



Cytokinetics

EMPOWERING
MUSCLE
EMPOWERING
LIVES

Forward Looking Statements

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Our Mission

We are developing potential medicines to improve the healthspan of people with devastating cardiovascular and neuromuscular diseases of impaired muscle function.

Sarcomere-Directed Research Goals

C
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ACTIVATE MYOSIN

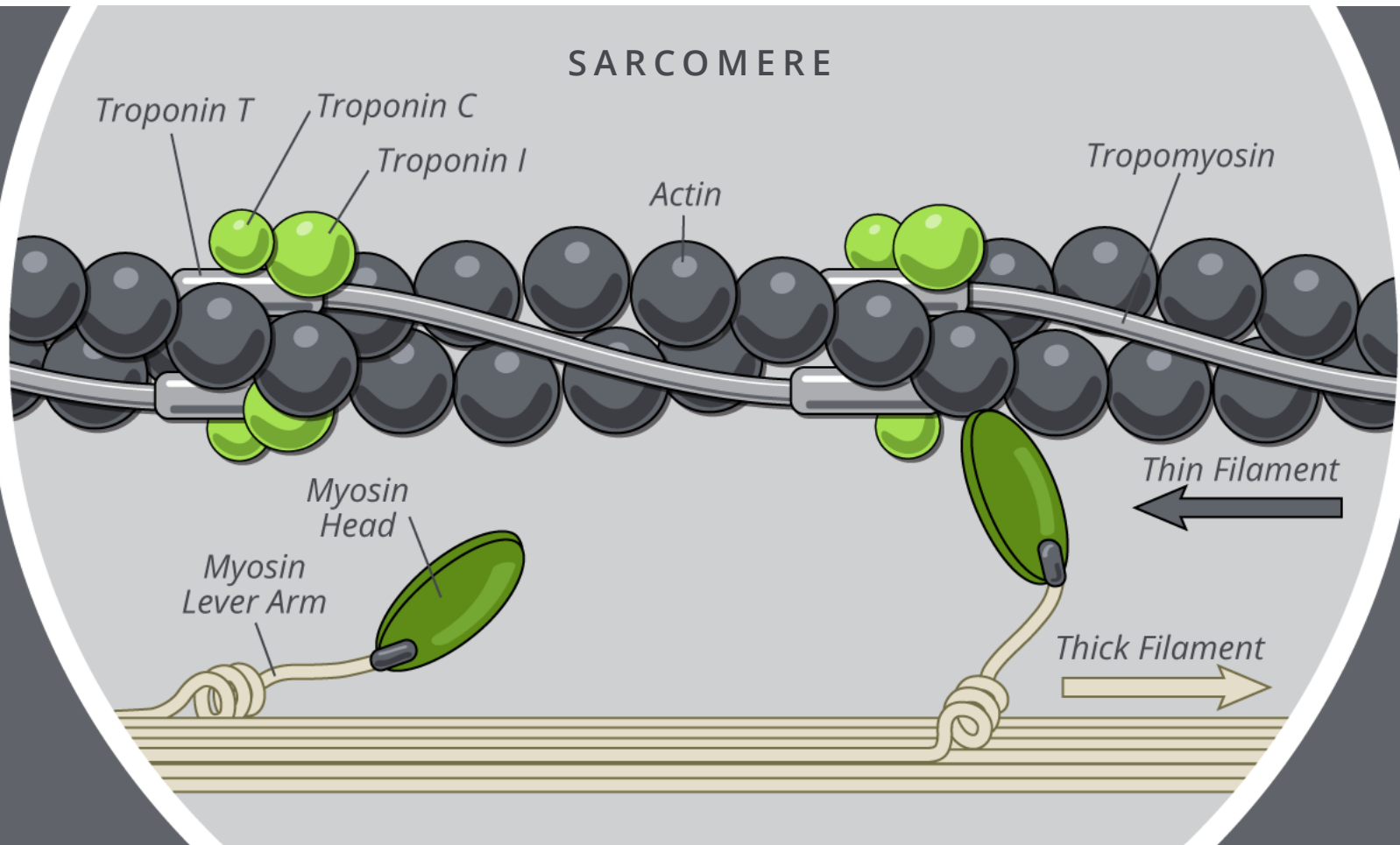
Omecamtiv Mecarbil

INHIBIT MYOSIN

CK-274

ACTIVATE TROPONIN

AMG 594



ACTIVATE TROPONIN

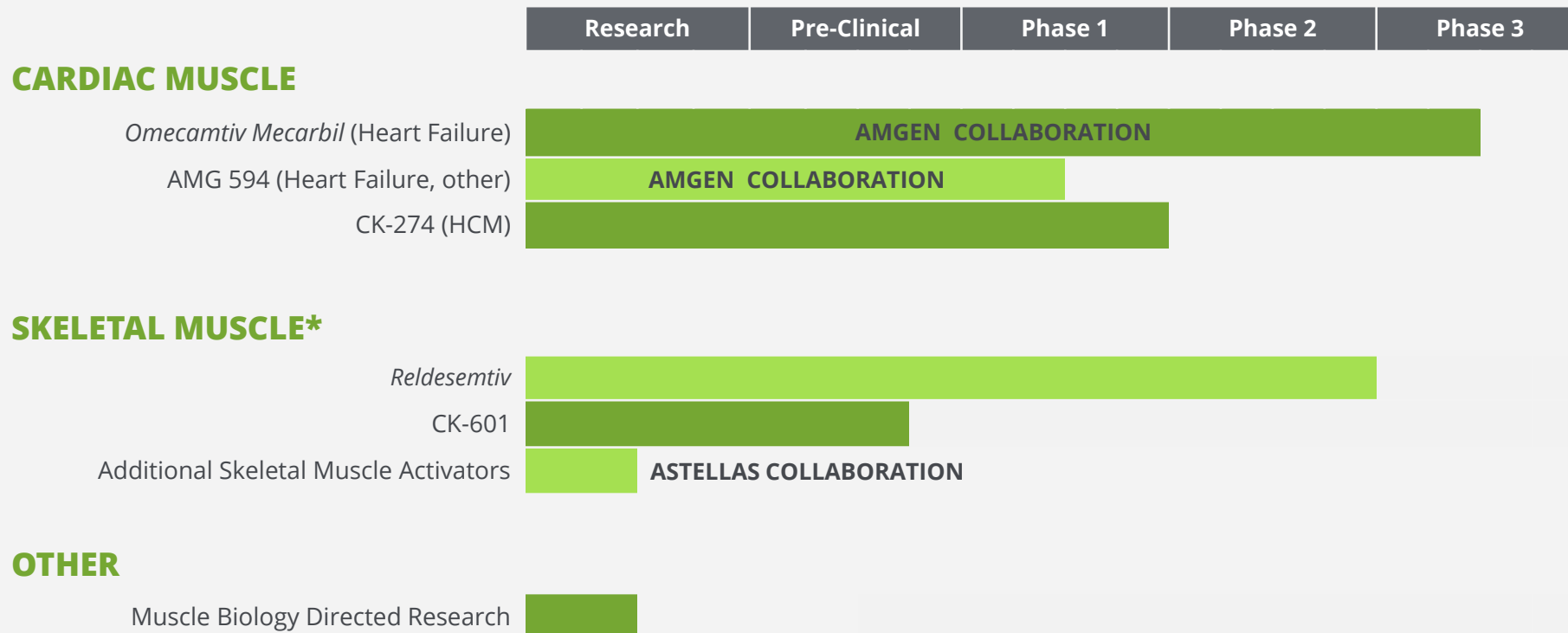
Reldesemtiv

ACTIVATE TROPONIN

CK-601

S
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Pipeline of Novel Muscle-Directed Compounds



Investigational products – not approved as safe or effective for any indication.
 *Development of *tirasemtiv* has been suspended. A managed access program remains underway for patients who completed participation in VITALITY-ALS.

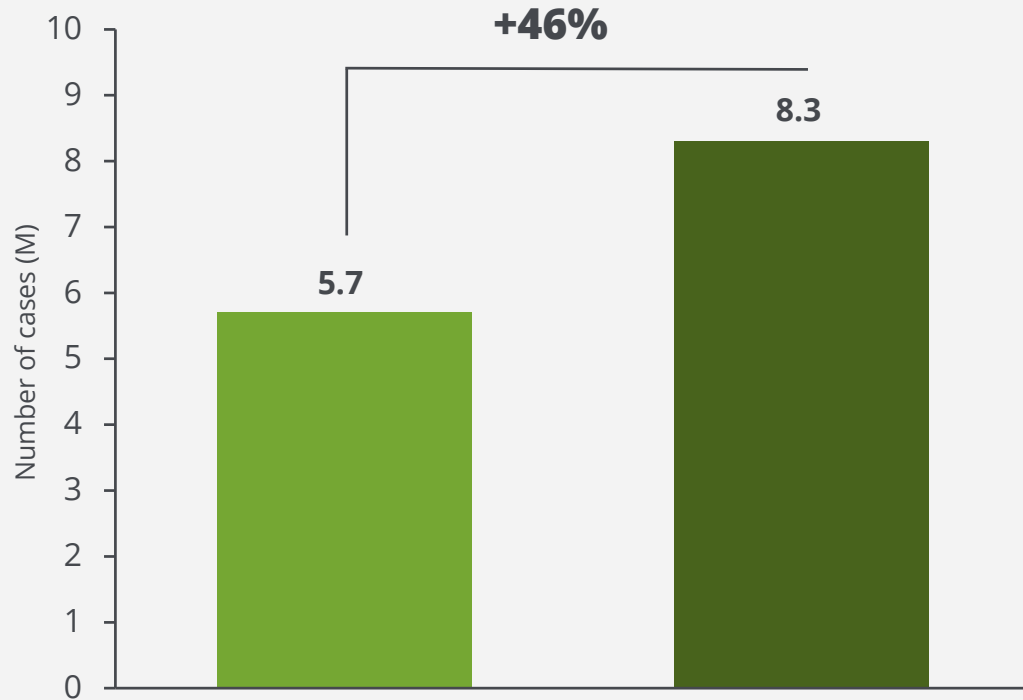
CARDIAC MUSCLE

Omecamtiv Mecarbil
CK-274



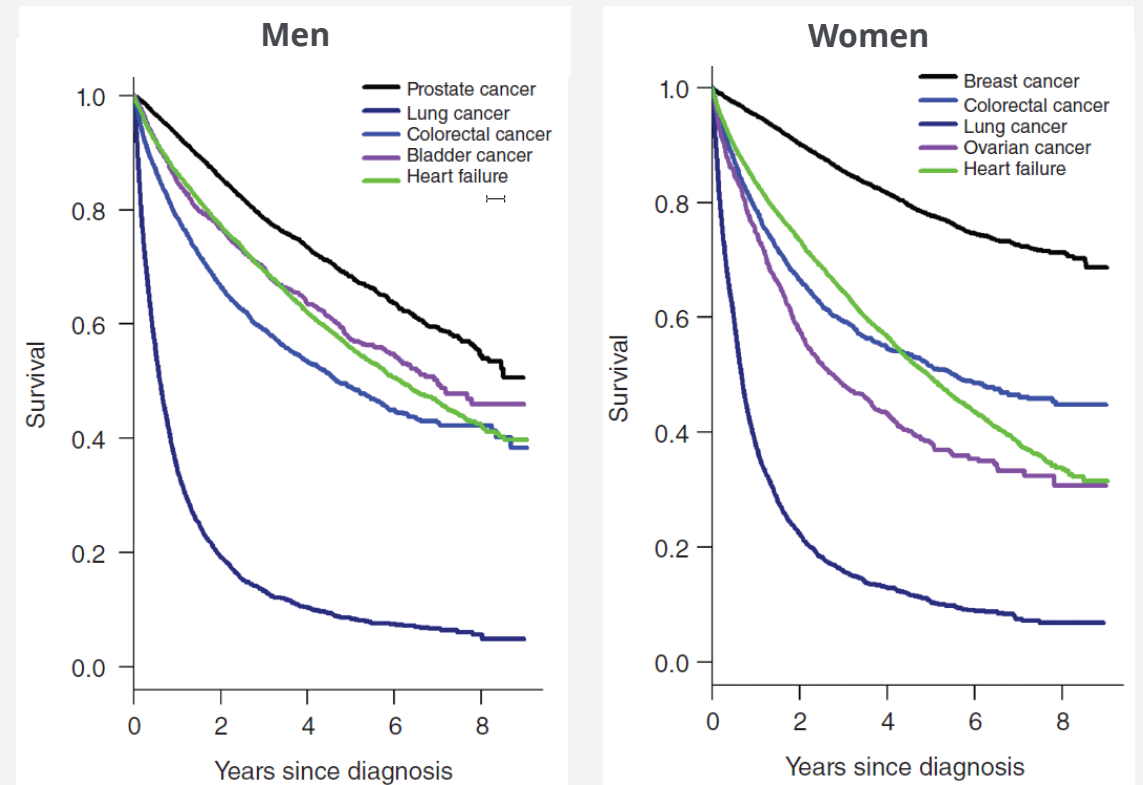
Heart Failure: Growing Prevalence and Low Survival Rate

