A First-in-Human, Single and Multiple Ascending Dose Study of CK-4021586, a Novel Cardiac Myosin Inhibitor

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INTRODUCTION

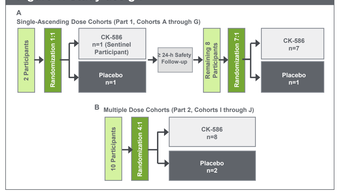
- Up to half of patients with heart failure have preserved left ventricular ejection fraction (LVEF), defined as LVEF ≥50%.[1]
- CK-4021586 (CK-586), a small-molecule cardiac myosin inhibitor (CMI), directly reduces cardiac contractility at the level of the cardiac sarcomere.
- The use of CMIs in heart failure with preserved ejection fraction (HFpEF) may yield advantages over current therapy as they directly address the underlying pathophysiology in patients with hypercontractility, thereby potentially improving myocardial energetics and promoting favorable cardiac remodeling.
- Preclinical pharmacology, pharmacokinetic (PK), and toxicology data support initiation of clinical studies of CK-586 towards the development of a novel therapy for patients with HFpEF.
- A first-in-human study was conducted to evaluate the PK, PK-pharmacodynamics (PKPD), safety, and tolerability of CK-586 in healthy adult participants.

METHODS

Study Design

- A double-blind, randomized, placebo-controlled study was conducted in 2 parts for CK-586 doses (**Figure 1**):
  - Part 1: 7 single ascending-dose cohorts of 10 mg, 30 mg, 90 mg, 135 mg, 250 mg, 350 mg, and 600 mg.
  - Part 2: 2 multiple ascending-dose cohorts of 100 mg and 200 mg once daily for 7 days.
- Healthy participants (N=10/cohort) were administered CK-586 orally under fasted conditions as a powder-in-capsule (n=8/cohort) or placebo (n=2/cohort).
- Participants were required to have LVEF ≥60% at screening

Figure 1: Study design



PK

- Intensive PK plasma sampling was conducted on Day 1 (Parts 1 and 2) and Day 7 (Part 2 only) for up to 168 h post dose for bioanalysis (HPLC/MS-MS) of CK-586 and its primary pharmacologically inactive metabolite (CK-4022235). Trough concentrations were assessed on Days 2–6 (Part 2 only).
- Urine was collected through 24 h post dose on Days 1 and 7 of Part 2 only.
- Plasma and urine PK parameters were estimated via non-compartmental analysis (Phoenix; v8.3.5).

PD, PKPD, and Safety

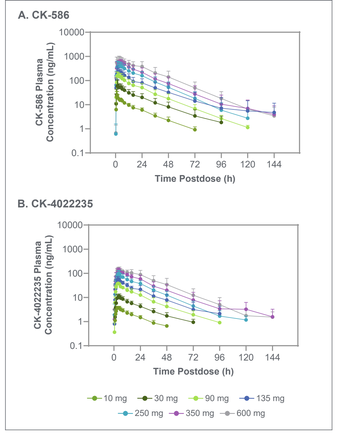
- Echocardiographic measurements were collected for up to 24 h post dose on Day 1 (Parts 1 and 2) and Day 7 (Part 2 only) for PD assessment of CK-586 effect on cardiac function.
- The PKPD relationships between CK-586 concentration and change from baseline in LVEF, LV fractional shortening (LVFS), and LV ejection time (LVET) were evaluated using simple linear regression.
- Safety and tolerability were assessed; all adverse events (AEs) were followed until resolved.

RESULTS

Single Ascending-Dose PK (Table 1, Figures 2 and 3)

- CK-586 was rapidly absorbed, with a median time to maximum plasma concentration (T_{max}) ranging 1.5 to 5.0 h.
- The median plasma elimination half-life ($T_{1/2}$) was consistent across the single-dose cohorts, ranging 14 to 17 h.
- Area under the plasma concentration–time curve (AUC) extrapolated to infinity (AUC_{inf}) was dose proportional from 10–600 mg.
- Proportionality of maximum plasma concentration (C_{max}) appears to be maintained in all but the 2 highest doses (350 and 600 mg).
- CK-4022235 $T_{1/2}$ was similar to parent, ranging 14 to 18 h.

