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

Donghong Xu, Justin Lutz, Punag Divanji, Kathleen Cheplo, Jianlin Li, Stuart Kupfer, Polina German

Cytokinetics, Incorporated, South San Francisco, CA, USA

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 vitro studies suggest aficamten is metabolized by CYP2C8, CYP2C9/19, CYP2D6, and CYP3A4.
- Given the theoretical potential for CYP3A inhibitors and P450 inducers to alter the PK of aficamten, a clinical drug-interaction study was conducted to determine the extent of any interaction with itraconazole (a strong CYP3A inhibitor) and carbamazepine (a P450 inducer).
- In vitro studies suggest that aficamten may inhibit P-glycoprotein (P-gp). To inform the use of aficamten with P-gp substrates, this study evaluated the effect of aficamten on the PK of dabigatran (administered as dabigatran etexilate, a sensitive P-gp probe).

OBJECTIVES

- **Primary objective:** To evaluate the effect of strong CYP3A inhibition (itraconazole) and P450 induction (carbamazepine) on the PK of aficamten, and the impact of aficamten on the PK of a sensitive P-gp substrate (dabigatran etexilate).
- **Secondary Objective:** To assess the safety and tolerability of aficamten administered alone and when coadministered with itraconazole, carbamazepine, or dabigatran etexilate in healthy participants.

METHODS

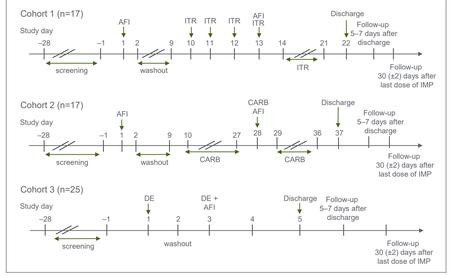
Study Design

- This was a Phase I, open-label, fixed-sequence study in healthy participants.
- Blood samples for concentrations of aficamten and its metabolites CK-3834282 and CK-3834283 were collected predose and up to 216 h post-dose.
- Blood sampling for free and total (free plus conjugated) dabigatran concentrations were collected predose and up to 48 h post-dose.
- Concentrations of study drugs were determined using validated LC-MS/MS methods.
- PK parameters were estimated using noncompartmental methods.
- A statistical analysis was conducted to investigate the drug–drug interaction effects.
  - A linear mixed-model analysis was applied to analyze the log-transformed primary PK parameters. The model included actual treatment as fixed effects, and participant as a random effect.
  - Estimates of GLSM ratios together with the corresponding 90% CIs were derived for the comparisons of the PK parameters between test and reference in each cohort.
- Safety and tolerability were monitored throughout the study.

Treatment Cohorts (Figure 1)

- Cohort 1: 17 participants were enrolled and completed the study.
  - Aficamten: single 10 mg dose on Days 1 and 13.
  - Itraconazole: 200 mg QD on Days 10–21.
- Cohort 2: 17 participants were enrolled, of which 13 completed the study.
  - Aficamten: single 20 mg dose on Days 1 and 28.
  - Carbamazepine: 100 mg BID on Days 10–12, 200 mg BID on Days 13–16, and 300 mg BID on Days 17–36.
- Cohort 3: 25 participants were enrolled and completed the study.
  - Aficamten: single 20 mg dose on Day 3.
  - Dabigatran etexilate: single 75 mg dose on Days 1 and 3.

Figure 1. Study design



For Cohort 1, AFI was administered 1 h after completing a standardized breakfast or 1 h after ITR administration, and ITR was administered within 5 min of completing a standardized meal.
Treatments for Cohorts 2 & 3 were administered within 5 min of completing a standardized meal.
AFI, aficamten; CARB, carbamazepine; DE, dabigatran etexilate; IMP, investigational medicinal product; ITR, itraconazole

RESULTS

Table 1. Summary of baseline demographics and clinical characteristics

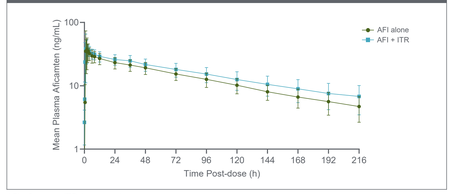
Demographics	Cohort 1 (n=17)	Cohort 2 (n=17)	Cohort 3 (n=25)
Sex, male, n (%)	7 (41.2)	11 (64.7)	8 (32.0)
Age, mean (SD), years	34.9 (6.90)	32.3 (6.83)	34.4 (7.44)
BMI, mean (SD), kg/m²	25.4 (2.60)	26.1 (3.05)	24.8 (2.67)
Race, n (%)			
White	11 (64.7)	7 (41.2)	19 (76.0)
Black or African American	4 (23.5)	9 (52.9)	5 (20.0)
Ethnicity, n (%)			
Hispanic or Latino	9 (52.9)	7 (41.2)	9 (36.0)
Not Hispanic or Latino	8 (47.1)	10 (58.8)	16 (64.0)

BMI, body mass index

Pharmacokinetics

- Weak inhibition of aficamten elimination was observed with itraconazole (strong CYP3A inhibitor) (**Figure 2, Table 2**).
- No change in aficamten metabolite AUC ratios with itraconazole indicates that CYP3A does not contribute significantly to the formation of circulating metabolites (**Figure 2, Table 2**).

