A First-in-Human Study of the **Cardiac Myosin Inhibitor, CK-3773274 (CK-274)**

Cytokinetics Clinical Study: CY 6011

ClinicalTrials.gov Identifier: NCT03767855

STUDY OBJECTIVES:

Primary:

- Determine the safety and tolerability of single and multiple ascending doses of CK-274 administered orally to healthy adult participants

**This study was not designed to identify a maximum tolerated dose*

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
- Assess the PK of CK-274 following a single dose administered to CYP2D6 poor metabolizers
- Evaluate the PK of CK-274 following single and multiple doses administered to healthy subjects in fed and fasted states

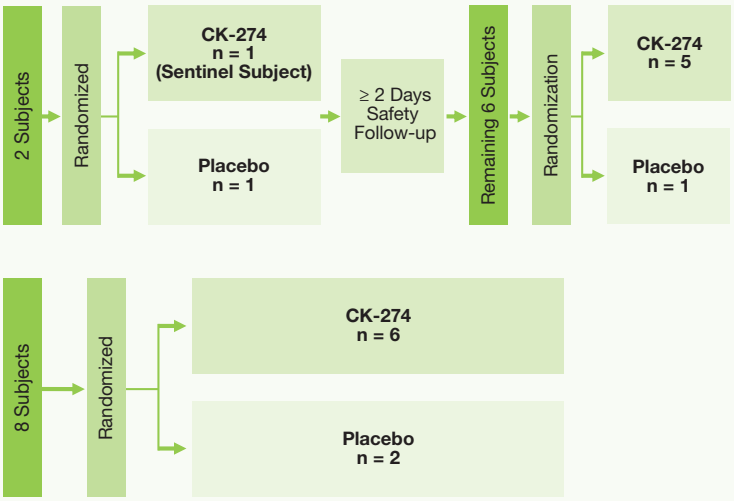
STUDY DESIGN:

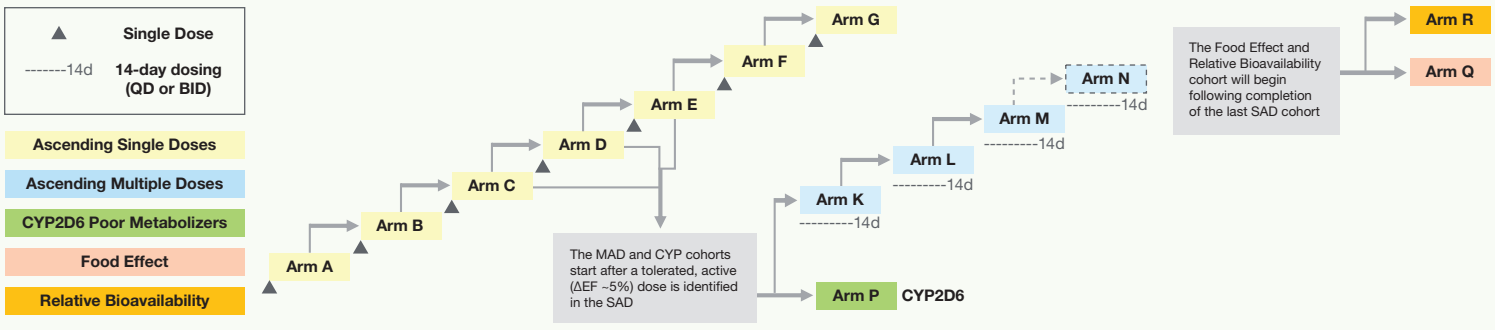
Single Ascending Dose (SAD)

- 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

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





References:

1. Robertson L, Armas DR, Robbie E, et al. A First in Human Study of the Selective Cardiac Myosin Inhibitor, CK-3773274. Poster session presented at Heart Failure Society of America Annual Scientific Meeting; 2019 Sept 13-16; Philadelphia, PA.
2. ClinicalTrials.gov. https://clinicaltrials.gov/ct2/show/NCT03767855

REDWOOD-HCM (Randomized Evaluation of Dosing With CK-3773274 in Obstructive Outflow Disease in HCM)

Cytokinetics Clinical Study: REDWOOD-HCM (CY 6021) ClinicalTrials.gov Identifier: NCT04219826

STUDY OBJECTIVES:

Primary Endpoint:

