Non-Interventional Study Protocol
B3461042

Vyndaqel Capsules Special Investigation
- Investigation on long-term use -

Statistical Analysis Plan

Version: 10.0

Author: PPD

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1. REVISION HISTORY

Version	Date	Author(s)	Summary of Changes/Comments
1.0	28-MAR-2014	PPD	First edition
2.0	21-Feb-2017	PPD	4.1 Statistical Hypotheses • Amended the description to "Not applicable.", because no statistical tests will be performed.
			5.1 Safety Analysis Set • Added a supplementary explanation about cases with no records on adverse events. • Added a supplementary explanation about patients with domino liver transplantation.
			5.2 Efficacy Analysis Set • Added a statement explaining analysis of patients registered for a non-target disease. • Updated the set of efficacy endpoints to include survival time.
			5.4 Patient Characteristics • Editorial revisions (deletion of duplications, etc.) • Added items for subgroup analyses.
			6.1 Safety Endpoints • Added "TTR amyloidosis-related symptoms other than peripheral neuropathy"
			6.2 Efficacy Endpoints • Added a supplementary explanation to the statement about NIS with editorial revisions. • Added a supplementary explanation to the statement about QOL-DN with editorial revisions. • Added a supplementary explanation to the statement about neurological assessment with editorial revisions. • Added a statement about the evaluation of survival time.
			6.4 Covariates • Editorial revisions
			7 HANDLING OF MISSING DATA • Editorial revisions • Made minor corrections about QOL-DN and added a supplementary explanation.

Version	Date	Author(s)	Summary of Changes/Comments
			8.1.3 Binary variables • Deleted the statement about statistical testing. • Added a statement about risk ratio.
			8.1.4 Repeatedly measured variables • Added this subsection.
			8.2.1 Description of patients • Editorial revisions in the part "Combination clinical practice" • Added a statement about patients after data linkage in the part "Constitution". • Corrected the analysis set used and time categories in the part "Discontinuation and dropouts".
			8.2.2 Patient characteristics and treatment history • Editorial revisions • Added factors for the analysis of patient characteristics. • In the part "Exposure of this drug", revised the definition of *duration of treatment* and added the item *total number of treatment weeks*.
			8.2.3.1 Adverse reactions • Added a summarization plan for selected adverse reactions. • Editorial revisions in "Major investigation items" • Modified the categorization of onset timing in "Onset timing of adverse reactions" • Deleted the statement specific to loperamide in "Association between concomitant medication and adverse reactions".
			8.2.3.1 Adverse events • Added analysis plans of presenting a tabulated list of deaths and summarizing SAEs by seriousness. • Added a plan of summarizing AEs leading to discontinuation.

Version	Date	Author(s)	Summary of Changes/Comments
			8.2.3.2 Subgroup analyses • Added a statement about risk ratio. • Editorial revisions in the statement on hepatotoxicity • Modifications in the summarization plan for liver transplantation and infections • Added a plan to perform subgroup analyses concerning patients with special characteristics.
			8.2.3.3 TTR amyloidosis-related symptoms other than peripheral neuropathy • Added this subsection.
			8.2.4.1 Time variations in NIS scores • Added plans regarding summarization at each time point, analysis of variance, and box plotting.
			8.2.4.2 Time variations in QOL-DN • Added plans regarding summarization at each time point, analysis of variance, and box plotting.
			8.2.4.3 Time variations in mBMI • Correction of printing errors
			8.2.4.6 Survival analysis • Added this subsection.
			8.2.4.7 Subgroup analyses • Added TQOL as an analysis item. • Added a plan to summarize scores at each time point. • Added a supplementary sentence concerning pretreatments and concomitant medications.
			CCI [redacted]
			CCI [redacted]
			9 LISTINGS • Updated the set of listing items to include mutant genotypes, deaths, pregnant women, non-target diseases, and liver transplantation.

