Effect of Moderate Hepatic Impairment on the Pharmacokinetics of Aficamten and its Metabolites

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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 human mass-balance study,[1] aficamten was predominantly cleared by metabolism with minimal parent-drug recovery from urine.
- CK-3834282 and CK-3834283 (pharmacologically inactive) are the main circulating metabolites in plasma.
- Because aficamten was anticipated to undergo hepatic metabolism and biliary excretion, this study evaluated the impact of moderate hepatic impairment (HI) on the pharmacokinetics (PK) of aficamten and its metabolites to inform dosing recommendations in patients with mild and moderate HI.

OBJECTIVES

- **Primary objective:** To evaluate the PK of aficamten and its metabolites CK3834282 and CK3834283 following a single oral dose in participants with moderate HI compared with participants with normal hepatic function.
- **Secondary Objective:** To assess the safety and tolerability of a single oral dose of aficamten in participants with moderate HI and with normal hepatic function.

METHODS

Study Design

- This was a single-dose, open-label, parallel-group study in participants with moderate HI (Child-Pugh class B, total score, 7 to 9 points) and participants with normal hepatic function.
- Participants in the moderate HI (n=8) and normal hepatic function (n=8) groups were matched for age (±10 years), sex, race, and BMI (±20%).
- Participants received aficamten 20 mg as a single oral dose under fasting conditions.
- Blood samples for concentrations of aficamten and its metabolites CK-3834282 and CK-3834283 were collected predose and up to 480 h postdose.
- Concentrations of study drugs were determined using validated LC-MS/MS methods.
- PK parameters were estimated using noncompartmental methods.

- ANCOVA was performed to compare the PK in participants with moderate HI (test) and matching participants with normal hepatic function (reference).
  - The natural-log (ln)-transformed PK parameters were analyzed using a model that included factor “HI group” and sex as fixed effects and the covariates age and BMI.
  - The LSM of primary PK parameters for each hepatic function group, difference in LSMs between the test and reference groups, and corresponding 90% CIs were calculated, and back-transformed to give the GLSM, ratio of GLSMs, and corresponding 90% CIs.
- Safety and tolerability were monitored throughout the study.

RESULTS

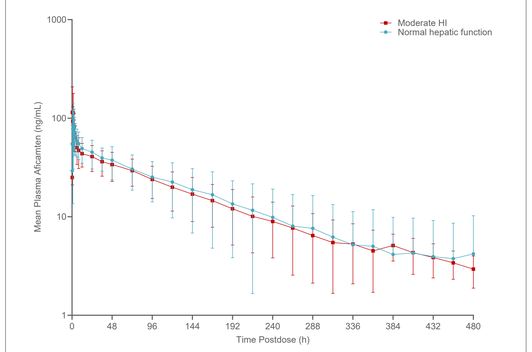
Table 1. Summary of baseline demographics and clinical characteristics

Demographics	Moderate HI (n=8)	Normal Hepatic Function (n=8)
Sex, male, n (%)	5 (62.5)	5 (62.5)
Age, mean (SD), years	57.1 (7.04)	57 (4.5)
BMI, mean (SD), kg/m²	31.4 (3.2)	29.7 (4.1)
Race, n (%)		
White	7 (87.5)	8 (100.0)
Black or African American	1 (12.5)	0 (0.0)
Ethnicity, n (%)		
Hispanic or Latino	6 (75.0)	7 (87.5)
Not Hispanic or Latino	2 (25.0)	1 (12.5)
Child-Pugh score, n (%)		
7	4 (50.0)	–
8	1 (12.5)	–
9	3 (37.5)	–

Pharmacokinetics

- Aficamten PK parameters in participants with moderate HI and normal hepatic function were generally comparable (**Figure 1, Table 2**).
- Similar metabolite: parent ratios were observed between participants with moderate HI and normal hepatic function (**Table 2**).
- Exploratory regression analyses indicated minimal to no correlation between the aficamten PK parameters and Child-Pugh classification parameters (**Figures 2–4**).

Figure 1. Mean (±SD) plasma aficamten concentration–time profile



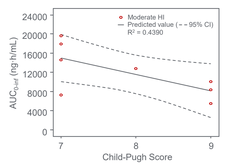
20 mg aficamten

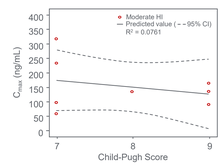
Table 2. PK parameters and statistical comparisons for aficamten administered in participants with normal hepatic function and moderate HI

