No Increase in Arrhythmia Burden Following Aficamten Treatment in Obstructive Hypertrophic Cardiomyopathy: Extended Ambulatory Electrocardiogram Analysis From FOREST-HCM

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BACKGROUND

- Aficamten is a next-in-class cardiac myosin inhibitor that is approved for use by the FDA, the European Commission, and China and has been demonstrated to improve left ventricular outflow obstruction, exercise capacity, and symptoms in obstructive hypertrophic cardiomyopathy (oHCM).[1]
- The impact of aficamten on subclinical arrhythmia burden is unknown and of high importance given the frequency of atrial fibrillation (AF) and non-sustained ventricular tachycardia (NSVT) in oHCM.

PURPOSE

- Assess the frequency of subclinical AF, NSVT, and high-risk NSVT before and after aficamten treatment as detected by ambulatory electrocardiogram (ECG) monitoring.

METHODS

- Patients with oHCM enrolled in the open-label extension FOREST-HCM trial underwent a 4–7 day ambulatory ECG at screening and at Weeks 48 and 96 of aficamten treatment.
- Occurrences of the following arrhythmias were compared from screening to 48 and 96 weeks:
  - Clinically detected and recurrent AF.
  - Subclinical AF (new-onset AF lasting ≥30 seconds that were not otherwise detected clinically).
  - NSVT (>3 consecutive ventricular beats at rate ≥120 bpm for <30 seconds in duration and terminating spontaneously).
  - High-risk NSVT (≥8 beats, >200 bpm, or ≥2 runs in 48 hours).[2,3]
- A subgroup analysis of patients who underwent withdrawal of beta-blocker (BB) therapy was performed comparing the most recent ambulatory monitor while on BB with the subsequent monitor after withdrawal.

RESULTS

Atrial Fibrillation

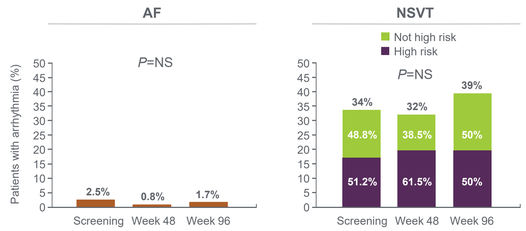
- In all, 122 patients with ≥24 h of interpretable ambulatory ECG data at screening, Week 48, and Week 96 were included.
- Mean age was 60.2 ± 13 years; maximum wall thickness was 20 ± 3.6; 19% of patients had prior implantable cardioverter defibrillator placement and 21% had prior clinical history of AF.
- Total ambulatory ECG monitoring duration was 1895 days; mean duration was 5.2 days per monitor per patient.
- Baseline rates of AF were low (2.5%) and there was no increase in AF episodes at Weeks 48 (0.8%; *P*=0.15) or 96 (1.7%; *P*=0.57) after aficamten initiation (**Table 1**, **Figures 1, 2**).
  - All episodes occurred in patients with prior clinical AF or history of AF.
  - There was 1 new clinical diagnosis of AF between baseline and Week 96 with subsequent AF detected on ambulatory monitoring. However, there was no newly identified subclinical AF based solely on ambulatory monitoring at 48 or 96 weeks.

Table 1: Change in AF from baseline to Week 96

Characteristic	Screening	Week 48	Week 96	*P* value	
				Week 0 vs 48	Week 0 vs 96
Duration, days	5.4 ± 1.4	4.9 ± 1.6	5.2 ± 1.4		
Atrial Fibrillation					
Presence	3 (2.5)	1 (0.8)	2 (1.7)	0.154	0.567
Average daily duration, hours	14.6 ± 11.8	24 (-)	21.9 ± 2.9	–	–

Data are presented as n (%) for categorical and mean ± SD for continuous data.
AF, atrial fibrillation.

Figure 1: Prevalence of AF and NSVT at screening and after 48 and 96 weeks of aficamten treatment



No difference in prevalence of AF at baseline (2.5%) vs Weeks 48 (0.8%) or 96 (1.7%) nor between high-risk (17.2% vs 19.7% vs 19.7%) or any NSVT (33.6%, 32%, 39.3%) at each timepoint.

