Transcript Details
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A Treatment for NYHA Class II-III Obstructive HCM Patients

ReachMD Announcer:
You're listening to ReachMD. This medical industry feature, titled "A Treatment for NYHA Class II-III Obstructive HCM Patients," is sponsored by Bristol Myers Squibb. This program is intended for U.S. healthcare professionals. Here's your host, Dr. Charles Turck.

Dr. Turck:
This is ReachMD, and I'm Dr. Charles Turck. Joining me to discuss an FDA-approved first-in-class cardiac myosin inhibitor for adult patients with New York Heart Association, or NYHA, class II-III obstructive hypertrophic cardiomyopathy, or HCM for short, is Dr. Amy Sehnert, who's the Vice President and Head of Cardiomyopathy and Heart Failure Clinical Development at Bristol Myers Squibb and a pediatric cardiologist. Dr. Sehnert, thanks for being here today.

Dr. Sehnert:
Thank you for having me.

Dr. Turck:
Dr. Sehnert, can you tell us a little bit more about this treatment option, called CAMZYOS, or mavacamten?

Dr. Sehnert:
Sure. For some background, HCM is a cardiovascular disease that causes thickening of the heart muscle and in some cases a blockage of blood flow from the heart, so-called 'obstruction'. HCM is a heterogeneous disease and can be a diagnostic challenge because the presentation is often variable, and the symptoms can be nonspecific and may develop very insidiously.[1]

CAMZYOS was developed as a disease-specific therapy and is the first and only cardiac myosin inhibitor approved in the U.S. and other countries, indicated for the treatment of adults with symptomatic NYHA class II-III obstructive HCM to improve functional capacity and symptoms.

Dr. Turck:
So before we continue, let's take a moment to review the indication and select safety information for CAMZYOS.

ReachMD Announcer:
CAMZYOS is indicated for the treatment of adults with symptomatic New York Heart Association (NYHA) class II–III obstructive hypertrophic cardiomyopathy (HCM) to improve functional capacity and symptoms. The full U.S. Prescribing Information for CAMZYOS includes a Boxed WARNING for the risk of heart failure. CAMZYOS reduces left ventricular ejection fraction (LVEF) and can cause heart failure due to systolic dysfunction. Echocardiogram assessments of LVEF are required prior to and during treatment with CAMZYOS. Initiation of CAMZYOS in patients with LVEF <55% is not recommended. Interrupt CAMZYOS if LVEF is <50% at any visit or if the patient experiences heart failure symptoms or worsening clinical status. Concomitant use of CAMZYOS with certain cytochrome P450 inhibitors or discontinuation of certain cytochrome P450 inducers may increase the risk of heart failure due to systolic dysfunction; therefore, the use of CAMZYOS is contraindicated with moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors, and moderate to strong CYP2C19 inducers or moderate to strong CYP3A4 inducers. Because of the risk of heart failure due to systolic dysfunction, CAMZYOS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CAMZYOS REMS PROGRAM. Please stay tuned to the end of this podcast for additional Important Safety Information including Boxed WARNING, and U.S. full prescribing information for CAMZYOS on this podcast web page.

Dr. Turck:
So, Dr. Sehnert, how does CAMZYOS work?

Dr. Sehnert:
In HCM, there is an over-activity of the proteins involved in contraction, that we refer to as hypercontractility. CAMZYOS is an allosteric and reversible inhibitor selective for one of those proteins called cardiac myosin. CAMZYOS modulates the number of myosin heads that can bind to actin and enter an "on actin" state. Excess myosin actin cross-bridge formation and dysregulation of the super-relaxed state are mechanistic hallmarks of HCM.[2] Thus, CAMZYOS reduces the probability of cross-bridge formation.

CAMZYOS shifts the overall myosin population towards an energy-sparing, recruitable, super-relaxed state. As a result, in obstructive HCM patients, myosin inhibition with CAMZYOS reduces dynamic left ventricular outflow tract obstruction, or LVOT, and improves cardiac filling pressures.[2]

Dr. Turck:
For those just joining us, this is ReachMD. I'm Dr. Charles Turk, and I'm speaking with Dr. Amy Sehnert about the treatment option CAMZYOS for adult patients with NYHA class II-III obstructive hypertrophic cardiomyopathy.

Now, Dr. Sehnert, what is the clinical trial data supporting CAMZYOS?

Dr. Sehnert:
So, there are data from two Phase 3 randomized-controlled trials that support CAMZYOS for symptomatic obstructive HCM.

