Non-Interventional Study Protocol

<B3461064>

Vyndaqel Capsules Special Investigation

- Investigation on Patients with Transthyretin Amyloid Cardiomyopathy -

Statistical Analysis Plan

Version: 6.0

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1. AMENDMENTS FROM THE PREVIOUS VERSION

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
1.0/ 21-June-2019/ PPD Before Enrollment	First edition
2.0/ 07-May-2021/ PPD Ongoing	• 2.1 The protocol amendments about the registration period and the patients who are subject to the investigation were reflected. • 5.1 "No administration information - Administration information not determined" was added to the inclusion/exclusion criteria for the safety analysis set based on the Criteria for Inclusion Ver 2.0. • 5.4 "Presence/absence of liver impairment" was added. • 8.2.1.3 For the tabulation of discontinued patients, a time point at 30 months was added to allow determination whether the investigation period was prolonged due to concurrent treatment. • 8.2.2.2 The tabulation of the total number of doses was changed to the tabulation of the number of doses per actual treatment period, and the tabulation of the dose per dose was changed to the tabulation of the dose per actual treatment period. The actual treatment period was defined as the treatment period excluding the non-treatment period. In addition, the statement that the treatment period would be tabulated as a categorical variable separately from its continuous variable was added. • 8.2.3.3 For the analysis of adverse reactions by subgroup, the description about the range subject to calculation of risk ratios was modified, and tabulations of adverse reactions by SOC and PT for each subgroup for specific factors were added. • 9 A listing of patients with adverse reactions for each safety specification was changed to a listing of adverse reactions for each safety specification. • 10.1 A1.1 For the NYHA Functional Classification at baseline, the statement that the case report form should be referred to for the time point at the start of treatment was added because the date of evaluation was not collected. • 10.3 The formula used to calculate mBMI was added. • Other minor description modifications were made.

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
3.0/ 21-April-2022/ PPD / Ongoing	• 2 and 2.2 A description about Vynmac was added. • 5.4 Gender was added as a factor for subgroup analyses for the safety evaluation. • 5.4 The factor "Dose change" for subgroup analyses for the efficacy evaluation was deleted (Because the effect to be truly evaluated will not be reflected by comparison of the presence/absence of dose changes if a temporary dose change is made frequently.) • 6.1 "Incorrect product selection between Vyndaqel and Vynmac" was added as an important potential risk in the safety specifications. • 8.2.2.2 A correction was made so that Vynmac can also be included in the tabulation of the administration status of this drug. • 8.2.3.3 A correction was made to include adverse reactions of Vyndaqel and Vynmac during the treatment periods before and after the switching to Vynmac. • 8.2.3 and 8.2.4 The statement that safety and efficacy will be evaluated using all data collected during the observation period without classifying the data into Vyndaqel and Vynmac unless otherwise specified was added. • Other minor description modifications were made.
4.0/ 08-June-2023/ PPD / Ongoing	• 2.1 Background information about a possible transfer to another hospital or department in this study was added. • 6.1 The name of the document separately describing the definitions of safety specifications was added instead of including descriptions of the definitions. • 7 The method of imputation of the end date of treatment in this study for patients continuing treatment with this drug was added. • 8.2.2.1 The periods for the use of concomitant medications and therapies to be tabulated were added. • 8.2.2.2 The method of tabulation of the administration records for transferred patients and the categorical variable of the initial dose were added. • 8.2.3.1.3 The number of days to onset and outcome were added to the tabulation of adverse reactions by item. • 9 A list of patients with adverse reactions in patients with variants was added. • 10 The REFERENCES section was added. • Other minor description modifications were made.

