IJBPAS, October, 2024, 13(10): 4981-4998

ISSN: 2277–4998

International Journal of Biology, Pharmacy and Allied Sciences (IJBPAS)

'A Bridge Between Laboratory and Reader'

www.ijbpas.com

MAVACAMTEN, A NOVEL DRUG FOR HYPERTROPHIC CARDIOMYOPATHY: REVIEW

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Received 24th July 2023; Revised 25th Sept. 2023; Accepted 17th Dec. 2023; Available online 1st Oct. 2024

https://doi.org/10.31032/IJBPAS/2024/13.10.8380

ABSTRACT

Introduction: Hypertrophic cardiomyopathy (HCM) is a common known monogenetic cardiovascular disorder which leads to dyspnea and exercise tolerance. Recent guidelines have different therapies. Hence, mavacamten is a small molecule modulator of beta cardiac myosin reduces hypercontractability which is the central mechanism of HCM. Hence, it is evaluated in phase 2 and 3 clinical trials for obstructive and non obstructive symptomatic HCM.

Purpose of Review: The pharmacological treatment for hypertrophic cardiomyopathy are limited and includes therapies such as beta blockers, non-dihydropyridine calcium channel blockers and disopyramide. They offer variable degree of symptomatic relief, suboptimal and are limited by side effects which addresses to molecular abnormalities of the disease.

Recent Finding: Mavacamten is novel, allosteric inhibitor of cardiac myosin ATPase, whichreduces actin-myosin cross bridge formation thus may reduce contractability and improves myocardialenergy consumption. The phase 2 and phase 3 demonstrates the efficacy and safety in reducing left ventricular outflow tract obstruction and exercise capacity in oHCM patients.

Summary: Mavacamten represent the first agent for HCM which is registered for clinical use, representing a change in paradigm in the pharmacological treatment of HCM. It is effective in obstructive HCM and non obstructive HCM.

Keywords: Hypertrophic cardiomyopathy, Mavacamten, Myosin, Left ventricular outflowobstruction, Therapy

INTRODUCTION:

Myocardial disorder which is characterized by hypertrophy of the left ventricle which may be due to any condition is called hypertrophic cardiomyopathy. It is a rare disorder. The prevalence is 1 in 200 in the

general population and is known as a monogenetic cardiovascular disorder **[1]**. One of the causes of HCM is autosomal inheritance. This includes genes with proteins like cardiac b-myosin heavy chain (MYH7) or myosin binding protein C3 (MYBPC3) **[2]**. This occurs without symptoms, then in higher stages, it may progress to symptoms like dyspnea and exercise. There are two types of HCM: they are obstructive hypertrophic cardiomyopathy and nonobstructive hypertrophic myopathy **[3]**.

Obstructive hypertrophic is most common around 70% and is defined as increased or frozen peak left ventricular outflow. This occurs when one or two of the mitral valve move during systolic pressure to increase blood flow in LVOT **[4]**. The treatment options start from lifestyle modification to pharmacological treatment. The pharmacological treatment includes beta blockers, calcium channel blockers, diuretics, etc. There are no guidelines for HCM treatment. They also include invasive management like surgical myectomy or trans-coronary alcohol septal ablation which is collectively calledseptal reduction therapy (SRT) **[5]**. This SRT is effective in symptomatical relief. Non-obstructive hypertrophic cardiomyopathy is around 30-40% and also needs more treatment management as it has nodisease-modifying therapy **[6]**.

Pharmacokinetics:

Mavacamten is the allosteric modulator of beta-cardiac myosin and also is a small molecule. This molecule is rapidly absorbed and distributed and has a long elimination phase. The mean elimination half-life is 8 days. The preclinical and clinical trials demonstrate decreased clearance, increased volume of distribution, long half-life, and excellent bioavailability **[7]**. Grillo *et al* studied the concentration-time profile from bolus IV administration which gives rapid distribution followed by the elimination phase which is by monoexponential decay. The clearance is low, where 2% is noted in dogs and 7-10% in mouse, rat, and monkey liver blood flow. It gave an increased volume of distribution and long t1/2 **[8]**. In oral administration the t1/2 is 4.8hrs. The maximum concentration is between 0.3-0.7 hrs, Cmax is 63ng/ml in monkeys and 564ng/ml in mice. Thus, they reported the mavacamten is well tolerated and safe. In PIONEER HCM, this drug decreases the concentration-dependent manner with a reduction in LVOT obstruction. In MAVERICK HCM, the mavacamten is discontinued as it decreases LVEF <45%. In

EXPLORER HCM also the patient is discontinued due to decreased LVEF **[9]**.

