Clinical Evaluation of the Effect of Aficamten on QT/QTc Interval in Healthy Participants

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INTRODUCTION

- Aficamten is a next-in-class small molecule, selective cardiac myosin inhibitor (CMI) in development for treatment of hypertrophic cardiomyopathy (HCM).
- The potential of aficamten to prolong the corrected QT (QTc) interval was evaluated in nonclinical studies, including an in vitro human ether-à-go-go-related gene (hERG) assessment (IC_{50}>10 µM) and a telemetry study in dogs (no drug-related effects on electrocardiogram [ECG] parameters at tested doses).
- This study was conducted in accordance with ICH E14 guidance to evaluate the effect of aficamten on the QTc interval in healthy participants and thereby exclude a clinically concerning effect on QTc interval at therapeutic concentrations.
- Evaluation of aficamten doses >50 mg was limited by potential systolic dysfunction in healthy participants.
- The main circulating metabolites in plasma (CK-3834282 and CK-3834283; pharmacologically inactive) were also included in the cardiodynamic evaluation.

OBJECTIVES

Primary Objectives

- Dose determination for Part B (TQT study) using pharmacokinetics (PK) and safety data from Part A (dose-finding study).
- Evaluate the effect of a single oral dose of aficamten on the QTc interval in healthy participants.
- Evaluate PK of aficamten (and its metabolites CK-3834282 and CK-3834283) following a single oral dose in healthy participants.

Secondary Objectives

- Evaluate the effects of a single aficamten oral dose on other ECG parameters.
- Assess the safety and tolerability of a single oral dose of aficamten.

Exploratory Objective

- Evaluate the effect of aficamten metabolites CK-3834282 and CK-3834283 on the QTc interval in healthy participants following a single oral dose of aficamten.

METHODS

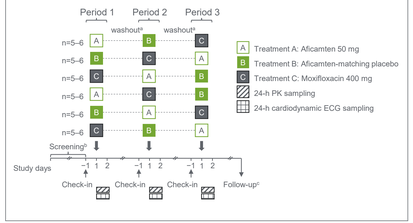
Study Design

- This was a phase 1, 2-part study in healthy participants.
  - Part A: dose-finding (n=10):
    - Open-label single-dose study to identify a dose for Part B (TQT study).
  - Part B: TQT study (n=34):
    - Randomized, double-blind, positive- and placebo-controlled single dose 3-way crossover study that minimizes potential decreases of LVEF <50% (**Figure 1**).

Study Endpoints

- PK parameters: area under concentration–time curve (AUC_{0-t}), maximum plasma concentration (C_{max}), and maximum time to plasma concentration (t_{max}), estimated using noncompartmental analysis.
  - Descriptive comparison of aficamten exposures with phase 3 (SEQUOIA-HCM, NCT05186818) PK data at steady state.
- Placebo-corrected change from baseline in QTc using Fridericia's correction (ddQTcF).
  - Primary analysis: Concentration-QTc interval (C-QT) evaluation using linear mixed-effects modeling.
    - Model components: Change from baseline QTcF (dQTcF) was used as the dependent variable, time-matched analyte plasma concentrations as explanatory variables, centered baseline QTcF as an additional covariate, and study treatment and time as fixed effects. A random intercept and slopes were reported per participant.
    - 5 C-QT models were explored: each analyte alone and a combination of the parent with each metabolite (aficamten + CK-3834282 and aficamten + CK-3834283).
    - Model with t-value <1.95 and the smallest Akaike information criterion (AIC) estimate were selected as the primary model.
    - Lack of QTc prolongation was concluded if the upper bound of the 2-sided 90% CI of least squares (LS) mean ddQTcF was <10 msec at the highest clinically relevant exposure (geometric mean C_{max}) of aficamten.
  - Secondary analysis: By time point:
    - Change in QTcF from baseline (central-tendency) between aficamten and placebo was estimated.
    - Aficamten was concluded not to prolong QTc interval if the upper bound of the 2-sided 90% CI of LS mean ddQTcF was <10 msec at all post-dose time points.

Figure 1: Study design



[a] There was a washout of ≥21 days between dosing in each period.
[b] Screening of study participants occurred within 28 days prior to first dosing.
[c] All participants who received ≥1 dose of study drug (including participants who terminated the study early) returned to the CRU 30 (± 2) days after the last dose for follow-up procedures, and to determine if any AE occurred since the last study visit.
AE=adverse event; CRU=clinical research unit; ECG=electrocardiogram; n=sample size; PK=pharmacokinetic(s).