Analyte	PK Parameter[a] (n=8)	Reference: Normal Hepatic Function	Test: Moderate HI	Test vs Reference[b]: Ratio of GLSM (90% CI)
Aficamten	$AUC_{0\text{-}inf}$ (h·ng/mL)	7990 (70.8)	7040 (42.3)	0.95 (0.64–1.41)
	AUC_{last} (h·ng/mL)	7360 (59.3)	6690 (41.0)	0.95 (0.66–1.36)
	C_{max} (ng/mL)	109 (48.6)	153 (56.0)	1.38 (0.84–2.30)
	$C_{max,u}$ (ng/mL)[d]	6.3 (60.1)	9.6 (49.2)	1.59 (0.92–2.73)
	t_{max} (h)	1.50 (1.00, 2.00)	0.75 (0.50, 1.25)	–
	$t_{1/2}$ (h)	88.2 (76.8, 102)	106 (69.9, 115)	0.7209[c]
CK-3834282	MR_{AUCinf}	0.5 (27.0)	0.5 (45.6)	0.87 (0.59–1.27)
CK-3834283	MR_{AUCinf}	0.9 (40.7)	0.9 (31.2)	1.12 (0.78–1.60)

[a] Arithmetic mean (%CV) statistics presented; t_{max} and $t_{1/2}$ are presented as median (Q1, Q3).
[b] The ratio of GLSMs and corresponding CIs were obtained by taking the exponential of the LSMs, differences in LSMs, and corresponding CIs on the natural log scale.
[c] p-value presented for $t_{1/2}$.
[d] $C_{max,u} = fu \times C_{max}$; free fractions ($f_u$, mean [SD]) for moderate HI and normal hepatic function were 6.4% [1.1] and 5.6% [0.7], respectively.

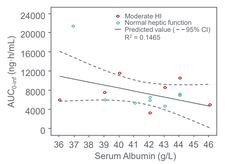
Figure 2. Plasma aficamten $AUC_{0\text{-}inf}$ and C_{max} vs Child-Pugh score

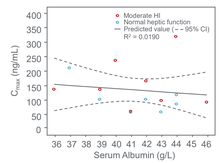




20 mg aficamten

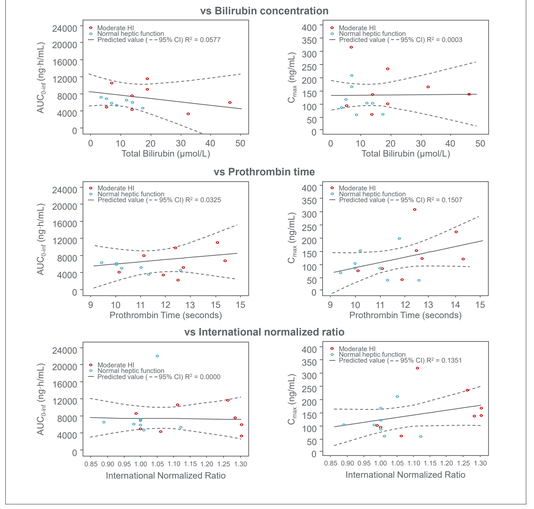
Figure 3. Plasma aficamten $AUC_{0\text{-}inf}$ and C_{max} vs serum albumin concentration





20 mg aficamten

Figure 4. Plasma aficamten $AUC_{0\text{-}inf}$ and C_{max}



20 mg aficamten

Safety

- There were no deaths, SAEs, AESIs, or other significant AEs during this study.
- Overall, 3 TEAEs were reported by 3 (18.8%) participants following a single oral dose of aficamten, including 2 (25.0%) participants with moderate HI and 1 (12.5%) participant with normal hepatic function.
  - All TEAEs were reported by ≤2 (12.5%) participants.
  - 2 events were mild in severity and 1 event (headache) was moderate.
- There were no safety concerns identified from the evaluation of clinical laboratory, vital signs, ECGs, or physical examinations in this study with respect to participant safety.

CONCLUSIONS

- No clinically relevant changes in the PK of aficamten were observed in participants with moderate HI.
- Aficamten was well tolerated after a single oral dose of 20 mg in participants with HI or normal hepatic function.
- No dose adjustment of aficamten in moderate or mild HI is warranted.

References

1. Xu D, et al. AAPS 2023; poster #M1430-10-69.

Disclosures

This study was funded by Cytokinetics, Incorporated. **DX, PD, AG, SK,** and **PG:** Employees of and hold stock in Cytokinetics, Incorporated. **EK, JL,** and **YB:** Paid consultants for Cytokinetics, Incorporated.

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Abbreviations

AE, adverse event; AESI, adverse event of special interest; ANCOVA, analysis of covariance; $AUC_{0\text{-}inf}$, area under the plasma concentration–time curve from 0 to infinity, AUC_{last}, area under the plasma concentration–time curve from time 0 to the time of the last quantifiable concentration; BMI, body mass index; C_{max}, maximum plasma concentration; $C_{max,u}$, unbound maximum plasma concentration; CV, coefficient of variation; ECG, electrocardiogram; f_u, fraction of drug unbound in plasma;GLSM, geometric least squares mean; HI, hepatic impairment; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LSM, least squares mean; MR_{AUCinf}, metabolite/parent ratio AUC_{inf}; PK, pharmacokinetics; Q, quartile; SAE, serious adverse event; $t_{1/2}$,half life; t_{max}, time of the maximum observed plasma concentration; TEAE, treatment-emergent adverse event.

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