Case Study

Navigating complexity in Phase III HOCM clinical trial

Background:

Hypertrophic cardiomyopathy (HCM) is the most common genetic heart disease in the US, with an estimated prevalence of 1 in 500. HCM is a chronic, progressive disease which over time results in tissue remodeling characterized histologically by myocyte hypertrophy and disarray, microvascular remodeling, and fibrosis. Two HCM types are obstructive HCM (oHCM or HOCM) and non-obstructive HCM that are recognized based on the presence or absence of obstruction of the left ventricular outflow tract (LVOT).

The role of imaging in HOCM

Various imaging modalities can be used to assess cardiac structure and function, the presence and severity of LVOT obstruction and tissue characteristics. Transthoracic echocardiography and cardiac MRI (CMR) remain the imaging modalities of choice in the diagnosis and clinical management of HOCM. In clinical trials, echocardiography and CMR can support eligibility criteria and efficacy endpoints.

Key Highlights:

Phase 3 trial for HOCM treatment

15 sites

Subjects:

130 screened

81 enrolled

Imaging supported screening and endpoint assessment:

Echocardiography

Cardiac MRI

Streamlined reviewer workflows minimized reader variability

Close collaboration throughout trial

Results:

Pivotal milestones met

Successful on-site inspection

Regulatory approval granted

Echocardiography

Echocardiography is a non-invasive imaging modality that has high diagnostic accuracy and is considered one of the most performed imaging tests to provide valuable information on the key features of HOCM. Echo is widely available and relatively inexpensive, making it attractive for collection of imaging data across multiple investigator sites participating in clinical trials. It can provide great insight on cardiac structure and function in patients with HOCM such as Left Ventricular (LV) myocardial thickness, changes in LV ejection fraction (LVEF), and LVOT peak pressure gradients.

Cardiac MRI

Cardiac MRI is valuable in evaluating disease severity and characterizing the morphological and functional pathology of HOCM.

Standard CMR images in cine mode can reliably assess cardiac structure and function, e.g., LV or left atrial (LA) volumes, LV wall thickness. Advanced CMR techniques can provide quantitative assessment in pathological changes due to HOCM at a cellular level. Late gadolinium (Gd) enhancement (LGE) imaging is used to quantify myocardial fibrosis mass. MRI methods such as T1 and T2 mapping can show myocardial injuries related to HOCM without using a contrast agent. T1 mapping with Gd-based contrast is utilized to measure the extracellular volume fraction, another critical imaging biomarker which is elevated due to cellular hypertrophy.

Study Implementation: Executing a complex imaging strategy

Perceptive Imaging supported a Phase III clinical trial in which the sponsor was evaluating a new treatment for symptomatic HOCM. The clinical trial included 15 sites with over 130 screened and 81 enrolled subjects. Both echocardiography and Cardiac MRI were included to support eligibility and efficacy assessments in the HOCM clinical trials.

Echocardiography was the modality of choice to screen patients, meet study primary and secondary endpoints, and support dose titration. The imaging protocol consisted of echo images obtained at rest and with Valsalva maneuvers which made the image acquisition complex. To ensure harmonization of all incoming imaging data, the Perceptive Imaging team worked with sites to train the sonographers on all aspects of image acquisition and patient preparation.

All echo images were analyzed by independent reviewers (cardiologists) who were trained on the study-specific image analysis protocol. To maintain independent reads in a standardized manner, the Perceptive study team monitored reviewer performance throughout the study, making sure that all readers adhered to the review assessment criteria and maintained reader-to-reader variability at an acceptable level. All resulting data was checked by the Perceptive team for accuracy and completeness prior to reporting.

Cardiac MRI supported secondary and exploratory endpoints of the clinical trial, for assessment of cardiac structure and function, myocardial fibrosis, and extracellular volume fraction. Perceptive developed a customized image acquisition protocol for this study, which included with both standardized and novel CMR imaging sequences. Because of the highly complex nature of the acquisition protocol and to maximize the consistency and quality of MRI images across all participating sites, Perceptive's Scientific and Medical team worked closely with each site to optimize the MRI protocol specific to the site's scanner and reviewed the quality of each MRI sequence in detail.

As the clinical trial included different types of CMR assessments and all assessments required contour placement, we streamlined a workflow to optimize the usage of the reviewers' time and minimize reader variability. To ensure the accuracy of CMR data review, Perceptive identified and recruited reviewers/cardiologists who are experts in the field, conducted thorough reviewer training on the assessment criteria, and continued monitoring reviewer performance.

Results

The Perceptive team collaborated closely with the sponsor's study team, investigative sites, and independent readers to support the imaging components of this pivotal study and deliver the critical data needed to demonstrate the efficacy of this compound in treating HOCM.

By applying their scientific and operational expertise in clinical trial imaging, Perceptive Imaging overcame the significant challenges that arose during the trial and delivered timely independent analysis results, enabling the sponsor to meet pivotal milestones, including database lock, NDA submission, and the successful completion of an on-site inspection.

As a result, the compound granted regulatory approval for the treatment of adults with symptomatic HOCM, and has since been licensed to a leading, global pharmaceutical company for further development and commercialization.

Contact hello@perceptive.com for more information on why you can rely on Perceptive Imaging for your clinical trial.