6M People Have HF; Prevalence Expected to Increase by 46% from 2012 - 2030



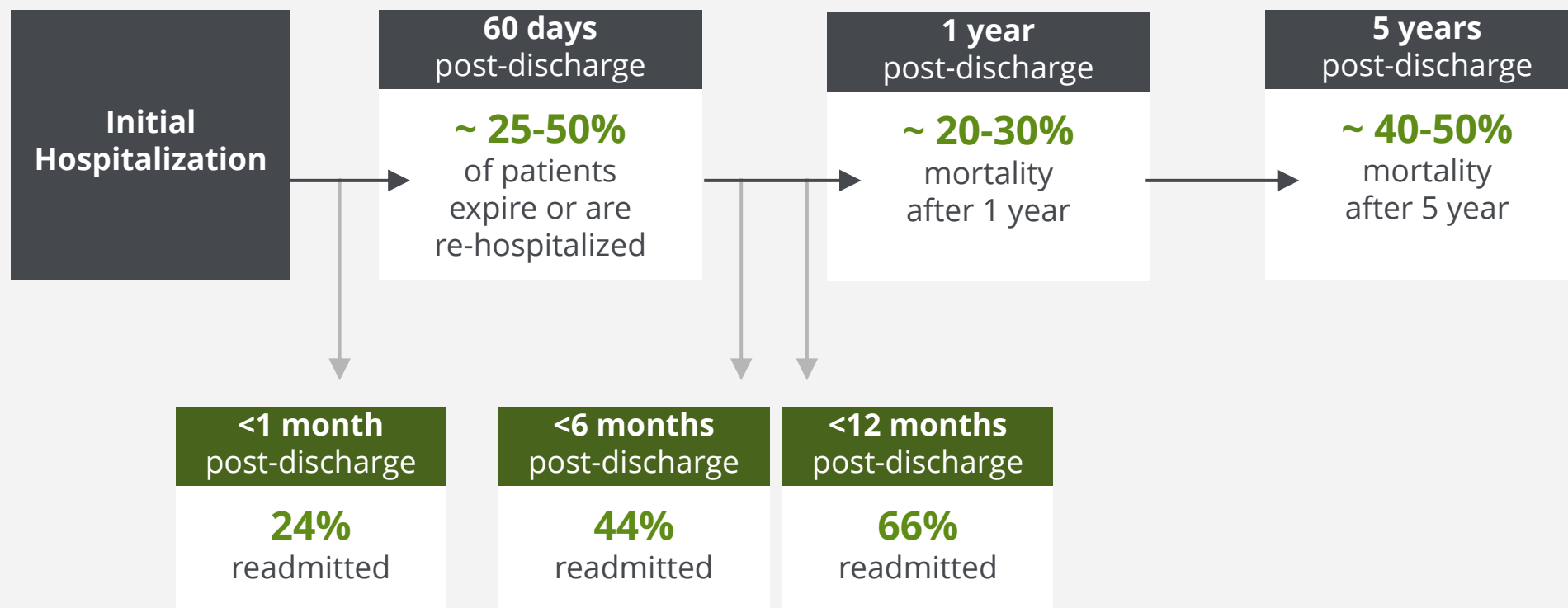
Mozzafarian, et al. *Circulation* 2016; 133: e38-360

HF Survival Rates Worse than Some Prevalent Cancers



Mamas MA, et al. Do patients have worse outcomes in heart failure than in cancer? *European Journal Heart Failure* 2017

High Mortality and Hospital Readmission Rates



Mozzafarian, et al. *Circulation* 2016; 133: e38-360
Shahar, et al. *J Card Fail* 2004 Oct 1;10(5):374-9.

Roger et al. *Circulation* 2012;125:32-220
Chen et al. *JAMA* 2011;306:1669-78

Mamas et al. *Eur J Heart Fail.* 2017 Sep;19(9):1095-104.
Adams et al. *Am Heart J* 2006; 149:209-16
Dickstein et al. *Eur Heart J* 2008;29:2388-442

Whellan et al. *Circulation* 2010 Jan;3(1):33-40.
Krumholz HM, et al. *Arch Intern Med* 1997;15799 - 105
Loehr et al. *Am J Cardiol* 2008;101:1016-22

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

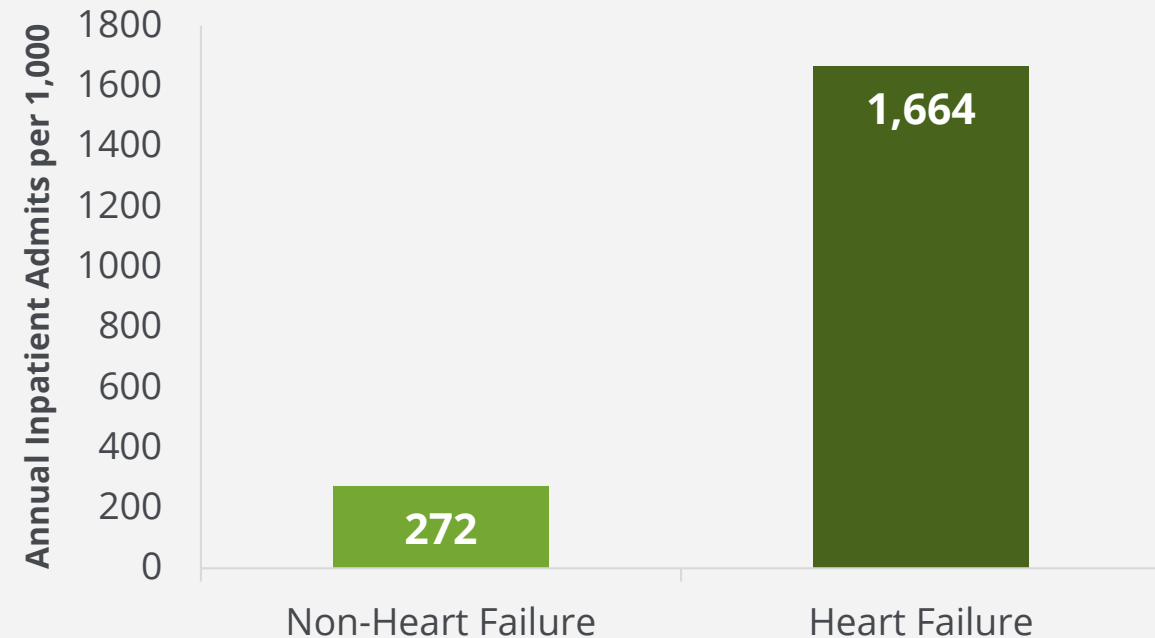
1 of 2 hospitalized HF patients are readmitted within 6 months

High Economic Burden of Heart Failure

Heart failure costs ~\$123 billion annually, which represents **33% of total Medicare budget**

Heart failure is the most frequent diagnosis for hospitalized Medicare patients in the US

Inpatient Admission Rates for HF Patients 6X Higher than Non-HF Patients



Source: Milliman Analysis of Medicare 5% Sample 2011-2012 (2012 index year, 2011 look back year)

Source: Milliman Analysis of Medicare 5% Sample (2014 index year, 2013 look back year) and Office of the Actuary 2016 Board of Trustees Report. The costs only include Part A & B costs.

Significant Unmet Need in Heart Failure with Reduced Ejection Fraction

Reduction in mortality & hospital visits

Physicians say Entresto has prolonged survival, decreased hospital visits, but still **see need for other therapies that reduce mortality**

Drugs that do not affect renal function

Most physicians recognize negative effect therapies such as aldosterone antagonists have **on renal function**

Drugs that do not affect BP

BP often limiting factor for up titration and therapy initiation; Need efficacious drugs **that do not result in hypotension**

Drugs with molecular targets & inotropic agents

Need drugs that target **novel/more specific molecular targets**;
Need targets other than the neurohormonal pathway;
Need for inotropic drugs as support agents

Disease modifying therapies

Need therapies **that offer contractile support**
Increased EF most frequently mentioned desired measure

Drugs that increase QoL

Patient management will improve **with drugs that increase QoL**;
Patient QoL decreases as they lose the ability to perform daily tasks