Figure 2: Plasma concentrations (mean [SD]) over time after single ascending doses of CK-586



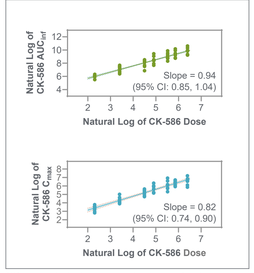
Timepoints with n<3 observable concentrations were excluded from depiction.

Table 1: Tabulated PK parameters after single ascending doses (n=8 per cohort on active treatment)

Single Ascending Doses	Cohort A 10 mg	Cohort B 30 mg	Cohort C 90 mg	Cohort D 135 mg	Cohort E 250 mg	Cohort F 350 mg	Cohort G 600 mg
CK-586							
$T_{1/2}$, h[a]	16.8 (15.1, 18.4)	17.3 (15.8, 20.7)	15.6 (13.1, 17.0)	15.2 (13.8, 17.4)	14.0 (13.0, 15.5)	13.8 (11.2, 17.6)	14.9 (13.9, 16.2)
T_{max}, h[a]	1.47 (1.00, 2.24)	2.51 (1.47, 4.50)	2.02 (1.47, 2.51)	3.01 (2.24, 4.00)	4.00 (2.24, 4.50)	4.99 (3.01, 5.52)	3.50 (2.51, 5.00)
C_{max}, ng/mL[b]	29.4 (31.4)	76.5 (45.7)	192 (30.3)	303 (44.4)	493 (52.9)	598 (27.5)	765 (40.0)
AUC_{last}, ng·h/mL[b]	377 (22.1)	1300 (43.6)	3140 (44.1)	5480 (59.9)	9510 (52.1)	13,300 (50.5)	20,200 (52.0)
AUC_{inf}, ng·h/mL[b]	398 (21.4)	1320 (42.8)	3160 (43.7)	5540 (61.1)	9530 (51.9)	13,400 (50.7)	20,200 (52.0)
CK-4022235							
$T_{1/2}$, h[a]	17.6 (16.8, 18.4)	16.2 (14.4, 22.7)	17.1 (13.2, 18.2)	15.7 (12.9, 18.3)	14.9 (13.6, 17.3)	14.2 (13.1, 18.0)	16.4 (14.3, 16.9)
T_{max}, h[a]	4.53 (3.50, 5.00)	4.51 (4.00, 5.00)	4.00 (4.00, 4.11)	3.51 (3.01, 4.00)	4.00 (4.00, 5.00)	4.49 (4.00, 5.01)	4.50 (4.00, 5.00)
C_{max}, ng/mL[b]	3.80 (18.3)	11.4 (27.7)	38.6 (13.7)	62.6 (24.5)	101 (35.1)	139 (16.8)	156 (23.2)
AUC_{last}, ng·h/mL[b]	74.6 (23.5)	249 (25.2)	760 (29.8)	1270 (38.4)	2100 (32.3)	3230 (40.1)	4600 (42.8)
AUC_{inf}, ng·h/mL[b]	90.8 (21.3)	270 (23.3)	780 (29.7)	1300 (38.3)	2120 (31.9)	3260 (40.1)	4620 (42.7)

[a] Median (25%ile, 75%ile).
[b] Mean (%CV).
%ile=percentile; AUC_{inf}=area under the plasma concentration–time curve from time zero to infinity; AUC_{last}=area under the plasma concentration–time curve from time zero to the last observable plasma concentration; C_{max}=maximum plasma concentration; CV=coefficient of variation; $T_{1/2}$=terminal elimination half-life; T_{max}=time to maximum plasma concentration.

Figure 3: Dose linearity of CK-586 AUC_{inf} and C_{max} after single ascending doses of CK-586 (10–600 mg)

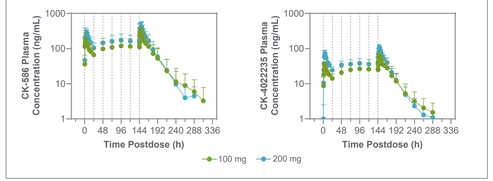


AUC_{inf}=area under the plasma concentration–time curve from time zero to infinity; C_{max}=maximum plasma concentration; LVEF=left ventricular ejection fraction.

