EDG-7500, a First-in-Class Cardiac Sarcomere Modulator, Demonstrates Favorable Tolerability, Safety, and Pharmacokinetics in Healthy Adults

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Background

EDG-7500 is a novel, orally bioavailable, first-in-class cardiac sarcomere modulator (CSM) being developed for the treatment of hypertrophic cardiomyopathy (HCM) and other diseases of diastolic dysfunction.

Preclinical models demonstrate that EDG-7500 improves left ventricular (LV) compliance and distensibility and ameliorates LV outflow tract (LVOT) pressure gradient, with minimal impact on LV ejection fraction (LVEF). (Kaplan et al. JACC 2023, Del Rio et al. Circ. 2023)

Based on preclinical data, 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.

Safety, tolerability, pharmacodynamic (PD) response by echocardiography, and pharmaco-kinetics (PK) of EDG-7500 were assessed in a Phase 1 study of healthy adults and in a Phase 2 study of patients with obstructive HCM (oHCM).

Study Design

Phase 1 First-in-Human Healthy Adult Study

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- Placebo-controlled, single ascending dose (SAD) and multiple ascending dose (MAD) cohort design
- 8 subjects per cohort (6 EDG-7500, 2 placebo), LVEF ≥ 60%.
- SAD: single-dose, 8 days post-dose follow-up
- MAD: once-daily dose x 14 days, 8 days post-dose follow-up

Phase 2 First-in-Patient oHCM Single Dose Study

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- Open-label, single dose, cohort design
- 3-5 oHCM patients per cohort, LVEF ≥ 60%.
- Single-dose, 24-hour post-dose follow-up with a final end of study safety visit ~7 days post-dose
- Efficacy Evaluable Population: LVOT-G (rest) ≥ 30 mmHg and LVOT-G (Valsalva) ≥ 50 mmHg at baseline (Day 1).

Baseline Characteristics

- **In healthy subjects, baseline characteristics were generally well balanced between the EDG-7500 and placebo cohorts.**
  - **Mean age: 36-42 years; mean weight: 75-83 kg; mean BMI: 27-28 kg/m^2; mean LVEF: 61-64%**
- **Baseline characteristics for oHCM study are shown below.**

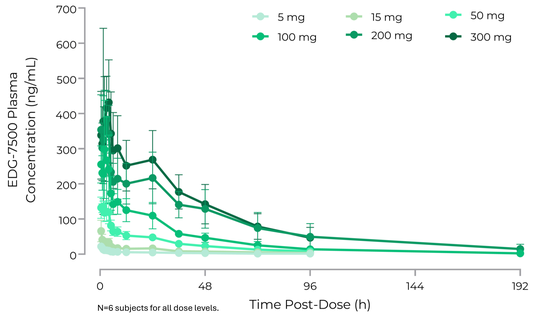
Baseline Characteristics of oHCM Patients	Safety (N=11)
Age, years	59 ± 15
Female (%)	73
Race – Black / White (%)	9 / 91
BMI (kg/M^2)	28 ± 3.9
NYHA Class – I / II / III (%)	27 / 45 / 27
Time from HCM diagnosis, years	5.0 ± 5.5
Max End-Diastolic LV Wall Thickness, mm	20 ± 6.2
LVOT-G (rest), mmHg	60 ± 28
LVOT-G (Valsalva), mmHg	88 ± 32
LVEF (%)	68 ± 3.8
Background Beta Blocker (%)	64

Mean ± STD unless specified otherwise.

Single Dose PK in Healthy Subjects

- **Exposures were generally dose proportional between 5-200 mg.**
- **Terminal half-life was ~ 30 hours (range: 25 – 39 hours).**
- **PK of EDG-7500 in oHCM patients was similar to healthy subjects.**

SAD: EDG-7500 Plasma Concentration Over Time (mean ± SD)

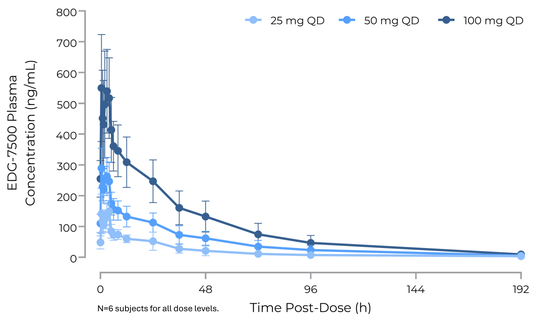


N=6 subjects for all dose levels.