The initial FDA approval, which was granted on April 28 in 2022, was based on the Phase 3 EXPLORER-HCM trial which met its primary composite functional endpoint in 251 adult patients with New York Heart Association class II and III obstructive HCM treated for 30 weeks with CAMZYOS versus placebo.[1]

Patients were on average 59 years old, who at baseline had left ventricular ejection fraction, or LVEF, of at least 55%, and at least one LVOT peak gradient greater than 50 millimeters of mercury at rest or with provocation.[2] Patients also had a Valsalva LVOT gradient great than or equal to 30 millimeters of mercury. 92% of patients in the trial were on background therapy with either a beta blocker or calcium channel blocker.[1] At baseline, 73% of the randomized patients were NYHA class II and 27% were NYHA class III.[2]

The primary composite functional endpoint assessed changes in both peak oxygen consumption, or pVO^2, determined by cardiopulmonary exercise testing and NYHA functional class. It was defined as either an improvement in pVO^2 of at least 1.5 milliliters per kilogram per minute and improvement of one or more NYHA class OR an improvement in pVO^2 by at least 3.0 milliliters per kilogram per minute and no worsening in NYHA class.[2]

37% of 123 patients in the CAMZYOS treatment arm met the primary composite functional endpoint, demonstrating significant benefit, compared to 17% of the 128 patients in the placebo arm. The difference was 19%, with a p-value of 0.0005.[2] A big takeaway from the EXPLORER-HCM trial was that 65% of patients on CAMZYOS improved by at least one NYHA class at week 30 compared to 31% of patients in the placebo group, which was a secondary endpoint of the trial.[2]

In terms of safety, adverse reactions that occurred in more than 5% of patients and more commonly in the CAMZYOS group than in the placebo group were dizziness in 27% vs 18% of patients, and syncope in 6% vs 2% of patients.[2]

Now more recently, on June 15 of 2023, the FDA approved BMS' supplemental New Drug Application. With this approval, positive data from the Phase 3 VALOR-HCM study, which is a randomized, double-blind, placebo-controlled, multicenter Phase 3 study that assessed the effect of CAMZYOS treatment in 112 adults with symptomatic, NYHA class II-III, obstructive HCM who met guideline eligibility criteria for septal reduction therapy, or SRT, and who had been referred or were under active consideration for this invasive procedure within the past 12 months, was added to the U.S. Prescribing Information for CAMZYOS.[2]

At baseline, patients were a mean of 60 years old, had at least one LVOT peak gradient greater than or equal to 50 millimeters of mercury at rest or with provocation, and LVEF of at least 60%. 93% of patients were greater than or equal to NYHA class III and 95% of patients were on background therapy of a beta blocker, calcium channel blocker, disopyramide, or a combination of these therapies.[2]

The primary composite functional endpoint was defined as the proportion of subjects who decided to proceed with SRT and those who remained SRT-guideline eligible at Week 16. SRT eligibility was defined as LVOT gradient greater than or equal to 50 millimeters of mercury and NYHA class III-IV or NYHA class II with history of exertional syncope or near syncope.[2]

After 16 weeks, 18% of CAMZYOS patients and 77% of placebo patients met guideline criteria for SRT or made a decision to proceed with SRT at or prior to Week 16. The difference was 59% with a p-value of less than 0.0001.[2]

The safety profile was similar to that seen in EXPLORER-HCM, and there were no new adverse reactions identified in VALOR-HCM. As a reminder, in EXPLORER-HCM, the adverse reactions occurring in at least 5% of patients and more commonly with CAMZYOS were dizziness in 27% of patients and syncope in 6% of patients.[2]

The data from this trial added to the label showed that treatment with CAMZYOS significantly reduced patient eligibility for SRT at Week 16 or the decision to proceed with SRT prior to or at Week 16, which was the primary composite endpoint of the study. This is an exciting milestone as CAMZYOS is now supported by safety and efficacy data from two Phase 3 trials in symptomatic obstructive HCM patients.[2]

We believe CAMZYOS is redefining the treatment landscape for symptomatic NYHA class II-III obstructive HCM. And we're excited to be able to offer this important option to appropriate patients and physicians.

Dr. Turck:
Thanks for sharing that with us, Dr. Sehnert. Also, I understand there's a REMS program in place for CAMZYOS. So can you tell our listeners more about this program?

