AFICAMTEN FOR SYMPTOMATIC OBSTRUCTIVE HYPERTROPHIC CARDIOMYOPATHY

By VTH UNIT

CHIEF - PROF.DR.A.SENTHAMARAI M.D.,

ASSISTANT PROFESSOR,

DR.P.SUDHA M.D.,

DR.M.J.SENTHILKUMAR M.D.

DR.S.SUGADEV M.D.

The NEW ENGLAND JOURNAL of MEDICINE

ORIGINAL ARTICLE

Aficamten for Symptomatic Obstructive Hypertrophic Cardiomyopathy

M.S. Maron, A. Masri, M.E. Nassif, R. Barriales-Villa, M. Arad, N. Cardim, L. Choudhury, B. Claggett, C.J. Coats, H.-D. Düngen, P. Garcia-Pavia, A.A. Hagège, J.L. Januzzi, M.M.Y. Lee, G.D. Lewis, C.-S. Ma, M. Michels, I. Olivotto, A. Oreziak, A.T. Owens, J.A. Spertus, S.D. Solomon, J. Tfelt-Hansen, M. van Sinttruije, J. Veselka, H. Watkins, D.L. Jacoby, S.B. Heitner, S. Kupfer, F.I. Malik, L. Meng, A. Wohltman, and T.P. Abraham, for the SEQUOIA-HCM Investigators*

Published on May 13 2024

INTRODUCTION :-

- HCM is one of the most common genetic heart diseases.
- HCM is characterized by a thickened, nondilated left ventricle and often causes exertional dyspnea and reduced exercise capacity, which can impair quality of life.
- Left ventricular outflow tract obstruction, which results from contact of the mitral valve with the ventricular septum during systole, is one of the principal determinants of HCM-related complications and therefore is an important target for therapy.
- Aficamten is a reversible inhibitor of cardiac myosin that reduces left ventricular contractility by decreasing the number of active actin–myosin 2 cross-bridges within the sarcomere.

BACKGROUND :-

- The pathology behind the exercise intolerance in obstructive hypertrophic cardiomyopathy, is because of elevated intracardiac pressure.
- Elevated intracardiac pressure resulting from the left ventriclar outflow tract obstruction.
- Aficamten is an oral selective cardiac myosin inhibitor that reduces left ventricular outflow tract gradients by minimizing cardiac hypercontractility.

STUDY DESIGN :-

- Phase III double blinded
- Randomised
- Placebo controlled
- Total patients - 282
- Aficamten group – 142 patients

1. Minimum dose of aficamten – 5mg
2. Maximum dose aficamten – 20mg

- Placebo group – 140 patients
- Duration of study – 24 weeks

INCLUSION CRITERIA :-

- Age – 18 - 85 yrs
- NYHA class – class II or III
- cardiopulmonary exercise testing (treadmill or cycle ergometer).
- Left ventricular wall thickness – atleast 15 mm in the absence of pressure overload
- Ejection fraction – atleast 60%
- decreased exercise capacity - defined by a predicted peak oxygen uptake of 90% or less on the basis of age & sex.
- left ventricular outflow tract gradients :–

1. at least 30 mm Hg at rest
2. at least 50 mm Hg after the Valsalva maneuver.

EXCLUSION CRITERIA :-

- The most common reasons for exclusion from trial participation were an inadequately elevated left ventricular outflow tract gradient after the Valsalva maneuver (**or)**not meeting cardiopulmonary exercise testing criteria.

TRIAL PROCEDURE :-

- Eligible patients were randomly assigned in a 1:1 ratio to receive aficamten or placebo.
- Randomization was performed according to the use of beta-blockers (yes or no) and the method of cardiopulmonary exercise testing (treadmill or cycle ergometer).
- Oral aficamten or placebo was administered once daily for 24 weeks.
- At each visit, NT-proBNP levels echo was performed to assess the left ventricular outflow tract gradient at rest and after the Valsalva maneuver and the left ventricular ejection fraction.
- The starting dose of aficamten was 5 mg, with three subsequent opportunities (at weeks 2, 4, and 6) to increase the dose by 5-mg increments, to a maximum dose of 20 mg.