- Assay sensitivity
  - Assessed based on C-QT analysis of moxifloxacin (positive control) using the same model as for the primary analysis of aficamten.
  - Assay sensitivity was established if the lower bounds of the 2-sided 90% CI of LS mean ddQTcF were >5 msec at the geometric mean C_{max} of moxifloxacin.
- Secondary ECG parameter analysis
  - Descriptive analysis: Change from baseline for QTc, QT, PR, RR, and QRS intervals and heart rate by treatment and time point.
  - Categorical analysis: Counts by treatment and time point for:
    - Absolute QTc interval: ≤450, >450, >480, and >500 msec.
    - Change from baseline in QTc interval: ≤30, >30, and >60 msec.
    - Other ECG parameters: PR, QRS, and heart rate.
  - Morphological analyses of ECG waveform.
- Safety and tolerability assessments
  - Treatment-emergent adverse events (TEAEs); changes in clinical laboratory tests, vital signs, and safety 12-lead ECGs; and left ventricular ejection fraction (LVEF) <50%.

RESULTS

Participants

- Baseline demographics of enrolled participants are provided in **Table 1**.
- All enrolled participants completed Part A, whereas 2 participants terminated early (before the start of period 3) in Part B.

Table 1: Summary of baseline demographics and clinical characteristics

Demographics	Part A (N=10)	Part B (N=34)
Sex (male / female), n	3 / 7	12 / 22
Age, mean (SD), y	32.8 (7.15)	35.3 (6.63)
BMI, mean (SD), kg/m^2	24.6 (2.74)	26.1 (2.65)
Race, n (%)		
Asian	1 (10)	2 (6)
Black or African American, Asian	1 (10)	9 (26)
White	8 (80)	22 (65)
White, Black or African American	0 (0)	1 (3)
Ethnicity, n (%)		
Hispanic or Latino	7 (70)	28 (82)
LVEF, mean (SD), %	66.2 (1.40)	67.0 (1.96)
BP (systolic / diastolic), mean (SD), mmHg	114 (16.6) / 69.4 (5.64)	114 (10.7) / 73.6 (9.00)

BMI=body mass index; SD=standard deviation.

Pharmacokinetics

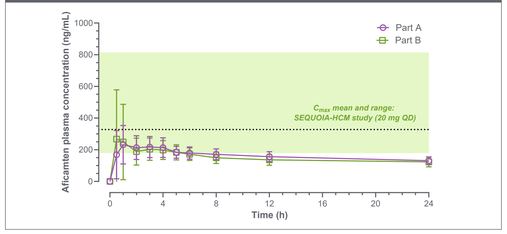
- Aficamten exposure in Part A was similar to that achieved following the highest planned clinical dose (20 mg once daily) in patients with obstructive HCM (oHCM; SEQUOIA-HCM) (**Table 2**); as such, the 50 mg dose was selected for Part B (TQT study).
- Aficamten PK was comparable between Parts A and B (**Table 2, Figure 2**).
- Moxifloxacin PK (C_{max} and AUC) was comparable to literature-reported values.[1]

Table 2: Comparison of exposures between TQT and SEQUOIA-HCM

Analyte	Part A (N=10)	Part B (N=33)	SEQUOIA-HCM[a] (N=68)
	C_{max}, ng/mL	C_{max}, ng/mL	C_{max} or $C_{2h\ postdose}$, ng/mL
Aficamten	310 (169, 448)	353 (124, 1660)	328 (179, 813)
CK-3834282	170 (52, 248)	136 (62.6, 213)	237 (31.6, 604)
CK-3834283	294 (106, 439)	228 (101, 343)	364 (60.4, 702)

Note: For Parts A and B, mean (min, max) C_{max} following aficamten 50 mg single dose are presented (N=33).
[a] For SEQUOIA-HCM, population PK-estimated mean (min, max) C_{max} at steady state for participants with aficamten 20 mg QD as the last titrated dose is presented for aficamten (N=65), while mean (min, max) $C_{2h\ postdose}$ observed for participants receiving aficamten 20 mg QD during the maintenance phase (Weeks 8–24) is presented for CK-3834282 and CK-3834283 (N=68).
C_{max}=maximum plasma concentration; $C_{2h\ postdose}$=concentration at 2 h post dose; max=maximum; min=minimum; PK=pharmacokinetic; QD=once daily.

Figure 2: Mean (SD) aficamten plasma concentrations following a single 50 mg dose in Parts A and B

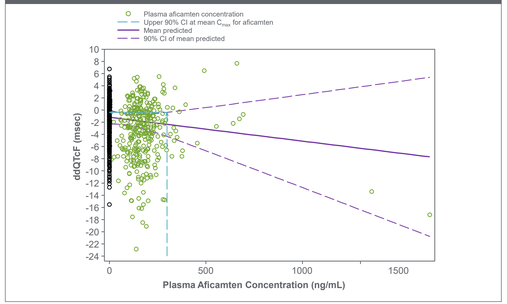


Mean (± SD) aficamten plasma concentrations following single 50 mg dose in Part A (N=10) and Part B (N=33) are presented.
The dotted line and green shaded portion depict the mean and range, respectively, of population PK-estimated C_{max} at steady state in participants treated with aficamten 20 mg QD as the last titrated dose (N=65) in SEQUOIA-HCM.
C_{max}=maximum plasma concentration; PK=pharmacokinetic; QD=once daily; SD=standard deviation.