Figure 2. Cohort 1 mean (SD) plasma aficamten concentration–time profile



AFI, aficamten; ITR, itraconazole

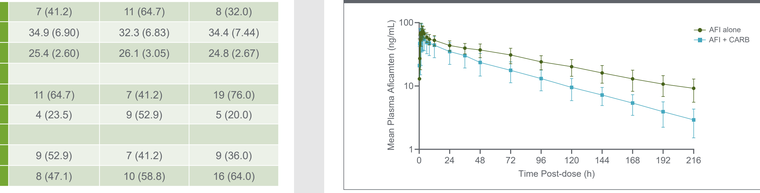
Table 2. PK parameters and statistical comparisons for aficamten administered alone and with CYP3A inhibitor itraconazole

Analyte	PK Parameter[a] (n=16[b])	Reference	Test	Test vs Reference[c]
		10 mg AFI	10 mg AFI + 200 mg QD ITR	Ratio of GLSM (90% CI)
Aficamten	AUC_{inf} (h·ng/mL)	3430 (27.6)	4420 (34.7)	1.26 (1.19–1.34)
	AUC_{last} (h·ng/mL)	2840 (22.0)	3380 (24.7)	1.18 (1.13–1.24)
	C_{max} (ng/mL)	58.0 (54.4)	50.4 (36.6)	0.93 (0.79–1.08)
	t_{max} (h)	2.00 (1.50, 3.00)	2.00 (1.00, 2.75)	–
	$t_{1/2}$ (h)	80.6 (64.8, 98.4)	91.7 (71.8, 120)	<0.0001[d]
CK-3834282	MR_{AUCinf}	0.717 (28.7)	0.774 (39.1)	1.04 (0.97–1.11)
CK-3834283	MR_{AUCinf}	1.06 (25.3)	1.06 (33.0)	0.98 (0.93–1.03)

[a] Arithmetic mean (%CV) statistics presented; t_{max} and $t_{1/2}$ are presented as median (Q1, Q3).
[b] One subject was excluded due to an unexplained decrease in aficamten PK with itraconazole.
[c] 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.
[d] *p*-value presented for $t_{1/2}$.
AFI, aficamten; ITR, itraconazole.

- Weak to moderate induction was observed with the constitutive androstane receptor (CAR)/pregnane X receptor (PXR)-agonist carbamazepine (**Table 3, Figure 3**).
  - Aficamten elimination can be induced by CAR- and/or PXR-mediated P450 metabolism.

Figure 3. Cohort 2 mean (SD) plasma aficamten concentration–time profile



AFI, aficamten; CARB, carbamazepine

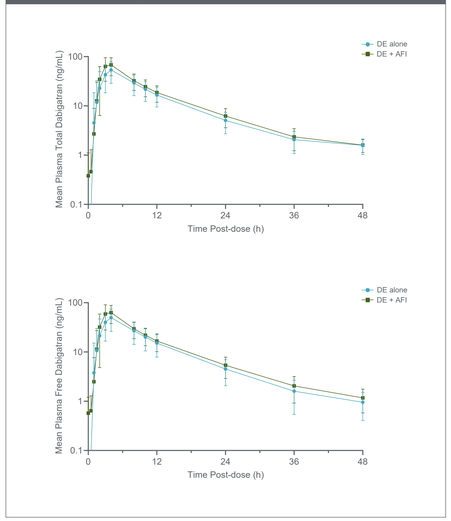
Table 3. PK parameters and statistical comparisons for aficamten administered alone and with P450 inducer carbamazepine

Analyte	PK Parameter[a] (n=15–17)	Reference	Test	Test vs Reference[b]
		20 mg AFI	20 mg AFI + 300 mg BID CARB	Ratio of GLSM (90% CI)
Aficamten	AUC_{inf} (h·ng/mL)	6740 (27.0)	3620 (35.4)	0.49 (0.36– 0.66)
	AUC_{last} (h·ng/mL)	5520 (22.9)	3390 (35.4)	0.55 (0.40–0.75)
	C_{max} (ng/mL)	107 (35.4)	81.2 (45.4)	0.69 (0.50–0.95)
	t_{max} (h)	1.50 (1.00, 3.00)	1.50 (0.500, 2.50)	–
	$t_{1/2}$ (h)	78.9 (67.5, 103)	52.3 (46.8, 60.7)	<0.0001[c]
CK-3834282	MR_{AUCinf}	0.597 (39.2)	0.819 (44.2)	1.27 (1.08–1.50)
CK-3834283	MR_{AUCinf}	1.07 (21.6)	1.57 (21.6)	1.48 (1.41–1.54)

[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 $t_{1/2}$.
AFI, aficamten; CARB, carbamazepine

- Aficamten demonstrated weak P-gp inhibition (**Table 4, Figure 4**).