Dr. Sehnert:
Sure. So the CAMZYOS REMS program has requirements in place for clinicians, patients, and pharmacies. Clinicians must be certified in the REMS program, which requires a one-time knowledge assessment, along with a review of the U.S. prescribing information and REMS program overview. The clinician is then responsible for ongoing patient education and timely submission of Patient Status Forms to support the appropriate dispensing of medication. The clinician must also assess patients' cardiovascular status, including measurement of LVEF and Valsalva LVOT gradient, using echocardiography before initiating and throughout treatment with CAMZYOS. It is also important to understand and screen for contraindications and drug interactions and pregnancy status, if applicable.[2]

In the U.S., CAMZYOS is available only from certified specialty pharmacies participating in the REMS Program.[2]

Now when it comes to patients, they must also enroll in the CAMZYOS REMS program to understand and comply with the ongoing echocardiogram monitoring requirements that are set forth by the dosing and administration algorithm that can be found in the Dosage and Administration section of the U.S. Full Prescribing Information.[2]

Patients also need to notify their clinicians about any changes in the medications they take in addition to CAMZYOS, including prescription and over-the-counter medicines, vitamins, and herbal supplements.[2]

Lastly, Bristol Myers Squibb offers various resources to help clinicians navigate the process of enrolling and participating in the CAMZYOS REMS program. These resources are available at www.camzyosrems.com.

Dr. Turck:
If one of our listeners who's a prescribing cardiologist is interested in getting an appropriate patient started on CAMZYOS, how should they proceed?

Dr. Sehnert:
Prescribing physicians can get their patients started in three steps. First, they need to enroll in the CAMZYOS REMS program that I just described.[2]

Second, they should educate their patients on the CAMZYOS REMS requirements and help them enroll in the program.[2]

Finally, physicians can prescribe CAMZYOS. In doing so, it's important to make sure that after you prescribe CAMZYOS you schedule follow-up visits with echocardiograms as outlined in the label and remind your patients of the importance of these appointments.[2]

Dr. Turck:
Well, it's great to know that there are resources available to help both patients and clinicians in the NYHA Class II-III obstructive HCM care journey. I want to thank my guest, Dr. Amy Sehnert, for helping us better understand the latest information in the treatment of obstructive HCM. Dr. Sehnert, it was great speaking with you today.

Dr. Sehnert:
You as well.

Dr. Turck:
I'm Dr. Charles Turck. Please stay tuned for some additional important safety information for CAMZYOS.

ReachMD Announcer:

INDICATION

CAMZYOS® (mavacamten) is indicated for the treatment of adults with symptomatic New York Heart Association (NYHA) class II-III obstructive hypertrophic cardiomyopathy (HCM) to improve functional capacity and symptoms.

IMPORTANT SAFETY INFORMATION

WARNING: RISK OF HEART FAILURE

CAMZYOS reduces left ventricular ejection fraction (LVEF) and can cause heart failure due to systolic dysfunction.

Echocardiogram assessments of LVEF are required prior to and during treatment with CAMZYOS. Initiation of CAMZYOS in patients with LVEF <55% is not recommended. Interrupt CAMZYOS if LVEF is <50% at any visit or if the patient experiences heart failure symptoms or worsening clinical status.

Concomitant use of CAMZYOS with certain cytochrome P450 inhibitors or discontinuation of certain cytochrome P450 inducers may increase the risk of heart failure due to systolic dysfunction; therefore, the use of CAMZYOS is contraindicated with the following:
Moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors
Moderate to strong CYP2C19 inducers or moderate to strong CYP3A4 inducers

Because of the risk of heart failure due to systolic dysfunction, CAMZYOS is available only through a restricted program under a Risk Evaluation and Mitigation Strategy (REMS) called the CAMZYOS REMS PROGRAM.

CONTRAINDICATIONS

CAMZYOS is contraindicated with concomitant use of:

- Moderate to strong CYP2C19 inhibitors or strong CYP3A4 inhibitors
- Moderate to strong CYP2C19 inducers or moderate to strong CYP3A4 inducers

WARNINGS AND PRECAUTIONS

Heart Failure
CAMZYOS reduces systolic contraction and can cause heart failure or totally block ventricular function. Patients who experience a serious intercurrent illness (e.g., serious infection) or arrhythmia (e.g., atrial fibrillation or other uncontrolled tachyarrhythmia) are at greater risk of developing systolic dysfunction and heart failure.

Assess the patient's clinical status and LVEF prior to and regularly during treatment and adjust the CAMZYOS dose accordingly. New or worsening arrhythmia, dyspnea, chest pain, fatigue, palpitations, leg edema, or elevations in N-terminal pro-B-type natriuretic peptide (NT-proBNP) may be signs and symptoms of heart failure and should also prompt an evaluation of cardiac function.