PHARMACODYNAMICS:

Enzymatic molecular motor, myosin is a cardiac sarcomere and it is a dimer. The myosin bond has adenosine triphosphate (ATP)ase hydrolyses the propel cyclical interaction with filament actin and the interaction is at sarcomere shortening less than 10% of myosin head are involved in contraction, and rest remains super relaxed in both domains which are inhibited and unable to bind or in adisordered state, thus energy consumption is optimized **[10]**. The HCM causes mutation acts as a doping form which may lead to increased interaction causing relaxation, hyperdynamic contraction, and increased energy consumption. The HCM is caused by mutation of one of the gene proteins: beta cardiac heavy chain and predominant myosin isoform **[11]**. More than 300 mutations in beta cardiac myosin heavy chain gene are known causes of HCM. These may lead to increased myosin lead. Half of the patients expand gene testing, a contraction. It also reduces contraction by decreasing the affinity. This helps in reverting the development of ventricular hypertrophy, cardiomyocyte disarray, and fibrosis **[12]**.

Efficacy:

In PIONEER HCM, 21 patients were enrolled, it was done in two sequential cohorts A and B for 12 weeks. In cohort A,

Safety and Tolerance:

Mavacamten is well tolerated and safe. In PIONEER HCM, this drug decreases LVEF in a concentration-dependent manner, with a reduction in LVOT obstruction occurring in plasma concentration between 350ng/ml and 695ng/ml. Higher plasma concentration was associated with an exaggerated decrease in LVEF, where 4 patients discontinued. However, in MAVERICK HCM, where 5 patients are discontinued. In EXPLORER HCM, where 9 patients discontinued **[12, 13]**. They have some adverse effect in PIONEER OLE, MAVERICK, and EXPLORER, which includes atrial fibrillation, ventricular tachycardia, angina pectoris, headache, dizziness, nausea, fatigue, rash, dyspnea, upper respiratory tract infection, urinary tract infection, and rash. Of these adverse effects, the frequency of adverse effects should be highlighted **[14]**. In PIONEER HCM, 4 patients were discontinued due to atrial fibrillation. In MAVERICK HCM, 2 patients were discontinued due to atrial fibrillation, and in EXPLORER HCM, 8 patients were discontinued due to atrial fibrillation **[15]**.

they could not be given background therapy and started a dose of 10mg/day. Incohort B, patients were given beta blockers at 2mg/day and increased to 5mg/day. The primary outcome was a change in post-exercise LVOT **[14-16]**. The secondary outcome was post-exercise LVOT, change in a numerical rating scale (NRS) dyspnea score, change in pVO and VE/VCO, change in resting and LVOT gradients, and change in resting LVEF. These changes are measured by scoring cohort A consisting of 11 patients with a mean intraventricular wall thickness of 1.7±0.2cm and NYHA class II-III. Cohort B consists of 10 patients with a mean intraventricular wall thickness of 2.5±0.2cm and NYHA class II-III. Background therapy consists of beta-blockers based on these results, mavacamten was evaluated in EXPLORER HCM **[16, 17]**.

The EXPLORER HCM had 251 patients whose plasma concentration was between 350- 700mg/ml. patients continued standard therapy with either beta-blockers or calcium channel blockers as amonotherapy. The primary endpoint is composed of either increase in pVO≥1.5ml/kg/min with a class NYHA class or an increase in pVO≥3.0ml/kg/min with no other class of NYHA. Secondary outcomes include the change in post-exercise of LVOT gradient and pVO ratio of patients with the improvement ofat least one NYHA class **[8, 18]**. Exploratory endpoints include serum concentration of NT proBPN and high-sensitivity cardiac troponin I. Thus the results gave effective, safe, and tolerated outcomes of mavacamten **[19]**. The different studies were conducted which is explained in **Table 1**.