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
5.0/ 28-May-2024/ PPD / Ongoing	• 2.1 The end date of the registration period was specified in association with the termination of registration only. In addition, the statement about registration only patients for investigation was deleted. • 5.1 The criteria for inclusion in the safety analysis set were added. • 5.2 The criteria for the efficacy evaluation in the efficacy analysis set and the description in the report were changed based on the latest version of the Guidance for Criteria for Inclusion in Analysis Sets and Data Handling in Use-result Surveys. • 5.3 The safety analysis set consisting of consented patients and the efficacy analysis set consisting of consented patients were added. • 5.4 Usage experience of this drug was added to and dose change was deleted from the subgroups. • 8.1.4 The method of handling a period data which includes interval-censored data was added. • 8.2 A description about the tabulation and analysis in the safety analysis set consisting of consented patients or the efficacy analysis set consisting of consented patients was added. • 8.2.1.1 The "Numbers of study sites and study patients by founder" section was deleted. • 8.2.1.1 The tabulation of patient disposition was changed from registered patients to patients with collected case report forms. • 8.2.2.1 The analysis sets for the breakdown of complications was changed to the safety analysis set only. In addition, the tabulation of the categories of concomitant medications was deleted. • 8.2.3 Adverse reactions and adverse events to be tabulated were changed from those occurring during the observation period to all of those collected. • 8.2.3.1.5 The "Relationship between concomitant medications and occurrence of adverse reactions" section was deleted. • 8.2.3.2.1 The "All adverse events" section was deleted. • 8.2.3.2.1 The section name was changed from "Serious adverse events" to "Adverse events by seriousness," and the method of tabulation of non-serious adverse events was added. • 8.2.4.3 The period for the tabulation of the number and proportion of deaths was specified. • A1.1 The method of handling of multiple values of the same endpoint at the same visit time was added. • Other minor description modifications were made.

Version/ Date/ Author(s)/ Status of Study	Summary of Changes/Comments
6.0/ 23-Jan-2025/ PPD Ongoing	• 8.2.3.1.3 The tabulation of serious adverse reactions by outcome was added. • 8.2.3.3 The subgroups to be tabulated for each SOC and PT were specified.

2. INTRODUCTION

This statistical analysis plan describes the statistical analysis plan for the special investigation of Vyndaqel or Vynmac (hereinafter, both drugs are collectively referred to as this drug unless otherwise specified). In this document, texts cited from the protocol are indicated in *italics*.

2.1. Study Design

Investigation period: March 2019 to September 2023 (From the start date of observation for the first subject to the end date of observation period for the last subject)

Registration period: March 2019 to March 2021 (From the start date of treatment for the first subject to the start date of observation period for the last subject)

Study patients: *This study will be conducted with all patients surveillance system that all patients will be registered until data are collected on a target number of patients.*

Target sample size: *The number of patients with ATTR-CM in Japan is estimated to be approximately 750. Of these, the proportion of patients who actually received the definitive diagnosis and were prescribed with this drug was estimated to be approximately 40% (approximately 300 patients). As a result, the target sample size was set at 300 subjects from the viewpoint of feasibility.* (300 patients to be evaluated for the safety of this drug)

Observation period: 30 months (Week 130) from the start of administration (Day 1). However, for patients who discontinued this drug during the observation period, the observation period will be until the first visit after the date of discontinuation.

Handling of patients transferred to another hospital or department: For the proper use of this drug, requirements for patients, institutions, and physicians have been specified by the Japanese Circulation Society[1], and it is necessary to meet all of these requirements to introduce this drug. However, since continued prescription at another institution is allowed in consideration of convenience, patients who have already started to receive this drug may be transferred to another hospital or department. *If the patient is transferred to another hospital or department (hereinafter referred to as hospital transfer) during the observation period, the patient will be newly registered even at the transferred site and the CRF will be completed. If the patient is transferred to another hospital, the patient registration number of the original*

site will be conveyed to the transferred site. Although the patient will be given a new patient registration number at the transferred site at the time of registration, he or she will be determined to be a transferred patient by reporting the patient registration number of the original site and his/her data will be handled as the same patient. However, registration is not necessary when the date of starting the treatment at the transferred site is on or after 01 April 2021. If the time point of 30 months after the start date of initial administration can be identified for the transferred patient, the observation period at the transferred site may be reset so that the total observation period of the patient in this study will become 30 months.

2.2. Study Objectives

The objective of this study is to comprehend information on the long-term safety (e.g., onset status of adverse reactions), etc. of patients who are treated with this drug for the treatment of ATTR-CM after the approval for the indication of this drug for ATTR-CM was obtained. When Vynmac is used, the study will be also conducted to grasp information on safety (e.g., onset status of adverse reactions), etc. during the observation period.