AF, atrial fibrillation; NSVT, non-sustained ventricular tachycardia.

Non-Sustained Ventricular Tachycardia

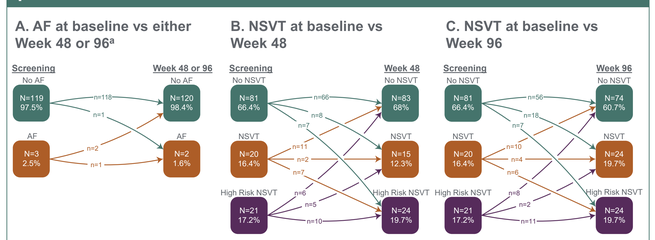
- NSVT was present at screening in 41 (33.6%), including 21 (17.2%) with high risk NSVT (**Table 2**).
  - Median of 0.4 runs/day (interquartile range 0.2–1.2).
  - Mean duration: 5.2 beats.
  - Median fastest NSVT rate per monitoring period: 143 bpm.
- After aficamten initiation, there was no increase in the proportion of patients with NSVT detected at Weeks 48 (32%, *P*=0.72) or 96 (39%, *P*=0.28) vs screening (**Table 2**, **Figure 2**).
  - There was no difference at Weeks 48 and 96 vs screening for NSVT in:
    - Number of runs/day (0.6 and 0.3 vs 0.4).
    - Average duration (6.6 and 5.3 vs 5.2 beats).
    - Median fastest speed (152 and 145 vs 143 bpm).
    - Proportion of patients with high-risk NSVT (19.7% each vs 17.2%).

Table 2: Change in NSVT from baseline to Week 96

Characteristic	Screening	Week 48	Week 96	*P* value	
				Week 0 vs 48	Week 0 vs 96
NSVT					
Presence	41 (33.6)	39 (32)	48 (39.3)	0.72	0.28
NSVT runs/day (in patients with NSVT)	0.4 [0.2–1.2]	0.6 [0.3–1.4]	0.3 [0.2–0.9]	0.512	0.627
Average length of NSVT runs per monitor, number of beats	5.2 ± 2.9	6.6 ± 6.3	5.3 ± 2.4	0.226	0.287
Rate of fastest NSVT run per monitor, bpm	143 [120–160]	152 [125–171]	145 [115–166]	0.568	0.302
Presence of high-risk NSVT	21 (17.2)	24 (19.7)	24 (19.7)	0.548	0.531

Data are presented as n (%) for categorical and mean ± SD or median [IQR] for continuous data.
IQR, interquartile range; NSVT, non-sustained ventricular tachycardia.

Figure 2. Arrythmias seen on ambulatory monitoring at screening as compared with Week 48 or 96 as proportion of cohort and on individual patient level



[a] All participants with AF on ambulatory ECG monitoring had a medical history of AF.
AF, atrial fibrillation; ECG, electrocardiogram; NVST, non-sustained ventricular tachycardia.

Beta-Blocker (BB) Discontinuation

- A subgroup of 16 patients from the overall cohort discontinued BB therapy during aficamten treatment.
  - Prior to BB withdrawal, 7 (43.8%) had NSVT.
  - After withdrawal 7 (43.8%) had NSVT (between group, *P*=non-significant).
- No AF was seen in these 16 patients before or after BB withdrawal

CONCLUSIONS

- This is the first prospective analysis of ambulatory ECG monitoring in patients treated with aficamten or other myosin inhibitors.
- In FOREST-HCM, the incidence of NSVT on ambulatory ECG monitoring was stable over time in patients with oHCM after 96 weeks of aficamten treatment compared with baseline.
- Prolonged arrythmia monitoring did not identify any new patients with subclinical AF, and showed no difference in AF incidence compared with baseline.
- There was no increase in frequency of arrhythmias after BB withdrawal.
- These data are consistent with the previously reported low incidence of clinically detected arrhythmias for patients with oHCM treated with aficamten.

References

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