Adverse effects:

In the PIONEER study, 99% of AE are mild or moderate which includes a decrease in LVEF, AF, ventricular tachycardia, angina pectoris, headache, dizziness, nausea, fatigue, rash, dyspnea, URTI, UTI, and rash. The serious AE is hospitalization and cardioversion due to AF which is due to discontinuation of the study drug **[27]**. In MAVERICK, 96% of AE are mild or moderate which includesAF, nausea, fatigue, dyspnea, IRTI, dizziness, palpitation, nasopharyngitis, constipation, abdominal distention, tooth abscess, and sinusitis **[28]**. They include 6 serious AE in 4 patients that include AF, systolic dysfunction, arthritis, mental status change, and renal failure. In EXPLORER, 8% of AE are noted which includes atrial fibrillation, syncope, stress, cardiomyopathy, diverticulitis, infection, confusion, and fracture **[29]**.

Ongoing Clinical Trial:

The ongoing studies include VALOR HCM and MAVALTE which enrolled patients from MAVERICK HCM, EXPLORER HCM, and PIONEER HCM. DISCOVER HCM, is a registry thathelps in assessing the safety and efficacy of symptomatic HCM. The different phases of mavacamten was given in **Table 2** and the ongoing studies are explained in **Table 3**.

Table 1: Efficacy of Mavacamten

STUDY NAME AND STATUS	MOLECULE	STUDY TYPE	POPULATION	PRIMARY ENDPOINT	SECONDARY ENDPOINT	REFERENCE
PIONEER- HCM STATUS: COMPLETED	MAVACAMTEN MYOKARDI A, INC	MULTI-CENTER, PHASE II OPEN- LABEL, NONRANDOMIZED. 2 SEQUENTIAL COHORTS (A AND B), EACH COMPRISING A 12- WEEK TREATMENTPHASE FOLLOWED BY A 4-WEEK POST-TREATMENT PHASE	21 OHCM, MEAN AGE IN COHORT A56 YEARS, MEAN AGE IN COHORT B58 YEARS, 57% MEN, 57% NYHA IIAND 43% NYHA III	IN COHORT A, MAVACAMTEN REDUCED MEAN POSTEXERCISE LVOT GRADIENT FROM 103 ±50 MMHG TO 19 ±13 MMHG AT 12WEEKS, (P = 0.008); IN COHORTB, LVOT GRADIENT DECREASED FROM 86 ±43 MMHG TO 64 ±26 MMHG (P= 0.020)	IN COHORT A, RESTING LVEF REDUCTION -15% (CI, -23% TO - 6%). PEAK VO2 INCREASED BY A MEAN OF 3.5 ML/KG/MIN (CI, 1.2 TO 5.9 ML/KG/MIN). IN COHORT B, MEAN CHANGE IN RESTING LVEFWAS -6% (CI, -10% TO -1%). PEAK VO2 INCREASED BY A MEAN OF 1.7 ML/KG/MIN (SD, 2.3) (CI, 0.03 TO 3.3 ML/KG/MIN). DYSPNEA SCORES IMPROVED IN BOTH COHORTS.	20