[Conditions for approval for Vyndaqel]

Because the number of study participants in Japan is very limited, the background information of patients using this drug should be grasped by conducting a use-result survey in all patients while the data on a certain number of patients is accumulated after marketing and data on the safety and efficacy of this drug should be collected early to take measures necessary for proper use of this drug.*

**: Vyndaqel*

[Conditions for approval for Vynmac]

*Because the number of study participants in Japan is very limited, the background information of patients using this drug** or Vyndaqel Capsules 20 mg should be grasped by conducting a use-result survey in all patients while the data on a certain number of patients is accumulated after marketing and data on the safety and efficacy of this drug or Vyndaqel Capsules 20 mg should be collected early to take measures necessary for proper use of this drug.*

***: Vynmac*

3. INTERIM AND FINAL ANALYSES

In this study, interim analyses for Periodic Safety Update Reports will be performed periodically. At the time of interim analyses, only the analyses necessary for Periodic Safety Update Report among the statistical analyses specified in this plan will be performed. In addition, the final analysis for the application for reexamination will be performed. At the time of the final analysis, all analyses specified in this plan will be performed.

4. HYPOTHESES AND DECISION RULES

This study is not a confirmatory investigation. Therefore, if a test is performed, an obtained result will be considered as exploratory.

4.1. Statistical Hypothesis

The p-value of test results will be evaluated as descriptive statistics. The significance level is not provided, but a threshold may be set afterwards for the purpose of screening.

4.2. Statistical Decision Rules

Not applicable.

5. ANALYSIS SETS

5.1. Safety Analysis Set

The safety analysis set is defined as the full analysis set that is as closer as possible to all patients treated with this drug. More specifically, the safety analysis set is defined as the population of patients registered or reported, excluding those who meet any of the following conditions:

1. The case report form could not be collected at all (Description in the report: "Case report form not collected")
2. There was a violation or deficiency in the contract (Description in the report: "Contract violation/deficiency")
3. There was a violation in the registration (Description in the report: "Registration violation")

   Registration criteria: *The purpose of treatment with this drug is ATTR-CM. *Patients who have participated in clinical studies of ATTR-CM and are willing to continue receiving treatment of ATTR-CM are eligible for the registration.*
4. Administration of the drug under investigation is not reported at all (Description in the report: "No administration information")
5. Information on adverse events is not reported at all - No visits after the first prescription day (Description in the report: "No adverse event information - No revisits")
6. Information on adverse events is not reported at all - There is a visit after the first prescription day but no description of information (Description in the report: "No adverse event information - No description")
7. Information on administration is not reported at all (Description in the report: "No administration information - Administration information not determined")

The "Guidance for Criteria for Inclusion in Analysis Sets and Data Handling in Use-result Surveys" will be followed for the details of each criterion.

5.2. Efficacy Analysis Set

The efficacy analysis set is defined as the population of patients in the safety analysis set, excluding those who meet any of the following conditions:

8. Efficacy cannot be evaluated appropriately because of insufficient conditions for efficacy evaluation (Description in the report: "Efficacy evaluation not possible").

5.3. Other Analysis Sets

5.3.1. Safety analysis set consisting of consented patients

Analysis population consisting of only the consented patients for the publication of results among the patients in the safety analysis set

5.3.2. Efficacy analysis set consisting of consented patients

Analysis population consisting of only the consented patients for the publication of results among the patients in the efficacy analysis set

5.4. Subgroups

Subgroup analyses of safety will be performed for the following patient characteristics and other factors. For the patient characteristics and other factors with those of specific categories underlined, a risk ratio will be calculated using each underlined category as the reference.

- Inpatient/outpatient status at the first prescription [inpatient, outpatient]
- *Severity of liver impairment [absent, mild, moderate, severe]
- Liver impairment [absent, present]
- Renal impairment [absent, present]
- Age [<15 years, ≥15 to <65 years, ≥65 years]
- *TTR genetic variant [wild-type, variant]
- NYHA functional classification [Class I/II, III/IV]
- NYHA functional classification [Class I, II, III, IV]
- Concomitant medication [absent, present]
- Non-drug therapy (device therapy) [absent, present]

- Complication [absent, present]
- Gender [male, female]
- Usage experience of this drug (administered this drug for the first time, transferred from clinical trials, transition from the treatment of ATTR-PN]

