CIRRUS-HCM: An Open-label Study to Evaluate the Safety, Tolerability, Pharmacokinetic, and Pharmacodynamic Effects of EDG-7500 in Adults with Hypertrophic Cardiomyopathy

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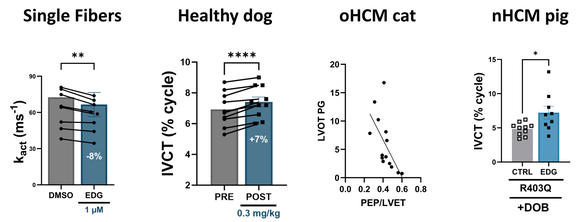
Background

Hypertrophic cardiomyopathy (HCM) is a chronic, progressive disease of the sarcomere characterized by excess myosin-actin crossbridge formation in systole and diastole leading to hyperdynamic contraction and impaired relaxation. Over time these abnormalities lead to tissue remodeling characterized histologically by myocyte hypertrophy, myofilament disarray, microvascular remodeling, and fibrosis. Clinically, patients experience fatigue, exertional dyspnea, and an increased risk of sudden cardiac death.[1]

EDG-7500 is a novel, orally bioavailable, first-in-class cardiac sarcomere modulator (CSM) designed to slow the rate of myocardial force generation in early systole and speed the rate of myocardial relaxation during early diastole. This molecule is being developed for the treatment of obstructive HCM (oHCM) and nonobstructive HCM (nHCM). Preclinical models demonstrate that EDG-7500 improves left ventricular (LV) compliance and distensibility and ameliorates LV outflow tract obstruction, with minimal impact on LV ejection fraction (LVEF).[2,3] In a Phase 1 study, once-daily dosing of EDG-7500 was well tolerated in healthy subjects for 14 days, and at plasma concentrations that exceed those demonstrating efficacy in nonclinical oHCM models, decreases in LVEF below normal (< 50%) were not observed.[4]

The CIRRUS-HCM study is a first-in-patient, open-label study that will evaluate safety, tolerability, pharmacokinetics (PK), and pharmacodynamics (PD) of EDG-7500 in patients with oHCM or nHCM. A dose range of EDG-7500 will be evaluated in cohorts of patients with oHCM (single dose, once-daily for 4 weeks) and nHCM patients (once-daily for 4 weeks). Long-term administration will be assessed over 48 weeks after completion of the initial 4-week study. Echocardiography will be used to assess the PD effects of EDG-7500 on myocardial systolic and diastolic function. Dose and exposure response relationships of the resulting echocardiography parameters along with safety and tolerability will be used to select doses for subsequent HCM patient studies. It is anticipated that participants in CIRRUS-HCM will be eligible for chronic administration of EDG-7500 in a long-term extension study.

Nonclinical Models



- In nonclinical models, EDG-7500 *slows the rate* of acto-myosin cross-bridge formation during isovolumic contraction, where obstruction formation starts.[5]
- In a cat model of oHCM, the IC_{50} of EDG-7500 was 125 ng/mL for a 50% reduction in LVOT gradient.
- In nonclinical models, EDG-7500 *speeds the rate* of acto-myosin cross-bridge detachment to improve relaxation rate and ventricular filling (data not shown).[3]

Healthy Subjects

- PK of EDG-7500 in healthy subjects is as expected based on non-clinical models, including a half-life of ~30 hrs and steady state achieved within ~4 days.
- EDG-7500 was well-tolerated, with no clinically significant changes in clinical chemistry, hematology, or ECGs.
- No meaningful reductions in LVEF were observed with up to 14 days of once-daily dosing.
- See Poster #1251 at ePoster Session 7, Monitor #15 on Sept 29th at 1:15 - 1:45 pm.

Objectives

EDG-7500

Edgewise plans to investigate fixed-dose regimens of EDG-7500 to determine whether echo-mediated dose titration and frequent long-term echo monitoring for adverse reductions in LVEF can be avoided.

CIRRUS-HCM Study Design

Part A: Single-dose Administration (oHCM)

Parts B/C: Multiple-dose Administration (oHCM and nHCM)

Part D: Long-term Administration (oHCM and nHCM)

- First-in-patient, open-label, dose-ranging, cohort design
- 3-part study in ~55 adults with HCM
  - Part A: Single-dose in ~15 patients with oHCM
  - Part B: Multiple-dose in ~20 patients with oHCM
  - Part C: Multiple-dose in ~20 patients with nHCM
  - Part D: Long-term administration (oHCM and nHCM)
- Fixed doses (no echocardiography-guided titration)
  - Part A: 50, 100 and 200 mg single doses
  - Part B/C: 50 mg QD for 4 weeks in first cohort
  - Part D: 50 mg QD for up to 48 weeks in first cohort
- Dose escalation directed by Data Monitoring Committee
- Dose reduction available in the event of intolerance or clinically significant safety event

Key Eligibility Criteria

- Male or nonpregnant female, age ≥ 18 years
- Diagnosis of HCM consistent with current ACC/AHA Guidelines:
  - Hypertrophied and non-dilated LV in absence of systemic or other cause
  - LV wall thickness ≥ 15 mm or LV wall thickness ≥ 13 mm with a positive family Hx of HCM, or in conjunction with a positive genetic test
- Left ventricular ejection fraction (LVEF) ≥ 60%
- NYHA Classification I-III at Screening
- If receiving β-blocker, must have stable dose ≥ 30 days prior to dosing
- No prior use of mavacamten or investigational cardiac myosin inhibitor
- LVOT peak gradient ≥ 30 mmHg measured at rest and ≥ 50 mmHg during the Valsalva maneuver at Screening (oHCM only)
- LVOT peak gradient < 30 mmHg measured at rest and < 50 mmHg during the Valsalva maneuver at Screening (nHCM only)
- Maximal exercise peak LVOT gradient < 50 mmHg (nHCM only)
  - Historical < 12 months prior to dosing or confirmed at Screening
- Mean early diastolic annular velocity ≤ 8 cm/s at Screening (nHCM only)
- If NYHA Classification I, must have positive pathologic/likely pathologic genotype (nHCM only)
- NT-proBNP ≥ 300 pg/mL and < 2000 pg/mL at Screening. (nHCM only)
- No Hx of diabetes with hemoglobin A1C ≥ 7.0% at Screening. (nHCM only)

Endpoints and Measures of Interest

- Safety and tolerability of EDG-7500 in adults with HCM
- LVOT gradient by Doppler echocardiography at rest and during the Valsalva maneuver (oHCM only)
- Cardiac biomarkers (hsTnI and NT-proBNP)
- Single and multiple-dose PK of EDG-7500
- Systolic and diastolic LV structure and function at rest
- NYHA functional classification and KCCQ-CSS
- Submaximal exercise echocardiography substudy (nHCM only)
- Cardiopulmonary exercise test substudy (Part D)

References

[1] Arbelo et al, EHJ (2023) 44, 3503–3626
[2] Kaplan et. al. JACC. 2023 Mar, 81 (8_Supplement) 349
[3] Del Rio et. al. Circulation. 2023; 148: A15822
[4] Dufton C et al, HFSA ASM 2024 poster #1251.
[5] Ro R et al. JACC. 2014;64:1984-1995.

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