Steady State PK in Healthy Subjects

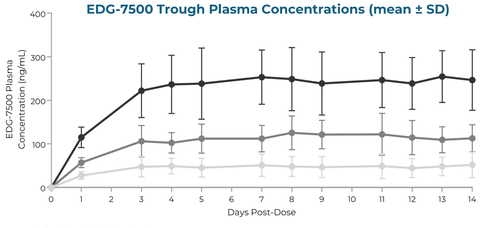
- **Exposures were generally dose proportional between 25-100 mg QD.**
- **Terminal half-life was ~ 30 hours (range: 23 – 34 hours).**
- **~2-fold accumulation was observed after 14 days of administration.**
- **Steady-state was achieved in ~4 days with once-daily dosing.**

MAD: EDG-7500 Plasma Concentration Over Time (mean ± SD)



N=6 subjects for all dose levels.

EDG-7500 Trough Plasma Concentrations (mean ± SD)



N=6 subjects for all dose levels. 25 mg QD 50 mg QD 100 mg QD

Adverse Events

- **In healthy subjects, nearly all AEs were mild and all resolved by end of study. No dose-response for AEs was observed (data not shown).**
  - **1 moderate AE (medical device site reaction) in SAD 100 mg cohort.**
- **In oHCM patients, all AEs were mild and considered unrelated to drug.**
  - **Parasomnia (50 mg), hypokalemia (50 mg), hypotension (100 mg), and paroxysmal AF (200 mg).**

TEAEs by body system and treatment after single ascending doses of EDG-7500 (n=6 per cohort on active)

System Organ Class	Pooled Placebo (N=12)	Overall (N=36)	EDG-7500 5 mg	15 mg	50 mg	100 mg	200 mg	300 mg
Any TEAE	**3 (25%)**	**9 (25%)**	0	1	4	2	0	2
Eye disorders	0	1 (3%)	0	0	0	0	0	1
Gastrointestinal disorders	1 (8%)	2 (6%)	0	0	1	1	0	0
General disorders and administration site conditions[1]	1 (8%)	3 (8%)	0	1	0	2	0	0
Infections and infestations	0	2 (6%)	0	0	1	0	0	1
Injury, poisoning and procedural complications	1 (8%)	0	0	0	0	0	0	0
Nervous system disorders	0	3 (8%)	0	0	1	1	0	1
Respiratory, thoracic and mediastinal disorders	0	1 (3%)	0	0	1	0	0	0

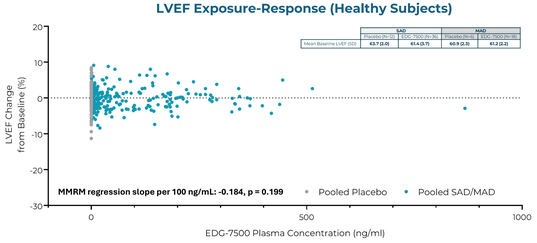
TEAEs by body system and treatment after daily EDG-7500 for 14 days (n=6 per cohort on active)

System Organ Class	Pooled Placebo (N=6)	Overall (N=18)	EDG-7500 25 mg QD	50 mg QD	100 mg QD
Any TEAE	**2 (33%)**	**6 (33%)**	3	3	0
General disorders and administration site conditions	1 (17%)	1 (6%)	1	0	0
Injury, poisoning and procedural complications	0	1 (6%)	1	0	0
Musculoskeletal and connective tissue disorders	0	3 (17%)	3	0	0
Nervous system disorders	1 (17%)	1 (6%)	1	0	0
Reproductive system and breast disorders	0	1 (6%)	1	0	0
Respiratory, thoracic and mediastinal disorders	0	1 (6%)	1	0	0
Skin and subcutaneous tissue disorders	0	3 (17%)	0	3	0

