Pharmacokinetics of EDG-7500, a First-in-Class Cardiac Sarcomere Modulator for the Treatment of Hypertrophic Cardiomyopathy

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1. Background

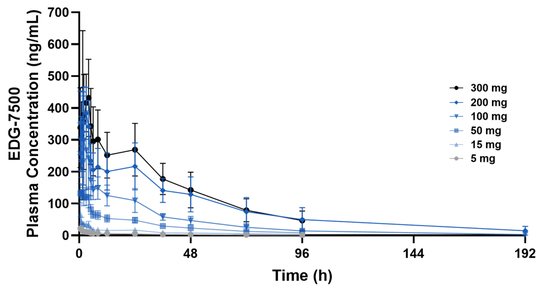
Hypertrophic cardiomyopathy (HCM) is a chronic, progressive disease of the cardiac sarcomere characterized by excessive contraction and impaired relaxation of the heart. EDG-7500 is a first-in-class, oral (PO) small molecule cardiac sarcomere modulator being developed for the treatment of HCM. The compound acts through a novel calcium-dependent mechanism that allows it to slow the rate of myocardial contraction and increase the rate of relaxation. The pharmacokinetics (PK), safety, and tolerability of EDG-7500 were assessed in a Phase 1, randomized, double-blinded, placebo-controlled, single and multiple-ascending dose study in healthy adults. The relative bioavailability (rBA) and potential effect of food on the PK of EDG-7500 were also assessed in an open-label, three-period, randomized crossover study.

2. Study Design

- Single Ascending Dose (SAD; n = 48): EDG-7500 PO (5, 15, 50, 100, 200, and 300 mg).
  - 8 healthy volunteers per cohort (6 EDG-7500, 2 Placebo)
  - Objective: safety, tolerability, and PK in healthy subjects
- Multiple Ascending Dose (MAD; n = 24): EDG-7500 PO once-daily x 14 days (25, 50, and 100 mg).
  - 8 healthy volunteers per cohort (6 EDG-7500, 2 Placebo)
  - Objective: safety, tolerability, and PK in healthy subjects
- Relative bioavailability (rBA) and food effect (FE) (n = 12): EDG-7500 PO (50 mg).
  - 12 healthy volunteers participated in an open-label, three-period, randomized crossover with at least a 5-day washout period in between treatment periods
  - Treatment Groups: 1) EDG-7500 single-dose suspension, fasted; 2) solid dose, fasted; 3) solid dose, fed
  - Objective: compare the PK of suspension vs. solid, and under fasted vs. fed conditions

3. SAD Pharmacokinetics

SAD Study: EDG-7500 single dose PK



EDG-7500 Dose Level	C_{max} (ng/mL)	$T_{1/2}$ (h)	$AUC_{0\text{-}24h}$ (h*ng/mL)	AUC_{INF} (h*ng/mL)
5 mg	22.1 (26.1)	25.9 (± 7.96)	165 (18.4)	335 (42.0)
15 mg	65.5 (42.3)	31.9 (± 12.5)	475 (26.3)	1,040 (45.6)
50 mg	156 (10.3)	31.5 (± 7.67)	1,590 (15.0)	3,360 (20.2)
100 mg	283 (30.8)	27.1 (± 6.29)	3,270 (27.0)	6,650 (28.9)
200 mg	462 (11.0)	38.8 (± 14.7)	5,440 (22.6)	15,200 (45.0)
300 mg	484 (37.0)	29.9 (± 8.73)	6,670 (32.8)	16,600 (46.5)

C_{max}, $AUC_{0\text{-}24h}$, and AUC_{INF} are presented as geometric mean (geometric %CV)
$T_{1/2}$ data represent arithmetic mean (± SD)

- Exposures were dose proportional from 5 – 200 mg and less so from 200 – 300 mg.
- Terminal half-life was ~ 30 hours.

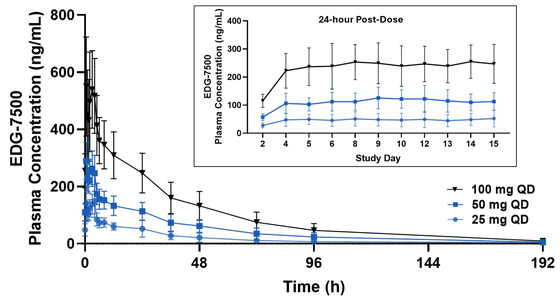
SAD Treatment Emergent Adverse Events

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

- All AEs were mild except for one in the 100 mg cohort (medical device site reaction that was moderate) and all resolved by the end of study.
- No clinically significant changes or trends in clinical chemistry, hematology, or echocardiograms were observed.

