Provisional Translation (as of December 2024)*

Points to consider in the clinical development of drugs for transthyretin amyloid cardiomyopathy (Early Consideration)

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1. Introduction

Transthyretin amyloid cardiomyopathy (ATTR-CM) is a type of systemic amyloidosis, a designated intractable disease, characterized by the deposition of transthyretin (TTR)-derived amyloid in the myocardium, leading to functional impairment.[1)] TTR exists in two forms: a wild-type with a normal amino acid sequence and a mutant type with enhanced fibril formation. The number of ATTR-CM patients in Japan is estimated to be approximately 1,500-1,800 (1,468-1,798 patients with wild-type TTR and 50-61 patients with variant type TTR).† Regardless of the presence or absence of TTR gene mutations, the prognosis of ATTR-CM is generally poor, with many patients dying from sudden cardiac death, heart failure and myocardial infarction,[2), 3)] etc.

ATTR-CM was traditionally considered to be a rare disease. However, advances in imaging diagnostic techniques and changes in diagnostic criteria have led to an increase in diagnosed cases of wild type ATTR-CM. This suggests that many cases may have previously gone undiagnosed.[4), 5)] In Japan, the TTR tetramer-stabilizers including tafamidis and tafamidis meglumine are the only medications currently approved for ATTR-CM; however, several other therapeutic agents are under development.

Given the above circumstances, the objective of this document is to outline the current considerations for the development of therapeutic drugs for ATTR-CM. It should be noted that the points to be considered in this document are based on current knowledge and may evolve with new findings in future.

2. Key considerations for overall development strategy

Though the goal of treatment in ATTR-CM is to improve prognosis, it could be challenging to conduct a confirmatory trial with mortality/morbidity events as the primary endpoint only in Japan. PMDA encourages Japan's participation in multiregional clinical trials (MRCT) from the early stage of development.

Recently, there have been changes in diagnostic methods and patient screening for ATTR-CM. When defining inclusion criteria for clinical trials and/or estimating the number of patients who can be enrolled, it is necessary to consider the latest clinical practice and epidemiological data.

If the intended target population includes both wild type and variant TTR ATTR-CM patients, it is desirable to include both patients groups in the confirmatory study. Since there are very few ATTR-CM patients with

* 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.
† The number of ATTR-CM patients in Japan was estimated based on the Medical Data Vision Co., Ltd. database (period: January 2010 to September 2018) (Cardiol Ther 2019; 8: 297-316).

variant TTR in Japan, data from non-Japanese cases would be included in the evaluation in these situations.

3. Considerations for confirmatory trials

3.1 General matters

Efficacy of ATTR-CM therapeutics should be evaluated in a randomized, double-blind controlled trial with an appropriate control group.

It is appropriate to select a comparator taking into account the anticipated clinical positioning of the investigational drug. When a placebo is used as a comparator, it is necessary to clarify whether or not the existing treatment for ATTR-CM can be used in combination with the investigational drug, ensuring the evaluation of the efficacy of the treatment regimen as it would be expected in actual clinical practice. It is also possible to select an existing therapeutic agent for ATTR-CM as a comparator, and to design the study to demonstrate the non-inferiority or superiority to the treatment.

3.2 Primary endpoint

Since improvement of morbidity/mortality is the true endpoint of efficacy assessment for ATTR-CM treatment, it is recommended that the primary endpoint for a confirmatory trial be death (all-cause or cardiovascular death), or a composite endpoint of death combined with “other events related to survival outcomes”.

“Other events related to survival outcomes” should be selected considering their relationship to the morbidity/mortality and their clinical importance. For example, hospitalization or urgent medical visits resulting from cardiovascular events could be considered as a component of the composite endpoint.

On the other hand, exercise tolerance (e.g., 6-minute walk test), quality of life (QOL), and biomarkers (e.g., troponin, N-terminal pro-brain natriuretic peptide (NT-proBNP)) are not recommended as a component of the primary endpoint, as their relationship with survival outcomes are not clearly established.

“Other events related to survival outcomes” should be defined as specifically as possible in a study protocol and evaluated in principle based on the results of a blinded central judgment by an independent adjudication committee in order to reduce the variability in judgments among study sites, countries or regions, and to ensure the objective evaluation. It is also recommended to collect objective supporting information (e.g., medical records) to validate reported events, if hospitalizations or urgent visits due to cardiovascular events are included in the primary endpoint as “other events related to survival outcomes”.

When using a composite endpoint as the primary endpoint, following points should be noted.

- The efficacy of the investigational drug should be demonstrated not only by the results of the composite endpoint, but also supported by each of its components.
- When the study is conducted as a MRCT, consistency of results for the composite endpoint between the overall population and the Japanese population must be demonstrated. Additionally, for clinically significant events within the composite endpoint, consistency of results between these populations is desirable.

Recent changes in the clinical practice, such as increased early diagnosis of ATTR-CM and reductions in

mortality rate among patients with ATTR-CM[6], should be considered when designing trials. Although the following strategies could be considered, given the complexity of trial design, it is strongly recommended to consult with PMDA to ensure the appropriateness of the study design.

- Including recurrent events as well as first events as part of "other events related to survival outcomes". In such cases, it is appropriate to also evaluate the event incident rates adjusted for observation period.
- Applying enrichment strategies, such as selecting patients with a higher risk of events to accumulate more events.

3.3 Efficacy endoints other than the primary endpoint

To include exercise tolerance (e.g., 6-minute walk test), QOL, and biomarkers (e.g., troponin, NT-proBNP) as secondary or exploratory endpoints in confirmatory trials may be valuable to demonstrate the efficacy and clinical relevance of the investigational drug, and assess the consistency of efficacy results between the overall population and the Japanese population.

3.4 Evaluation period

It is recommended that the evaluation period in a confirmatory study be set appropriately based on the characteristics of the investigational drug and the time required for the drug to demonstrate its therapeutic effects in the target population.‡

3.5 Statistical analysis

In the comparison of morbidity/mortality between groups, it is generally appropriate to perform a comparison of the incidence of events during the evaluation period or a survival analysis for the time to event.

In case where a composite endpoint is used as the primary endpoint and the clinical importance between components varies, it may be appropriate to use an analytic methods that takes into account the clinical importance of each component.

In the case of MRCT, it is needed to determine the target sample size for Japanese patients considering the probability of demonstrating the consistent results for the primary endpoint and components between the overall population and the Japanese population, as already mentioned in section 3.2. It is appropriate to consider the feasibility of the study based on the number of patients in Japan, the number of study sites, and the period required for the study, taking into account the recent clinical practice system and epidemiological data for ATTR-CM as needed.

4. References

1) Circ J. 2020; 84: 1610-1671
2) Am J Med. 1996; 101: 395-400
3) Mayo Clin Proc. 1984; 59: 547-55

‡ In previous developments, the evaluation period was generally about 30 months (N Engl J Med. 2018; 379: 1007-16, N Engl J Med. 2024; 390: 132-42, N Engl J Med. 2024; doi: 10.1056/NEJMoa2409134).

4) J Am Coll Cardiol. 2019; 73: 2872-91
5) Circulation. 2017; 135: 1357-77
6) Circulation. 2022; 146: 1657-70