Proprietary Market Research Suggests
Need for Novel
Therapy

Omecamtiv Mecarbil: Clinical Trials Program

11

Phase 1 Studies

324

Subjects Enrolled

**Well characterized safety,
tolerability and PK/PD data**

**Robust
Clinical
Trials
Program**

7

Phase 2 Studies

1,414

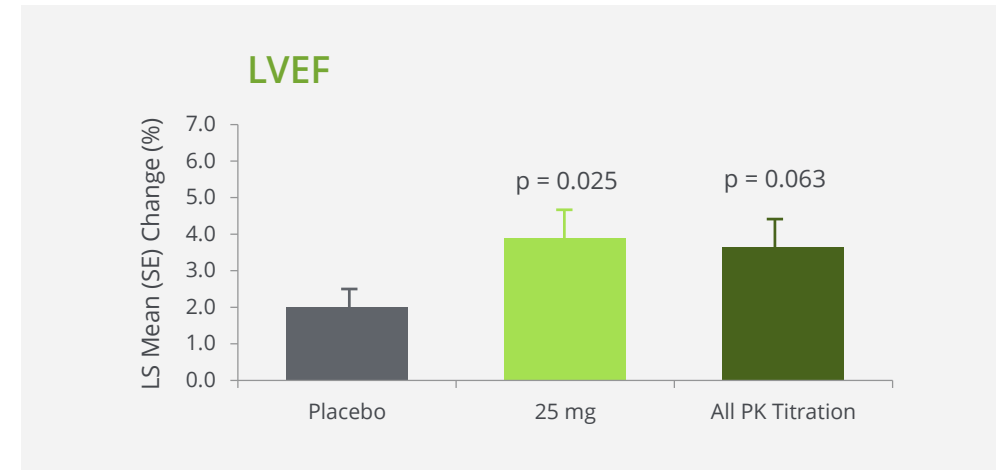
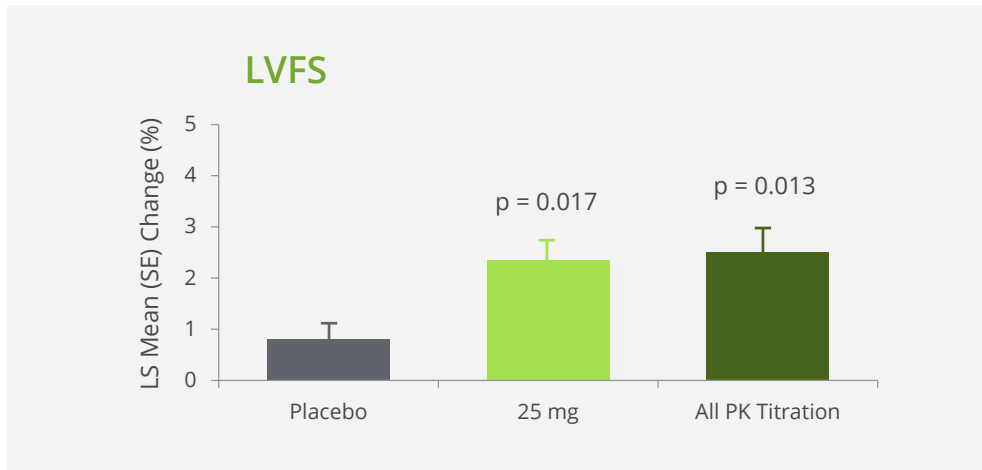
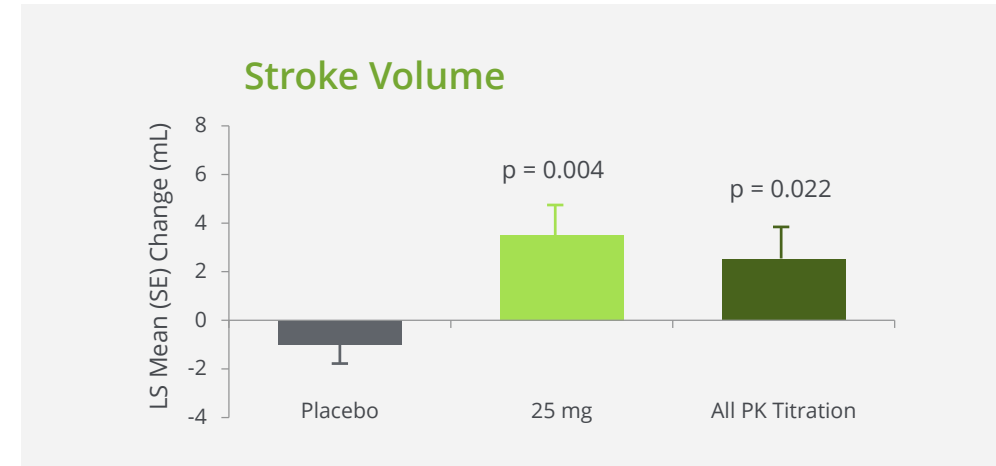
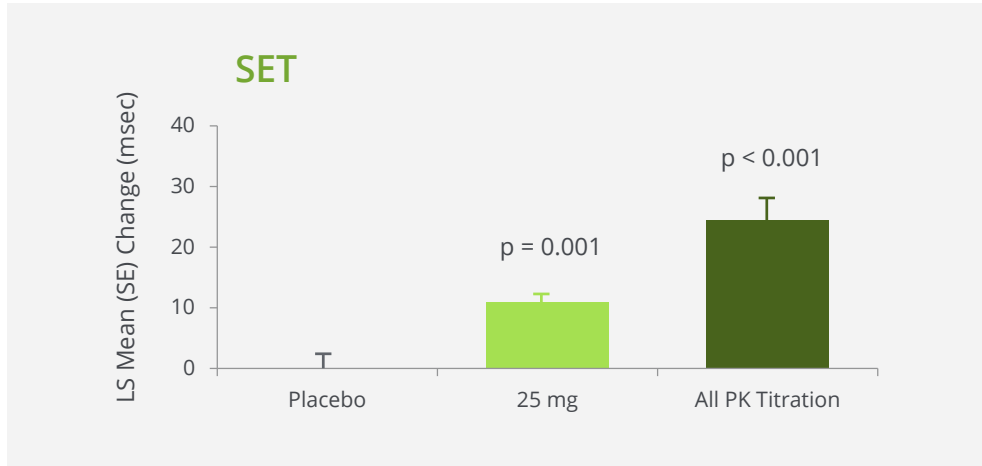
Subjects Enrolled

**COSMIC-HF showed statistically
significant improvements in
measures of cardiac function**

Dose-Dependent Increases Observed in Cardiac Output

Pharmacodynamic Data Observed

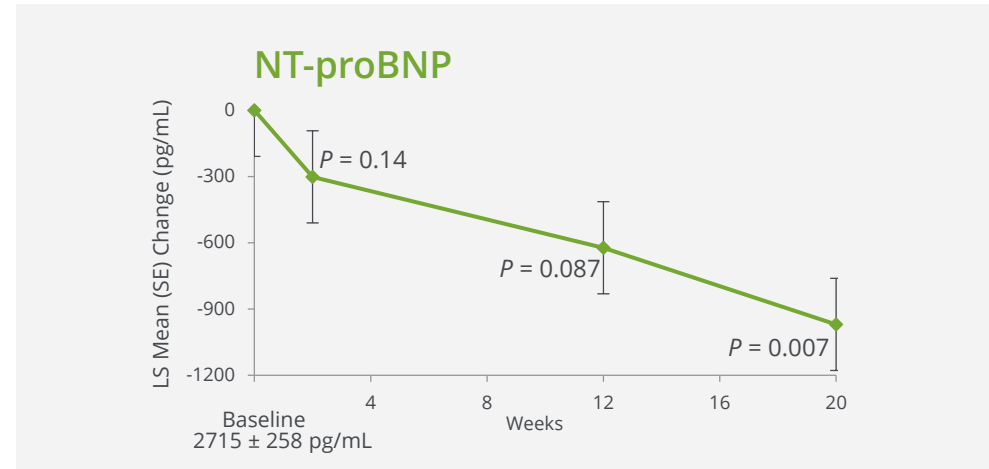
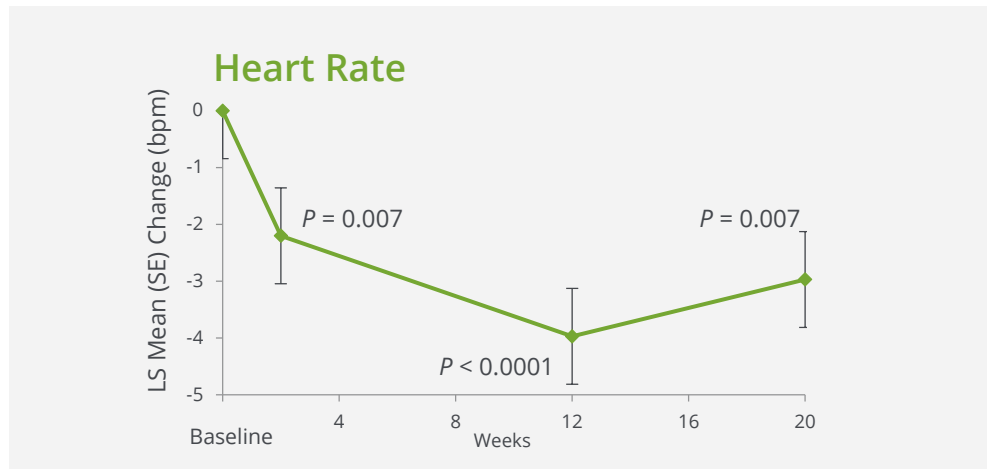
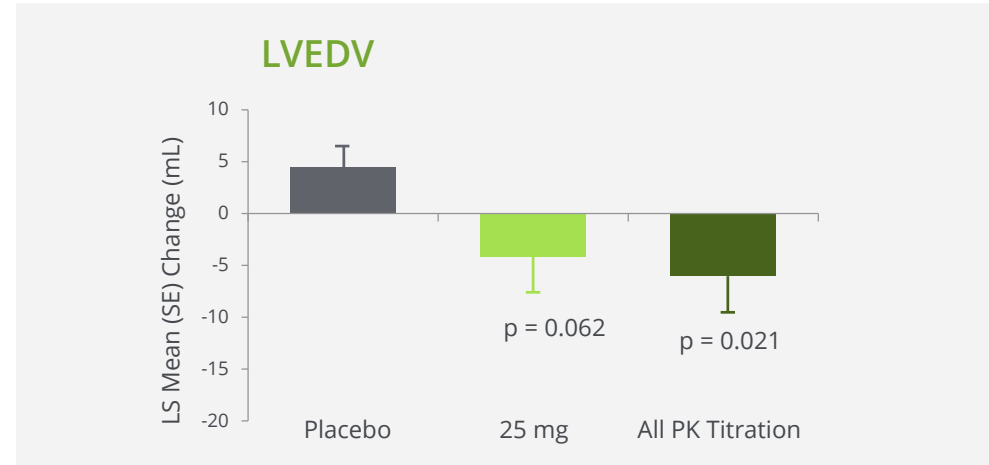
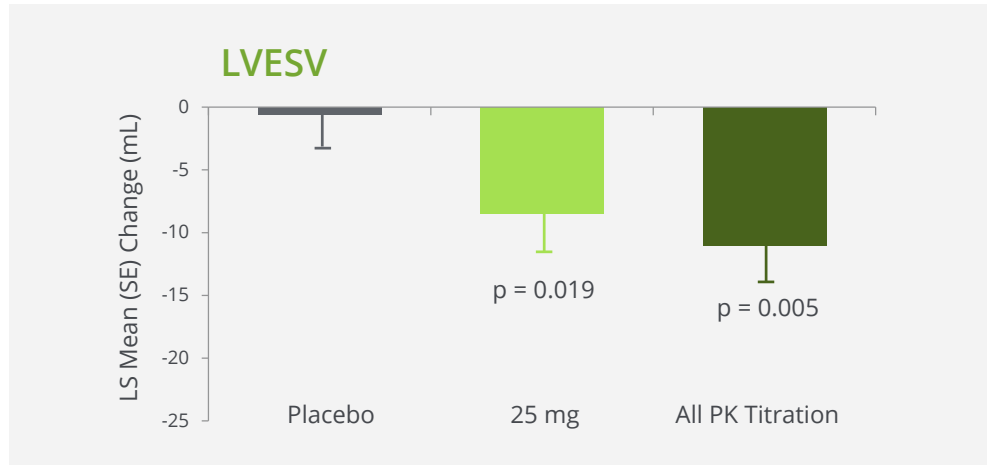
LVEF, left ventricular ejection fraction; LVFS, left ventricular fractional shortening; SE, standard error; SET, systolic ejection time; all p values are nominal without multiplicity adjustment.