END POINT :-

- This study has three end points,
- **Primary end point**
- **Secondary end point**
- **Exploratory end point**

- **Primary end point**: is about peak oxygen uptake by cardiopulmonary exercise testing at wk 24 (ml/kg/hr) .
- **Exploratory end point**

Exploratory end point about geometric mean proportional change in NT-proBNP at wk 24

Secondary end point :-

1. KCCQ-CSS at wk 24
2. Improvement of ≥1 NYHA functional class at wk 24
3. Left ventricular outflow tract gradient after the Valsalva maneuver at wk 24
4. Left ventricular outflow tract gradient of <30 mm Hg after the Valsalva maneuver at wk 24
5. Total duration of septal reduction therapy eligibility during treatment period
6. KCCQ-CSS at wk 12 & Improvement of ≥1 NYHA functional class at wk 12
7. Left ventricular outflow tract gradient after the Valsalva maneuver at wk 12
8. Left ventricular outflow tract gradient of <30 mm Hg after the Valsalva maneuver at wk 12
9. Total workload during cardiopulmonary exercise testing at wk 24
10. Exploratory end point: geometric mean proportional change in NT-proBNP at wk 24

PEAK OXYGEN UPTAKE :-

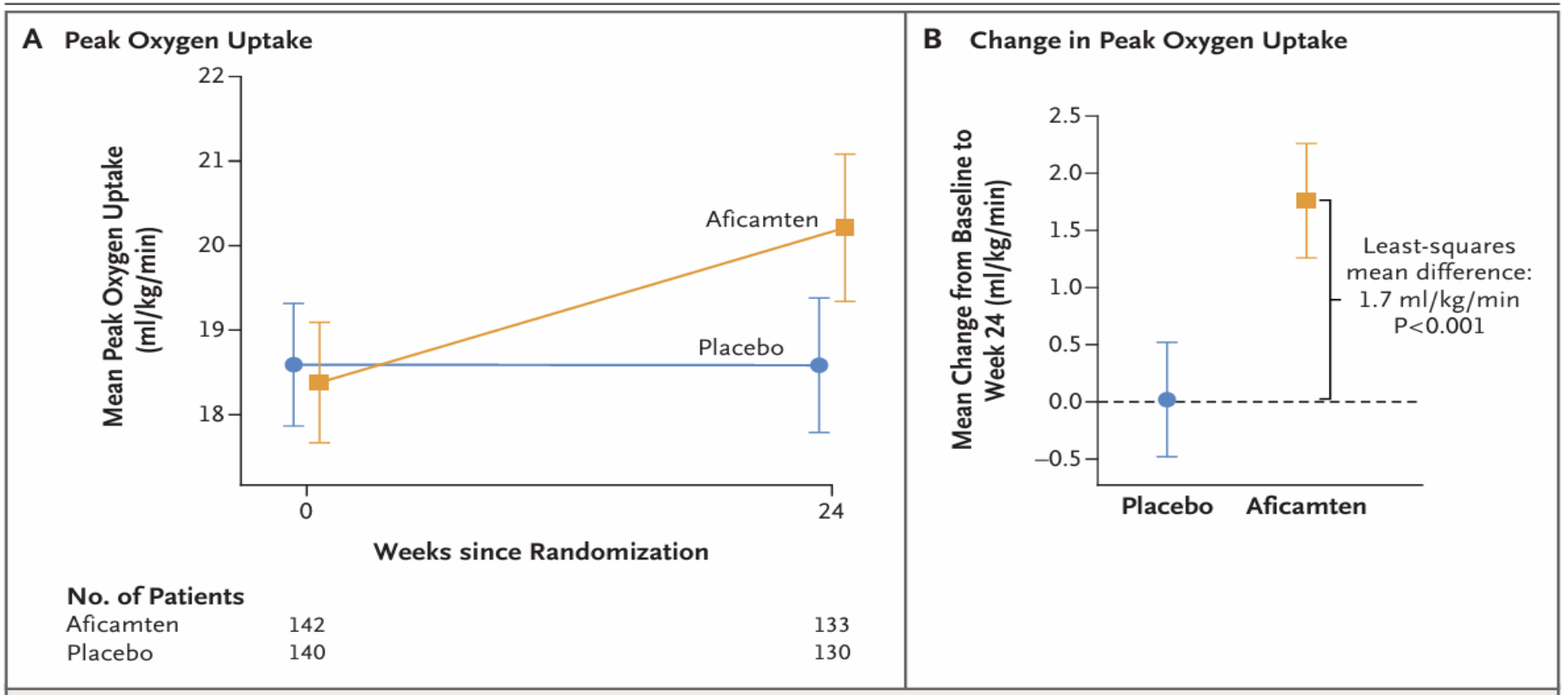


Figure 1. Changes in Exercise Capacity from Baseline to Week 24.

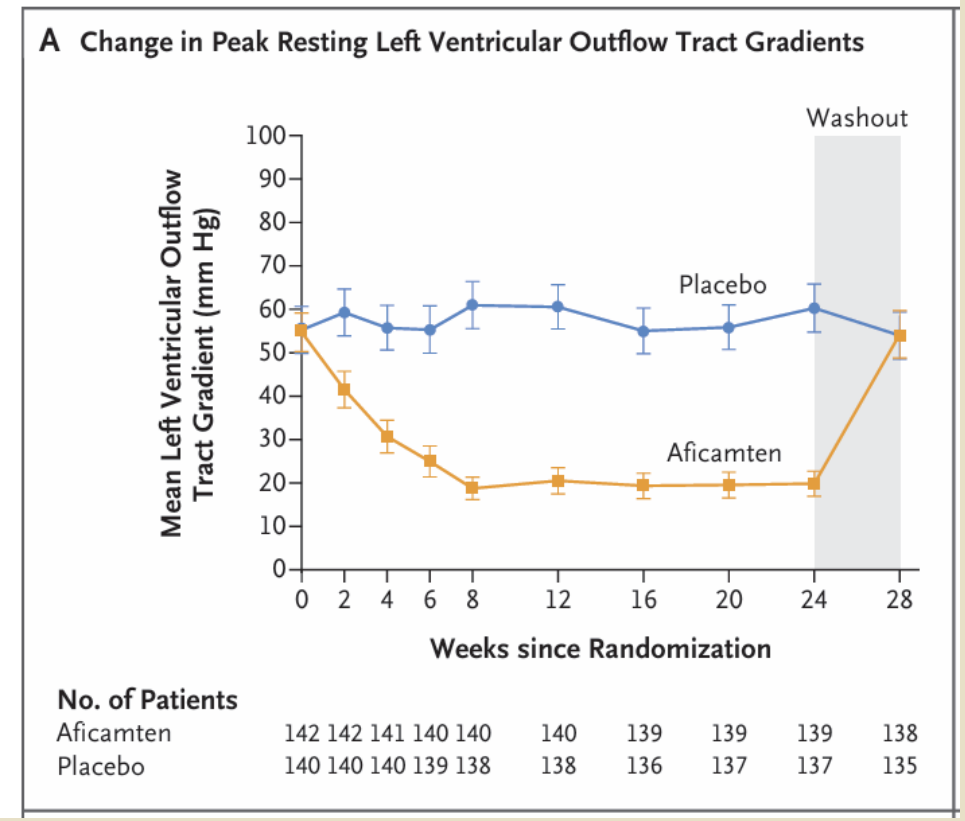
Panel A shows the mean peak oxygen uptake values at baseline and at week 24. Panel B shows the least-squares mean estimate of change in the peak oxygen uptake. I bars denote 95% confidence intervals.