*Evaluation of the important missing information (safety in patients with severe liver impairment and patients with variants)

Subgroup analyses of efficacy will be performed for the following patient characteristics:

- TTR genetic variant [wild-type, variant]
- NYHA functional classification [Class I/II, III/IV]
- NYHA functional classification [Class I, II, III, IV]

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

- Adverse reactions: Adverse events assessed as related to this drug by the physician
- Adverse events: Adverse events of any causality
- Serious adverse events or adverse reactions: Adverse events or adverse reactions assessed as serious by the physician
- Safety specifications: Events to be handled as safety specifications will be specified according to the latest version of the "Rationale for Safety Specifications and Events to be Defined based on the Risk Management Plan."
  - Important potential risks:
    - Hepatotoxicity
    - Hypersensitivity reactions
    - Reproductive and developmental toxicity
    - Infection
    - Incorrect product selection between Vyndaqel and Vynmac
- Laboratory tests

6.2. Efficacy Endpoints

- Change in NYHA functional classification
- Change in cardiac biomarker values (NT-pro BNP, BNP, troponin I, troponin T)
- Survival time

6.3. Other Endpoints

Not applicable.

7. HANDLING OF MISSING DATA

If treatment with this drug is continued even after the end of the observation period and the end date of treatment is missing, the end date of observation will be handled as the end date of treatment in this study.

If the seriousness, causal relationship, and action taken and outcome regarding adverse events are missing, these data will be handled as "unknown" for tabulation.

For the efficacy endpoints and laboratory test values, if there is no measurement within the time window for each evaluation time point (Appendix 1), data will be handled as missing, and the missing data will not be complemented.

The strategy for handling data with uncompleted cleaning is described below:

- Items of missing data: The items will be handled as missing (category of categorical variables is "unknown") for both tabulation and listing.
- Items of inconsistent data: The items will be handled as missing for both tabulation and listing. However, a list of data handling should be prepared separately.
- No signature: Any entry in a case report form without the signature of the contracted physician (including a case report form with the signature of an uncontracted physician only) will be handled as missing for both tabulation and listing. If there is no date of signature in the field for the date of signature or if there is inconsistency in the date entered (e.g., date before the start date of treatment, future date), the entry in the case report form will be regarded as having no signature.

8. STATISTICAL METHODS AND STATISTICAL ANALYSIS

8.1. Statistical Methods

8.1.1. Analysis of continuous data

Summary statistics (number of patients, mean, standard deviation, median, maximum, minimum) will be calculated.

8.1.2. Analysis of categorical data

The frequency (e.g., number of patients) and proportion of each category will be calculated in the tabulation at each evaluation time point.

For the evaluation of a change from baseline in the number of patients at each evaluation time point after the start of treatment, the number and proportion of patients (the number of patients in each category at baseline is used as the denominator) will be calculated using a cross table.

8.1.3. Analysis of binary data

The frequency and its proportion will be calculated. When the confidence interval of the proportion is calculated, the two-sided 95% confidence interval (exact method) will be calculated.

When the proportion is compared between subgroups, the risk ratio and its 95% confidence interval (Wald method) will be calculated.

8.1.4. Analysis of period data (time to event onset)

The median, first quartile, and third quartile will be calculated by the Kaplan-Meier method. For period data which includes interval-censored data, the median, first quartile, and third quartile will be calculated based on the EMICM algorithm. In addition, Kaplan-Meier plots will be prepared.

8.1.5. Analysis of longitudinal data measured repeatedly

When longitudinal data is analyzed using a mixed model repeated measure (MMRM), parameters will be estimated using the restricted maximum likelihood estimation method (REML), and an unstructured variance-covariance structure will be assumed for within-subject variation. If the model fails to converge, a different available optimization method will be tried. If the problem of convergence is still not resolved, estimation will be performed by changing the assumption of variance-covariance structure in the order of TOEPH, ARH(1), AR(1), and CS. The model-adjusted mean change from baseline at each evaluation time point will be summarized using the least squares mean and its 95% confidence interval.

When individual data are graphically presented, the time-courses of all measured values will be presented using line graphs.