Decreases Observed in Physiology & Cardiac Risk

Reductions in Heart Volume, Oxygen Demand & Wall Stress

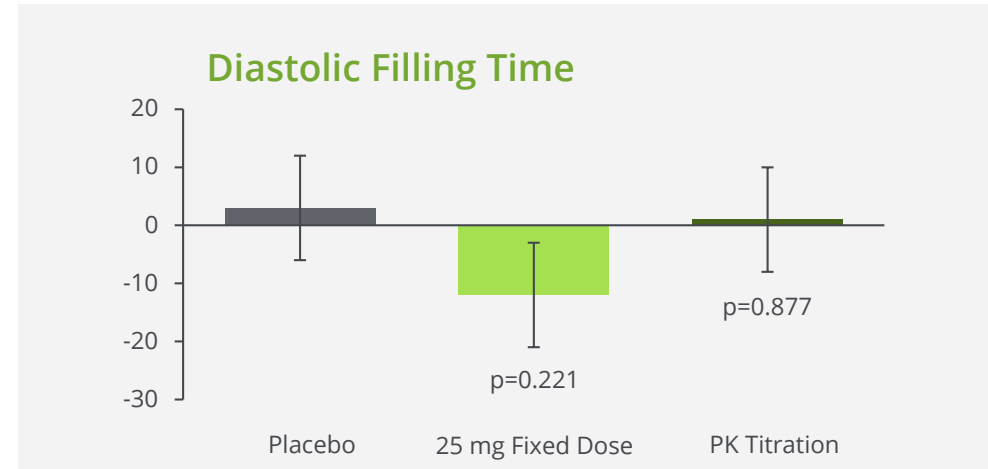
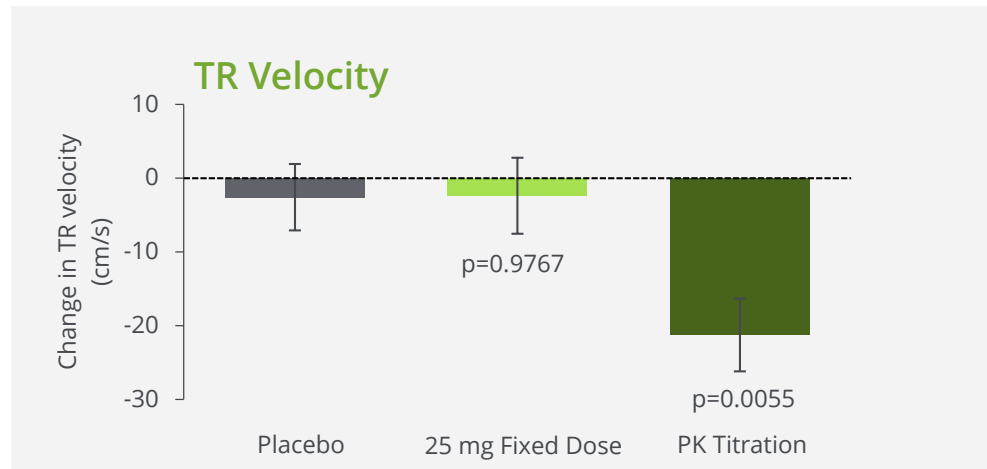
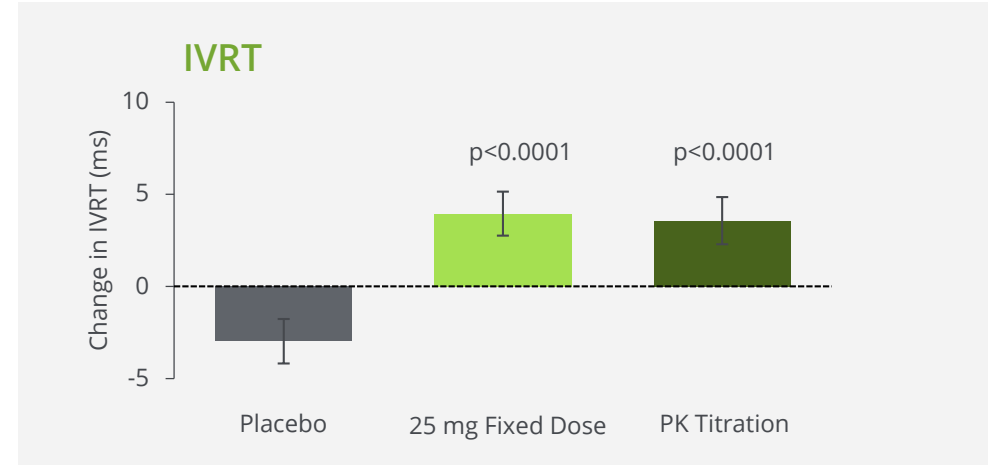
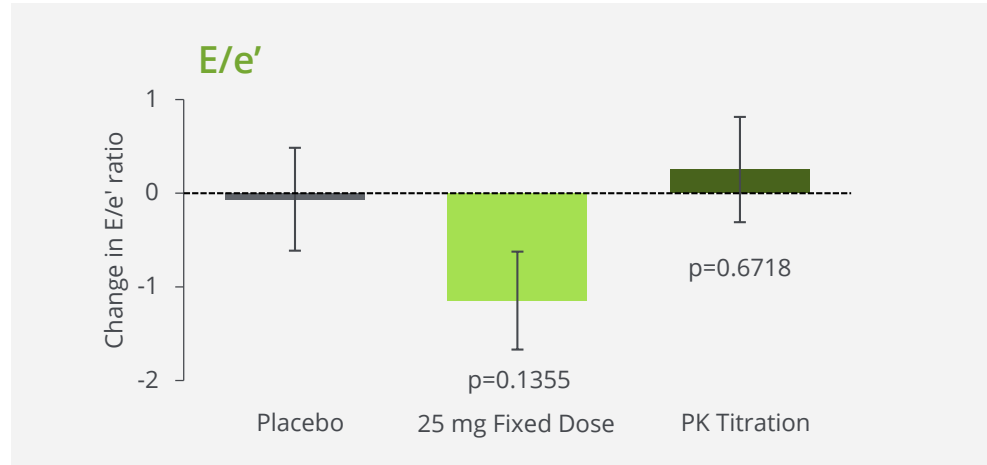
LVESV left ventricular end systolic volume
 LVEDV left ventricular end diastolic volume
 All p values are nominal without multiplicity adjustment



Neutral or Improved Measures of Diastolic Function

Improved Systolic Function With No Negative Impact on Diastolic Function

IVRT=isovolumic relaxation time
TR=tricuspid regurgitation



Prognostic Implications: NT-proBNP and Remodeling

Prognostic Implications of Changes in N-Terminal Pro-B-Type Natriuretic Peptide in Patients With Heart Failure

Michael R. Zile, MD,^a Brian L. Claggett, PhD,^b Margaret F. Prescott, PhD,^c John J.V. McMurray, MD,^d Milton Packer, MD,^e Jean L. Rouleau, MD,^f Karl Swedberg, MD,^g Akshay S. Desai, MD,^b Jianjian Gong, PhD,^c Victor C. Shi, MD,^c Scott D. Solomon, MD,^c



ABSTRACT

BACKGROUND Natriuretic peptide levels and changes in NP from baseline is

OBJECTIVES The authors assess the relationship between a decrease in HF hospitalization and

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doi:10.1016/j.jacc.2010.05.011

QUARTERLY FOCUS ISSUE: HEART FAILURE

Quantitative Evaluation of Drug or Device Effects on Ventricular Remodeling as Predictors of Therapeutic Effects on Mortality in Patients With Heart Failure and Reduced Ejection Fraction

A Meta-Analytic Approach

Daniel G. Kramer, MD,* Thomas A. Trikalinos, MD, PhD,† David M. Kent, MD, MS,† George V. Antonopoulos, MD,* Marvin A. Konstam, MD,* James E. Udelson, MD*
Boston, Massachusetts

Objectives The purpose of this study was to quantitatively assess the relationship between therapy-induced changes in left ventricular (LV) remodeling and longer-term outcomes in patients with left ventricular dysfunction (LVD).

Background Whether therapy-induced changes in left ventricular ejection fraction (LVEF), end-diastolic volume (EDV), and end-systolic volume (ESV) are predictors of mortality in patients with LVD is not established.

Zile et al. JACC 2016; 68(22): 2425-2436 Kramer et al. JACC 2010;56(5):392-406

Analysis of PARADIGM-HF showed decreases from baseline in NT-proBNP were strongly correlated with reductions in combined endpoint of time to first HF hospitalization or CV death

Meta-analysis of 30 mortality trials of 25 drugs/device therapies found that in patients with left ventricular dysfunction, short-term therapeutic effects of a drug or device on left ventricular remodeling were associated with longer-term effects on mortality



Phase 3 Clinical Trial Completed Enrollment

Study Overview

- Enrolled over 8,200 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

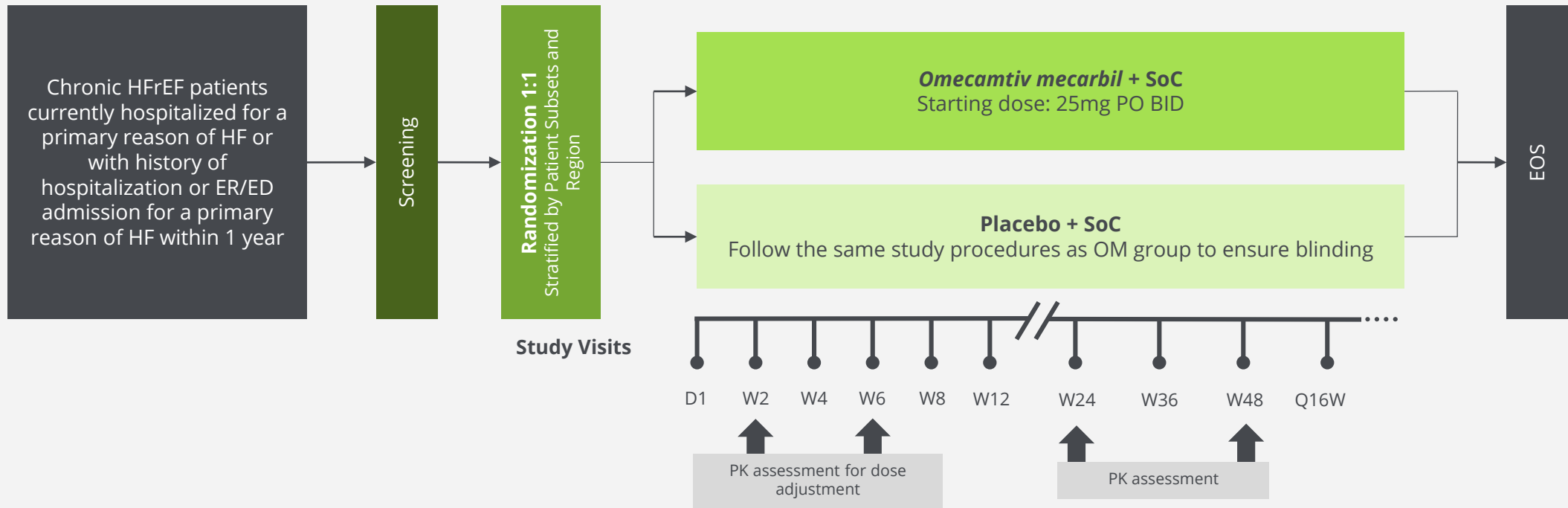
- Dose optimization based on trough concentration of *omecamtiv mecarbil* at 2 weeks and 6 weeks
 - Starting Dose = 25 mg BID
 - Escalation (or not) at Week 4 to 37.5 mg or 50 mg BID based on plasma concentration of *omecamtiv mecarbil* at Week 2
 - Recheck at Week 6, adjust dose downward if necessary
- 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

GALACTIC-HF
Continuing
Following Planned
Interim Analysis
Conducted by DMC

Second Interim
Analyses Expected
in Q1 2020

Clinical Trial Overview

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





Second Phase 3 Clinical Trial Underway

Primary endpoint

- Change in peak VO_2 on 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

Multicenter Exercise Tolerance Evaluation of *Omecamtiv Mecarbil* Related to Increased Contractility in Heart Failure

9 Countries 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)

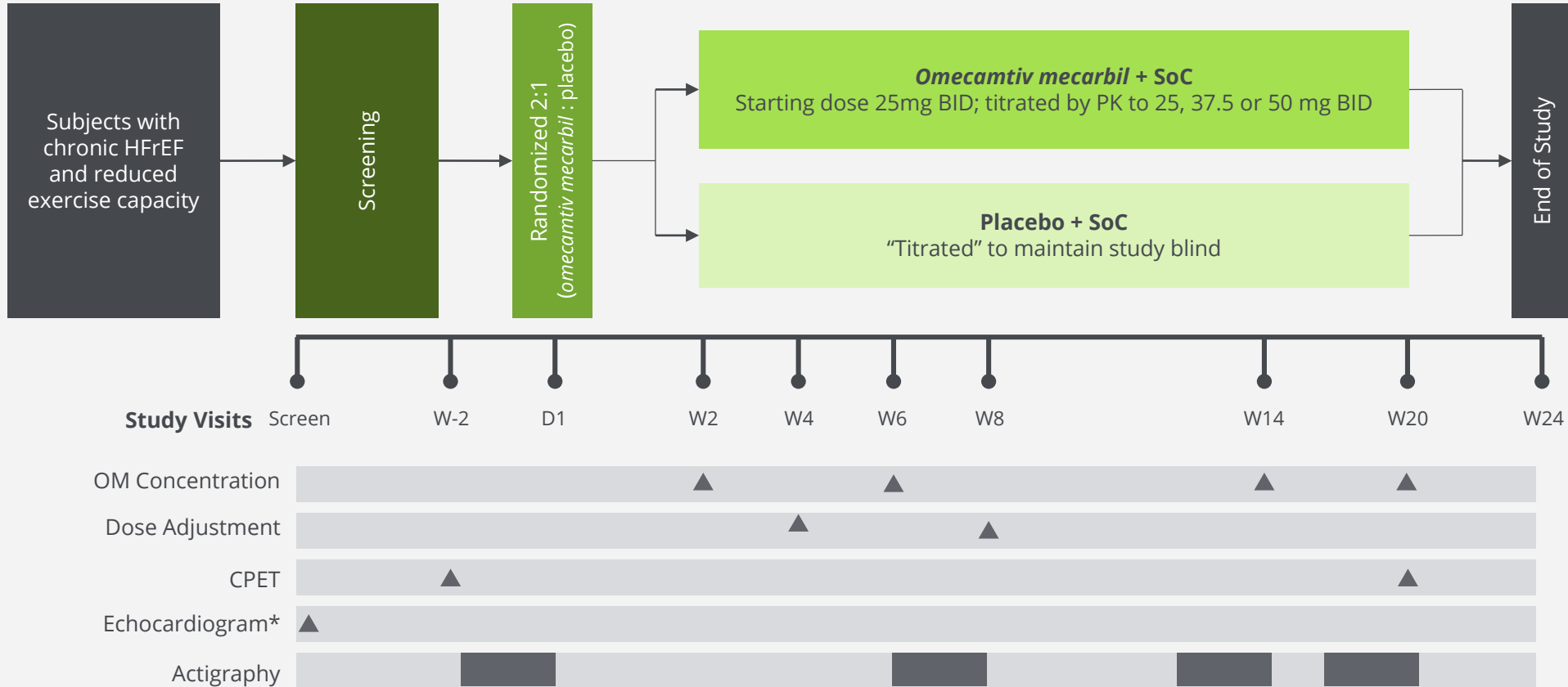
Alain Cohen-Solal (France)