Version	Date	Author(s)	Summary of Changes/Comments
			10.1 Appendix 1: Details of Data Extraction • Modifications in visit timing; editorial revisions
			Other • Editorial revisions
3.0	25-Apr-2018	PPD	5.4. Subgroups • "Patient characteristics": Added "Body weight". • "Patient characteristics": Deleted "Mutant genotype 1". • "Patient characteristics": Modified the plan regarding past history of liver transplantation.
			6.1. Safety Endpoints • "Adverse reactions": Deleted "Adverse reactions as assessed by company". • Added "Serious adverse events or serious adverse reactions"
			8.2.2. Patient characteristics and treatment history • "Patient characteristics": Added "Body weight" and "History of pregnancy during study period" • "Patient characteristics": Editorial revisions in the categorization of target diseases • "Patient characteristics": Modified the categorization for "Mutant genotype 1" • "Patient characteristics": Added the analysis item "Disposition of non-V30M mutations" • "Patient characteristics": Editorial revisions in the categorization for "Past history of liver transplantation" • "Patient characteristics": Editorial revisions and an addition in the categorization for "Timing of liver transplantation"
			8.2.3.3. TTR amyloidosis-related symptoms other than peripheral neuropathy • Modifications in the analysis plan
4.0	18-Feb-2019	PPD	8.2.1 Description of patients • Updated the procedure to identify possible patients with combination clinical practice to include "mutant genotype" and "names of sites after patient transfer" as information to be considered; and modified a statement so that it reads that the identification will be determined at a case conference.

Version	Date	Author(s)	Summary of Changes/Comments
5.0	03-Oct-2019	PPD	6.1. Safety Endpoints, and 6.3. Other Endpoints • Integrated the part "TTR amyloidosis-related symptoms other than peripheral neuropathy" in Section 6.1 to the part "Medical assessments of physical symptoms" in Section 6.3 as an editorial revision.
			Addition of "8.1.5. Time data".
			8.2.1. Description of patients • Added the summarization plan for patients who complete the study period.
			8.2.2 Patient characteristics and treatment history, and 8.2.3.1 Adverse reactions • Divided the time category "≥52 to <104 weeks" into "≥52 to <78 weeks" and "≥78 to <104 weeks" in the analysis plans of duration of treatment in "8.2.2 Exposure of this drug" and onset timing of adverse reactions in "8.2.3.1 Adverse reactions".
			8.2.3. Safety analysis, 8.2.5. Other analyses, and 10.1 Appendix 1 • Moved the content of "TTR amyloidosis-related symptoms other than peripheral neuropathy" in Section 8.2.3 to Section 8.2.5 with a change of analysis plan to that based on cross-classification after modifications in survival analysis and time points for the summarization. • In association with the above, deleted the definition of time points in A1.4, Section 10.1, and added *medical assessments of physical symptoms* to the set of endpoints defined in A1.1.
			8.2.4.6. Evaluation of survival time • Editorial revisions in association with the addition of Section 8.1.5
			Added "10.3.1. Analysis of interval censored data".
			Other • Editorial revisions
6.0	13-May-2020	PPD	5.4. Subgroups, 8.2.2. Patient characteristics and treatment history and 8.2.3.3. Subgroup analyses • Integrated different age categorizations to a single one.

Version	Date	Author(s)	Summary of Changes/Comments
			8.2.1. Description of patients • Deleted the plan to summarize studied sites and patients by type of site establisher. (This summarization had been included as data required for re-examination but became no longer needed.)
			8.2.2. Patient characteristics and treatment history • Changed the analysis sets used for the analyses of disposition of non-V30M mutations and method of diagnosis of FAP to the SAS alone.
			5.4. Subgroups • Added a categorization for concomitant medications and pretreatments.
			8.2.3.1. Adverse reactions • Added a statement that important potential risks will be summarized by making a tabulated list of events (instead of in terms of n and proportion) if n is very small for each event.
			8.2.4.1. Time course of NIS and 8.2.4.2. Time course of QOL-DN • CCI [redacted]
			CCI [redacted]
			9. Listings • Deleted “Patients with AEs” and “Patients with SAEs” from the set of listing items; and made editorial revisions concerning Attachment Forms.
			Other: Editorial revisions
7.0	21-Oct-2020	PPD	5.2. Efficacy Analysis Set • Deleted the plan of the efficacy analysis in patients with non-target disease because this analysis is unnecessary.