Asymptomatic LVEF reduction, intercurrent illnesses, and arrhythmias require additional dosing considerations.

Initiation of CAMZYOS in patients with LVEF <55% is not recommended. Avoid concomitant use of CAMZYOS in patients on disopyramide, ranolazine, verapamil with a beta blocker, or diltiazem with a beta blocker as these medications and combinations increase the risk of left ventricular systolic dysfunction and heart failure symptoms and clinical experience is limited.

CYP450 Drug Interactions Leading to Heart Failure or Loss of Effectiveness
CAMZYOS is primarily metabolized by CYP2C19 and CYP3A4 enzymes. Concomitant use of CAMZYOS and drugs that interact with these enzymes may lead to life-threatening drug interactions such as heart failure or loss of effectiveness.

Advise patients of the potential for drug interactions, including with over-the-counter medications (such as omeprazole, esomeprazole, or cimetidine). Advise patients to inform their healthcare provider of all concomitant products prior to and during CAMZYOS treatment.

CAMZYOS Risk Evaluation and Mitigation Strategy (REMS) Program
CAMZYOS is only available through a restricted program called the CAMZYOS REMS Program because of the risk of heart failure due to systolic dysfunction. Notable requirements of the CAMZYOS REMS Program include the following:

- Prescribers must be certified by enrolling in the REMS Program.
- Patients must enroll in the REMS Program and comply with ongoing monitoring requirements.
- Pharmacies must be certified by enrolling in the REMS Program and must only dispense to patients who are authorized to receive CAMZYOS.

- Wholesalers and distributors must only distribute to certified pharmacies.

Further information is available at www.CAMZYOSREMS.com or by telephone at 1-833-628-7367.

Embryo-Fetal Toxicity
CAMZYOS may cause fetal toxicity when administered to a pregnant female, based on animal studies. Confirm absence of pregnancy in females of reproductive potential prior to treatment and advise patients to use effective contraception during treatment with CAMZYOS and for 4 months after the last dose. CAMZYOS may reduce the effectiveness of combined hormonal contraceptives (CHCs). Advise patients using CHCs to use an alternative contraceptive method that is not affected by CYP450 enzyme induction or to add nonhormonal contraception. Advise females of reproductive potential about the potential risk to the fetus with maternal exposure to CAMZYOS during pregnancy.

ADVERSE REACTIONS

In the EXPLORER-HCM trial, adverse reactions occurring in >5% of patients and more commonly in the CAMZYOS group than in the placebo group were dizziness (27% vs 18%) and syncope (6% vs 2%). There were no new adverse reactions identified in VALOR-HCM.

Effects on Systolic Function
In the EXPLORER-HCM trial, mean (SD) resting LVEF was 74% (6) at baseline in both treatment groups. Mean (SD) absolute change from baseline in LVEF was -4% (8) in the CAMZYOS group and 0% (7) in the placebo group over the 30-week treatment period. At Week 38, following an 8-week interruption of trial drug, mean LVEF was similar to baseline for both treatment groups. In the EXPLORER-HCM trial, 7 (6%) patients in the CAMZYOS group and 2 (2%) patients in the placebo group experienced reversible reductions in LVEF <50% (median 48%: range 35-49%) while on treatment. In all 7 patients treated with CAMZYOS, LVEF recovered following interruption of CAMZYOS.

DRUG INTERACTIONS

Potential for Other Drugs to Affect Plasma Concentrations of CAMZYOS
CAMZYOS is primarily metabolized by CYP2C19 and to a lesser extent by CYP3A4 and CYP2C9. Inducers and inhibitors of CYP2C19 and moderate to strong inhibitors or inducers of CYP3A4 may affect the exposures of CAMZYOS.

Impact of Other Drugs on CAMZYOS:

- Moderate to Strong CYP2C19 Inhibitors or Strong CYP3A4 Inhibitors: Concomitant use increases CAMZYOS exposure, which may increase the risk of heart failure due to systolic dysfunction. Concomitant use is contraindicated.
- Moderate to Strong CYP2C19 Inducers or Moderate to Strong CYP3A4 Inducers: Concomitant use decreases CAMZYOS exposure, which may reduce CAMZYOS' efficacy. The risk of heart failure due to systolic dysfunction may increase with discontinuation of these inducers as the levels of induced enzyme normalizes. Concomitant use is contraindicated.
- Weak CYP2C19 Inhibitors or Moderate CYP3A4 Inhibitors: Concomitant use with a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor increases CAMZYOS exposure, which may increase the risk of adverse drug reactions. Initiate CAMZYOS at the recommended starting dose of 5 mg orally once daily in patients who are on stable therapy with a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor. Reduce dose of CAMZYOS by one level (i.e., 15 to 10 mg, 10 to 5 mg, or 5 to 2.5 mg) in patients who are on CAMZYOS treatment and intend to initiate a weak CYP2C19 inhibitor or a moderate CYP3A4 inhibitor. Schedule clinical and echocardiographic assessment 4 weeks after inhibitor initiation, and do not up-titrate CAMZYOS until 12 weeks after inhibitor initiation. Avoid initiation of concomitant weak CYP2C19 and moderate CYP3A4 inhibitors in patients who are on stable treatment with 2.5 mg of CAMZYOS because a lower dose is not available.