Multiple Ascending Dose (Table 2, Figure 4)

- Following multiple-dose administration, CK-586 PK appears linear with time:
  - Steady state was achieved by Day 7.
  - Median CK-586 T_{max} and $T_{1/2}$ at Day 7 was consistent with single dosing: 2 to 4 h and 15 to 18 h, respectively.
  - Mean AUC over the dosing interval (AUC_τ) accumulation ratio from Days 1 to 7 was 1.49 to 1.69.
  - Mean peak C_{max} to trough ratio was ~3 at steady state.
- Urine excretion of unchanged CK-586 was minimal (<1%; data not shown).
- CK-4022235 circulated in plasma with mean AUC, metabolite-to-parent ratios of 0.26 to 0.27 at Day 7.
- CK-4022235 $T_{1/2}$ was similar to parent, ranging 17 to 19 h.

Figure 4: Plasma concentrations (mean and SD) over time after 2 ascending doses of daily CK-586 for 7 days



Timepoints with n<3 observable concentrations were excluded from depiction.
Vertical dashed lines represent daily dosing events.

Table 2: Tabulated PK parameters after 2 ascending doses of daily CK-586 for 7 days (n=8 per cohort on active treatment)

Multiple Daily Dosing – Day 7	Cohort I 100 mg	Cohort J 200 mg
CK-586		
$T_{1/2}$, h[a]	18.0 (12.8, 20.2)	14.7 (13.5, 18.0)
T_{max}, h[a]	2.02 (1.48, 3.00)	4.00 (2.52, 5.50)
C_{max}, ng/mL[b]	312 (40.3)	457 (33.2)
C_{trough}, ng/mL[b]	115 (64.1)	164 (51.8)
Peak-to-trough ratio[c]	3.05 (35.6)	2.99 (25.2)
AUC_τ, ng·h/mL[b]	4220 (50.2)	6520 (42.7)
AUC_τ accumulation ratio[c]	1.69 (20.9)	1.49 (21.8)
CK-4022235		
$T_{1/2}$, h[a]	19.4 (14.6, 22.7)	16.8 (14.5, 20.2)
T_{max}, h[a]	3.07 (3.01, 4.00)	3.50 (3.00, 4.00)
C_{max}, ng/mL[b]	65.5 (33.6)	114 (16.8)
C_{trough}, ng/mL[b]	28.0 (47.7)	40.3 (33.8)
Peak-to-trough ratio[c]	2.49 (30.9)	2.94 (26.7)
AUC_τ, ng·h/mL[b]	948 (31.6)	1530 (21.9)
AUC_τ accumulation ratio[c]	1.89 (19.8)	1.60 (21.9)
AUC_τ metabolite-to-parent ratio[c]	0.26 (31.0)	0.27 (30.7)

[a] Median (25%ile, 75%ile).
[b] Mean (%CV).
[c] Geometric mean (geometric %CV).
%ile=percentile; AUC_τ=area under the plasma concentration–time curve from time zero to time tau; C_{max}=maximum plasma concentration; C_{trough}=plasma concentration immediately before dosing; CV=coefficient of variation; $T_{1/2}$=terminal elimination half-life; T_{max}=time to maximum plasma concentration.

PKPD in LVEF, LVFS, and LVET (Table 3, Figure 5)

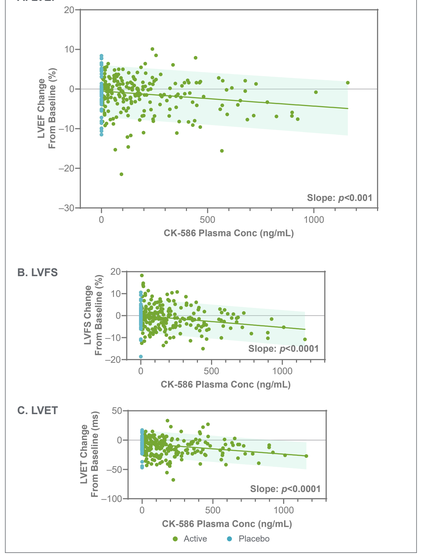
- All 3 markers of contractility demonstrated a consistent decrease from baseline with increasing dose.
- CK-586 plasma concentration demonstrated shallow and predictable PKPD relationships:
  - ~1% decrease from baseline in LVEF for every 264 ng/mL increase in CK-586.
  - ~1% decrease from baseline in LVFS for every 187 ng/mL increase in CK-586.
  - ~1-ms decrease from baseline in LVET for every 55 ng/mL increase in CK-586.