Version	Date	Author(s)	Summary of Changes/Comments
			8.2.2. Patient characteristics and treatment history • Deleted “Mutant genotype 2”, a factor that had been included in the factors for which summarization will be performed, because the summarization for this factor can be covered by that for “Mutant genotype 1”.
			8.2.3.1. Adverse reactions • Added a statement that summarization for pre-specified events will be separately performed, as necessary, because it will be covered by the tabulation for all adverse reactions.
			8.2.4.6. Evaluation of survival time • For the determination of survival rate at specified time points performed in align with plotting of Kaplan-Meier's curve, changed the time points to those determined by considering each evaluation period.
			9. Listings • Like in Section 5.2, deleted “Results of efficacy evaluation in patients with non-target disease” from the set of listing items, because it is unnecessary.
8.0	07-May-2021	PPD	8.2.1. Description of patients • Modified the categorization of the timing of last visit used for the summarization described in “Discontinuation and dropouts” to “<52 weeks, ≥52 to <78 weeks, ≥78 to <104 weeks, ≥104 to <156 weeks” and explicitly stated that patients who complete the study period of this study will not be included in this summarization.
			8.2.2. Patient characteristics and treatment history • Changed the categorization of “Duration of treatment” in “Exposure of this drug” to “<52 weeks, ≥52 to <78 weeks, ≥78 to <104 weeks, ≥104 to <156 weeks, ≥156 weeks”.
9.0	21-April-2022	PPD	CCI [redacted]

Version	Date	Author(s)	Summary of Changes/Comments
			10.3.2. Analysis of repeated measures data • Added a sample SAS code to show how the percent change described in Section 8.2.4.8 will be calculated.
			Other: Minor corrections • Made a terminological change from “study period” to “observation period”. • In “Evaluation of survival time”, Section 6.2, clarified the explanation of when survival will be determined.
10.0	13-Mar-2023	PPD	5.4. Subgroups • Changed the reference category for pretreatments and concomitant medications to “absent”. • Identified the pretreatments and concomitant medications for which subgroup analysis will be performed.
			6.1. Safety Endpoints • Amended the name of the document referred to to identify the events covered by each major investigation item, in accordance with the name of the document submitted to PMDA.
			6.2. Efficacy Endpoints • In “Evaluation of survival time”, added the definition of FAP-related death. • In “Evaluation of survival time”, deleted “Time from birthdate to event” from the set of items evaluated as time to event.
			7. HANDLING OF MISSING DATA • In “Evaluation of Survival Time”, added how to handle cases in which cause of death is missing.
			8.2.1. Description of patients • In “Constitution”, added a summarization plan by planned observation time (Weeks 78 and 156). • Deleted the plan of summarizing the patients who complete the study period.
			8.2.2. Patient characteristics and treatment history •In “Other”, added what period data of concomitant medications, concomitant non-drug therapies, and pretreatments will be collected; and added definition of past medical history and complications.

Version	Date	Author(s)	Summary of Changes/Comments
			8.2.3.1. Adverse reactions • In "Onset timing of adverse reactions", added definition of the denominator to calculate the proportion of patients with an adverse reaction.
			8.2.3.3. Subgroup analyses • Deleted the statement "risk ratio and its confidence interval will not be calculated for pretreatments and concomitant medications".
			8.2.4.6. Evaluation of survival time • Deleted the statement about "time from birthdate to event".
			CCI [redacted]
			8.2.6.1. Measurement of plasma concentration of tafamidis in patients with severe hepatic impairment • Added in what condition plasma concentrations of tafamidis will be tabulated.
			9. LISTINGS • Added "Efficacy endpoints" and "Medical assessments of physical symptoms" to the set of listing items.
			CCI [redacted]
			Other • Editorial revisions

2. INTRODUCTION

This document describes the statistical analysis plan for the non-interventional study entitled “Vyndaqel Capsules Special Investigation - Investigation on long-term use -”. In this SAP, citations from the corresponding protocol are indicated in *italics*.

