**Introduction**

Hypertrophic cardiomyopathy (HCM), the most prevalent genetic heart disease, arises from cardiac sarcomere gene variants, resulting in left ventricular hypertrophy (LVH) and myocardial fibrosis. The causes behind its progression remain unclear. Prior studies indicate angiotensin II receptor blockers (ARBs), such as losartan and valsartan, could curb HCM's advancement, particularly when administered early. Despite neutral results from a losartan trial in mid-age adults with HCM, the Valsartan for Attenuating Disease Evolution in Early Sarcomeric HCM (VANISH) trial demonstrated ARB valsartan's potential in mitigating phenotypic progression in young, early-stage HCM patients. In our research, we examine preclinical HCM patients – sarcomere variant carriers without LVH – from a parallel VANISH cohort. We aim to observe short-term disease progression and potential valsartan effects, informing strategies to prevent preclinical HCM's evolution to an overt disease state.

**Methods**

*Design*

The VANISH trial was a multicenter, double-blind, randomized clinical trial investigating the effect of 2-year valsartan treatment on asymptomatic sarcomere variant carriers. It included two parallel cohorts: primary (early-stage HCM) and exploratory (preclinical stage without LVH).

*Participants*

Preclinical HCM cohort participants were 10-25 years old, carrying a sarcomere gene variant associated with HCM, and exhibited early phenotypic manifestations.

*Trial procedures*

Following a 2-6 week active run-in period for valsartan titration, participants were randomized to valsartan or placebo. Study visits were conducted at baseline, 1 and 2 years.

*Trial outcomes*

Treatment effect was assessed using a primary composite outcome z-score, integrating nine biological components of cardiac structure and function. Progression to developing LVH and overt HCM was analyzed to identify transition predictors.

*Statistical Analyses*

Analysis involved a mixed linear regression model, and standardized differences were used for baseline characteristic comparisons. Post-hoc simulations were performed to estimate future trial sizes under three scenarios.

*Ethics*

The trial was NIH-funded, overseen by an independent Data Safety Monitoring Board, and approved by ethics committees at all sites. Novartis Pharmaceutical Corporation donated study medications but was uninvolved in design, analyses, or publication decisions. For more on statistical analyses, see Supplementary Methods S1.

**Results**

*Baseline Characteristics*

In the VANISH trial conducted from 2014 to 2019, 212 subjects from 17 sites across four countries participated. Of these, 34 were preclinical hypertrophic cardiomyopathy (HCM) patients, randomized into two groups: placebo (16 subjects) and valsartan (18 subjects). The study was completed by all preclinical HCM subjects. The treatment groups were comparably matched, except for minor differences in left atrial (LA) volume and detectable troponin T concentrations, both of which were higher in the valsartan group.

*Exploratory Trial Outcomes*

No significant differences were observed between the valsartan and placebo groups in terms of phenotypic progression. The primary composite outcome showed no substantial difference between the two groups. Post-hoc simulations estimated this exploratory trial had 30% power if the effect seen in the early-stage HCM cohort had been replicated. Valsartan treatment was safe and well-tolerated, with no significant change in blood pressure and no instances of hyperkalemia or renal insufficiency.

*Natural History of Preclinical HCM*

All 34 participants were combined for analysis to characterize the natural history of preclinical HCM, as no apparent treatment effect was identified. Overall, metrics remained relatively static over 2 years, with modest progression seen only in LA volume index. Lower baseline LV ejection fraction and larger LV end-systolic volume, maximal LVWT, and LVWT to LV cavity diameter ratio were associated with more phenotypic progression.

*Natural History of Preclinical vs Early-Stage HCM*

Comparing preclinical HCM participants to the early-stage HCM cohort showed less phenotypic progression over 2-years in preclinical participants. However, phenotypic progression was more pronounced in early-stage HCM, which appeared to be attenuated by valsartan administration in patients with early disease.

*Transition from Preclinical HCM to Developing LVH and Clinically Overt HCM*

During the 2-year trial period, 9 preclinical HCM participants developed left ventricular hypertrophy (LVH), with 6 transitioning to clinically overt HCM. Participants who developed LVH had larger body size, higher diastolic blood pressure, larger indexed LA volumes, and greater septal wall thickness.

*Estimation of Cohort Sizes Needed for Future Trials of Disease Modification*

Computer simulations were performed to determine sample size requirements for future trials. The simulations covered three scenarios, and depending on the assumed treatment effect and rate of phenotypic progression, estimated that sample sizes of 130 to over 500 would be needed to achieve 80% power.

**Discussion:**

During the two-year study, preclinical Hypertrophic Cardiomyopathy (HCM) sarcomere variant carriers exhibited minimal phenotypic progression, complicating the assessment of valsartan's impact on cardiac remodeling. Post-hoc simulations suggested a substantial sample size of 220-500 preclinical HCM participants would be needed to match the power of the early-stage HCM cohort. Despite limited short-term phenotypic progression, nine participants unexpectedly exhibited increased left ventricular wall thickness (LVWT), six transitioning to overt HCM. Greater baseline left atrial volume and LV wall thickness were associated with phenotypic evolution and disease development.

In this preclinical HCM cohort, phenotypic progression was slow, with the rate of cardiac remodeling significantly lower than early-stage HCM. Markers of cardiac remodeling remained relatively static, except for the indexed left atrial volume showing a slight increase, potentially an early disease progression indicator. In the early-stage HCM cohort, valsartan seemed to slow phenotypic progression, evidenced by an improved composite z-score. Preliminary analyses highlighted that preclinical HCM participants receiving placebo had less cardiac remodeling than early-stage HCM on placebo. Conversely, valsartan-treated early-stage and preclinical HCM participants showed similar cardiac remodeling levels, indicating valsartan might stabilize and slow early-stage HCM phenotypic progression.

The small preclinical HCM cohort and minimal phenotypic progression challenge the identification of a valsartan treatment response. Simulations suggested over 500 patients would be required to achieve adequate power, indicating that future trials will require larger participant numbers, longer follow-ups, and more responsive outcome measures to identify possible therapeutic effects. Detecting disease progression in the earliest stages is critical for disease prevention trials to be feasible, as overt disease progression takes years to manifest.

Despite slow overall phenotypic progression, 26% of preclinical HCM participants developed LVH during the study, with 18% transitioning to clinically overt HCM. This conversion rate, unaffected by valsartan, was more than double the rate previously reported in long-term family screening clinics. This discrepancy could be due to the VANISH trial's prospective nature and the preclinical cohort's slightly older age. Indexed left atrial volume, LV wall thickness to diameter ratio, and LV wall thickness showed promise as early markers of LVH and HCM development.

This exploratory trial was underpowered to detect a moderate to large treatment response, with the number of participants, follow-up duration, and slow phenotypic progression in the preclinical stage posing challenges to identifying valsartan's therapeutic impact. Precise metrics are required to accurately assess phenotypic progression. In conclusion, preclinical HCM showed minimal progression over two years, and no impact of valsartan on cardiac remodeling was observed in this small, exploratory cohort. This study underscores the need for better understanding of disease transition, longitudinal follow-up of at-risk sarcomere variant carriers, and more dynamic metrics to monitor phenotypic progression or response to treatments. These findings reinforce the importance of monitoring genetically susceptible individuals for HCM emergence.