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Disposition and Metabolism of the Cardiac Myosin Inhibitor *Aficamten* in Humans

Donghong Xu, Punag Divanji, Kathleen Cheplo, Jianlin Li, Polina German

Cytokinetics, Incorporated. South San Francisco, CA USA

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BACKGROUND

- *Aficamten* is a next-in-class, small-molecule, selective cardiac myosin inhibitor in Phase 3 development as a potential treatment for hypertrophic cardiomyopathy.
- In a first-in-human study in healthy participants, *aficamten* exhibited linear pharmacokinetics (PK) over the evaluated single dose range of 1 to 75 mg, and multiple once-daily doses of 5 to 10 mg administered for 14–17 days; *aficamten* median half-life was ~75–85 h.[1,2]

OBJECTIVES

- **Primary:** To determine the absorption, metabolism, and excretion of a single oral dose of [^{14}C]-*aficamten* and identify and characterize the metabolites present in plasma, urine, and feces in healthy male participants.
- **Secondary:** To assess the safety and tolerability of [^{14}C]-*aficamten* when administered to healthy male participants.

METHODS

- This was a Phase 1 open-label study conducted in 8 healthy male participants (**Table 1**).
- Participants received a single oral 20-mg dose containing ~100 µCi of [^{14}C]-*aficamten*, administered after an overnight fast of ≥10 h.
- Participants were confined until meeting protocol pre-specified discharge criteria:
  - ≥90% mass balance recovery, and
  - ≤1% of the total radioactive dose recovered in combined excreta (urine and feces) in 2 consecutive 24-h periods in which both collections occur, and
  - plasma radioactivity falls below the lower limit of detection for 2 consecutive collections.
- PK sampling was performed as follows:
  - Whole blood and plasma: predose, 0.25, 0.5, 1, 1.5, 2, 2.5, 3, 4, 6, 8, 12, 16, 24, 36, and 48 h post-dose, then at 24-h intervals until discharge.
  - Urine: predose (–12 to 0 h), 0–4, 4–8, 8–12, and 12–24 h post-dose, then at 24-h intervals until discharge.
  - Feces: predose (from check-in to 0 h), then at 24-h intervals until discharge.
- Samples analyzed for:
  - Total radioactivity: liquid scintillation counting.
  - Metabolite profiling and identification: radiometric detection in liquid chromatography (LC) and LC-tandem mass spectrometry (LC-MS/MS).
- Safety and tolerability evaluated throughout the study: adverse events, vital signs, electrocardiograms (ECGs), and clinical laboratory and physical examination data.

Table 1. Summary of baseline demographics and clinical characteristics

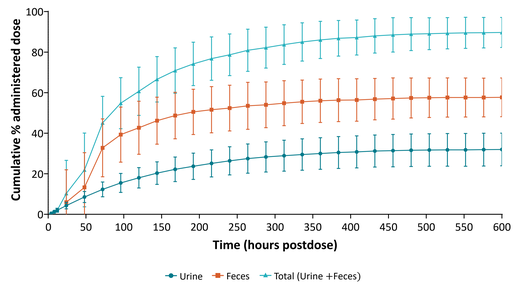
Parameter, unit	20 mg [^{14}C]-*aficamten* (N=8)
Male, n (%)	8 (100)
Age, mean (SD), y	33.3 (7.78)
BMI, mean (SD), kg/m^2	26.7 (2.68)
Race, n (%)	
White	4 (50)
Black or African American	4 (50)
Ethnicity, n (%)	
Not Hispanic or Latino	7 (87.5)
Hispanic or Latino	1 (12.5)

BMI, body mass index.

RESULTS

- Mean recovery of radioactivity in urine and feces samples was 89.7% (57.7% in feces and 32.0% in urine) (**Figure 1**).
- Most of the recovered radioactivity (85%) was excreted by 336 h postdose.

Figure 1. Mean (±SD) cumulative urinary and fecal radioactivity excretion



- Moderately rapid absorption and steady formation of metabolites CK-3834282 (M1a) and CK-3834283 (M1b) were observed (**Figure 2**, **Table 2**).

Figure 2. Mean (±SD) plasma concentration–time profiles

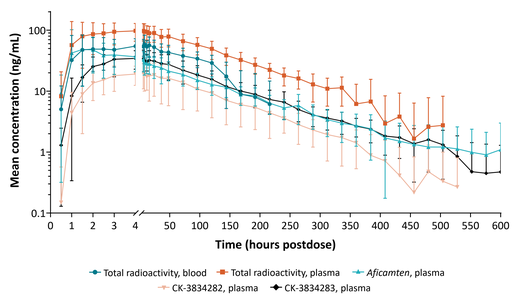


Table 2. Summary of pharmacokinetic parameter estimates

Parameter (unit)	20 mg [^{14}C]-*aficamten* (N=8)		
	Aficamten	CK-3834282	CK-3834283
$AUC_{0\text{-last}}$, h·ng/mL	4300 (32.1)	2740 (59.0)	4810 (34.9)
AUC_{inf}, h·ng/mL	4630 (31.0)	2920 (54.5)	5010 (33.5)
C_{max}, ng/mL	70.9 (63.8)	24.9 (33.0)	43.8 (28.2)
T_{max}, h	2.00 (1.00, 6.00)	5.00 (3.00, 36.0)	5.00 (3.00, 36.0)
$t_{1/2}$, h	99.6 (81.5, 209)	94.8 (76.8, 208)	95.4 (77.6, 180)
$MRAUC_{inf}$	–	0.611 (39.4)	1.06 (23.6)