8.1.6. Analysis based on the person-years method

The incidence rate per exposure period will be calculated using the following formula:

Incidence rate (per 100 person-years) = $100 * y / PT$

y: Number of patients with event

PT: Total exposure period (years)

Where the exposure period is the period from the first date of administration to the date of last observation in this study for patients with no event and the period from the first date of administration to the first date

of confirmation of the event in this study for patients with an event. The 95% confidence interval will be calculated using the following formula:

$$\left[\frac{100}{PT}\cdot\frac{1}{2}\chi^2_{2y}\left(\frac{\alpha}{2}\right),\frac{100}{PT}\cdot\frac{1}{2}\chi^2_{2(y+1)}\left(1-\frac{\alpha}{2}\right)\right]$$

y: Number of events

$\chi^2_{2y}(\alpha / 2)$: $\alpha / 2$ percent point of the chi-square distribution with $2y$ degrees of freedom

8.2. Statistical Analysis

The analyses to be performed on the safety analysis set or the efficacy analysis set, shown below, will also be performed on the safety analysis set consisting of consented patients or the efficacy analysis set consisting of consented patients. Applicable analyses will be specified separately. When these analyses are performed, the analysis populations will be replaced with the safety analysis set consisting of consented patients or the efficacy analysis set consisting of consented patients.

8.2.1. Overview of patients

8.2.1.1. Patient disposition

For patients with collected case report forms, the number of patients completing the study, the number of patients in the safety analysis set, and the number of patients in the efficacy analysis set will be tabulated. In addition, the numbers of patients excluded from the safety analysis set and the efficacy analysis set and the number of patients by reason for exclusion will be tabulated.

8.2.1.2. List of discontinuations and dropouts

For the safety analysis set and the efficacy analysis set, the number and proportion of discontinuations will be tabulated by timing [<12 months, ≥12 to <24 months, ≥24 to <30 months, ≥30 months]. In addition, the number and proportion of patients by reason for discontinuation will be tabulated.

8.2.1.3. List of excluded patients by patient

A listing of patients excluded from the safety analysis, patients excluded from the efficacy analysis, and reasons for exclusion will be prepared.

8.2.2. Patient characteristics and history of treatment

8.2.2.1. Patient characteristics

For the safety analysis set and the efficacy analysis set, the following patient characteristics will be tabulated as described in Section 8.1:

- Target disease [ATTR-CM, others]
- Gender [male, female]

- Age (continuous variable)
- Age [<15 years, ≥15 to <65 years, ≥65 years]
- Inpatient/outpatient status at the first prescription [inpatient, outpatient]
- Body height (continuous variable)
- Body weight (continuous variable)
- BMI [<18.5, ≥18.5 to <25, ≥25]
- TTR genotype [wild-type, variant, unknown]
- NYHA functional classification [Class I, II, III, IV]
- mBMI (continuous variable, see Section 11.3 for the calculation method)
- Severity of liver impairment [mild, moderate, severe, unknown]
- Liver impairment [absent, present, unknown]
- Renal impairment [absent, present, unknown]
- Complication [absent, present]
- Usage experience of this drug (administered this drug for the first time, transferred from clinical trials, transition from the treatment of ATTR-PN, no information]
- Pregnancy status [absent, present]
- Concomitant drug therapy [absent, present]
- Concomitant non-drug therapy (device therapy) [absent, present]

For the safety analysis set, the number and proportion of the following patients will be tabulated by System Organ Class (SOC) and Preferred Term (PT):

- Breakdown of complications

For the safety analysis set, the number and proportion of patients for each of the following breakdowns will be tabulated:

- Breakdown of concomitant medications (Concomitant medications are defined as drugs used between the start date of administration of this drug and the date of discontinuation or end date of administration of this drug among those entered in the drug therapy section of the case report form.)
- Breakdown of concomitant non-drug therapies (device therapies) (Concomitant non-drug therapies are defined as non-drug therapies (device therapies) performed between the start date of administration of

this drug and the date of discontinuation or end date of administration of this drug among those entered in the non-drug therapy (device therapy) section of the case report form.)

- The classification of device therapies (pacemaker, implantable cardioverter defibrillator [ICD], cardiac synchronization therapy [CRTP], biventricular pacing implantable cardioverter defibrillator [CRTD], other) will be tabulated. Other breakdowns will be listed.

