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A First-in-Human Study of the Selective Cardiac Myosin Inhibitor, CK-3773274

Laura A. Robertson,[1] Danielle R. Armas,[2] Edward Robbie,[1] Anna Osmukhina,[1] Hanbin Li,[3] Fady I. Malik,[1] Scott D. Solomon[4]

[1]Cytokinetics, Inc., South San Francisco, CA; [2]Celerion, Inc., Tempe, AZ; [3]Certara, Inc., Menlo Park, CA; [4]Brigham and Women's Hospital, Boston, MA

INTRODUCTION

- Hypercontractility of the cardiac sarcomere appears to underlie pathological hypertrophy, outflow obstruction, and fibrosis in select genetic hypertrophic cardiomyopathies (HCM)[1]
- CK-3773274 (CK-274) decreases cardiac contractility in preclinical models by directly binding to the cardiac myosin motor domain and inhibiting the myosin ATPase, stabilizing the motor in a non–force-producing state[2]
- The preclinical pharmacologic and pharmacokinetic properties of CK-274 were optimized to facilitate the potential ease of dose titration and related therapeutic window in patients[2]
- In preclinical models of cardiac function, including the R403Q mouse model of HCM, CK-274 reduced cardiac contractility in a predictable dose and exposure dependent fashion[3]
- Here we report on the first-in-human experience of single and multiple dosing with CK-274

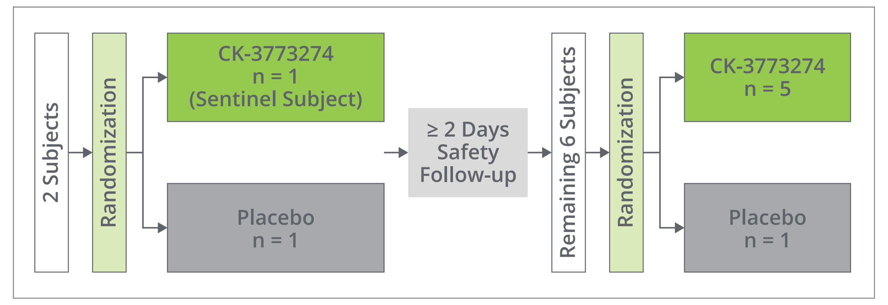
STUDY OBJECTIVES

- **Primary**
 - Determine the safety and tolerability of single and multiple ascending doses of CK-274 administered orally to healthy adult participants
- **Secondary**
 - Evaluate the pharmacokinetics (PK) of CK-274 following single and multiple oral doses
 - Identify dose(s) of CK-274 that reduce left ventricular ejection fraction (LVEF)
 - Describe the pharmacokinetic-pharmacodynamic (PK/PD) relationship between CK-274 and cardiac function
- This study was not designed to identify a maximum tolerated dose

METHODS

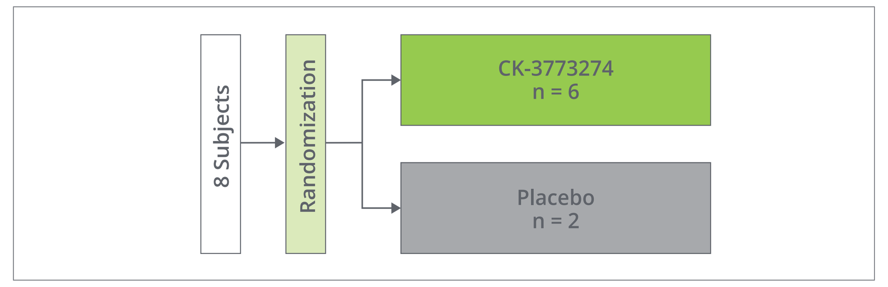
Single Ascending Dose (SAD)

- The SAD cohort design incorporated a sentinel group
- PK sampling occurred on Days 1, 2, 3, 4, 5, and 10 following dosing
- Echocardiography was performed pre-dose, at 1.5 hours, 4 hours, or 6 hours depending on cohort, and at 24 hours following dosing


2 Subjects
Randomization
CK-3773274
n = 1
(Sentinel Subject)
Placebo
n = 1
≥ 2 Days
Safety
Follow-up
Remaining 6 Subjects
Randomization
CK-3773274
n = 5
Placebo
n = 1

Multiple Ascending Dose (MAD)

