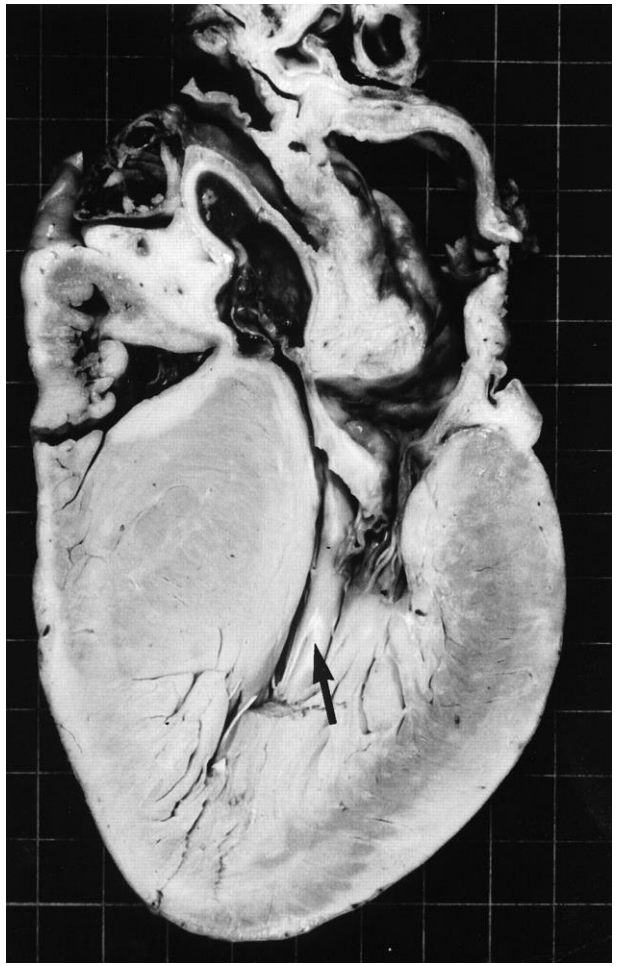
Therapeutic Hypothesis

A cardiac sarcomere inhibitor will counteract the pathologic effects of mutations in the sarcomere that lead to HCM

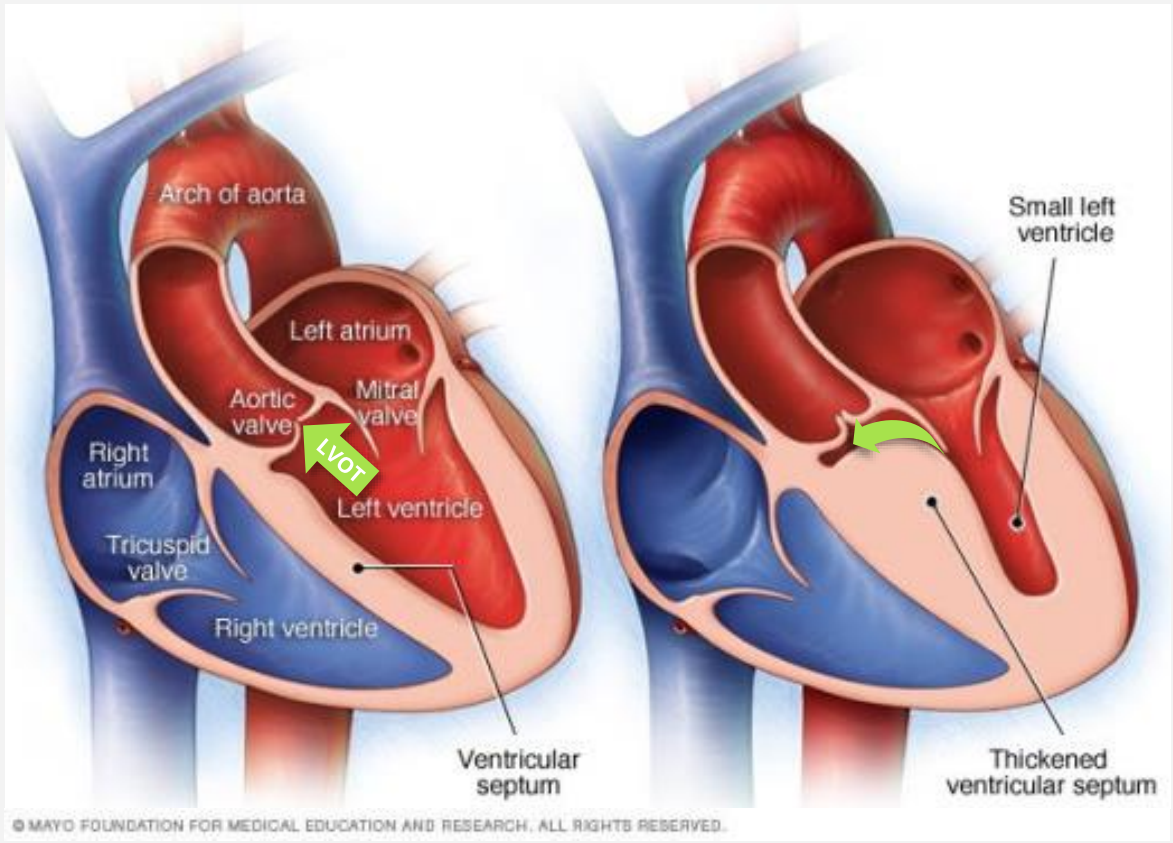
- Hyperdynamic contraction and obstruction of blood flow out of the LV
- Cardiac hypertrophy, small LV cavity, small stroke volume
- Impaired relaxation and high LV filling pressures



