Evaluation of the Pharmacokinetics, Pharmacodynamics, Safety, and Tolerability of *Aficamten* in Healthy Japanese and Caucasian Participants

Donghong Xu[1], Tyrell J. Simkins[2], Alex Ng[3], Wendy Xie[4], Eric Yu[4], Youcef Benattia[5], Adrienne Griffith[1], Daniel L. Jacoby[2], Stuart Kupfer[2], and Polina German[1]

[1]Department of Clinical Pharmacology; [2]Department of Clinical Research; [3]Department of Clinical Operations; [4]Department of Biostatistics; [5]Department of Drug Safety and Pharmacovigilance, Cytokinetics, Incorporated, South San Francisco, CA, USA

Cytokinetics®

Poster 602

INTRODUCTION

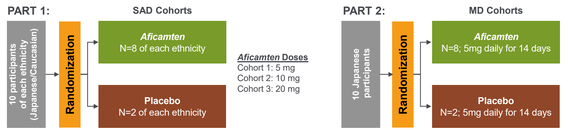
- *Aficamten* is a next-in-class cardiac myosin inhibitor in development as a potential chronic, oral treatment for patients with hypertrophic cardiomyopathy (HCM)
- *Aficamten* exhibits characteristics indicative of low ethnic sensitivity,[1,2] including a predictable pharmacokinetic (PK) profile[3]; expected high oral bioavailability[4]; and low and/or manageable potential for drug–disease, drug–diet, or drug–drug interactions[5,6]
- A Phase 1 study was conducted to definitively characterize and compare PK, pharmacodynamics (PD), and short-term safety and tolerability of *aficamten* in healthy Japanese participants and to compare these findings to Caucasian participants
- These data were generated to support *aficamten* clinical development in Japanese patients with HCM

METHODS

Study Design

- A double-blind, randomized, placebo-controlled study was conducted in 2 parts (**Figure 1**):
  - **PART 1:** 3 single-ascending dose (SAD) cohorts in healthy Japanese and Caucasian participants
  - **PART 2:** 1 multiple-dose (MD) cohort in healthy Japanese participants

Figure 1. Study Design



- Japanese and Caucasian participants were matched by sex and body weight (± 20%)
  - Japanese participants: must have been born in Japan; have both parents and 4 grandparents of Japanese descent, and have not lived outside of Japan for more than 5 years
  - Caucasian participants: must have both parents and 4 grandparents who are Caucasian
- *Aficamten* was administered orally under fasted conditions
- Participants were required to have left ventricular ejection fraction (LVEF) ≥60% at screening

PK assessments

- Serial plasma samples were collected predose and up to 216 hours postdose for SAD cohorts and 24 hours postdose for MD cohort to measure the concentrations of *aficamten* and its inactive metabolites CK-3834282 and CK-3834283, using validated liquid chromatography–tandem mass spectrometry methods
- PK parameters were estimated using noncompartmental analysis
- Single-dose PK comparison between Japanese and Caucasian participants was conducted using an analysis of variance (ANOVA)
- PK data from the MD cohort were summarized and compared descriptively with historical data

PD and Safety assessments

- Multiple echocardiographic measurements were collected for PD assessment of *aficamten* effect on cardiac function, including LVEF and left ventricular fractional shortening (LVFS), with a PD comparison between Japanese and Caucasian participants
- Safety and tolerability were assessed throughout the study
- Appropriate echocardiogram and adverse event (AE)–based stopping criteria were in place to ensure safe dose escalation between cohorts

RESULTS

Study Demographics

- A total of 70 participants (40 Japanese and 30 Caucasian) were enrolled and completed the study
- Overall, demographic characteristics were comparable between Caucasian and Japanese participants (**Table 1**)