Piotr Ponikowski (Poland)

Michael Böhm (Germany)

Marco Metra (Italy)

Clinical Trial Overview



~270 subjects
90% power

5 months of treatment (same as COSMIC-HF)

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

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

Collaborations & Agreements

Amgen Collaboration

Purchase Option: 2006
Exercise Option Ex-Japan: 2009
Expanded to Include Japan/Purchase Equity: 2013
Received >\$220M over 12 Years

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

Cytokinetics could earn over \$600 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

Royalty Pharma Agreement

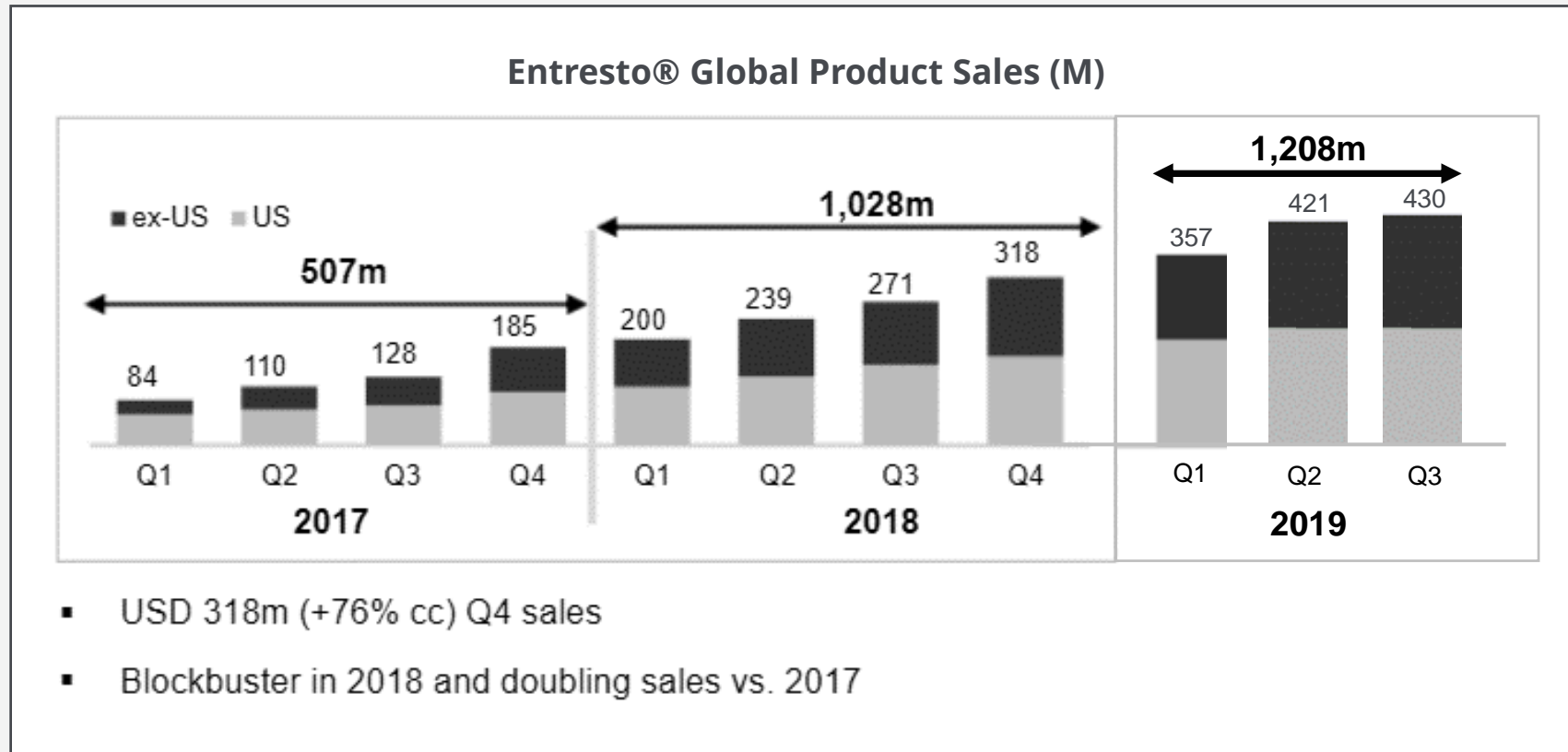
Paid \$100M for 4.5% royalty on worldwide sales of *omecamtiv mecarbil*: 2017

Cytokinetics gains right to co-promote *omecamtiv mecarbil*, if approved, in institutional care settings in North America, with reimbursement from Amgen for certain sales force activities

Joint commercial operating team responsible for commercialization program

- Royalty rate may increase up to additional 1% associated with timing of US approval
- Cytokinetics agreed to exercise option to co-invest \$40M in Ph 3 development program in exchange for up to incremental 4% royalty on increasing worldwide sales outside of Japan
- Cytokinetics retains right to receive >\$600M in additional potential milestone payments and escalating double-digit royalties that may exceed 20% on tiered worldwide sales outside Japan; lower royalty rate in Japan

Commercial Opportunity for New Heart Failure Therapy

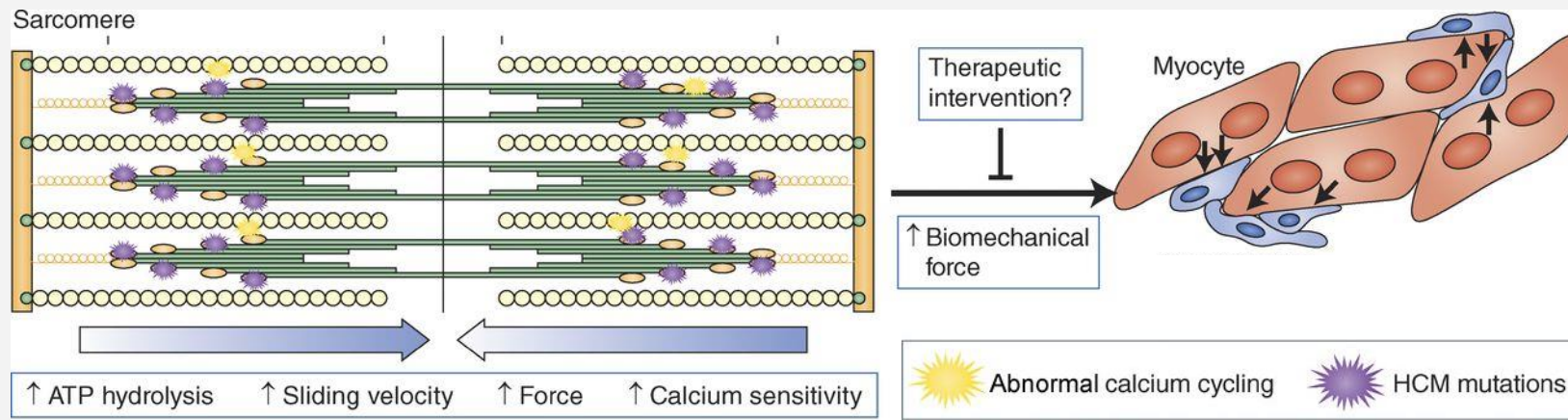


Sources: Novartis Q4 and FY18 results presentation, January 2019; Novartis Q1 2019 results presentation, April 2019; Novartis Q2 2019 results presentation, July 2019; Novartis Q3 2019 results presentation, October 2019

*As with all products in P3, the product profile achieved by omecamtiv mecarbil in GALACTIC-HF is required to provide a better understanding of the expected revenue.

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

CK-274: Potential Next-In-Class Cardiac Myosin Inhibitor

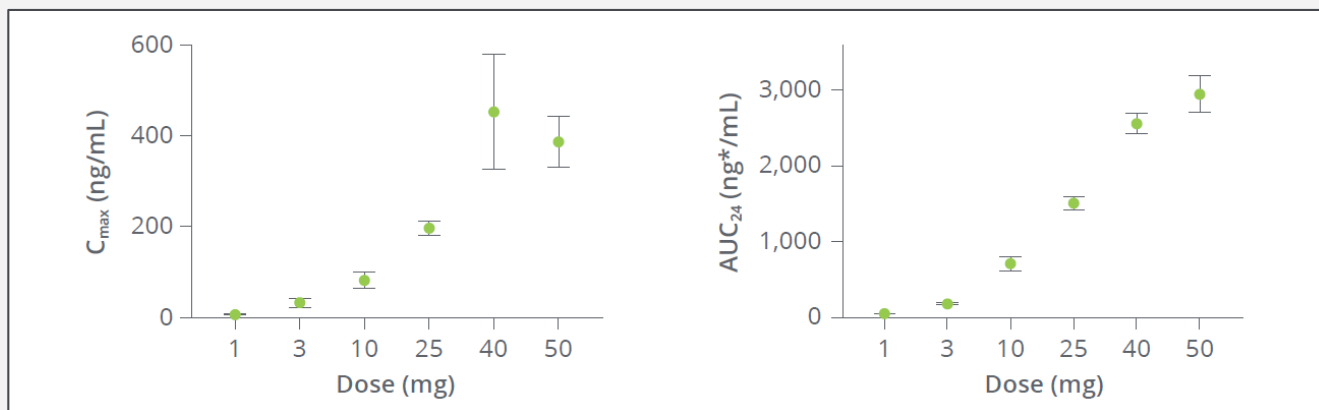
- Favorable pharmacokinetic / pharmacodynamic properties and other candidate selection criteria
 - Selective allosteric inhibitor of cardiac myosin
 - Potential *in vivo* pharmacodynamic advantages related to distinctive binding
 - No inhibition of smooth muscle myosin observed
 - Favorable ADME properties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

Discovered by
Company Scientists
Independent of
Collaborations

Selected from
Multiple Potential
Development
Candidates (PDCs)

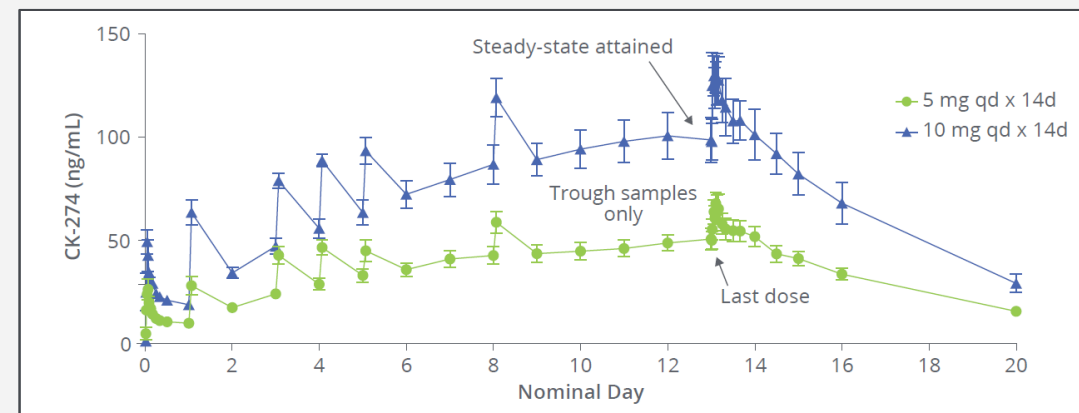
Phase 1 Study: SAD & MAD Pharmacokinetics

SAD Pharmacokinetics Appeared Generally Dose Proportional



Data points represent mean \pm standard error of the mean.
 C_{max} , maximum drug plasma concentration; AUC_{24} , area under the plasma concentration curve;
SAD, single ascending dose.