- The MAD cohorts started following completion of SAD Arm D
- Participants received study drug once daily for 14 days (5 and 10 mg) or 17 days (7.5 mg)
- PK sampling occurred daily during dosing, daily for 3 days after the end of dosing, with a final sample 7 days after the completion of dosing
- Echocardiography was performed pre-dose, at Days 2, 4, 9, 14, or 17 depending on cohort, and at 24 hours following dosing


8 Subjects
Randomization
CK-3773274
n = 6
Placebo
n = 2

- Additional cohorts to assess the effect of CYP2D6 poor metabolizer genotype and food on the PK of CK-274 were also performed but are not reported here

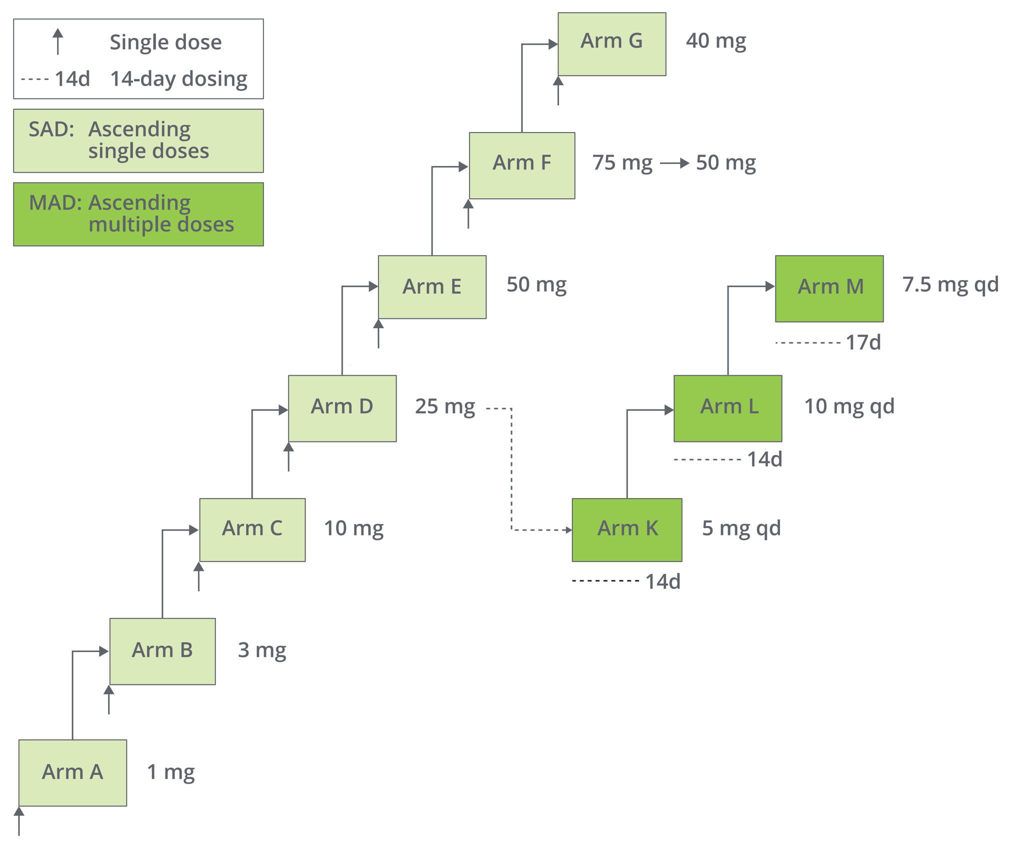
Key Inclusion Criteria (SAD/MAD Cohorts)

- Males and females (of non-childbearing potential) between 18 and 55 years of age, inclusive
- Body weight > 55.0 kg and body mass index within 18.0 to 32.0 kg/m^2, inclusive
- Normal cardiac structure and function, or if abnormalities are present, they are deemed not clinically significant
- SAD Arms A–D: LVEF ≥ 60%
- SAD Arms E–G and MAD Arms: LVEF ≥ 65%
- Normal electrocardiogram (ECG) or, if abnormalities are present, they are deemed not clinically significant
- Clinical laboratory findings within normal range
- Does not have CYP2D6 poor metabolizer genotype