Source: Teekakirikul et al., JCB 2012



HCM: Left ventricular outflow tract (LVOT) obstruction

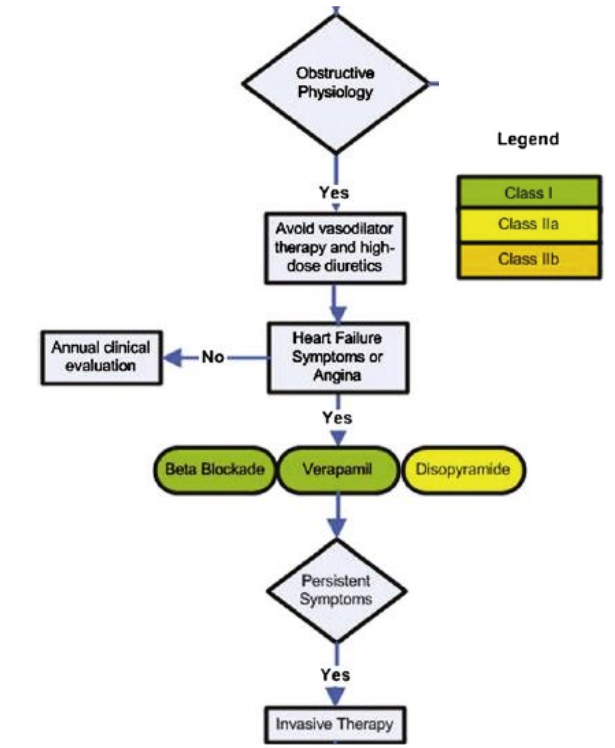


Thickening of the left ventricular septum narrows the LV outflow tract, creating resistance to blood flow. This leads to symptoms, reduces exercise tolerance, and can be quantified by echocardiography

Unmet Need in oHCM

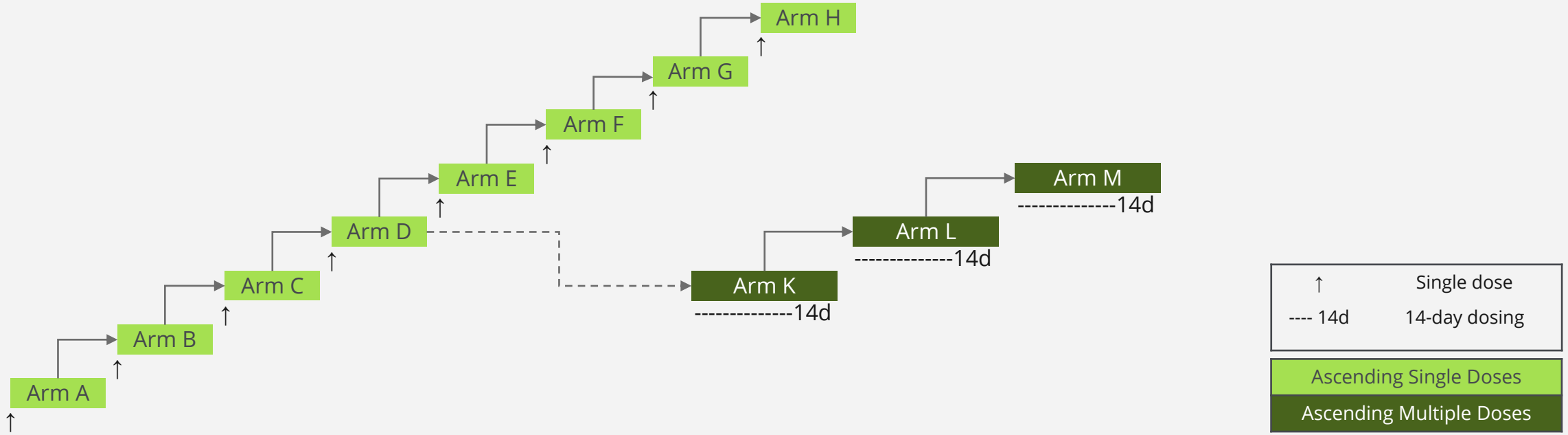
Targeted Oral Therapy to Reduce Daily Symptoms and Stop Disease Progression

