Provisional Translation (as of January 2026)*

Consideration in the development of drugs for hypertrophic cardiomyopathy (Early Consideration)

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1. Introduction

Hypertrophic cardiomyopathy (HCM) is a disease characterized by hypertrophy of the left or right ventricular myocardium and impairment of left ventricular diastolic function due to the hypertrophy. Clinically, HCM is diagnosed when echocardiography or cardiac magnetic resonance imaging demonstrates a maximum left ventricular wall thickness of 15 mm or greater (or 13 mm or greater in individuals with a family history of HCM), and other diseases that may cause myocardial hypertrophy are excluded[1]. HCM is a designated intractable disease under the Japanese health system. As of fiscal year 2023, 4,388 HCM patients were reported based on the number of Intractable Disease Medical Treatment Recipient Certificates issued[2].

The etiology of HCM is heterogeneous, and mutations in sarcomere-related genes are identified in approximately half of the patients. HCM is broadly classified into obstructive HCM (oHCM) and non-obstructive HCM (nHCM) according to the degree of left ventricular outflow tract (LVOT) obstruction, and it has been suggested that the prognosis may differ between oHCM and nHCM[3].

In Japan, pharmacotherapy for both oHCM and nHCM is primarily symptomatic treatment. β-blockers and calcium channel blockers are administered to improve symptoms such as chest pain, exertional dyspnea, shortness of breath and palpitations, which are considered to result from impaired left ventricular relaxation. In oHCM, sodium channel inhibitors may also be used. The cardiac myosin inhibitor mavacamten has been approved as a therapeutic agent directly acting on the disease mechanism; however, its indication is limited to oHCM. When these pharmacological treatments are insufficient, non-pharmacological interventions such as septal reduction therapy may be considered as alternative treatment options in patients with oHCM.

The purpose of this document is to present the current considerations for clinical development strategies of HCM therapeutics in Japan. It should be noted that these considerations are based on currently available knowledge and may change as new findings emerge.

2. Considerations for Overall Development Strategy

Because oHCM and nHCM differ in pathophysiology and may have different prognoses, it is

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* This English version of the Japanese Early consideration is provided for reference purposes only. In the event of any inconsistency between the Japanese original and the English translation, the former shall prevail.

considered appropriate to conduct confirmatory studies separately for each phenotype when evaluating therapeutic agents intended for both oHCM and nHCM.

As oHCM and nHCM are rare diseases with a limited number of patients, it may be challenging to conduct confirmatory trials solely within Japan. Therefore, participation in multi-regional clinical trials should be actively considered from the early stages of development.

When considering development in Japan in situations where (i) clinical data demonstrating efficacy are already available from overseas confirmatory trials, or (ii) an overseas confirmatory trial is ongoing but participation from Japan is not feasible, it may be acceptable to adopt a development strategy that includes conducting a clinical trial (a domestic trial or an multi-regional clinical trial excluding countries/regions participating in the overseas confirmatory trial) to compare and assess the similarity of efficacy and safety between Japanese and non-Japanese populations, while referring to the results of the overseas trial to support the evaluation of efficacy and safety in Japanese patients. In such a strategy, the study design for evaluating the similarity of efficacy and safety should be as consistent as possible with that of the reference overseas confirmatory trial. If a different design is employed, the rationale for the differences and justification for the comparability of results despite the design discrepancies should be clearly explained.

As HCM also occurs in pediatric patients, development plans should take pediatric indications into account. It is recommended to formulate a development plan that includes clinical trials to explore appropriate pediatric dosage and administration, as well as the establishment of pediatric formulations.

3. Considerations for Confirmatory Trials

3.1 Study Design

In general, confirmatory trials should be designed as randomized, double-blind, parallel-group comparative studies with an appropriate control group. Confirmatory trials should be conducted by maintaining appropriate standard therapies such as β-blockers, in accordance with the current treatment recommendations described in relevant guidelines[1], and using placebo as the control. However, when a therapeutic agent with a similar mechanism of action or place in therapy is already available, superiority or non-inferiority of the investigational product to the active comparator may be evaluated. In such cases, the appropriateness of the comparator should be justified, taking into account the anticipated clinical positioning of the investigational product under development.