Dose Escalation Criteria

- Dose escalation recommendations were provided by the study team and reviewed by an unblinded Dose Level Review Committee (DLRC)
 - The DLRC included an external cardiologist (S. Solomon) with relevant expertise and designated staff members of the study sponsor (or designee) representing clinical science, safety science, clinical pharmacology, and biostatistics
- The following rules were applied to dose escalation decisions:
 - No participants have experienced cardiac serious adverse events (SAEs) related to the study drug
 - No two participants have experienced similar, non-cardiac SAEs in the same organ system that appear to be related to the study drug
 - No two participants treated with CK-274 have a decrease in LVEF > 15% from last pre-dose value (determined by the DLRC)
 - No more than two participants have an LVEF < 50% (unless determined not to be related to the study drug by the DLRC and investigator) and have symptoms of decreased cardiac output
 - No participant has an LVEF < 45% (unless determined not to be related to the study drug by the DLRC and investigator) and has symptoms of decreased cardiac output
 - The investigator and DLRC both approve the escalation and the next dose level based on their clinical judgment

Study Conduct


Single dose
14d 14-day dosing
SAD: Ascending single doses
MAD: Ascending multiple doses
Arm A 1 mg
Arm B 3 mg
Arm C 10 mg
Arm D 25 mg
Arm E 50 mg
Arm F 75 mg → 50 mg
Arm G 40 mg
Arm K 5 mg qd
14d
Arm L 10 mg qd
14d
Arm M 7.5 mg qd
17d

- Criteria to stop dose escalation were met in the SAD 75-mg dose cohort
 - One participant in sentinel group had LVEF < 45% at 1.5 hours, asymptomatic and recovered to normal EF at 6 hours
- Criteria to stop dose escalation were met in the MAD 10-mg dose cohort
 - Two participants had LVEF < 50% at 14 days, asymptomatic and recovered to normal EF within 24–48 hours

Stopping criteria were evaluated based on initial read of echocardiogram prior to the final core lab determination.
d, day; MAD, multiple ascending dose; qd, once daily; SAD, single ascending dose.

RESULTS

Baseline Characteristics

Characteristic Mean (SD)*	SAD (n = 57)	MAD (n = 24)
Age (years, mean [range])	39.6 (18–55)	40.4 (28–54)
Sex (male, %)	72	75
Weight (kg)	79.4 (10.3)	77.0 (9.1)
BMI (kg/m^2)	27.8 (2.7)	27.0 (2.3)
LVEF (%)	65.8 (2.44)	67.5 (1.24)
SBP (mmHg)	113.6 (9.69)	114 (7.38)
DBP (mmHg)	71.5 (6.72)	72.6 (4.94)
HR (bpm)	63.3 (8.42)	61.3 (6.80)

* Except where noted otherwise.
BMI, body mass index; DBP, diastolic blood pressure; HR, heart rate; MAD, multiple ascending dose; SAD, single ascending dose; SBP, systolic blood pressure; SD, standard deviation.

Safety

SAD Adverse Events Occurring in Two or More Participants

Preferred Term n (%)	Pooled Placebo (n = 15)	CK-274 1 mg (n = 6)	CK-274 3 mg (n = 6)	CK-274 10 mg (n = 6)	CK-274 25 mg (n = 6)	CK-274 40 mg (n = 6)	CK-274 50 mg (n = 11)	CK-274 75 mg (n = 1)	Total (n = 57)
Headache	1 (6.7)	–	–	1 (16.7)	2 (33.3)	–	1 (9.1)	–	5 (8.8)
Ejection fraction decreased	–	–	–	–	–	1 (16.7)	1 (9.1)	1 (100)	3 (5.3)
Abdominal pain upper	–	–	–	–	2 (33.3)	–	–	–	2 (3.5)
Abdominal tenderness	–	–	–	–	1 (16.7)	–	1 (9.1)	–	2 (3.5)
Chest pain	–	–	–	–	–	–	1 (9.1)*	1 (100)†	2 (3.5)
Dyspepsia	–	–	–	–	1 (16.7)	–	1 (9.1)	–	2 (3.5)
Flatulence	–	–	–	–	1 (16.7)	–	1 (9.1)	–	2 (3.5)
Nausea	–	–	–	–	2 (33.3)	–	–	–	2 (3.5)
Upper respiratory tract infection	2 (13.3)	–	–	–	–	–	–	–	2 (3.5)

- 17 participants experienced TEAEs
- There were no SAEs; all AEs were of mild or moderate severity