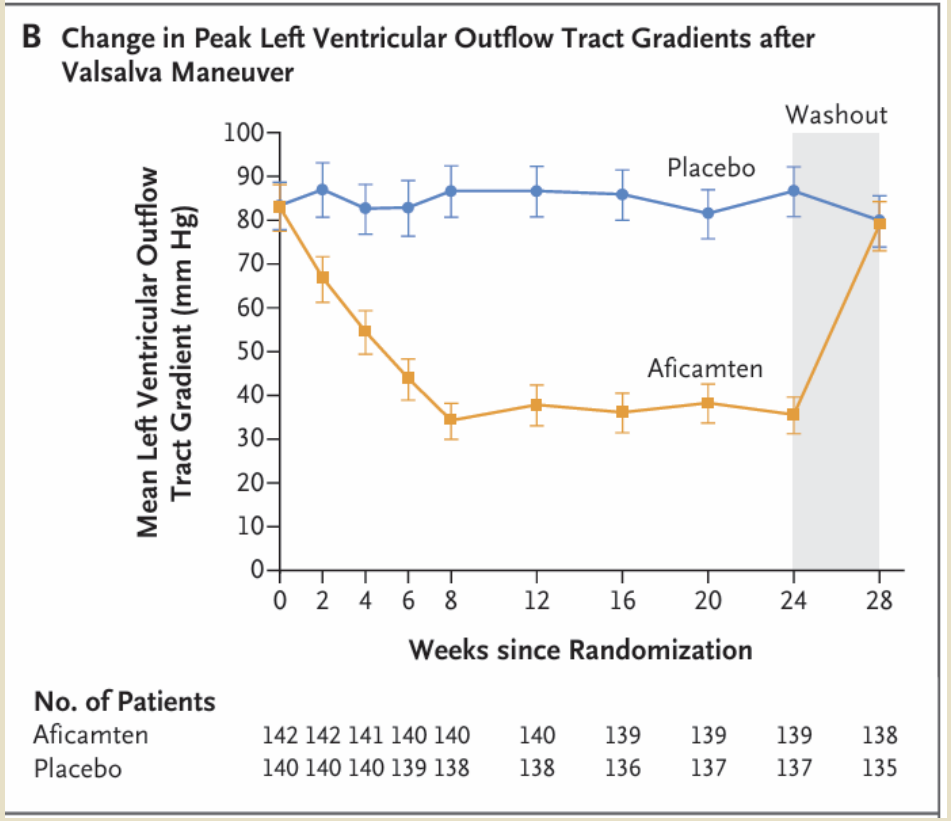
END POINT :-

Table 2. Primary, Secondary, and Exploratory End Points and Adverse Events.*

Variable	Aficamten (N=142)		Placebo (N=140)		Difference (95% CI)†	P Value
	Patients	Mean Change from Baseline (95% CI)	Patients	Mean Change from Baseline (95% CI)		
	no. (%)		*no. (%)*			
Primary end point: peak oxygen uptake by cardiopulmonary exercise testing at wk 24 — ml per kilogram per minute	133 (93.7)	1.8 (1.2 to 2.3)	130 (92.9)	0.0 (−0.5 to 0.5)	1.7 (1.0 to 2.4)	<0.001
Secondary end points						
KCCQ-CSS at wk 24	138 (97.2)	11 (9 to 14)	137 (97.9)	5 (3 to 7)	7 (5 to 10)	<0.001
Improvement of ≥1 NYHA functional class at wk 24	83 (58.5)	NA	34 (24.3)	NA	34.2 (23.4 to 45.0)	<0.001
Left ventricular outflow tract gradient after the Valsalva maneuver at wk 24 — mm Hg	137 (96.5)	−47.6 (−54 to −41)	134 (95.7)	1.8 (−4 to 8)	−50 (−57 to −44)	<0.001
Left ventricular outflow tract gradient of <30 mm Hg after the Valsalva maneuver at wk 24	70 (49.3)	NA	5 (3.6)	NA	45.7 (36.9 to 54.5)	<0.001
Total duration of septal reduction therapy eligibility during treatment period — days‡	32 (22.5)	36.5 (27.0 to 46.1)	29 (20.7)	114.2 (93.6 to 134.8)	−78 (−100 to −56)	<0.001
KCCQ-CSS at wk 12	140 (98.6)	11 (9 to 13)	136 (97.1)	5 (3 to 7)	7 (5 to 10)	<0.001
Improvement of ≥1 NYHA functional class at wk 12	69 (48.6)	NA	25 (17.9)	NA	30.8 (20.6 to 41.0)	<0.001
Left ventricular outflow tract gradient after the Valsalva maneuver at wk 12 — mm Hg	139 (97.9)	−44.8 (−51 to −39)	137 (97.9)	2.8 (−3 to 8)	−48 (−55 to −42)	<0.001
Left ventricular outflow tract gradient of <30 mm Hg after the Valsalva maneuver at wk 12	74 (52.1)	NA	8 (5.7)	NA	46.4 (37.3 to 55.5)	<0.001
Total workload during cardiopulmonary exercise testing at wk 24 — watts	134 (94.4)	14.1 (9.5 to 18.6)	129 (92.1)	1.4 (−2.3 to 5.1)	12.2 (6.4 to 18.0)	<0.001
Exploratory end point: geometric mean proportional change in NT-proBNP at wk 24§	133 (93.7)	0.20 (0.17 to 0.22)	133 (95.0)	1.00 (0.91 to 1.07)	0.20 (0.17 to 0.23)	—