Table 1. Summary of Demographic and Baseline Characteristics

0	Japanese					Caucasian			
	SAD			MD		SAD			
	Cohort 1	Cohort 2	Cohort 3	Cohort 4	Pooled	Cohort 1	Cohort 2	Cohort 3	Pooled
	5 mg	10 mg	20 mg	5 mg QD X 14 days	Placebo	5 mg	10 mg	20 mg	Placebo
	(N=8)	(N=8)	(N=8)	(N=8)	(N=8)	(N=8)	(N=8)	(N=8)	(N=6)
Sex, male n (%)	5 (62.5)	4 (50.0)	4 (50.0)	6 (75.0)	7 (87.5)	5 (62.5)	5 (62.5)	5 (62.5)	2 (33.3)
Age, mean (min, max), years	29.6 (22, 35)	32.3 (22, 45)	32.9 (19, 44)	29.6 (20, 39)	33.9 (22, 44)	33.5 (27, 41)	35.3 (26, 43)	34.5 (21, 41)	36.2 (28, 45)
Weight, mean (min, max), kg	66.8 (49.0, 83.9)	64.7 (47.4, 76.7)	59.9 (53.4, 64.6)	61.7 (46.6, 93.0)	67.8 (54.8, 84.3)	68.5 (54.8, 88.4)	77.0 (56.4, 90.1)	63.7 (56.2, 72.8)	64.0 (49.6, 75.5)

SAD, single ascending dose; max, maximum; MD, multiple dose; min, minimum.

SAD PK in Japanese and Caucasian Participants

- *Aficamten* PK was generally comparable between Japanese and Caucasian participants (**Figure 2; Table 2**)
  - The 90% CIs for the GMR for C_{max}, AUC, and metabolite to parent ratio AUC_{inf} (MR_{AUCinf}) crossed 100% in most comparisons, except for higher *aficamten* C_{max} and MR_{AUCinf} in Japanese participants at the 5 mg dose
  - Given the comparability of these parameters at the 10 mg and 20 mg doses, the 5 mg observation was likely a chance finding
  - Similar t_{max} and $t_{1/2}$ between Japanese and Caucasian participants across all 3 cohorts
- Linear PK from 5 to 20 mg single doses in Japanese and Caucasian participants was observed (**Figure 3**), consistent with that observed in other Phase 1 studies in the Caucasian population[3]

Figure 2. *Aficamten* Mean (SD) Concentration-time Profiles in Japanese and Caucasian Participants

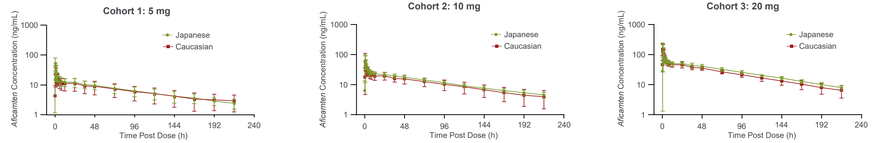
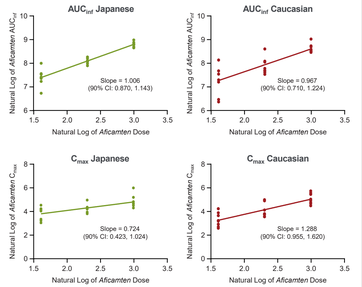


Table 2. Statistical PK Comparisons for *Aficamten* and Metabolites in Japanese and Caucasian Participants