* "Bubbling sensation to the left chest" consistent with a gastrointestinal association rather than a cardiac association.
† Onset approximately 60 hours post dose.
AE, adverse event; SAD, single ascending dose; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

MAD Adverse Events

Preferred Term n (%)	Pooled Placebo (n = 6)	CK-274 5 mg qd x 14d (n = 6)	CK-274 7.5 mg qd x 17d (n = 6)	CK-274 10 mg qd x 14d (n = 6)	Total (n = 24)
Headache	1 (16.7)	–	–	1 (16.7)	2 (8.3)
Chapped lips	–	1 (16.7)	–	–	1 (4.2)
Cough	–	1 (16.7)	–	–	1 (4.2)
Feeling hot	1 (16.7)	–	–	–	1 (4.2)
Nausea	1 (16.7)	–	–	–	1 (4.2)
Salivary hypersecretion	–	1 (16.7)	–	–	1 (4.2)
Upper respiratory tract infection	–	–	–	1 (16.7)	1 (4.2)
Vomiting	1 (16.7)	–	–	–	1 (4.2)

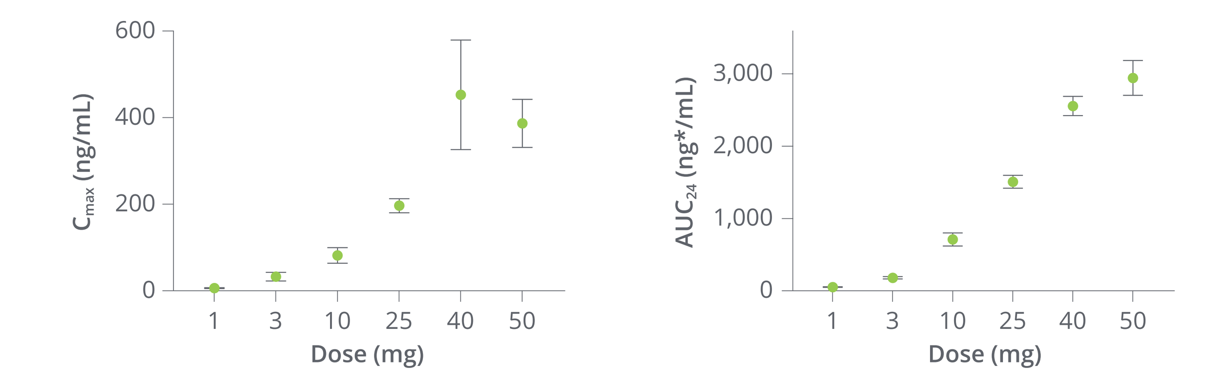
- Four participants experienced TEAEs
- There were no SAEs; all AEs were of mild severity

AE, adverse event; d, day; MAD, multiple ascending dose; qd, once daily; SAE, serious adverse event; TEAE, treatment-emergent adverse event.

- No clinically meaningful changes in ECG, laboratory test results, or vital signs in both SAD and MAD cohorts