- HCM gene mutations are common; the clinical course is variable
  - Prevalence is 1:500
  - A subset of patients have progressive symptoms, atrial fibrillation, stroke and/or sudden death
- Current medical treatments include beta blockers, verapamil and disopyramide
  - Not targeted to the underlying cause of HCM
  - Variable efficacy, often inadequate
  - Systemic side effects: hypotension, bradycardia, heart block
- Invasive therapy to reduce septal thickness is effective
  - Surgical myectomy or percutaneous ablation
  - Indicated for the most severely affected and refractory patients
  - Available only at a small number of institutions



(AHA 2011 guidelines)

CK-274 Phase 1 Study Design: Nested SAD and MAD in Healthy Subjects



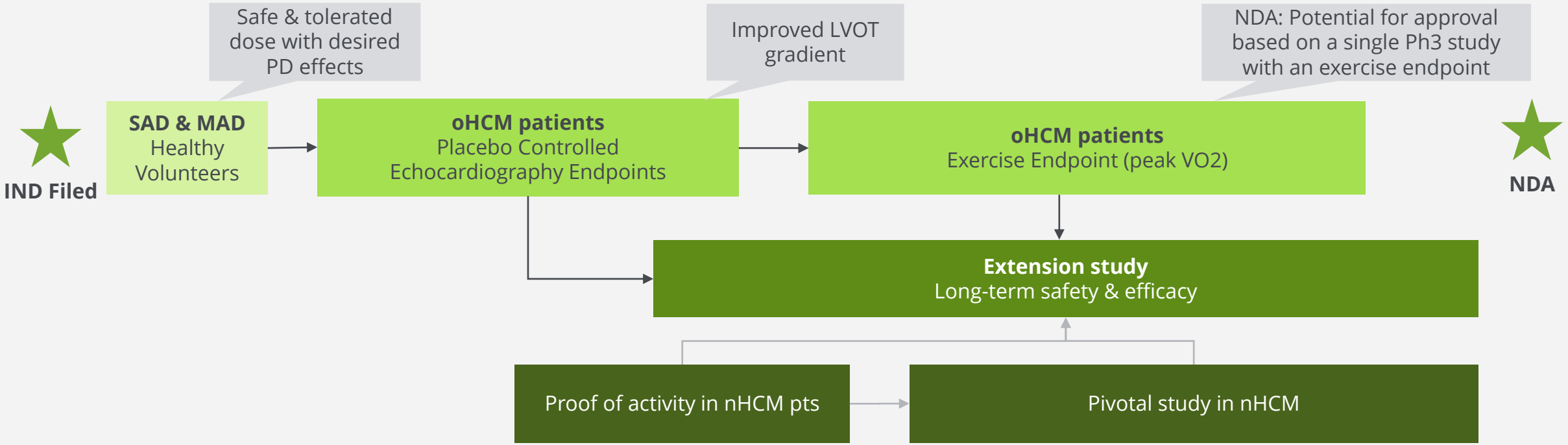
Randomized, placebo-controlled, double-blind, multi-part, single center study in ~96 healthy subjects

- Part 1: 8 single ascending oral doses (SAD)
- Part 2: 3 multiple ascending oral doses (MAD)

Objectives	Endpoints
Safety and tolerability	AEs, SAEs, LVEF
Pharmacokinetics	C_{max}, T_{max}, AUC, $t_{½}$, other
PK-PD Relationship	LVEF, LVFS, LVOT-VTI, other

CK-274: Efficient Clinical Development Plan for HCM

Phase 1 Safety, PK & PD	Phase 2 Proof of Concept, Dose Finding	Phase 3 Pivotal Studies