	Aficamten SD (N=8)	Population		Japanese vs. Caucasian
		Japanese (N=8)	Caucasian (N=8)	GMR (90% CI)
Cohort 1: 5 mg				
Aficamten	AUC_{inf} (h·ng/mL)	1750 (34.8)	1730 (54.1)	1.11 (0.72, 1.73)
	C_{max} (ng/mL)	54.3 (48.5)	31.6 (61.4)	1.77 (1.07, 2.93)
	t_{max} (h)	0.50 (0.50, 0.86)	1.50 (0.50, 2.50)	-
	$t_{1/2}$ (h)	82.6 (63.0, 96.3)	87.9 (74.1, 112)	-
CK-3834282	MR_{AUCinf}	0.91 (19.9)	0.62 (40.6)	1.54 (1.18, 2.02)
CK-3834283	MR_{AUCinf}	1.33 (48.2)	0.82 (20.2)	1.54 (1.18, 2.01)
Cohort 2: 10 mg				
Aficamten	AUC_{inf} (h·ng/mL)	3230 (13.5)	2850 (42.2)	1.19 (0.94, 1.51)
	C_{max} (ng/mL)	73.5 (43.5)	68.3 (67.9)	1.19 (0.78, 1.83)
	t_{max} (h)	1.01 (0.75, 1.50)	0.75 (0.50, 1.50)	-
	$t_{1/2}$ (h)	87.4 (71.8, 102)	82.1 (70.6, 97.4)	-
CK-3834282	MR_{AUCinf}	0.84 (15.8)	0.71 (39.5)	1.27 (0.96, 1.68)
CK-3834283	MR_{AUCinf}	1.12 (16.5)	1.12 (29.6)	1.04 (0.81, 1.33)
Cohort 3: 20 mg				
Aficamten	AUC_{inf} (h·ng/mL)	6730 (10.4)	5800 (20.7)	1.17 (1.03, 1.34)
	C_{max} (ng/mL)	152 (72.2)	177 (46.6)	0.81 (0.52, 1.25)
	t_{max} (h)	1.25 (0.75, 1.75)	1.00 (0.50, 1.25)	-
	$t_{1/2}$ (h)	75.7 (61.9, 84.3)	66.5 (54.7, 84.3)	-
CK-3834282	MR_{AUCinf}	0.93 (30.5)	0.73 (28.7)	1.29 (0.98, 1.70)
CK-3834283	MR_{AUCinf}	1.23 (23.0)	1.09 (27.4)	1.14 (0.90, 1.45)

Data presented as mean (%CV), except t_{max} and $t_{1/2}$ as median (25th percentile, 75th percentile); data presented to 3 significant figures.
PK, pharmacokinetic; SD, single dose; AUC_{inf}, area under the plasma concentration–time curve from time 0 to infinity; C_{max}, maximum plasma concentration; T_{max}, time to C_{max}; $t_{1/2}$, half-life; MR, metabolite:parent ratio; CV, coefficient of variation; GMR, geometric least squares mean ratio; CI, confidence interval; SAD, single ascending doses.

Figure 3. Dose Linearity of *Aficamten* AUC_{inf} and C_{max} Following SAD 5 to 20 mg *Aficamten*



MD PK in Japanese Participants

Figure 4. *Aficamten* Mean (SD) Concentration–Time Profiles Following Once Daily Oral Doses of 5 mg *Aficamten* in Japanese participants (Day 14)

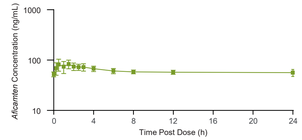


Table 3. Summary of Plasma PK of *Aficamten* and Metabolites Following MD

	Aficamten MD 5 mg QD × 14 days	Japanese[a] (N=8)	Historical Data[b] (N=6)
Aficamten	AUC_{tau} (h·ng/mL)	1460 (10.0)	1348 (22.4)
	C_{max} (ng/mL)	93.6 (19.5)	70.4 (21.1)
CK-3834282	MR_{AUCtau}	0.754 (34.6)	0.747 (18.0)[c]
CK-3834283	MR_{AUCtau}	1.20 (14.7)	1.31 (17.7)[c]

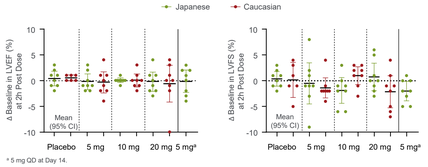
Data presented as mean (%CV);]; data presented to 3 significant figures; MD, multiple dose; QD, once daily; AUC_{tau}, area under the concentration–time curve over the dosing interval; C_{max}, maximum plasma concentration; CV, coefficient; MR, metabolite:parent ratio.
[a] 10% w/w in tablet; [b] 5% w/w granules in capsule; [c] 10 mg QD × 14 days.