EXPLORER-HCM STATUS: COMPLETED	MAVACAMTEN MYOKARDI A, INC	MULTI-CENTER,PHASE III, RANDOMISED, DOUBLE-BLIND, PLACEBO- CONTROLLED	251 OHCM, MEAN AGE 58 ± 11 YEARS, 59% MEN	IMPROVEMENT IN SYMPTOM SEVERITY FROM BASELINE TOWEEK 30 ASSESSED BY NYHA FUNCTIONAL CLASS AND INCREASE IN EXERCISE CAPACITY FROM BASELINE TOWEEK 30 AS ASSESSED BY MEASUREMENT OF PVO 2 OF ≥1.5 ML/MIN/KG; OR NO WORSENING IN NYHA FUNCTIONAL CLASS AND INCREASE IN EXERCISE CAPACITY AS A PVO 2 OF ≥3.0 ML/MIN/KG	CHANGE IN POST-EXERCISE LVOT GRADIENT; NYHA CLASS;PVO 2 ; PATIENT-REPORTED OUTCOMES (KANSAS CITY CARDIOMYOPATHY)	21,22
MAVERIK- HCM STATUS: COMPLETED	MAVACAMTEN MYOKARDI A, INC	MULTI-CENTER,PHASE II, RANDOMIZED, DOUBLE-BLIND,PLACEBO-CONTROLLED	59 NON- OBSTRUCTIVE HCM, MEAN AGE 54 ± 14 YEARS, 58%WOMEN	SERIOUS ADVERSE EVENTS OCCURRED IN 10% OF MAVACAMTEN AND IN 21% OFPLACEBO GROUP. FIVE PARTICIPANTS ON MAVACAMTEN HAD REVERSIBLE REDUCTION INLVEF ≤45%.	NTPROBNP DECREASED BY 53% IN THE MAVACAMTEN GROUP VS1% IN THE PLACEBO GROUP, (P = 0.0005). TROPONIN I DECREASEDBY 34% IN THE MAVACAMTEN GROUP VS A 4% INCREASE IN THE PLACEBO, (P = 0.009).	23
VALOR-HCM STATUS: ON-GOING	MAVACAMT EN MYOKARDI A, INC	MULTI-CENTER, PHASE III, RANDOMIZED, DOUBLE-BLIND, PLACEBO- CONTROLLED	OHCM	NUMBER OF SUBJECTS WHO PROCEED OR REMAIN GUIDELINE ELIGIBLE FOR SRT WITHIN WEEK 16	NUMBER OF SUBJECTS WHO PROCEED OR REMAIN GUIDELINE ELIGIBLE FOR SRT WITHIN WEEK 32; CHANGE FROM BASELINE TO WEEK 16 IN NYHA, KCCQ-23, NTPROBNP, TROPONIN, LVOT GRADIENT	24
MAVA-LTE STATUS: ON-GOING	MAVACAMT EN MYOKARDI A, INC	MULTI-CENTER, PHASE III, RANDOMIZED	A LONG-TERM SAFETY EXTENSION STUDY OF MAVACAMTEN IN WHO HAVE COMPLETED THE MAVERICK-HCM OR EXPLORER-HCM TRIALS	FREQUENCY AND SEVERITY OF TREATMENT-EMERGENT ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS		25
REDWOOD-HCM STATUS: ON- GOING	CK-274 CYTOKINETI CS INC.	MULTI-CENTER, PHASE II, RANDOMIZED, PLACEBO-CONTROLLED, DOUBLE-BLIND	OHCM	SAFETY AND TOLERABILITY	CONCENTRATION-RESPONSE AND DOSE-RESPONSE ON THE RESTING AND POST-VALSALVA LVOT GRADIENT; EFFECT ON NTPROBNP AND NYHA.	26