Summary

- CK-274 is a novel, oral, small molecule, allosteric cardiac myosin inhibitor
  - Intended to counteract the pathologic effects of mutations in the sarcomere that cause HCM
- Preclinical results
  - PD effects support a potential for best-in-class safety and efficacy
  - PK projections are consistent with daily dosing and rapid titration to a personalized dose
- Advancing into clinical development
  - IND filed
  - Efficient clinical development plan with robust PD assessments in early development

CK-274 is a cardiac myosin inhibitor with best-in-class potential for the treatment of patients with hypertrophic cardiomyopathy

PANEL DISCUSSION

A New Generation of Cardiovascular Therapies

MODERATOR

Fady Malik, MD, PhD

EVP, Research & Development
Cytokinetics

John Teerlink, MD

Professor of Clinical Medicine, University of California, San Francisco; Director of Heart Failure and Director of Echocardiography, San Francisco Veterans Affairs Medical Center

Greg Lewis, MD

Section Head, Heart Failure; Medical Director, Heart Transplant Program and Director of Cardiopulmonary Exercise Testing, Massachusetts General Hospital

SUMMARY

AND

THE LOOK AHEAD

Robert Blum
President &
Chief Executive Officer

Amgen Collaboration

Purchase Option: 2006
Exercise Option Ex-Japan: 2009
Expanded to Include Japan/Purchase Equity: 2013
Received >$200M over 11 Years

Amgen responsible for development and commercialization subject to Cytokinetics' participation rights*

Cytokinetics can earn over $650 mm in milestone payments

*Servier has a sub-license from Amgen to commercialize *omecamtiv mecarbil* in Europe and certain other countries.

COMMERCIALIZATION:

- Cytokinetics may receive escalating double-digit royalties
- Cytokinetics to co-fund Phase 3 development program
- Co-fund enables co-promote NA
- Cytokinetics reimbursed for certain sales force activities

Astellas Collaboration

Original Deal: 2013
Expanded to include SMA: 2014
Expanded to Include ALS: 2016
>$200M in Upfront Payments/R&D Sponsorship

- Collaborative research program on next-generation skeletal muscle activators through 2019 (under Astellas' sponsorship)
- Development of *reldesemtiv* in non-neuromuscular and neuromuscular indications (e.g., SMA and ALS)
- Cytokinetics conducts Phase II clinical trials of *reldesemtiv* in SMA and ALS (at Astellas' expense)
- Astellas primarily responsible for development; Cytokinetics' option to co-fund (e.g., SMA) and co-funding obligation (e.g., ALS)
- Cytokinetics has option to conduct early-stage development for certain indications at its expense, subject to reimbursement