Table 3: Change from baseline in LVEF, LVFS, and LVET at 1.5 h post dose, by cohort (n=8 per cohort on active treatment)

Dose	Δ LVEF, Mean (%)	Δ LVFS, Mean (%)	Δ LVET, Mean (ms)
Part 1: SAD (Day 1)			
Pooled Placebo (n=14)	–0.85 (5.27)	–0.40 (7.24)	–8.98 (11.14)
10 mg	–0.18 (4.28)	1.35 (8.11)	–2.18 (13.23)
30 mg	–1.00 (3.37)	1.62 (6.10)	–13.71 (12.03)
90 mg	–3.50[a] (8.52)	–3.21 (4.60)	–14.70 (9.67)
135 mg	–1.34 (3.97)	1.78 (4.21)	–23.12 (13.71)
250 mg	–6.38[a] (4.41)	–2.27 (7.73)	–11.24 (14.89)
350 mg	–2.70 (4.49)	–3.49 (3.57)	–15.72 (13.47)
600 mg	–4.44[a] (4.64)	–2.10 (5.60)	–24.03[a] (12.67)
Part 2: MAD (Day 7)			
Pooled Placebo (n=4)	–0.60 (0.96)	–1.23 (1.41)	–2.77 (5.45)
100 mg	–0.17 (2.41)	–1.78 (2.17)	–7.23 (10.83)
200 mg	–1.28 (2.79)	–2.82 (5.28)	–10.47 (8.12)

[a] Statistically significant ($p<0.05$) from pooled placebo.
LVEF=left ventricular ejection fraction; LVFS=left ventricular fractional shortening; LVET, left ventricular ejection time; MAD=multiple ascending dose; SAD=single ascending dose.

Figure 5: Change from baseline in LVEF, LVFS, and LVET as a function of coincidental CK-586 plasma concentrations



Line and shaded area are estimated mean and 90% prediction interval, respectively.
Conc=concentration; LVEF=left ventricular ejection fraction; LVET=left ventricular ejection time; LVFS=left ventricular fractional shortening.

Safety (Tables 4 and 5)

- CK-586 was generally safe and well tolerated across all cohorts; no serious AEs nor AEs of special interest were observed.
- 1 participant experienced an asymptomatic decrease in LVEF <50% (specifically 48%) after single-dose administration of 250 mg, with a return to baseline within 3 h.
- Stopping criteria were not met in this study.

Table 4: SAD TEAEs by body system and treatment

n (%)	CK-586 n=56	Placebo n=14
Number of participants with TEAEs	**15 (26.8)**	**3 (21.4)**
System Organ Class		
Nervous system disorders	6 (10.7)	1 (7.1)
General disorders and administration site conditions	5 (8.9)	1 (7.1)
Gastrointestinal disorders	3 (5.3)	0 (0)
Musculoskeletal and connective tissue disorders	3 (5.3)	0 (0)
Investigations	2 (3.6)	1 (7.1)
Skin and subcutaneous tissue	2 (3.6)	0 (0)
Cardiac disorders	1 (1.8)	0 (0)
Eye disorders	1 (1.8)	0 (0)
Psychiatric disorders	1 (1.8)	0 (0)

SAD=single ascending dose; TEAE=treatment-emergent adverse event.

Table 5: MAD TEAEs by body system and treatment

n (%)	CK-586 n=16	Placebo n=4
Number of participants with TEAEs	**9 (56.3)**	**1 (25.0)**
System Organ Class		
Gastrointestinal disorders	6 (37.5)	0 (0)
Musculoskeletal and connective tissue disorders	2 (12.5)	1 (25.0)
Nervous system disorders	2 (12.5)	0 (0)
General disorders and administration site conditions	1 (6.3)	0 (0)
Metabolism and nutrition disorders	1 (6.3)	0 (0)
Respiratory, thoracic and mediastinal disorders	1(6.3)	0 (0)
Vascular disorders	1(6.3)	0 (0)

MAD=multiple ascending dose; TEAE=treatment-emergent adverse event.

CONCLUSIONS

- CK-586 demonstrated ideal clinical pharmacologic properties for once-daily fixed-dose administration:
  - Half-life of 14–17 h.
  - Dose- and time-linearity over a wide range of exposures.
  - Modest and predictable PKPD relationship with LVEF, LVFS, and LVET.
- CK-586 was safe and well tolerated across all doses studied.
- These results provide key insights for future phase 2 evaluations of CK-586 in patients with HFpEF.

Reference

1. Dunlay, S, et al. Nat Rev Cardiol 2017;14:591-602. doi: 10.1038/nrcardio.2017.65.

Disclosures

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