3.2 Efficacy Endpoints

The treatment goal for HCM is improvement of long-term prognosis. However, since HCM is a rare disease with limited patient numbers, it may be difficult to conduct confirmatory trials using mortality-related events as primary efficacy endpoints.

When it is not feasible to use endpoints related to survival improvement as primary endpoints, the use of peak oxygen uptake (pVO_2) as the primary efficacy endpoint is recommended,

considering the following factors:

(i) Assessment of exercise tolerance is useful for determining treatment strategies and evaluating therapeutic response

(ii) exercise tolerance provides an objective measure of treatment effect

(iii) pVO_2, an indicator of exercise tolerance, has been reported to correlate with prognosis in patients with HCM[4].

When exercise tolerance is used as the primary endpoint, it is important to include endpoints related to survival improvement as secondary endpoints and to confirm that the investigational product does not adversely affect survival outcomes in patients with HCM.

Because improvement in clinical symptoms such as exertional dyspnea and shortness of breath is also an important treatment objective, it is recommended to include subjective symptom assessment measures—such as the Kansas City Cardiomyopathy Questionnaire Clinical Summary Score (KCCQ-CSS) and the New York Heart Association (NYHA) functional classification—as secondary endpoints, and to evaluate the overall efficacy of the investigational product based on these results as well.

oHCM is defined as a phenotype with a resting or provoked left ventricular outflow tract (LVOT) pressure gradient of ≥30 mmHg. Most existing therapies are intended to improve disease condition by reducing this pressure gradient. Considering that LVOT pressure gradient is used to assess disease severity and guide treatment decisions in oHCM[1], and that its association with prognosis and exercise tolerance has been reported[5], evaluation of LVOT pressure gradient as a biomarker related to therapeutic effect is considered useful in oHCM.

3.3 Evaluation Period

The evaluation period in confirmatory trials should be appropriately determined, taking into account the characteristics of the investigational product and the time required for the therapeutic effect to manifest in the target population.

For drugs expected to be used for long-term management in clinical practice, the safety and efficacy of long-term administration should also be appropriately evaluated.

3.4 Study Population

Because confirmatory trials are expected to include patients receiving standard treatment, measures should be implemented to minimize the potential impact of changes in standard therapy on the efficacy and safety evaluation of the investigational product—for example, by enrolling patients for whom it is unlikely that the dosage and regimen of their standard therapy will change during the study period. If discontinuation, modification, or addition of standard therapies occurs during the trial, such changes should be recorded in detail to allow assessment of their potential impact on the efficacy and safety outcomes of the investigational product.

For investigational products with a mechanism of action that suppresses myocardial hypercontractility, such as myosin inhibitors, the risk of heart failure due to reduced left ventricular contractile function should be carefully considered. Enrollment of patients with left ventricular ejection fraction (LVEF) below the reference range should be avoided or clearly justified with adequate risk mitigation measures, and regular echocardiographic monitoring should be performed during treatment to ensure appropriate safety management.

3.5 Dosage and Administration

Given that oHCM and nHCM differ in pathophysiology and may exhibit different therapeutic responses and safety profiles, it is desirable that the dosage and administration for confirmatory trials be determined based on the results of dose-response studies or other relevant data, conducted for each phenotype. When the dosage and administration for confirmatory trials in patients with one phenotype is determined based on the results of a dose-response studies conducted in patients with the other phenotypes, the appropriateness of this approach should be sufficiently justified.

4. Reference

1) JCS 2018 Guideline on Diagnosis and Treatment of Cardiomyopathies.
2) https://www.nanbyou.or.jp/wp-content/uploads/2025/07/2023koufu_age.pdf (Accessed 2026 Jan 27.)
3) Martin S Maron, et al. Contemporary Natural History and Management of Nonobstructive Hypertrophic Cardiomyopathy. J Am Coll Cardiol 2016; 67: 1399-409
4) Isabela Landsteiner, et al. Cardiopulmonary Exercise Testing for Characterization of Hypertrophic Cardiomyopathy: A Meta-Analysis. J Am Heart Assoc 2025; 14: e039551
5) Martin S. Maron, et al. Effect of Left Ventricular Outflow Tract Obstruction on Clinical Outcome in Hypertrophic Cardiomyopathy. N Engl J Med 2003; 348: 295-303