Left Ventricular Ejection Fraction

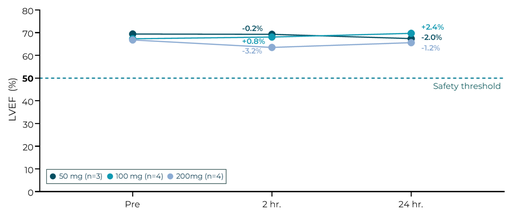
- **No healthy subjects in the SAD or MAD studies had a post-dose LVEF value < 50% or an LVEF absolute decrease from baseline ≥ 10%.**
- **No oHCM patients had a post-dose LVEF value < 50% or an absolute decrease from baseline in LVEF ≥ 10%.**
- **There was no correlation between EDG-7500 plasma concentration and LVEF change in healthy subjects (p=0.199).**

LVEF Exposure-Response (Healthy Subjects)



Data presented as mean absolute change from baseline.

LVEF Group Mean Values (oHCM patients)

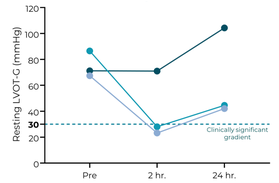


Safety Population (N=11); Data presented as mean absolute change from baseline.

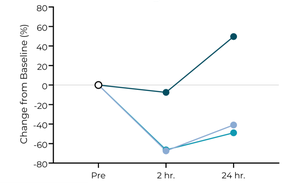
LVOT Peak Gradient and NT-proBNP

- **EDG-7500 led to a meaningful reduction in resting LVOT-G of 67% for the combined 100/200 mg cohorts.**
- **EDG-7500 led to a meaningful reduction of Valsalva LVOT-G of 55% for the combined 100/200 mg cohorts.**

LVOT-G (Rest) Group Mean Values

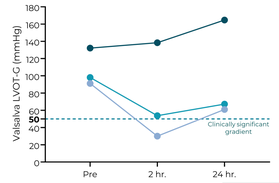


LVOT-G (Rest) Percent Change from Baseline

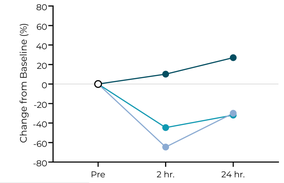


Efficacy Evaluable Population (N=7). 50 mg (n=2) 100 mg (n=3) 200mg (n=2)

LVOT-G (Valsalva) Group Mean Values



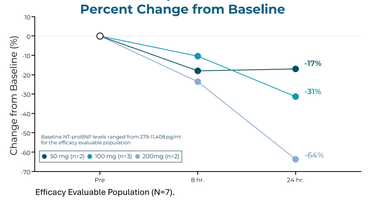
LVOT-G (Valsalva) Percent Change from Baseline



Efficacy Evaluable Population (N=7). 50 mg (n=2) 100 mg (n=3) 200mg (n=2)

- **EDG-7500 led to a robust reduction in mean NT-proBNP of up to 64% In the 200 mg cohort.**

NT-proBNP Percent Change from Baseline



Efficacy Evaluable Population (N=7).

Conclusions

- Once-daily EDG-7500 was well-tolerated for up to 14 days in healthy subjects and as a single dose in oHCM patients.
- The PK of EDG-7500 supports once-daily dosing with steady-state plasma levels achieved in ~4 days.
- No meaningful reductions in LVEF < 50% were observed in healthy subjects receiving once-daily EDG-7500 up to 14 days and in oHCM patients receiving a single dose of EDG-7500.
- No correlation between the LVEF change from baseline and EDG-7500 plasma concentration was observed in healthy subjects over a wide range of exposures.
- In patients with oHCM, a single dose of EDG-7500 led to meaningful reductions in LVOT peak gradient and NT-proBNP without reductions in LVEF.