4. MAD Pharmacokinetics

MAD Study: EDG-7500 PO once-daily PK (Day 14)



EDG-7500 Dose Level	C_{max} (ng/mL)	$T_{1/2}$ (h)	$AUC_{0\text{-}24h}$ (h*ng/mL)	AR $AUC_{0\text{-}24h}$
25 mg QD	166 (40.4)	23.9 (± 11.6)	1,710 (± 27.6)	1.80
50 mg QD	311 (17.8)	31.7 (± 10.8)	3,600 (± 25.3)	2.00
100 mg QD	556 (28.4)	33.3 (± 6.59)	7,920 (± 25.5)	2.30

C_{max}, $AUC_{0\text{-}tau}$ are presented as geometric mean (geometric %CV); $T_{1/2}$ data represent arithmetic mean (± SD); AR = Accumulation ratio

- Exposure was linear and dose proportional.
- ~2-fold accumulation after 14 days of administration QD.
- Terminal half-life was ~ 30 hours.
- Steady-state was generally achieved in 3 – 4 days.

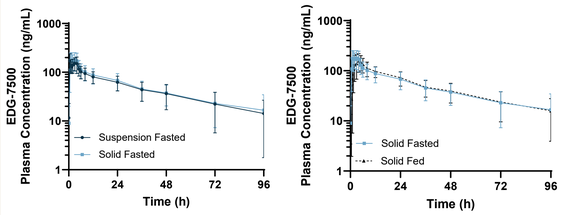
MAD Treatment Emergent Adverse Events

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

- All AEs were mild and resolved by the end of study.
- No dose-response for AEs was observed.
- No clinically significant changes or trends in clinical chemistry, hematology, or echocardiograms were observed.

5. rBA/FE Pharmacokinetics

rBA: EDG-7500 single dose suspension or tablet (fasted)
FE: EDG-7500 single dose tablet fasted vs. fed



Parameter (unit)	Treatment: Geometric Least-Squares Mean, EDG-7500 (50 mg)—Fasted State: Solid	(n)	Suspension	(n)	Geometric Mean Ratio (%)	90% Confidence Interval	Intra-subject CV%
$AUC_{0\text{-}t}$ (ng*hr/mL)	4,200	11	3,810	10	110	101 - 120	10.9
$AUC_{0\text{-}inf}$ (ng*hr/mL)	4,950	11	4,470	10	111	101 - 122	11.8
C_{max} (ng/mL)	214	11	185	10	116	101 - 133	17.7

Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100 × (test/reference)
Intra-subject CV% was calculated as 100 × square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.

Parameter (unit)	Treatment: Geometric Least-Squares Mean, EDG-7500 (50 mg): Fed	(n)	Fasted	(n)	Geometric Mean Ratio (%)	90% Confidence Interval	Intra-subject CV%
$AUC_{0\text{-}t}$ (ng*hr/mL)	4,420	9	4,200	11	105	95.9 – 116	10.9
$AUC_{0\text{-}inf}$ (ng*hr/mL)	5,200	9	4,950	11	105	95.0 – 117	11.8
C_{max} (ng/mL)	190	9	214	11	88.7	76.3 – 103	17.7

Parameters were ln-transformed prior to analysis.
Geometric least-squares means (LSMs) are calculated by exponentiating the LSMs from the ANOVA.
Geometric Mean Ratio (GMR) = 100 × (test/reference)
Intra-subject CV% was calculated as 100 × square root(exp[MSE]-1), where MSE = Residual variance from ANOVA.

- No significant difference in relative bioavailability of EDG-7500 was observed between the suspension and tablet forms.
- No food effect was observed.

6. Conclusions

- The PK of EDG-7500 supports once-daily dosing with steady-state plasma levels achieved in 3 – 4 days.
- Solid oral dose form performance supports outpatient studies.
- Safety and exposure profiles support advancement of EDG-7500 to Phase 2 studies in HCM patients.

- Disclosures: MMM, MM, CD, JM, and JAS are all employees and stockholders of Edgewise Therapeutics (EWTX); ME and MJS were employees at EWTX at the time the work was conducted; DDG is a consultant for EWTX; ALH and MV have no disclosures.
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