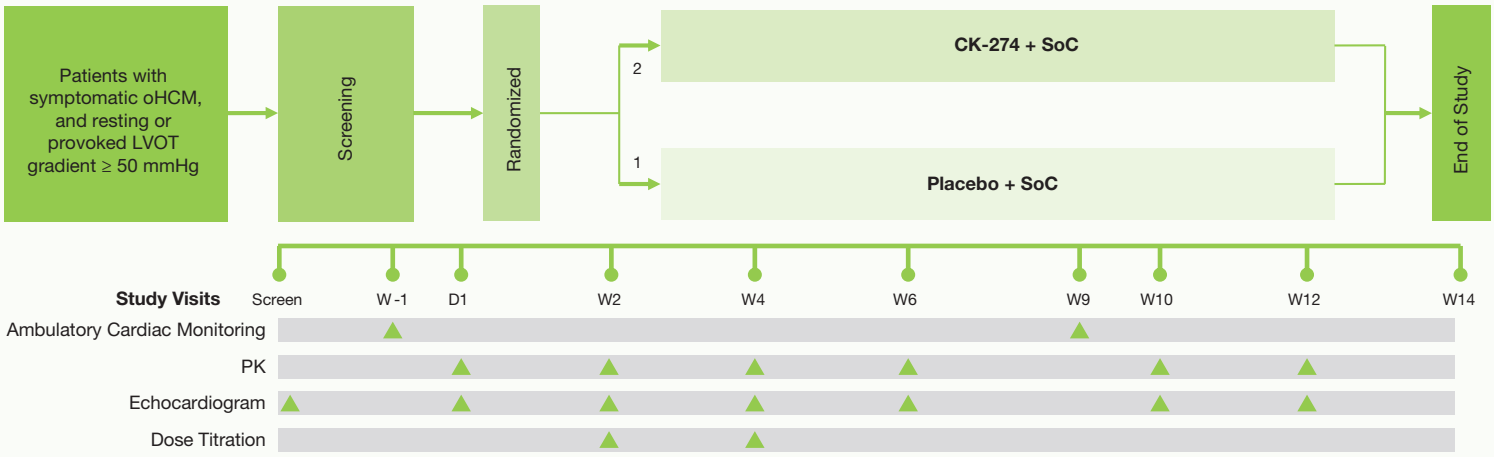
- Assess the safety and tolerability of CK-274

Secondary Endpoint:

- Assess the PK and PD of CK-274, guided by echocardiography, with two-week dose titration

**CK-274 will be added to stable background medical therapy*

STUDY DESIGN:



Inclusion Criteria:

- Males and females between 18 and 70 years of age at screening.
- Body weight is ≥45 kg at screening.
- Diagnosed with oHCM per the following criteria:
  - Has left ventricular (LV) hypertrophy with non-dilated LV chamber in the absence of other cardiac disease.
  - Has minimal wall thickness ≥15 mm at time of initial diagnosis (minimal wall thickness ≥13 mm is acceptable with a positive family history of HCM or with a known disease-causing gene mutation).
- Adequate acoustic windows for echocardiography.
- Has LVOT-G during screening as follows:
  - Resting gradient ≥50 mmHg OR
  - Resting gradient ≥30 mmHg and <50 mmHg with post-Valsalva LVOT-G ≥50 mmHg
- LVEF ≥60% at screening.
- NYHA Class II or III at screening.
- Patients on beta-blockers, verapamil, diltiazem, or ranolazine should have been on stable doses for >4 weeks prior to randomization and anticipate remaining on the same medication regimen during the study.

Exclusion Criteria:

- Aortic stenosis or fixed subaortic obstruction.
- Known infiltrative or storage disorder causing cardiac hypertrophy that mimics oHCM (eg, Noonan syndrome, Fabry disease, amyloidosis).
- History of LV systolic dysfunction (LVEF <45%) at any time during their clinical course.
- Documented history of current obstructive coronary artery disease (>70% stenosis in one or more epicardial coronary arteries) or documented history of myocardial infarction.
- Has been treated with septal reduction therapy (surgical myectomy or percutaneous alcohol septal ablation) or has plans for either treatment during the study period.
- Has been treated with disopyramide or antiarrhythmic drugs that have negative inotropic activity within 4 weeks prior to screening.
- Documented atrial fibrillation during the Screening period.
- Paroxysmal atrial fibrillation or flutter requiring treatment (eg, anti-coagulation or antiarrhythmic therapy including disopyramide) documented within the 6 months prior to Screening.
- History of syncope or sustained ventricular tachyarrhythmia with exercise within 6 months prior to Screening.
- Has received prior treatment with CK-274 or is currently receiving mavacamten.
- Subject is a CYP2D6 poor metabolizer.

Abbreviations:

D=day; ECG=electrocardiogram; oHCM= obstructive hypertrophic cardiomyopathy; LVOT=left ventricular outflow tract; PD=pharmacodynamics; PK=pharmacokinetics; SoC=standard of care; W=week

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