Table 2: different Phase of Mavacamten

DRUG(S)	INDICATION	PHASE	STATUS	LOCATION	SPONSOR(S)	IDENTIFIER	REFERENCE
MAVACAMTEN, PLACEBO	SYMPTOMATIC OHCM	3	ACTIVE	USA	MYOKARDIA, INC.	NCT04349072; VALOR-HCM	30
MAVACAMTEN, PLACEBO	SYMPTOMATIC OHCM	3	ACTIVE	CHINA	LIANBIO	NCT05174416; EXPLORER-CN; CTR20212890	31
MAVACAMTEN, PLACEBO	SYMPTOMATIC OHCM	3	COMPLETED	GLOBAL	MYOKARDIA, INC.	NCT03470545; EXPLORER-HCM; EUDRACT 2017-002530-23	32
MAVACAMTEN	OHCM, NHCM	2 OR 3	ACTIVE	GLOBAL	MYOKARDIA, INC.	NCT03723655; MAVA-LTE; EUDRACT 2018-004039-64	33.34
MAVACAMTEN	SYMPTOMATIC OHCM	2	ACTIVE	USA	MYOKARDIA, INC.	NCT03496168; PIONEER-OLE	35
MAVACAMTEN	SYMPTOMATIC OHCM	2	COMPLETED	USA	MYOKARDIA, INC.	NCT02842242; PIONEER-HCM	36
MAVACAMTEN, PLACEBO	SYMPTOMATIC NHCM	2	COMPLETED	USA	MYOKARDIA, INC.	NCT03442764; MAVERICK-HCM	37
MAVACAMTEN	HF WITH PRESERVED EJECTION FRACTION	2	ACTIVE	USA	MYOKARDIA, INC.	NCT04766892; EMBARK-HFPEF	38

Table 3: Ongoing Studies

NCT NO.	POPULATION	CLINICAL STUDY	DRUG OR INTERVENTION	OUTCOME MEASURES	STATUS	REFERENCE
NCT03537183	80 HCM PATIENTS ≥ 18 YEARS	INTERVENTIONAL, RANDOMIZED, DOUBLE BLIND.	MODERATE INTENSITY EXERCISE TRAINING FOR 12 WEEKS (3 H A WEEK) VS. 12 WEEKS OF USUAL ACTIVITY LEVEL.	CHANGE FROM BASELINE TO FOLLOW-UP IN PCWP AT 25 W;PULMONARY CAPILLARY WEDGE PRESSURE;WORKLOAD ADJUSTED PULMONARY CAPILLARY WEDGE PRESSURE ;SYSTEMIC VASCULAR RESISTANCE, ARTERIO-VENOUS DIFFERENCE; CLINICAL PARAMETERS: EXERCISE CAPACITY, HEART RATE, BLOOD PRESSURE, CARDIAC INDEX,VO2 MAX	RECRUITING	39
NCT03335332	20 HCM PATIENTS ≥ 18 YEARS	INTERVENTIONAL, RANDOMIZED, SINGLE BLIND	HIGH INTENSITY EXERCISE VS. MODERATE INTENSITY EXERCISE	CARDIORESPIRATORY FITNESS; FUNCTIONAL DIASTOLIC RESERVE; SAFETY - NUMBER OF ADVERSE EVENTS; SAFETY - NUMBER OF ARRHYTHMIC EVENTS	RECRUITING	40
NCT03470545	220 HOCM PATIENTS ≥ 18 YEARS	INTERVENTIONAL, RANDOMIZED, QUADRUPLE BLIND. PHASE 3	MAVACAMTEN VS. PLACEBO	PERCENTAGE OF PARTICIPANTS ACHIEVING A CLINICAL RESPONSE (IMPROVEMENT IN NYHA FUNCTIONALAND IN PVO2 DETERMINED BY CPET FROM BASELINE TO WEEK 30)	RECRUITING COMPLETED	41
NCT01332162	80 HOCM PATIENTS ≥ 18 YEARS.	INTERVENTIONAL, RANDOMIZED, OPEN LABEL. PHASE 2	CRT-P OR CRT-D VS. NO PACING THERAPY DURING THE FIRST YEARAND LATER VS. PACING THERAPY AAI IN THE SECOND YEAR.	CHANGE FROM BASELINE IN LEFT VENTRICULAR MASS AND RESTING LEFT VENTRICULAR OUTFLOW TRACT GRADIENT; CHANGE FROM BASELINE IN CLINICAL EVALUATION OF NYHA, QOL,6MWT, INTERVENTRICULAR SEPTUM THICKNESS, POSTERIOR WALLTHICKNESS, PROVOKED LEFT VENTRICULAR OUTFLOW TRACT GRADIENT, MITRAL REGURGITATION GRADE	RECRUITING	42
NCT03953989	26 HCM PATIENTS AGE: 18–80 YEARSOLD	INTERVENTIONAL, OPEN LABEL. PHASE 2	RANOLAZINE PR (PROLONGED RELEASE)500 MG 1 TABLET BIS IN DIE AND 750 MG 1 TABLET BIS IN DIE.	MYOCARDIAL BLOOD FLOW DURINGHYPEREMIA; CORONARY FLOW RESERVE; CORONARY RESISTANCE;SYMPTOMS	RECRUITING	43