Potential for CAMZYOS to Affect Plasma Concentrations of Other Drugs
CAMZYOS is an inducer of CYP3A4, CYP2C9, and CYP2C19. Concomitant use with CYP3A4, CYP2C19, or CYP2C9 substrates may reduce plasma concentration of these drugs. Closely monitor when CAMZYOS is used in combination with CYP3A4, CYP2C19, or CYP2C9 substrates where decreases in the plasma concentration of these drugs may reduce their activity.

Hormonal Contraceptives: Progestin and ethinyl estradiol are CYP3A4 substrates. Concomitant use of CAMZYOS may decrease exposures of ethinyl estradiol and progestin, which may lead to contraceptive failure or an increase in breakthrough bleeding. Advise patients to use a contraceptive method that is not affected by CYP450 enzyme induction (e.g., intrauterine system) or add nonhormonal contraception (such as condoms) during concomitant use and for 4 months after the last dose of CAMZYOS.

Drugs That Reduce Cardiac Contractility

Expect additive negative inotropic effects of CAMZYOS and other drugs that reduce cardiac contractility. Avoid concomitant use of CAMZYOS in patients on disopyramide, ranolazine, verapamil with a beta blocker, or diltiazem with a beta blocker as these medications and combinations increase the risk of left ventricular systolic dysfunction and heart failure symptoms and clinical experience is limited.

If concomitant therapy with a negative inotrope is initiated, or if the dose of a negative inotrope is increased, monitor LVEF closely until stable doses and clinical response have been achieved.

SPECIFIC POPULATIONS

Pregnancy
CAMZYOS may cause fetal harm when administered to a pregnant female. Advise pregnant females about the potential risk to the fetus with maternal exposure to CAMZYOS during pregnancy. There is a pregnancy safety study for CAMZYOS. If CAMZYOS is administered during pregnancy, or if a patient becomes pregnant while receiving CAMZYOS or within 4 months after the last dose of CAMZYOS, healthcare providers should report CAMZYOS exposure by contacting Bristol Myers Squibb at 1-800-721-5072 or www.bms.com.

Lactation
The presence of CAMZYOS in human or animal milk, the drug's effects on the breastfed infant, or the effects on milk production are unknown. The developmental and health benefits of breastfeeding should be considered along with the mother's clinical need for CAMZYOS and any potential adverse effects on the breastfed child from CAMZYOS or from the underlying maternal condition.

Females and Males of Reproductive Potential
Confirm absence of pregnancy in females of reproductive potential prior to initiation of CAMZYOS. Advise females of reproductive potential to use effective contraception during treatment with CAMZYOS and for 4 months after the last dose. Use of CAMZYOS may reduce the effectiveness of CHCs. Advise patients using CHCs to use an alternative contraceptive method or add nonhormonal contraception.

Please see US Full Prescribing Information, including Boxed WARNING, in the additional content on this page.

ReachMD Announcer:
This program was sponsored by Bristol Myers Squibb. If you missed any part of this discussion, visit ReachMD.com/industryfeature. This is ReachMD. Be Part of the Knowledge.

References:

1. Ommen SR, Mital S, Burke MA, et al. 2020 AHA/ACC Guideline for the Diagnosis and Treatment of Patients With Hypertrophic Cardiomyopathy: A Report of the American College of Cardiology/American Heart Association Joint Committee on Clinical Practice Guidelines. *Circulation*. 2020;142(25):e558-e631.
2. CAMZYOS [package insert]. Princeton, NJ: Bristol-Myers Squibb Company; 2023.
3. Desai MY, Owens A, Geske JB, et al. Myosin Inhibition in Patients With Obstructive Hypertrophic Cardiomyopathy Referred for Septal Reduction Therapy. *J Am Coll Cardiol*. 2022;80(2):95-108.