- Breakdown of TTR genotypes (variant only)

8.2.2.2. Administration status of this drug

For the safety analysis set, the following administration status of this drug will be tabulated:

- For a patient receiving Vynmac, the dose of Vyndaqel will be used in the tabulation of doses; 61 mg of Vynmac will be considered equivalent to 80 mg of Vyndaqel. Treatment period (continuous variable, unit = month)

  1. Treatment period for any product
  2. Treatment period with Vyndaqel before the initial switching to Vynmac
  3. Treatment period with Vynmac after the initial switching to Vynmac

- Treatment period (categorical variable, [<12 months, ≥12 to <24 months, ≥24 to <30 months, ≥30 months])

  1. Treatment period for any product
  2. Treatment period with Vyndaqel before the initial switching to Vynmac
  3. Treatment period with Vynmac after the initial switching to Vynmac

- Initial dose (categorical variable, [20 mg, 40 mg, 60 mg, 80 mg]; for an initial dose >80 mg, a subcategory of >80 mg will be used.)

- Number of doses per actual treatment period (excluding the washout period from the treatment period) (total number of doses/actual treatment period [days]) (continuous variable)

- Dose per actual treatment period (excluding the washout period from the treatment period) (total dose/actual treatment period [days]) (continuous variable)

- Number and proportion of patients with dose reductions*

  *Including a dose change from Vynmac 61 mg to Vyndaqel ≤60 mg.

- Number and proportion of patients with dose increases**

  ** Including a dose change from Vyndaqel ≤60 mg to Vynmac 61 mg.

- Breakdown of reduced doses (categorical variable)

  The frequency and proportion will be tabulated for each dose pattern (maximum dose => minimum dose) during the observation period* [80 mg => 60 mg, 80 mg => 40 mg, 80 mg => 20 mg, 60 mg => 40 mg, 60 mg => 20 mg, 40 mg => 20 mg, no change].

Treatment period is defined as the period from the first date of administration to the last date of confirmation of administration in this study, including washout period.

If the treatment period overlaps between the administration records collected before and after transfer for a transferred patient, the patient will be handled as having received this drug at one of the sites if the number of doses per day and the administered dose during the overlapping period are the same. If there is any inconsistency in the number of doses per day or the administered dose during the overlapping period, the patient will not be included in the tabulation of the number of doses and the administered dose per actual treatment period or the dose increases and reductions, and the such action taken will be described in the report.

8.2.3. Safety analysis

All adverse reactions and adverse events occurring after the start of administration of this drug will be summarized in listings. The listings will include all events reported in this study. Safety will be evaluated using all data collected after the start of administration of this drug without classifying the data into Vyndaqel and Vynmac unless otherwise specified was added.

8.2.3.1. Adverse reactions

8.2.3.1.1. All adverse reactions

The number and proportion of patients with adverse reactions will be tabulated by SOC and PT.

8.2.3.1.2. Serious adverse reactions

The number and proportion of patients with serious adverse reactions will be tabulated by SOC and PT.

8.2.3.1.3. Details of adverse reactions

The number and proportion of patients with adverse reactions will be tabulated by SOC and PT for each of the following items:

- Seriousness [serious, non-serious]
- Number of days to onset [<26 weeks, ≥26 weeks and <52 weeks, ≥52 weeks and <78 weeks, ≥78 weeks and <104 weeks, ≥104 weeks and <130 weeks, ≥130 weeks] (For the tabulation of incidence, the number of patients receiving at least one dose of this drug in each period category will be used as the denominator.)
- Action taken [suspended, dose reduced, dose increased, discontinued]

- Outcome [recovered/resolved, recovering/resolving, recovered/resolved with sequelae, not recovered/not resolved, fatal, unknown]

For outcomes, the number and proportion of patients with serious adverse reactions will be tabulated by SOC and PT.

If the same adverse reaction (of the same PT) occurs more than once in the same patient, it will be handled as follows in the tabulation of the number of patients with events:

- Seriousness: If both serious and non-serious events are reported, the event will be regarded as serious.
- Number of days to onset: Defined as the number of days to the first event.
- Action taken: If multiple types of actions were taken, one action will be adopted in the order of priority of discontinued, suspended or dose reduced, and other (none, dose increased).
- Outcome: The outcome of the last occurring event will be used.