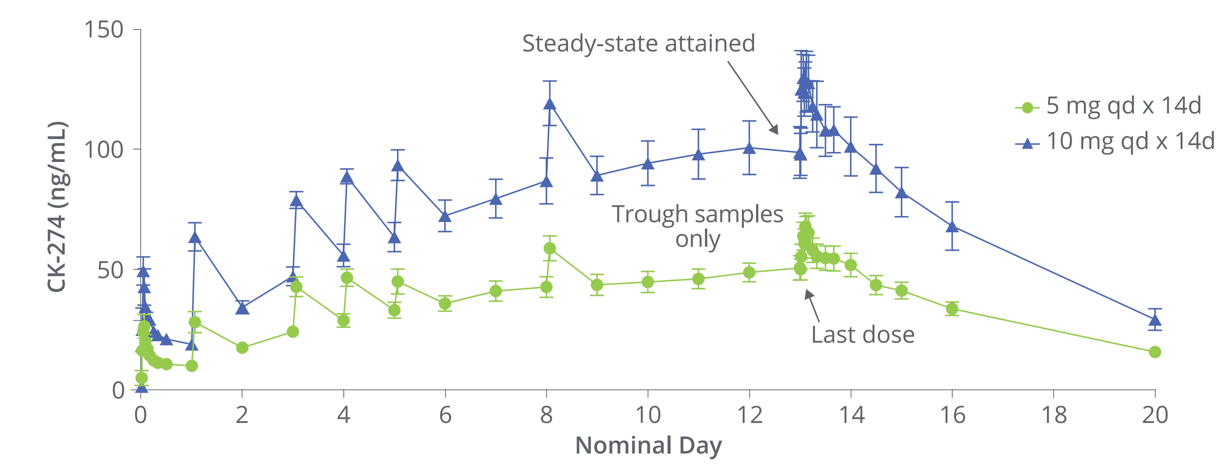
Pharmacokinetics

SAD Pharmacokinetics Are Generally Dose Proportional


600
400
200
0
C_{max} (ng/mL)
1 3 10 25 40 50
Dose (mg)
3,000
2,000
1,000
0
AUC_{24} (ng*/mL)
1 3 10 25 40 50
Dose (mg)

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

Steady-state Appears Evident After 14 Days of Dosing


150
100
50
0
CK-274 (ng/mL)
0 2 4 6 8 10 12 14 16 18 20
Nominal Day
Steady-state attained
Trough samples only
Last dose
5 mg qd x 14d
10 mg qd x 14d

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

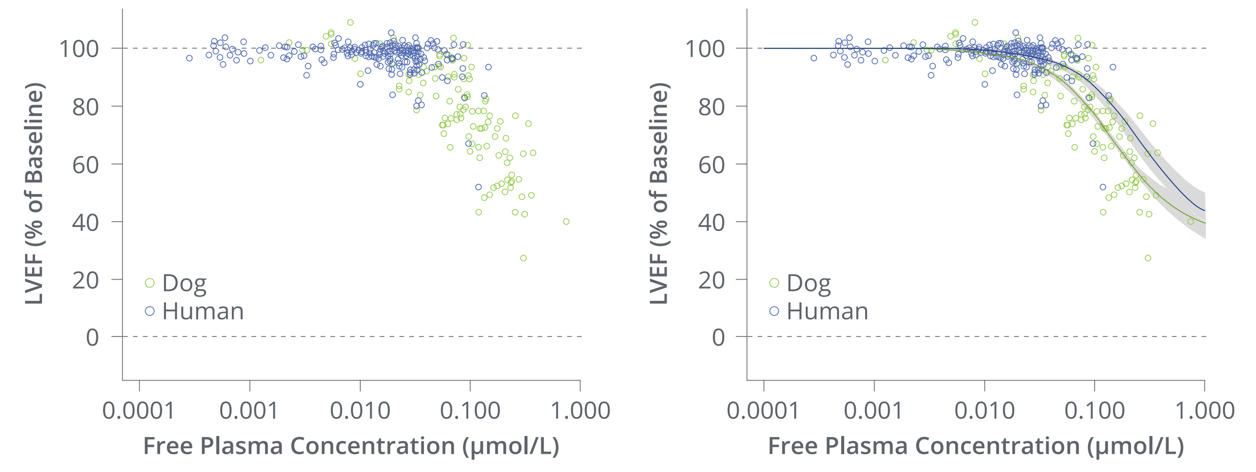
MAD Pharmacokinetic Parameters

Dose (n)	C_{max} (ng/mL)	t_{max} (h)	AUC_{24} (ng•h/mL)	$t_{½}$ (h)	AR
	PK Parameter, Geometric Mean (%CV)*				
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

- Half-life of CK-274 at steady-state is ~81 hours (3.4 days) on average

* Except data for t_{max} shown as median (minimum-maximum), and $t_{½}$ shown as the arithmetic mean (standard deviation). AR (accumulation ratio) calculated as (AUC_{24} on Day 14 or 17)/(AUC_{24} on Day 1).
%CV, percent coefficient of variation; C_{max}, maximum plasma concentration; AUC_{24}, area under the plasma concentration curve; MAD, multiple ascending dose; $t_{½}$, apparent plasma terminal elimination half-life; t_{max}, time to maximum observed plasma concentration.