Steady-State Appeared Evident After 14 Days of Dosing



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

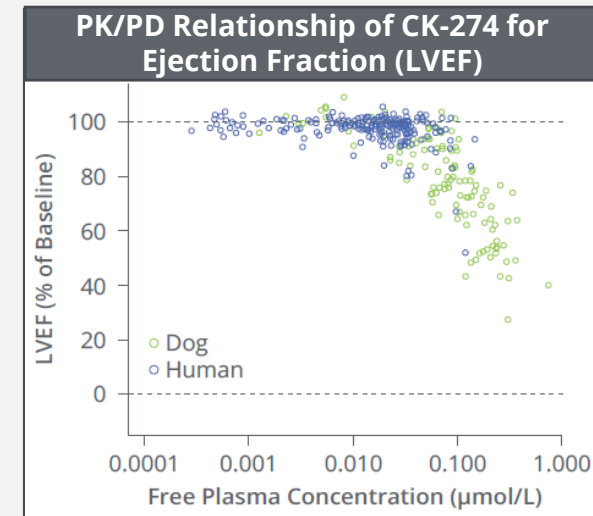
Phase 1 Study: MAD Pharmacokinetic Parameters

Half-Life of CK-274 at Steady-State was ~81 hours (3.4 days) On Average

Shallow Exposure-Response Relationship Observed Preclinically Appears to Have Translated to Humans, May Enable Flexible Dose Optimization in Humans

Dose (n)	PK Parameter, Geometric Mean (%CV)*				
	C _{max} (ng/mL)	t _{max} (h)	AUC ₂₄ (ng•h/mL)	t _{1/2} (h)	AR
5 mg (6)	69 (23.2%)	2.75 (1.5–4)	1,320 (23.0%)	86.3 (11.9)	4.71
7.5 mg (6)	148 (39.5%)	1.0 (0.5–5)	2,518 (25.8%)	76.9 (14.5)	4.50
10 mg (6)	141 (19.7%)	2.5 (0.5–3)	2,631 (22.8%)	79.7 (14.1)	4.79

* Except data for t_{max} shown as median (minimum-maximum), and t_{1/2} shown as the arithmetic mean (standard deviation). AR (accumulation ratio) calculated as (AUC₂₄ on Day 14 or 17)/(AUC₂₄ on Day 1). %CV, percent coefficient of variation; C_{max}, maximum plasma concentration; AUC₂₄, area under the plasma concentration curve; MAD, multiple ascending dose; t_{1/2}, apparent plasma terminal elimination half-life; t_{max}, time to maximum observed plasma concentration.



- Graphs show LVEF as a function of exposure; data points represent observed values in dogs and humans
- Decrease in LVEF as function of exposure is similar in humans and dogs

CK-274: Phase 1 Data Support Progression to Phase 2

- CK-274: well tolerated in healthy participants; no SAEs; no clinically meaningful changes in vital signs, ECGs, or lab tests
- Criteria for stopping dose escalation were reached after single dose of 75 mg and after 14 days of a daily 10 mg dose
- Decreases in ejection fraction below 50% readily reversible within 6 hours following single doses, within 24-48 hours following 14 days of dosing
- Pharmacokinetics (C_{max} and AUC_{24}) generally dose linear; steady-state appeared evident after 14 days of daily dosing
- Shallow exposure-response relationship observed preclinically appears to have translated to humans and may enable flexible dose optimization in humans
- Phase 1 data support progression into placebo-controlled, double-blind Phase 2 study in patients with oHCM who:
 - Remain on their background therapy for HCM
 - Can undergo echo-guided dose titration every 2 weeks

REDWOOD-HCM: Phase 2 Clinical Trial Design



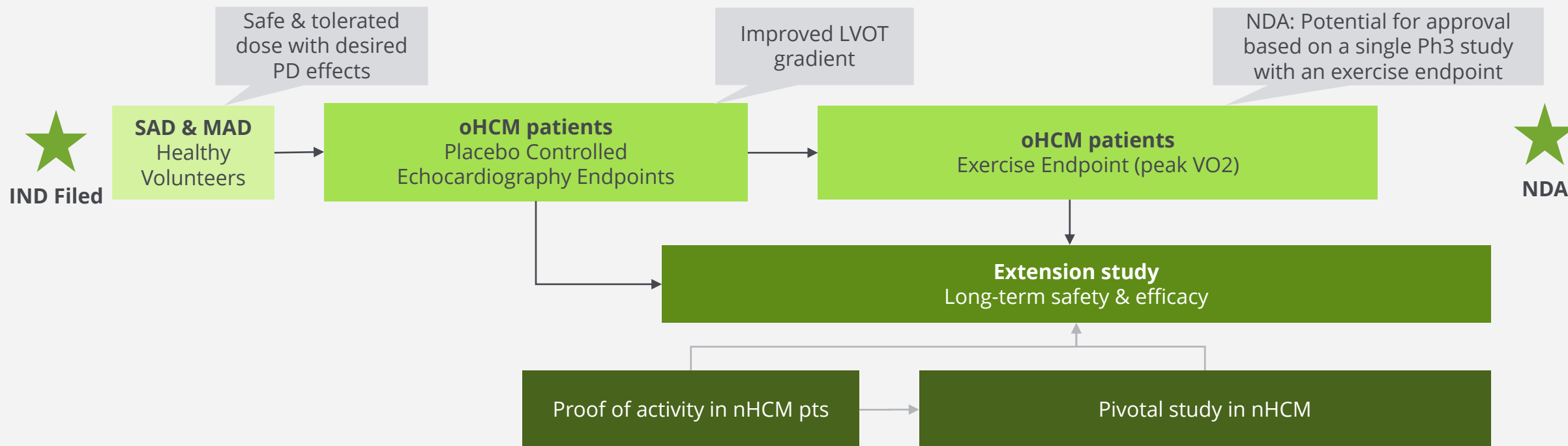
REDWOOD-HCM
Expected to Begin
in Q4 2019

CK-274: Clinical Development Plan for HCM

Phase 1
Safety, PK & PD

Phase 2
Proof of Concept, Dose Finding

Phase 3
Pivotal Studies



Cardiac Muscle: Upcoming Milestones

Continue to Conduct GALACTIC-HF through 2019;
Expect Second Interim Analyses in Q1 2020

Continue Enrollment in METEORIC-HF Through 2019

Expect to Initiate REDWOOD-HCM in Q4 2019

Continue to Conduct Phase 1 Study of AMG 594 through 2019

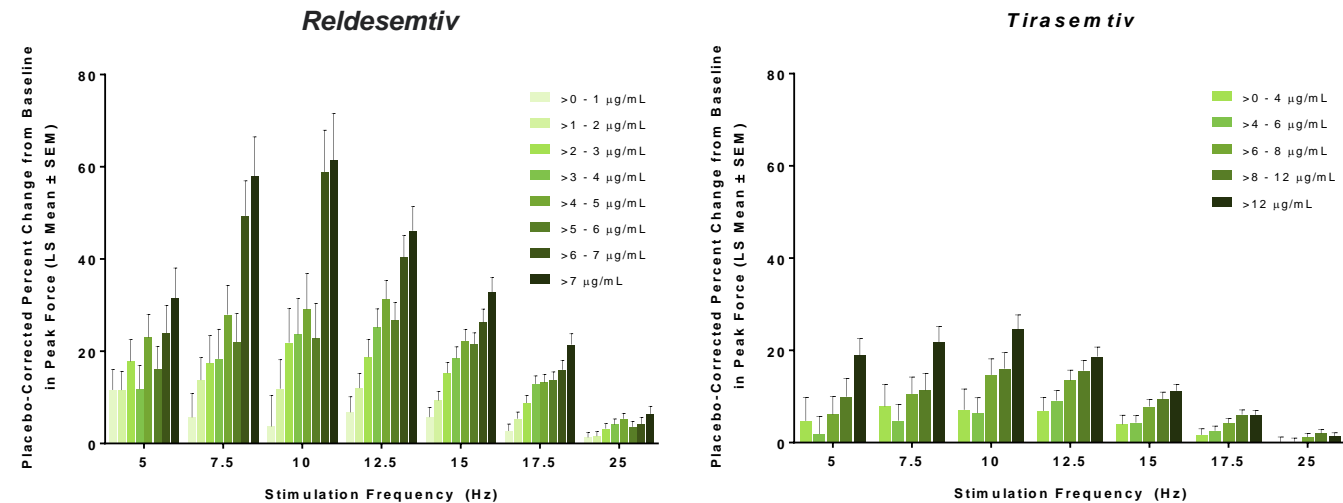
SKELETAL MUSCLE

Reldesemtiv



Reldesemtiv: Potentially More Potent, Well Tolerated Than *Tirasemtiv*

- *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

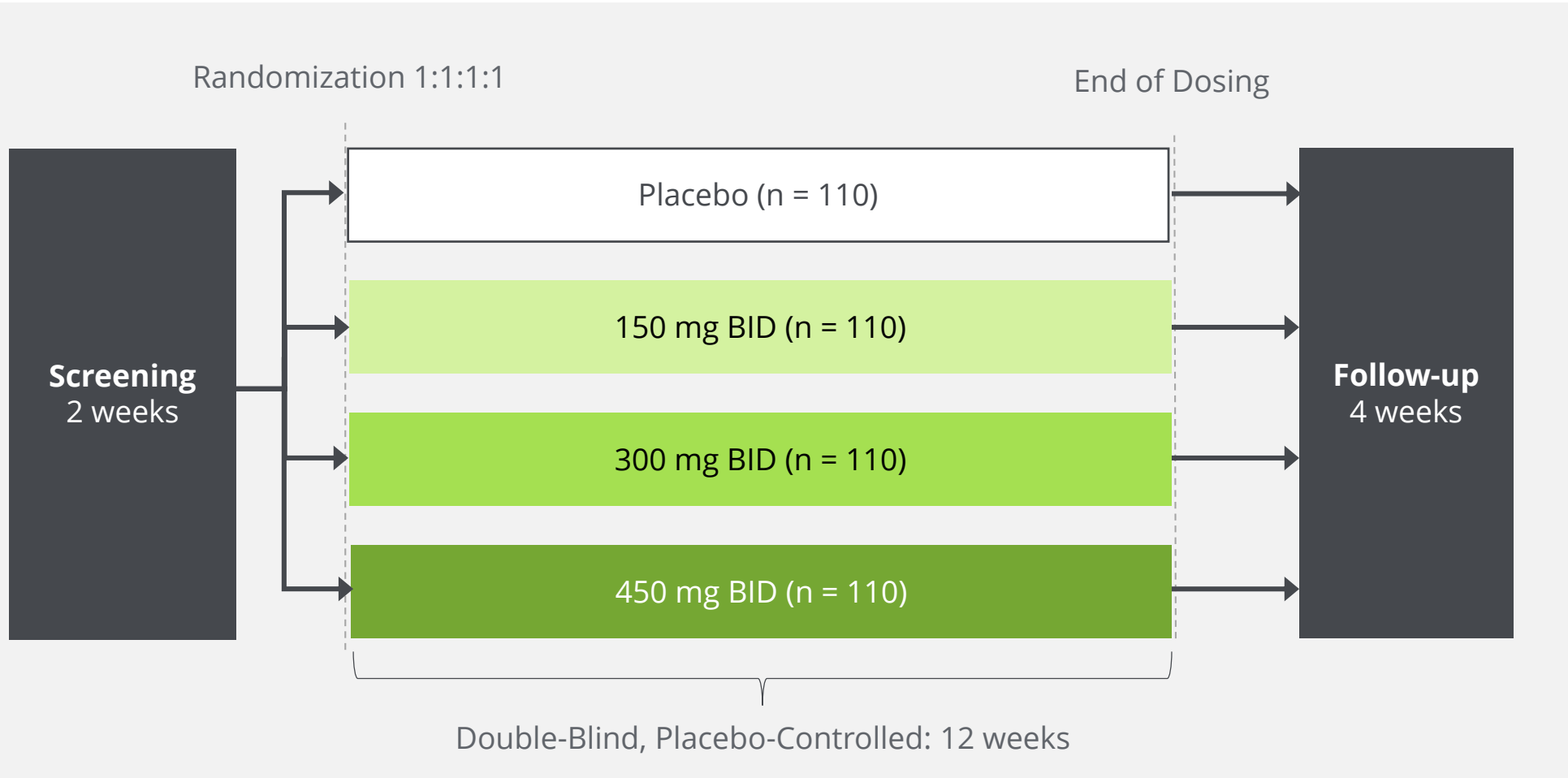


Results from Three Phase 1 Studies of *Reldesemtiv* Published in *Muscle & Nerve*

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.