8.2.3.1.4. Safety specifications

For the safety specifications shown in Section 6.1, the number and proportion of patients will be tabulated. The number and proportion of patients with safety specifications will be tabulated by SOC and PT for each action taken and outcome.

In addition, safety specifications will be analyzed, taking into account the difference in exposure period, as described in Section 8.1.4.

8.2.3.1.5. Occurrence status of adverse reactions by inclusion/exclusion in the safety analysis set

For patients with collected case report forms, a listing of adverse reactions in patients excluded from the safety analysis set will be prepared. In addition, the number of patients with adverse events will be tabulated by SOC and PT.

8.2.3.2. Adverse events

8.2.3.2.1. Adverse events by seriousness

The number and proportion of patients with serious adverse events will be tabulated by SOC and PT. Non-serious adverse events will also be tabulated in the same manner. However, the threshold for incidence will be set as necessary, and only events with an incidence at or above the threshold will be tabulated.

8.2.3.3. Exploratory analysis

For each of the factors specified in Section 5.4, the number and proportion of patients with at least one adverse reaction (incidence of any type of adverse reactions) will be tabulated, and for the incidence, the risk ratio among subgroups for each factor will be calculated as described in Section 8.1.3. However, after reconsidering the classification of a category with <10 patients, if calculation of a risk ratio is difficult, the

risk ratio to the category will not be calculated. In addition, unknown data will be excluded from the evaluation of risk ratios.

Serious adverse reactions and serious adverse events will also be analyzed in the same manner as above.

Adverse reactions will be tabulated by SOC and PT for each of the following subgroups:

- Liver impairment [absent, present]
- Renal impairment [absent, present]
- Age [<15 years, ≥15 to <65 years, ≥65 years]
- Pregnancy status [absent, present]
- NYHA functional classification [Class I, II, III, IV]

The onset status of adverse reactions will be evaluated for each product (Vyndaqel or Vynmac) during the treatment period until the first switching to Vynmac for Vyndaqel and during the treatment period after the first switching to Vynmac for Vynmac.

This drug is contraindicated to patients with a history of hypersensitivity to any of its ingredients. Because of limitations in evaluation in this study, no tabulation regarding contraindications will be performed. However, if hypersensitivity to any of its ingredients is reported as an adverse reaction, it will be presented in a listing.

Additional analyses may be performed as necessary. The exploratory analysis will be reported only when results giving important interpretation are obtained.

8.2.4. Efficacy analysis

Efficacy will be evaluated using all data collected during the observation period without classifying the data into Vyndaqel and Vynmac unless otherwise specified.

8.2.4.1. NYHA functional classification

The NYHA functional classification at each evaluation time point [at baseline, Month 12, Month 30, discontinuation] will be summarized as described in Section 8.1.2.

The NYHA functional classification at each evaluation time point after the start of treatment [at Month 12, Month 30, discontinuation) will be summarized using a cross table as described in Section 8.1.2.

8.2.4.2. Cardiac biomarkers

For NT-pro BNP, BNP, troponin I, and troponin T each, the following analyses will be performed:

Measurements of each biomarker at each evaluation time point [at baseline, Month 6, Month 12, Month 18, Month 24, Month 30, discontinuation] will be summarized as described in Section 8.1.1. In addition, a

change from baseline in each biomarker at each evaluation time point [at Month 12, Month 30, discontinuation] will be summarized as described in Section 8.1.1.

A change from baseline in each biomarker at each evaluation time point will be summarized, as described in Section 8.1.5, using an MMRM with patient as a random effect; TTR genetic variant [wild-type, variant], NYHA functional classification [I/II, III/IV], and evaluation time point [Month 6, Month 12, Month 18, Month 24, Month 30] as fixed effects; and baseline value as a covariate. The analysis will be performed on values measured on the nearest day to each time point for the evaluation using the model.

Evaluation time points may be changed depending on the status of data accumulation.

In addition, measured values at all time points in each patient will be used to prepare spaghetti plots for the entire observation period, as described in Section 8.1.5. (Figures using different colors [or separated by line type] will be prepared for both TTR genetic variant [wild-type, variant] and NYHA functional classification [I, II, III, IV].)

Preparation of an MMRM and figures will not be included in the subgroup analysis.