NCT03877731	**100 HOCM PATIENTS AGE:18–80 YEARS OLD**	**INTERVENTIONAL, RANDOMIZED, OPEN LABEL**	**ISOLATED SEPTAL MYECTOMY ; SEPTAL MYECTOMY + EDGE-TO-EDGE MITRAL VALVE REPAIR ; SEPTAL MYECTOMY + POSTERIOR LEAFLET SLIDING PLASTY ; SEPTAL MYECTOMY + SECONDARY CHORDAE TRANSECTION**	**EVENT-FREE SURVIVAL;RESIDUAL LEFT VENTRICULAR OUTFLOW TRACTGRADIENT; MITRAL REGURGITATION;PAPILLARY MUSCLES FUNCTION; MITRAL VALVE GEOMETRY**	**RECRUITING**	**44**
NCT03532802	**32 HCM PATIENTS ≥ 18 YEARS.**	**INTERVENTIONAL, RANDOMIZED, TRIPLE BLIND. PHASE 2**	**METOPROLOL SUCCINATE VS.PLACEBO**	**PULMONARY CAPILLARY WEDGE PRESSURE (REST-EXERCISE) ;VO2-MAX,CORONARY FLOW RESERVE, LVOT GRADIENT DURING MAXIMUM EXERCISE; NTPROBNP, CHANGES OF SYMPTOMS AND QUALITY OF LIFE WITH KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE**	**RECRUITING**	**45**
NCT03251287	**18 HCM PATIENTS AGE:18–80 YEARS OLD**	**INTERVENTIONAL, RANDOMIZED, QUADRUPLE BLIND. PHASE 1**	**SODIUM NITRATE VS. PLACEBO;DIAGNOSTIC TEST: 1ST VISIT PHOSPHOROUS MAGNETIC RESONANCE SPECTROSCOPY; DIAGNOSTIC TEST: 2ND VISIT**	**CARDIAC ENERGETIC STATUS; SKELETAL MUSCLE MITOCHONDRIALOXIDATIVE CAPACITY/ENERGETIC STATUS; CARDIAC DIASTOLIC AND SYSTOLIC FUNCTION ON EXERCISE**	**RECRUITING**	**46**
NCT03767855	**96 SYMPTOMATIC HOCM PATIENTS AGE: 18–55 YEARS.**	**INTERVENTIONAL, RANDOMIZED, TRIPLE BLIND. PHASE 1**	**EXERCISE STRESS ECHOCARDIOGRAM; CK-3773274 VS. PLACEBO**	**CARDIAC DIASTOLIC AND SYSTOLIC FUNCTION AT REST; PLASMA LEVELS OF NITRATE/NITRITE/NOX NCT03767855A SINGLE AND MULTIPLE ASCENDING DOSE STUDY OF CK-3773274 IN HEALTHY ADULT SUBJECTS. 96 SYMPTOMATIC HOCM PATIENTS AGE: 18–55 YEARS. INTERVENTIONAL, RANDOMIZED, TRIPLE BLIND. PHASE 1 CK-3773274 VS. PLACEBO ; INCIDENCE OF ADVERSE EVENTS AND SAFETY SIGNALS OBSERVED DURING SINGLE AND MULTIPLE ASCENDING DOSES OF CK-3773274 ADMINISTERED ORALLY TO HEALTHY ADULT SUBJECTS.; CMAXOF CK-3773274 AFTER SINGLE AND MULTIPLE ASCENDING DOSES; CHANGE IN ABSOLUTE REDUCTION IN EJECTION FRACTION RELATIVE TO BASELINE WITH DOSES OF CK-3773274; ASSESS THE EFFECT OF CYP2D6 GENETIC VARIANTS OF ON THE PK OF CK-3773274**	**RECRUITING**	**47**