For informational purposes only: no head-to-head studies have been conducted comparing *reldesemtiv* to *tirasemtiv*. Differences between the two studies may limit the conclusions that can be drawn from comparisons.

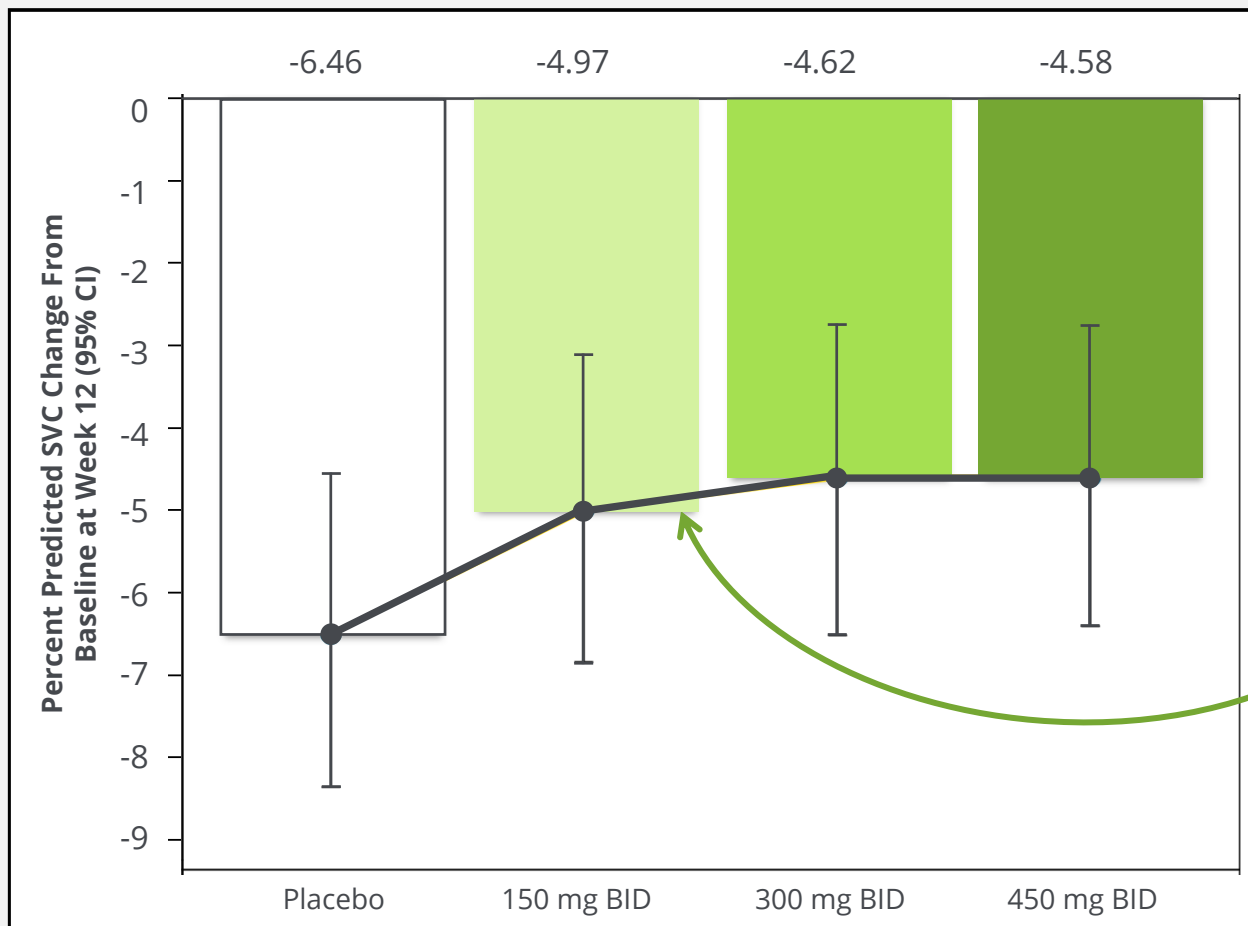
Phase 2 Clinical Trial in ALS



Functional
Outcomes in a
Randomized
Trial of
Investigational
Treatment with CK-107
to **U**nderstand
Decline in
Endpoints in
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

Primary Endpoint: SVC



Primary Analysis

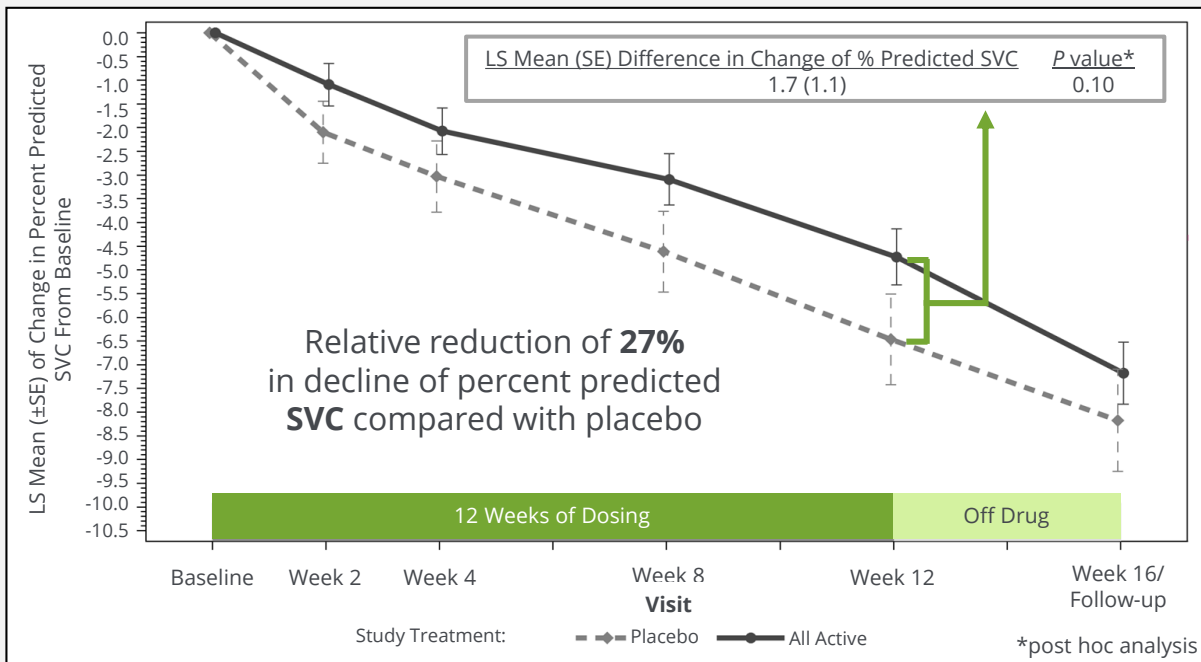
P = 0.11
for weighted
dose-response
relationship*

Change from
Baseline in
Percent
Predicted SVC
at Week 12

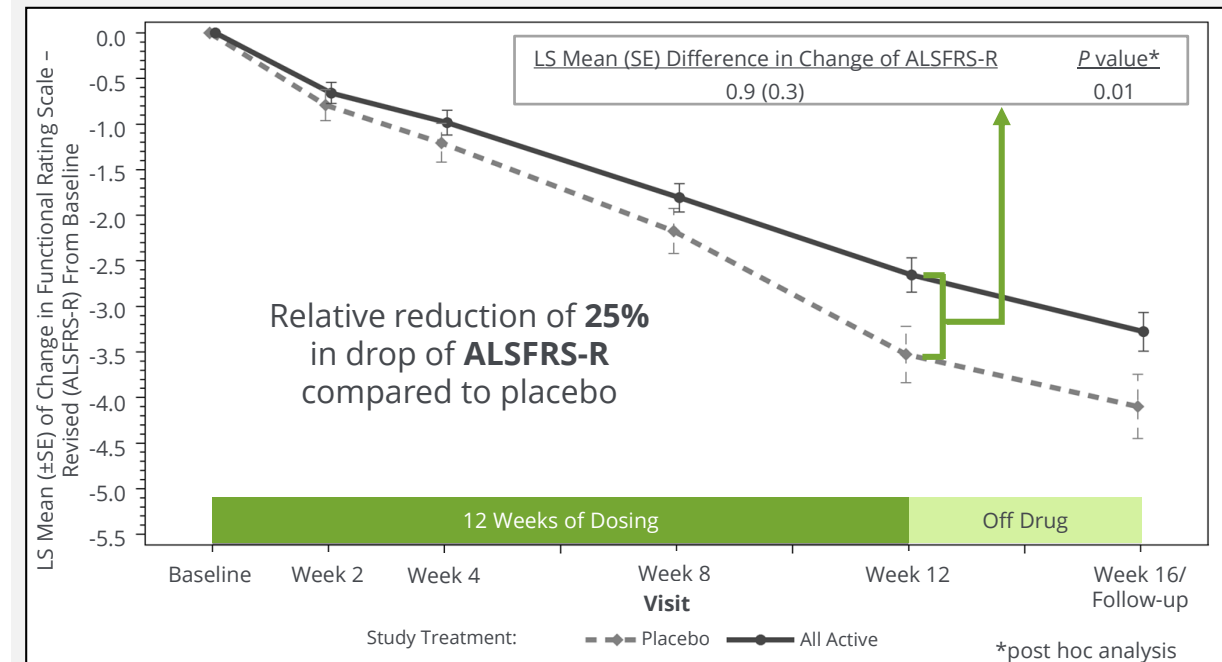
*Based on Mixed Model for Repeated Measures (MMRM) with the contrasts of (-5, -1, 3, 3) for placebo, reldesemtiv 150 mg, 300 mg and 450 mg BID, respectively

Change From Baseline: All Active vs Placebo*

SVC Change From Baseline (All Active vs Placebo)