8.2.4.3. Survival time

For the period from the start of administration of this drug to the end date of the observation period, the number and proportion of patients experiencing death of any cause and deaths related to cardiovascular events will be tabulated separately. In addition, each event will be summarized as described in Section 8.1.4. In the analysis in Section 8.1.4, data will be censored at the last date of confirmation of survival. If the date of death is unknown and the last date of confirmation of survival and date of death information obtained are known, data will be handled as interval censored. The handling of patients in the survival analysis is outlined below.

Non-English text

8.2.4.4. Exploratory analysis

For each of the factors specified in Section 5.4, subgroup analyses will be performed for the efficacy analyses described in Section 8.2.4. Kaplan-Meier estimation will be used to analyze the survival time by using the factors shown in Section 5.4 as stratification variables.

Additional analyses may be performed as necessary. The exploratory analysis will be reported only when results giving important interpretation are obtained.

9. LISTINGS

The following listings will be prepared:

- Listing of patients
- Listing of patients experiencing adverse events
- Listing of patients experiencing adverse reactions
- Listing of patients excluded from the safety analysis experiencing adverse reactions
- Listing of patients with a contraindication experiencing adverse reactions
- Listing of patients experiencing serious adverse reactions
- Listing of patients experiencing serious adverse events
- Listing of patients with TTR variants experiencing adverse reactions
- Listing of patients with severe liver impairment experiencing adverse reactions
- Listing of patients with renal impairment experiencing adverse reactions
- Listing of patients experiencing adverse reactions resulting in dose reduction
- Listing of pediatric patients (aged <15 years) experiencing adverse reactions
- Listing of elderly patients (aged ≥65 years) experiencing adverse reactions
- Listing of adverse reactions by safety specification
- Listing of laboratory test values
- Listing of efficacy evaluations

In addition, a form necessary for reexamination application (PSEHB/PED Notification No. 1128-2 dated November 28, 2017 issued by the Director of Pharmaceutical Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare) will be prepared.

Furthermore, a form necessary for Periodic Safety Update Reports (PSEHB/PED Notification No. 1128-5 and PSEHB/SD Notification No. 1128-4, dated November 28, 2017 issued jointly by the Director of Pharmaceutical Evaluation Division and the Director of Safety Division, Pharmaceutical Safety and Environmental Health Bureau, Ministry of Health, Labour and Welfare) will be prepared.

10. REFERENCES

1. Japanese Circulation Society. A Statement on Requirements for Medical Institutions and Physicians for the Proper Use of Vyndaqel in Patients with Transthyretin Amyloid Cardiomyopathy. March 30, 2019: https://www.j-circ.or.jp/old/topics/83thjcs_statement_dr_fukuda_r.pdf.

11. APPENDICES

11.1. Appendix 1: Details of Data Extraction

A1.1 Definition of Efficacy Evaluation Time Points

Visit time	Endpoints	Definition [Time window]
At baseline	Laboratory tests, efficacy endpoints	Between 30 days before the first date of administration (start date of administration) and the start date of administration in this study. For NYHA functional classification, the evaluated value of NYHA functional classification entered in the "Target disease" page of the case report form will be adopted.
Month 6	Laboratory tests, efficacy endpoints	Between 3 months and 9 months after the start of administration
Month 12	Laboratory tests, efficacy endpoints	Between 9 months and 15 months after the start of administration
Month 18	Laboratory tests, efficacy endpoints	Between 15 months and 21 months after the start of administration
Month 24	Laboratory tests, efficacy endpoints	Between 21 months and 27 months after the start of administration
Month 30	Laboratory tests, efficacy endpoints	Between 27 months and 39 months after the start of administration
At discontinuation	Laboratory tests, efficacy endpoints	1 month before or after the last date of administration in this study

If there are multiple values of the same endpoint at the same visit time, the value measured on the closest day to each visit time will be adopted. If there are multiple values measured on the closest day, the value measured at a later date will be adopted.

11.2. Appendix 2: Example of Risk Ratios of Subgroups to the Incidence of Adverse Reactions

11.3. Calculation of Modified Body Mass Index (mBMI)

mBMI = (serum albumin [g/dL] / 10) × BMI

BMI = body weight [kg] / (body height [cm] / 100)^2