SECONDARY END POINT :-





SECONDARY END POINT :-

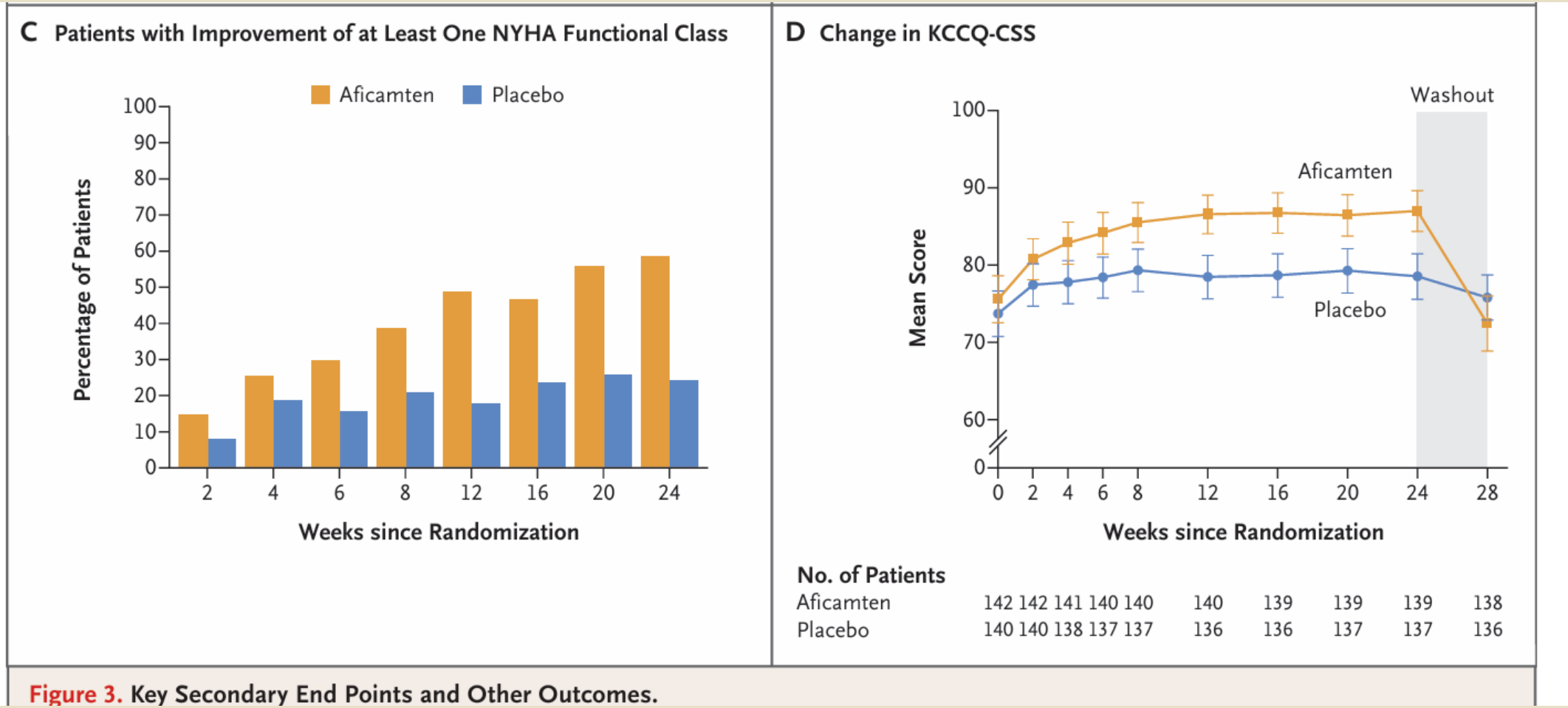


Figure 3. Key Secondary End Points and Other Outcomes.

SAFETY :-

- **Earlier discontinuation :-**

1. paranoia features in aficamten patient, resulted in early discontinuation of aficamten,
2. syncope & acute lymphocytic leukemia resulted in early discontinuation of placebo.

- **Temporary discontinuation :-**

1. acute cholecystitis in 1 patient in the aficamten group
2. bronchopneumonia & verrucous carcinoma removal in 1 patient each in the placebo group.

RESULT :-

- **PRIMARY END POINT :-**
- Increase in peak O2 uptake in aficamten group at 24 weeks – 1.8ml/kg/min
- Increase in peak O2 uptake in placebo group at 24 weeks – 0ml/kg/min.
- **SECONDARY END POINT :-**
- Improvement in patients NHYA class at 24 weeks occur in 58.5% of aficamten group & 24.3% in placebo group.
- NT-proBNP level at 24 weeks in aficamten group – 0.2
- NT-proBNP level at 24 weeks in placebo group – 1.0
- KCCQ-CSS at 24 weeks in aficamten group – 11
- KCCQ-CSS at 24 weeks in placebo group - 5

CONCLUSION :-

- Among patients with symptomatic obstructive HCM, treatment with aficamten resulted in a significantly greater improvement in peak oxygen uptake than placebo.
- The efficacy of aficamten was evident by week 12, with significantly greater improvements in left ventricular outflow tract gradients, health status, and symptoms.

DISCUSSION :-

- Aficamten was associated with other favorable outcomes, including a significantly greater improvement in limiting symptoms and a substantially greater reduction in the serum NT-proBNP level than placebo.
- The shorter half-life of aficamten enables more rapid dose escalation, which results in the ability to identify an effective dose within weeks, providing timely clinical benefit.
- the treatment effects of aficamten appeared to be similar with or without background betablocker use (WHICH IS NOT POSSIBLE IN MAVACAMTEM) and independent of the presence of a pathogenic sarcomere gene variant.
- In addition, no patient in the aficamten group who had a left ventricular ejection fraction of less than 50% had an interruption of treatment or an exacerbation of heart failure.

LIMITATION :-

- Limitations of this trial include the relatively short treatment period, precluding assessment of longer-term cardiovascular outcomes.
- The patients in the trial were from North America, Europe, Israel, and China.

THANK YOU.