Cardiodynamic Analysis

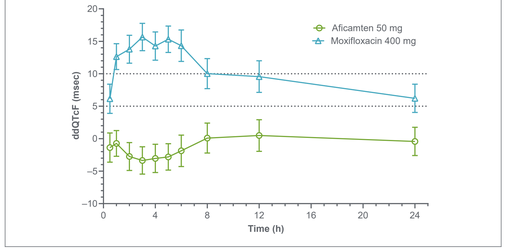
- All 5 C-QT models were comparable (t-value <1.95, similar AIC [range: 3966.7–4011.9]); as such, results for the aficamten alone model are presented in **Figure 3**.
- Aficamten did not cause QTc prolongation as the upper bounds of 2-sided 90% CI estimates were <10 msec using C-QT (up to 1660 ng/mL; **Figure 3**) and by time-point analysis.
  - Predicted ddQTcF of aficamten at its geometric mean C_{max} (298.3 ng/mL) was −1.82 msec (90% CI: −3.43, −0.214 msec).
  - Lack of QTcF prolongation was also noted for CK-3834282 (−1.74 msec [90% CI: −3.57, 0.088]) and CK-3834283 (−1.81 msec [90% CI: −3.76, 0.145].
- Assay sensitivity was established as the lower bound of the 2-sided 90% CI of ddQTcF for moxifloxacin was >5 msec using C-QT and by time-point analyses (**Figure 4**).
  - Predicted ddQTcF of moxifloxacin at its geometric mean C_{max} (2533 ng/mL) was 15.2 msec (90% CI: 14.3, 16.2 msec).
- Absolute QTcF and change from baseline in QTcF remained within normal limits (**Table 3**).
- No remarkable observations in mean values for heart rate, PR, and QRS parameters.
- No significant observations in the categorical or waveform analyses.

Figure 3: ddQTcF vs time-matched aficamten plasma concentrations using C-QT model



The solid and dashed purple lines denote model predicted mean ddQTcF and 90% CI, respectively, calculated as *ddQTcF = −1.1750 – 0.0039 × aficamten*.
The green and black circles denote time-matched observed plasma concentrations and estimated ddQTcF for aficamten and placebo, respectively.
C_{max}=maximum plasma concentration; ddQTcF=placebo-corrected change from baseline in QTc using Fridericia's correction.

Figure 4: Mean (90% CI) ddQTcF vs timepoint for aficamten and moxifloxacin



The dotted lines denote the regulatory threshold of concern applicable to aficamten (10 msec) and moxifloxacin (5 msec).
CI=confidence interval; ddQTcF=placebo-corrected change from baseline in QTc using Fridericia's correction.

Safety

- There were no deaths, serious adverse events, or discontinuation due to TEAEs.
- In Part A, 6 TEAEs of mild severity were reported by 1 (10%) participant following aficamten 50 mg single dose; there were no occurrences of LVEF <50%.
- In Part B, 44 TEAEs were reported by 18 (53%) participants, including 13 (39%) participants following aficamten 50 mg, 5 (15%) following placebo, and 7 (21%) following moxifloxacin 400 mg; most were of mild severity, except 5 events that were deemed to be of moderate severity.
  - The most common TEAE was decreased ejection fraction, reported in 6 (18%) and 1 (3%) of aficamten- and placebo-treated participants, respectively.
- 6 participants who received aficamten in Part B experienced asymptomatic occurrences of LVEF <50% (range 44–48%) after a 50 mg single dose; all returned to baseline value without any intervention.

Table 3: Cardiodynamic categorical summary by treatment

Parameter	Category	Treatment		
		Aficamten 50 mg (N=33)	Placebo (N=34)	Moxifloxacin 400 mg (N=33)
Absolute QTcF, n (%)	≤450 msec	32 (97.0)	33 (97.1)	30 (90.9)
	>450 msec	1 (3.0)	1 (2.9)	3 (9.1)
	>480 msec	0 (0)	0 (0)	0 (0)
	>500 msec	0 (0)	0 (0)	0 (0)
Change from baseline in QTcF, n (%)	≤30 msec	33 (100)	34 (100)	32 (97.0)
	>30 msec	0 (0)	0 (0)	1 (3.0)
	>60 msec	0 (0)	0 (0)	0 (0)

QTcF=corrected QT using Fridericia's correction.

CONCLUSIONS

- This was the first study to evaluate the effects of a CMI in healthy participants to categorically ascertain the impact on QT interval.
- Following 50 mg single dose, aficamten and its metabolites achieved generally comparable exposure to 20 mg once daily dosing in patients with obstructive HCM at steady state (SEQUOIA-HCM).
- Aficamten did not cause QTc prolongation as the upper bound of the 2-sided 90% CI estimates were <10 msec threshold using C-QT (up to aficamten concentration of 1660 ng/mL) and by time point analyses.
- Administration of aficamten at a dose of 50 mg was safe and well tolerated.

Reference

1. Avelox (moxifloxacin) prescribing information. Bayer Health Care; 2016.

Disclosures

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