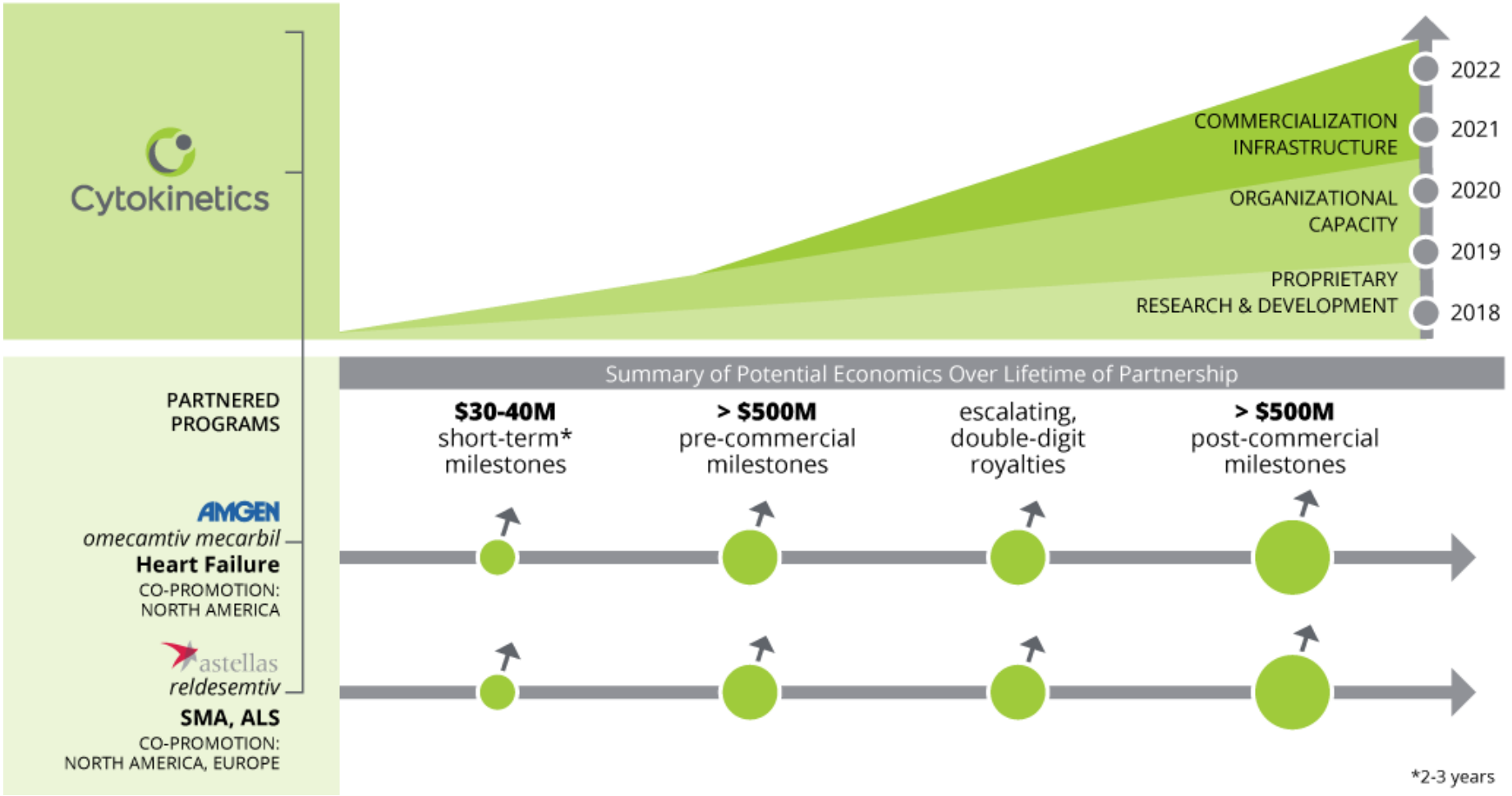
Astellas to commercialize products subject to Cytokinetics' option to co-promote for neuromuscular indications in US, Canada, and Europe; **Cytokinetics** has the option to co-promote for all other indications in the US and Canada

Astellas will reimburse Cytokinetics for certain expenses associated with co-promotion activities

Cytokinetics eligible to receive over $600 mm in pre-commercialization and commercialization milestones plus royalties, which are increased for co-funded products

Corporate Development Strategy

Leveraging Partnerships to Fund R&D and Commercialization



Cytokinetics Financing History

Strategic Partners and Institutional Investors Have Committed Approximately Equal Amounts of Capital to Cytokinetics

		Equity	Upfront Cash, Option, and Milestones	R&D Reimbur.	Total
Investors	Private Investors (VCs)	$116M			
	IPO	$94M			
	Public Post-IPO/Other	$414M			
	Total	**$625M**			**$625M**
Strategic Partners & Grants	Astellas	$10M	$130M	$75M	$215M
	Amgen	$43M	$145M	$29M	$217M
	Royalty Pharma	$10M	$90M		$100M
	GSK	$24M	$22M	$33M	$78M
	AstraZeneca			$2M	$2M
	MyoKardia			$2M	$2M
	Global Blood			$2M	$2M
	Grants (ALS Assoc / NINDS / other)		$6M		$6M
	Total	**$87M**	**$393M**	**$143M**	**$623M**

Note: Figures above exclude current debt outstanding of $42M.

Summary

- 20 years of demonstrated **leadership** in cytoskeletal and muscle biology
- Senior R&D management team: uncommon continuity, **pioneering expertise**
- **Unrivaled experience** in discovery/clinical research directed to muscle pharmacology
- Broad experience across multiple programs; **leverage and import/export learnings**
- **Monetized** progress and promise while **retaining** key rights and economics

Upcoming Milestones

2018	Begin Patient Enrollment in METEORIC-HF in Q4 2018	Initiate Phase 1 Studies for CK-274 and AMG 594 in Q4 2018	Type C Feedback from FDA regarding SMA in Q4 2018
2019	First Interim Analysis in GALACTIC-HF in 1H 2019	Complete Patient Enrollment in GALACTIC-HF in 1H 2019	Results from FORTITUDE-ALS Expected in 1H 2019

Cytokinetics

THANK YOU