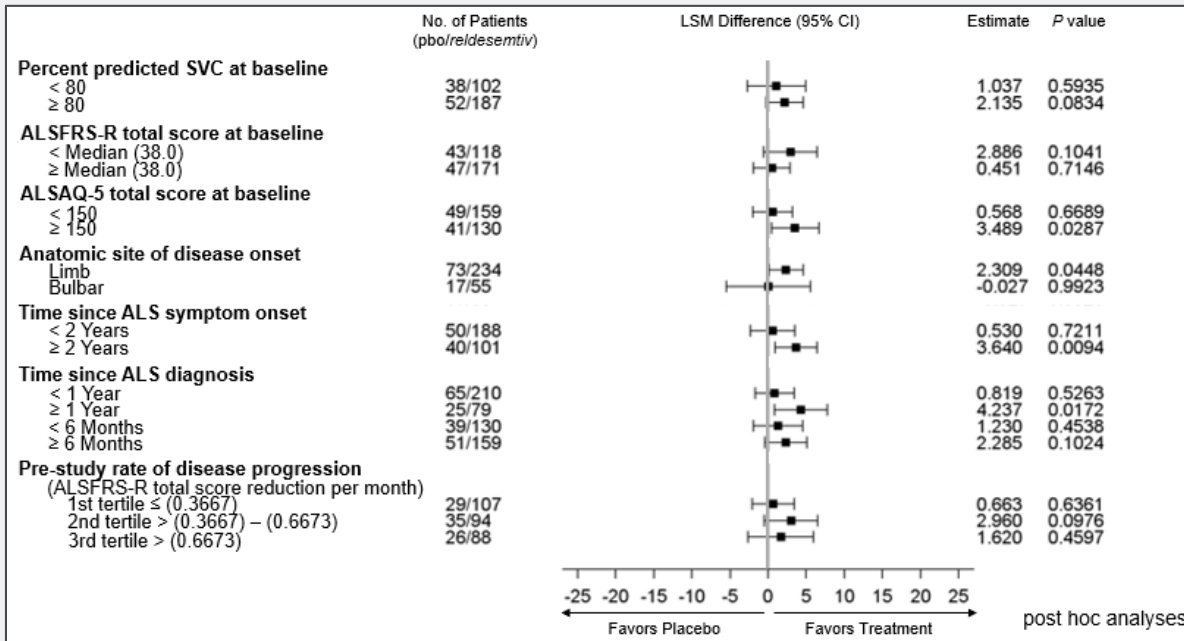


ALSFERS-R Change From Baseline (All Active vs Placebo)

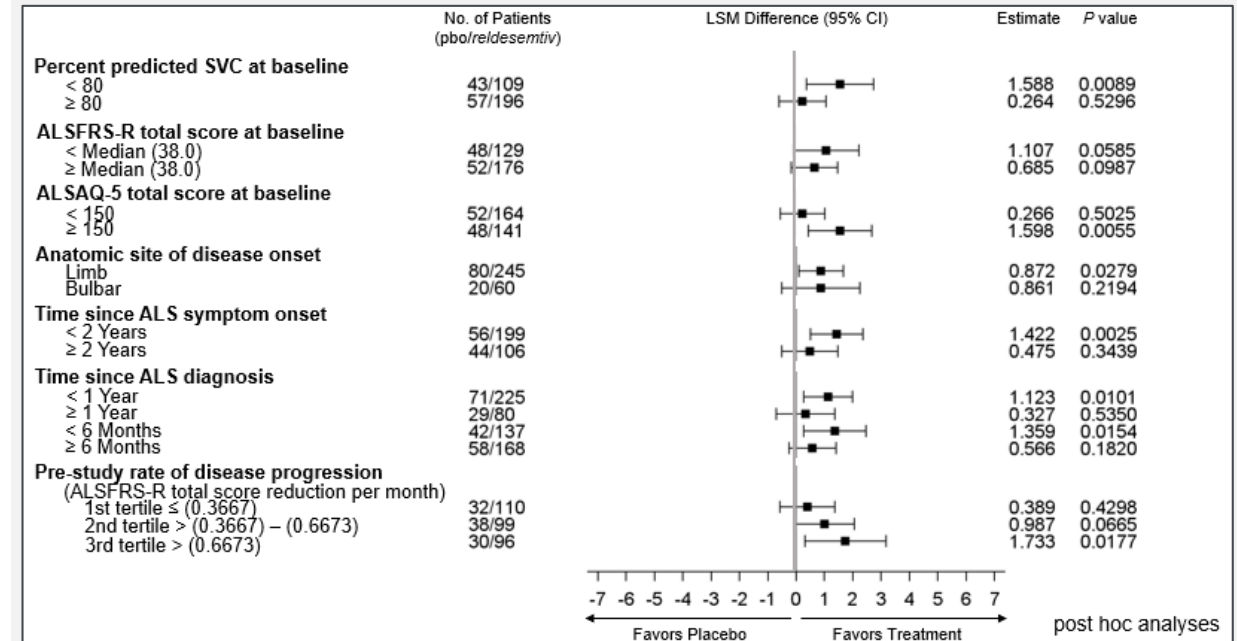


*FORTITUDE-ALS did not achieve statistical significance, but patients on all dose groups of *rel-desemtiv* declined less than patients on placebo

Percent Predicted SVC

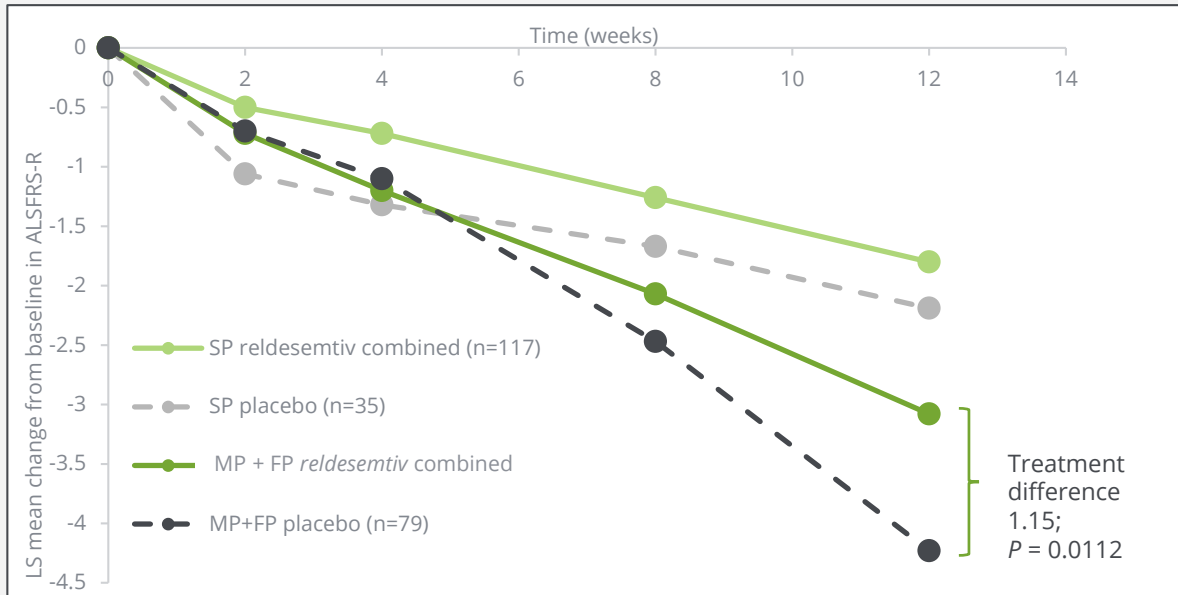


ALSFRS-R Total Score



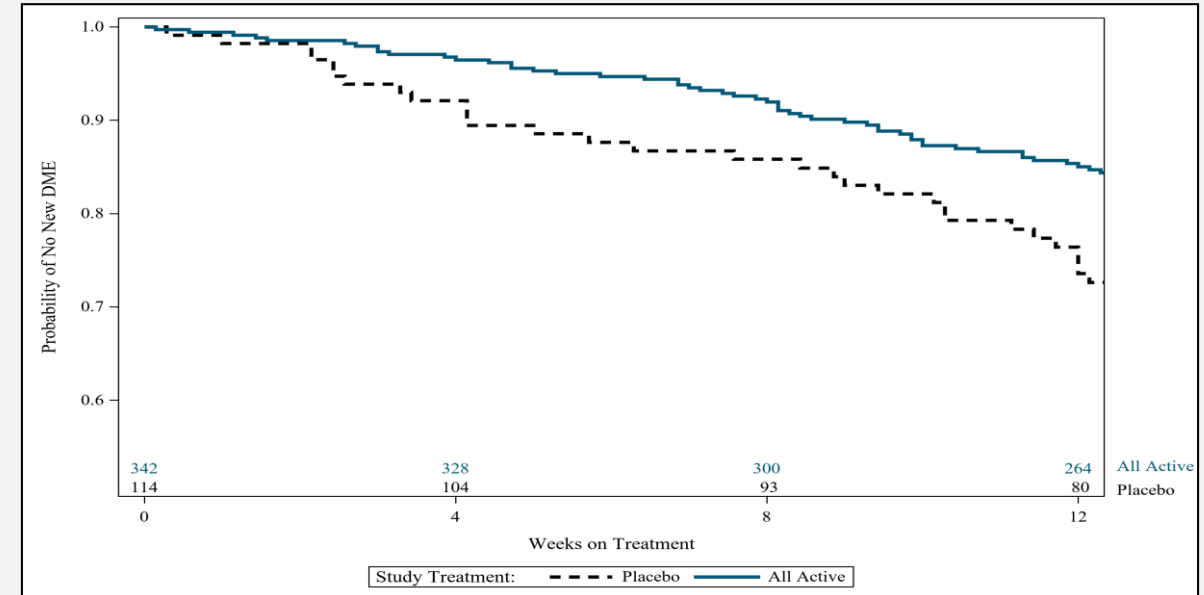
*FORTITUDE-ALS did not achieve statistical significance, but patients on all dose groups of *reldesemtiv* declined less than patients on placebo

Change From Baseline in ALSFRS-R by Progressor Tertiles



Probability of No New DME Use Over Time With *Reldesemtiv*

(DME: Manual wheelchair, power wheelchair, NIV, Augmentative Language Device, PEG)



CORPORATE
PROFILE

Cytokinetics Financing History

Capital Raised
Through
Combination of
Strategic Partners
and Institutional
Investors

	Financing	Equity	Upfront Cash, Option, Milestones	R&D Reimbur.	Total
Investors	Private Investors (VCs)	\$116M			
	IPO	\$94M			
	Public Post-IPO/Other	\$420M			
	Term Loan	\$45M			
	Convertible Debt (net)*	\$120.5M			
	Total	\$165.5M	\$630M		
*Net of fees and expenses					
Strategic Partners & Grants	Astellas	\$10M	\$130M	\$92M	\$232M
	Amgen	\$43M	\$145M	\$40M	\$228M
	Royalty Pharma	\$10M	\$90M		\$100M
	GSK	\$24M	\$22M	\$33M	\$79M
	AstraZeneca			\$2M	\$2M
	MyoKardia			\$2M	\$2M
	Global Blood			\$2M	\$2M
	Grants (ALS Assoc / NINDS / other)			\$6M	\$6M
	Total		\$87M	\$393M	\$171M

Q3 2019 Condensed Balance Sheet

	9/30/19 (in millions)
Cash and investments	\$166.0
Other assets	<u>\$21.4</u>
Total assets	\$187.4
Debt	\$44.8
Liability related to sale of future royalties	\$137.7
Other liabilities	<u>\$24.8</u>
Total liabilities	\$207.3
Working capital	\$155.0
Accumulated deficit	-\$834.4
Stockholders' Equity (Deficit)	-\$19.9
Basic shares outstanding	58.6

2019 Financial Guidance

	(in millions)
Cash Revenue	\$28 - 32
Cash Operating Expenses	\$110 - 115
Net	~\$90

Over 24 Months of
Cash Based on
2019 Guidance

Financial guidance confirmed on May 9, 2019 earnings call

Upcoming Milestones

Continue to Conduct
GALACTIC-HF through 2019;
Expect Second Interim
Analyses in Q1 2020

Continue Enrollment
in **METEORIC-HF**
through 2019

Expect to Initiate
REDWOOD-HCM
in Q4 2019

Continue to Evaluate Results
of **FORTITUDE-ALS**
& to Prepare for Potential
Phase 3 Clinical Trial

Continue to Conduct
Phase 1 Study of **AMG 594**
through 2019



Cytokinetics

**THANK
YOU**