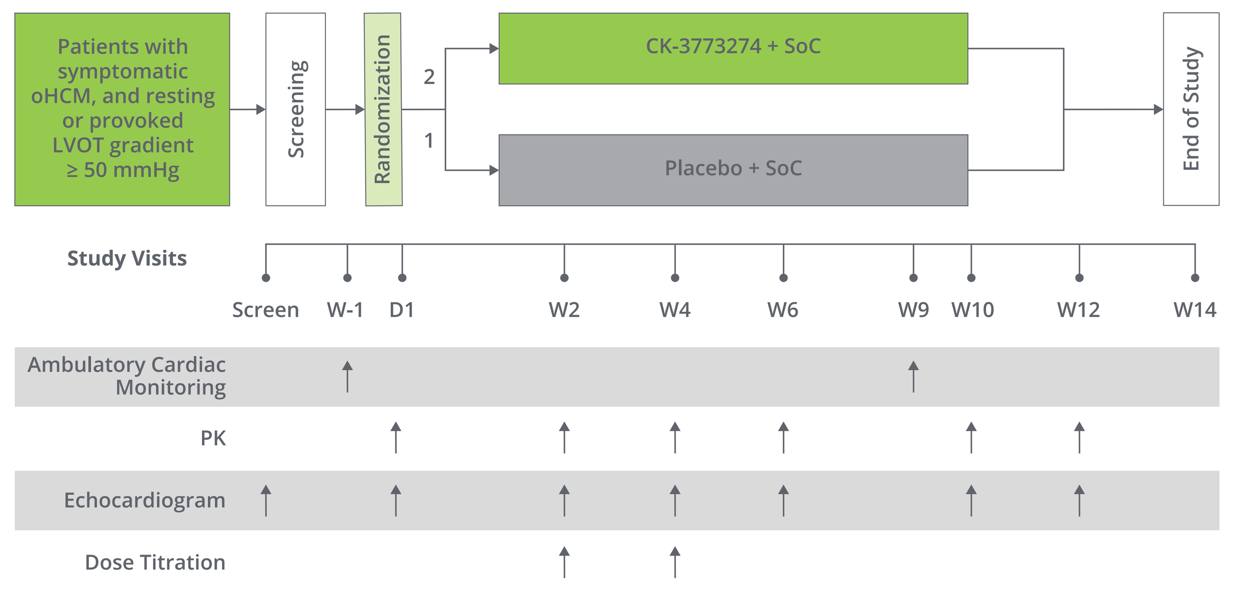
PK/PD Relationship of CK-274 for Ejection Fraction (LVEF)


LVEF (% of Baseline)
100
80
60
40
20
0
Dog
Human
0.0001 0.001 0.010 0.100 1.000
Free Plasma Concentration (μmol/L)
LVEF (% of Baseline)
Dog
Human
0.0001 0.001 0.010 0.100 1.000
Free Plasma Concentration (μmol/L)

- Decrease in LVEF as function of exposure is similar in humans and dogs
 - Right panel shows model prediction curves with solid lines representing fitted model for dog (green curve) and human (blue curve), and shaded areas represent 90% confidence intervals of the model prediction
- The PK/PD relationship for CK-274 observed in humans was similar to that observed preclinically when adjusted for differences in protein binding

PHASE 2 OVERVIEW

Study Schema


Patients with symptomatic oHCM, and resting or provoked LVOT gradient ≥ 50 mmHg
Screening
Randomization
2
1
CK-3773274 + SoC
Placebo + SoC
End of Study
Study Visits
Screen W-1 D1 W2 W4 W6 W9 W10 W12 W14
Ambulatory Cardiac Monitoring
PK
Echocardiogram
Dose Titration

- **Primary objective:** safety and tolerability
- **Secondary objectives:** PK and PD
- **Dose titration:** every 2 weeks guided by echocardiography

oHCM, obstructive hypertrophic cardiomyopathies; LVOT, left ventricular overflow tract; SoC, standard of care.

Study Population

- Men and women between 18 and 70 years of age
- Patients with obstructive HCM with:
 - Resting left ventricular overflow tract gradient (LVOT-G) ≥ 50 mmHg
 OR
 - Resting LVOT-G ≥ 30 mmHg and < 50 mmHg + post-Valsalva LVOT-G ≥ 50 mmHg
- LVEF ≥ 60%
- New York Heart Association class II or III
- Stable background medical therapy allowed

CONCLUSIONS

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

Acknowledgments

We wish to thank the participants and their families for their contributions to this clinical trial.

References

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Disclosures

Robertson, **Robbie**, **Osmukhina**, and **Malik** are employees of and own stock in Cytokinetics, Inc. **Armas** is an employee of Celerion, Inc., where the CY 6011 study was conducted. **Li** is an employee of Certara, Inc. and a consultant to Cytokinetics, Inc. **Solomon** has received research support from and is a consultant to Cytokinetics, Inc.

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