Figure 4, Cohort 3 mean (SD) plasma total and free dabigatran concentration–time profile



AFI, aficamten; DE, dabigatran etexilate

Table 4. PK parameters and statistical comparisons for DE administered alone and with aficamten

Analyte	PK Parameter[a] (n=25)	Reference	Test	Test vs Reference[b]
		75 mg DE	75 mg DE + 20 mg AFI	Ratio of GLSM (90% CI)
Total dabigatran	AUC_{inf} (h·ng/mL)	519 (41.4)	637 (39.1)	1.26 (1.12–1.41)
	AUC_{last} (h·ng/mL)	500 (42.7)	618 (39.9)	1.27 (1.13–1.44)
	C_{max} (ng/mL)	58.6 (42.3)	72.2 (39.9)	1.27 (1.11–1.45)
	t_{max} (h)	4.00 (3.00, 4.00)	4.00 (3.00, 4.00)	–
	$t_{1/2}$ (h)	7.36 (6.58, 8.57)	7.93 (7.03, 8.98)	0.0024[c]
Free dabigatran	AUC_{inf} (h·ng/mL)	477 (44.4)	577 (41.0)	1.24 (1.11–1.39)
	AUC_{last} (h·ng/mL)	467 (44.6)	563 (41.3)	1.24 (1.10–1.40)
	C_{max} (ng/mL)	54.8 (43.3)	66.8 (41.7)	1.25 (1.10–1.43)
	t_{max} (h)	4.00 (3.00, 4.00)	3.00 (3.00, 4.00)	–
	$t_{1/2}$ (h)	7.51 (6.83, 8.73)	8.81 (6.98, 9.20)	0.0045[c]

[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 $t_{1/2}$.
AFI, aficamten; DE, dabigatran etexilate

Safety

- There were no deaths or SAEs reported across the 3 cohorts.
- There were no notable trends in the mean or individual participant clinical chemistry, hematology, or urinalysis data during the study across all 3 cohorts.
- In Cohorts 1 and 3, there were no TEAEs leading to discontinuation.
- In Cohort 2, there were 7 TEAEs reported by 4 (23.5%) participants leading to discontinuation (1 due to COVID, 2 due to elevated AST/ALT related to carbamazepine, and 1 with thrombocytopenia related to carbamazepine).
- All TEAEs across all 3 cohorts had resolved by the end of the study.

CONCLUSIONS

- CYP3A plays a minor role in the elimination of aficamten. The 26% increase in aficamten AUC_{inf} in the presence of itraconazole suggests CYP3A is responsible for only ~20% of aficamten elimination.
- Aficamten elimination can be induced by CAR- and/or PXR-mediated pathway(s).
- Aficamten is a weak inhibitor of P-gp.
- Single oral doses of 10 mg and 20 mg aficamten were safe and well tolerated by the healthy participants.
- Aficamten can be administered with CYP3A inhibitors and P-gp substrates.

Disclosures

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

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Abbreviations

ALT/AST, alanine/aspartate aminotransferases; AUC_{inf}, area under the serum concentration–time curve from 0 to infinity; AUC_{last}, area under the serum concentration–time curve from time 0 to the time of the last quantifiable concentration; BID, twice daily; CAR, constitutive androstane receptor; CARB, carbamazepine; CI, confidence interval; C_{max}, maximum serum concentration; CV, coefficient of variation; CYP3A, cytochrome P450, family 3, subfamily A; DAB, dabigatran; DE, dabigatran etexilate; GLSM, geometric least squares mean; ITR, itraconazole; LC-MS/MS, liquid chromatography with tandem mass spectrometry; LSM, least squares mean; MR_{AUCinf}, metabolite/parent ratio AUC_{inf}; P450, cytochrome P450; P-gp, P-glycoprotein; PK, pharmacokinetics; PXR, pregnane X receptor; Q, quartile; QD, once daily; SAE, serious adverse event; $t_{1/2}$, half life; TEAE, treatment-emergent adverse event; t_{max}, time of the maximum observed concentration

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