Data presented as arithmetic mean (%CV), except for T_{max} and $t_{1/2}$, which are presented as median (range) and reported to 3 significant figures. $AUC_{0\text{-last}}$, area under the concentration–time curve from time 0 to last measurement; AUC_{inf}, AUC extrapolated to infinity; C_{max}, maximum plasma concentration; %CV, % coefficient variation; percent $MRAUC_{inf}$, metabolite:parent ratio based on AUC_{inf}; T_{max}, time to maximum plasma concentration; $t_{1/2}$, half-life.

- There were no major (>10% of dose) urine metabolites of *aficamten* (**Table 3**).
- A major fecal metabolite was M18 (CK-4017583; 44.1% of dose).
- CK-3834282 and CK-3834283 were the major circulating components (46.9% of the total exposure) (**Table 4**).
  - Not pharmacologically active at therapeutic exposures.

Table 3. Mean percentage recovered in excreta after a single PO dose of [^{14}C]-*aficamten*

	% of Administered [^{14}C]-*Aficamten* Dose		
Analyte	Mean Urinary Recovery	Mean Fecal Recovery	Total
Total radioactivity	32.0	57.7	89.7
Aficamten	ND	5.07	5.07
CK-3834282	6.16	–	6.16
CK-3834283	2.85	–	2.85
M18	–	44.1	44.1

ND, not detected; PO, oral administration.

Table 4. Summary of circulating [^{14}C]-*aficamten* and metabolites in plasma

Analyte	% of Total Radioactivity $AUC_{0\text{-t}}$
Aficamten	19.8
CK-3834282	10.5
CK-3834283	36.4
M5	10.3

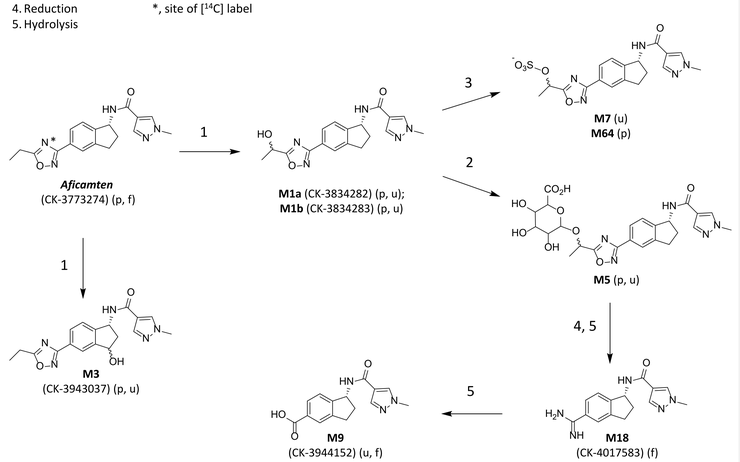
$AUC_{0\text{-t}}$, area under the concentration–time curve from time 0 to the last measurable concentration; M5, glucuronide of CK-3834282 and CK-3834283.

- M1a and M1b are hydroxylated metabolites of *aficamten* (**Figure 3**).
- M5 is a glucuronide conjugate of M1a/M1b detected in plasma and urine, but not in feces (**Figure 3**).
- M18 is the only major fecal metabolite observed and is proposed to be formed metabolically as indicated in **Figure 3**.[3]

Figure 3. Proposed biotransformation pathways of *aficamten* in male humans

1. Oxidation
2. Glucuronidation
3. Sulfonation
4. Reduction
5. Hydrolysis

p: plasma
u: urine
f: feces
*, site of [^{14}C] label



RESULTS

Safety

- 1 mild treatment-emergent adverse event (TEAE) was reported by 1 (12.5%) participant, which resolved by the end of the study, and was deemed not related to study drug.
- There were no serious adverse events reported during the study.
- No one discontinued the study due to a TEAE.
- There were no other laboratory measures, vital signs, or ECG parameters of concern, or other clinically significant adverse events.

CONCLUSIONS

- *Aficamten* is eliminated mainly by metabolism and, to a lesser extent, by fecal excretion.
- *Aficamten* metabolites accounted for ~ 80% of the recovered dose, resulting in the major non-circulating metabolite M18 in the feces (44.1%).
  - No major metabolites in urine.
- The major circulating (inactive) metabolites in plasma were the hydroxylated metabolites CK-3834282 (M1a) and CK-3834283 (M1b), followed by the subsequently formed ether-linked glucuronide metabolite M5.
- M18 is proposed to be formed from the metabolism of M5.[3]

REFERENCES

1. Malik FI, et al. *JACC Basic Transl Sci* 2022;7:763-75.
2. Robertson LA, et al. HFSA 2019; poster #10.
3. Sukhun R, et al. AAPS 2023; poster #W1130-10.

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