NCT03450252	**25 HCM PATIENTS ≥ 18 YEARS**	**INTERVENTIONAL, RANDOMIZED, TRIPLE BLIND.**	**ACTIVE PACING VSBACK-UP PACING**	**INVASIVE GRADIENT (MMHG); SYMPTOMATIC ASSESSMENT VIA SF36 AND VIA KANSAS CITY CARDIOMYOPATHY QUESTIONNAIRE; SYMPTOMATIC ASSESSMENT VIA CALCULATION OF NYHA FUNCTIONAL CLASS; EXERCISE PERFORMANCE ASSESSED BY 6MWT; EXERCISE PERFORMANCE ASSESSED BY CPET STRESS ECHOCARDIOGRAPHY; LEVELSOF BRAIN NATRIURETIC PEPTIDE**	**RECRUITING**	**48**
NCT01912534	**211 HCM PATIENTS AGE:8–45 YEARS**	**INTERVENTIONAL, RANDOMIZED, TRIPLE BLIND. PHASE 2**	**VALSARTAN VS.PLACEBO**	**A COMBINED SINGLE COMPOSITE Z- SCORE AS PRIMARY SURROGATE ENDPOINT TO MONITOR RESPONSE TO VALSARTAN TREATMENT; IMPACT OF VALSARTAN ON DISEASE PATHOLOGY;CLINICAL OUTCOMES AND ASSESSMENT OF SYMPTOM BURDEN; INCIDENCE OF ADVERSE DRUG REACTIONS, FREQUENCY OF SUBJECT DROP-OUT, AND RESPONSES TO VALIDATED QUALITY OF LIFE METRICS BETWEEN VALSARTAN AND PLACEBO-TREATED GROUP.**	**ONGOING**	**49**
NCT01614717	**25 HOCM PATIENTS ≥ 18 YEARS**	**INTERVENTIONAL, RANDOMIZED, SINGLE BLIND**	**CRT-P IMPLANT**	**TO EVALUATE THE PERCENTAGE OF HOCM PATIENTS WITH SEVERE LVOTOBSTRUCTION IMPLANTED WITH A CRT-P DEVICE THAT HAVE SYMPTOMATIC IMPROVEMENT AT 12**	**ONGOING**	**50**
				MONTHS		
NCT03442764	**60 HCM PATIENTS ≥ 18 YEARS**	**INTERVENTIONAL, RANDOMIZED, QUADRUPLE BLIND. PHASE 2**	**MAVACAMTEN VS. PLACEBO**	**FREQUENCY AND SEVERITY OF TREATMENT-EMERGENT ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS.**	**ONGOING**	**51**

Future prospectives:

The mavacamten will have to demonstrate efficacy and safety in the real world, for OHCM patients. The long-term clinical benefit that demonstrates the disease. The important point is it isnot developed as a drug to treat obstruction but rather is a "magic bullet" which may target the abnormal function, energetic and structural remodeling of the heart and brings it to normal. The therapeutic strategy allosteric cardiac myosin may inhibit the different scenarios, to broaden the indications of HCM.This may include the pediatric onset of OHCM, non-obstructive HCM, and is selected with HF with preserved ejection fraction (HEpEF). Another selective allosteric myosin inhibitor has a different pharmacokinetic profile-CK274 and hence it is undergoing phase II clinical trial and increases the pharmacological armamentarium.

CONCLUSION:

EXPLORER HCM is used in myocardial disease. This targets the core molecular mechanism of disease, used in cardiovascular medicines and also witnessed in oncology over the past 10 yrs. The mavacamten demonstrated that it is technically feasible and may be economically sustained for the benefitof patients. Thus, it may truly be the end of the adequate pharmacological treatment of cardiomyopathies. Mavacamten, a direct myosin inhibitor, is a new class of therapeutic in clinical trials that may help in improving symptoms, and functional capacity and reduce LVOT obstruction with few SAE.

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