- MD PK is consistent with historical data[3] in healthy participants (**Table 3**)
- Steady-state PK was consistent with single-dose PK, indicating the PK behavior did not change over time in Japanese participants (**Tables 2 and 3**)

PD in Japanese and Caucasian Participants

- Changes from baseline in LVEF and LVFS were similar between the two groups (Figure 5)
- No PKPD relationship was observed as expected given the low doses

Figure 5. Change From Baseline in LVEF and LVFS vs. *Aficamten* Dose



[a] 5 mg QD at Day 14.

Safety

- *Aficamten* was safe and well tolerated across all cohorts; no serious AEs or AEs of special interest were observed (**Table 4**)
- No participant experienced LVEF <50% or met prespecified stopping criteria

Table 4. Summary of TEAEs

Event	Participants, n (%)
Enrolled	70 (100)
≥1 TEAE	8 (11.43)
≥1 TESAE	0 (0)
≥1 TEAE leading to early termination	0 (0)
≥1 related TEAE	1 (1.43)
≥1 moderate TEAE	1 (1.43)
≥1 severe TEAE	0 (0)
Death during the study	0 (0)

TEAE, treatment-emergent adverse event; TESAE, treatment-emergent serious adverse event.

CONCLUSIONS

- ***Aficamten* PK *was generally comparable between Japanese and Caucasian participants***
  - Comparable *aficamten* exposures and similar $t_{1/2}$
  - Linear PK and predictable accumulation to steady state in Japanese participants
  - MD PK in Japanese participants is consistent with historical data in healthy participants
- ***Changes from baseline in LVEF and LVFS were similar between the 2 populations***
- ***Aficamten was safe and well tolerated across all cohorts. No participant experienced serious AEs, LVEF <50%, or met prespecified stopping criteria***

These results are supportive of the low risk of ethnic sensitivity of *aficamten* and the progression of *aficamten* into clinical studies in Japanese patients with HCM

References:

1. Zhao X, et al. Safety, tolerability, pharmacokinetics, and pharmacodynamics of single and multiple doses of aficamten in healthy Chinese participants: a randomized, double-blind, placebo-controlled, phase 1 study. *Front. Pharmacol.* 2023;14:1227470.
2. Xu D, et al. Toward a quantitative understanding of aficamten clinical pharmacology: population pharmacokinetic modeling. *CPT Pharmacometrics Syst Pharmacol.* Published online August 17, 2025. doi:10.1002/psp4.70099.
3. Malik FI, et al. A phase 1 dose-escalation study of the cardiac myosin inhibitor aficamten healthy participants. *JACC Basic Transl Sci.* 2022;7:763-775.
4. Xu D, et al. Pharmacokinetics, disposition, and biotransformation of the cardiac myosin inhibitor aficamten in humans. *Pharmacol Res Perspect.* 2024;12: e70006.
5. Xu D, et al. Drug-drug interaction study to evaluate the effect of strong CYP3A inhibition and P450 induction on the pharmacokinetics of aficamten, and the effect of aficamten on p-glycoprotein, in healthy participants. Paper presented at American Society for Clinical Pharmacology & Therapeutics (ASCPT24): March 27–29, 2024, Colorado Springs, CO, USA.
6. Maharao N, et al. Evaluation of cytochrome P450 2C9, 2C19, and 2D6 inhibition on the pharmacokinetics of aficamten in healthy participants. March 29–31, 2025. Paper presented at American College of Cardiology (ACC25): Chicago, IL, USA.

Acknowledgments: Editorial support for the preparation of this poster was provided by Elyse Smith, PhD, CMPP. No contributions were made to content.

Disclosures: Cytokinetics, Inc. sponsored this research. All authors are employees and shareholders of Cytokinetics, Incorporated.

Scan the QR code to obtain a PDF of this poster. No personal information is stored.

Presented at the American College of Clinical Pharmacology (ACCP) Annual Meeting | Phoenix, AZ, USA | September 14-16, 2025.