2.1. Study design

Target patients

All patients who received/used this drug will be targeted in this study.

Dosage and administration

The usual adult dosage for oral use is 20 mg of tafamidis meglumine once daily.

Observation period

3 years from the first day of treatment with this drug (156 weeks)

However, the observation period for patients who started to receive this drug after May 2018 will be 1.5 years (78 weeks).

Major investigation items

Hepatotoxicity should be evaluated in this study as a major investigation item and, if information on hepatotoxicity is obtained, it will be separately investigated in detail.

[Rationale for setting]

Although necrosis and hypertrophy of hepatocytes were observed in the repeated-dose toxicity study in mice, since the Japanese clinical data at the time of approval application are limited, hepatotoxicity was set as the major investigation item in this study to confirm the post-marketing safety profile.

Study size and its rationale

[Planned sample size]

All patients who received/used this drug will be targeted in this study.

[Rationale for sample size]

On the basis of the review of data on patients with familial amyloid polyneuropathy who were registered in the database from the Amyloidosis Clinical Survey Forms of the Specific Diseases Treatment Research Program by the Ministry of Health, Labour and Welfare for 3 years from 2003 to 2005, it is reported that the number of patients with familial amyloid polyneuropathy is 64 to 88 patients/year, and the estimated prevalence of familial amyloid polyneuropathy in Japan is 0.87 to 1.1 per population of 1 million people after the number of patients was corrected and calculated from the acquisition rate of data 1). When this

prevalence is multiplied by the Japanese population (127.54 million, as of November 2012), the estimated number of patients with TTR-FAP (hereinafter referred to as this disease) is approximately 111 to 140. On the website of the Japan Intractable Diseases Information Center, the estimated annual number of patients treated for this disease is approximately 130 on the basis of the nationwide epidemiological survey conducted in 1991. As described above, considering that this disease is a rare disease and the safety and efficacy information of this drug based on Japanese clinical studies are limited, all patients who received/used this drug will be collected as much as possible.

Planned period covered by this study

Duration of study: November 2013 to May 2021 (7.5 years)

Registration period: November 2013 to November 2019 (6 years)

A contract will be concluded after the start date of the study period, and then, the patient registration will be started.

2.2. Research Objectives

To understand information on the safety (e.g., onset status of adverse reactions) and efficacy of this drug in the long-term use under the post-marketing actual use in all patients receiving this drug.

Review on the onset status of hepatotoxicity will be set as a major investigation item in this study.

3. INTERIM AND FINAL ANALYSES

In this study, interim analyses for the purpose of Japan Periodic Safety Update Report (J-PSUR) will be conducted on a regular basis. For an interim analysis, only necessary items selected from the full analysis items defined in this SAP will be analyzed. A final analysis will be conducted to support the application of reexamination. For the final analysis, the full items defined in this SAP will be analyzed.

4. HYPOTHESES AND DECISION RULES

4.1. Statistical Hypotheses

Not applicable.

4.2. Statistical Decision Rules

Not applicable.

5. ANALYSIS SETS

5.1. Safety Analysis Set

Safety analysis will be performed using the safety analysis set (SAS) that consists of all registered patients who had their CRF collected and received at least one dose of this drug.

Patients who meet any of the criteria below, however, should be excluded from the SAS:

- Contract deficiency
- Contract violation
- Contract withdrawal
- Registration violation
- No information recorded on adverse events (Patients who had no record or made no visit even after reinvestigation was conducted because there was no record of AEs or of lack of AEs)

Although patients will not be excluded from the SAS just because reinvestigation could not be conducted, patients whose all records concerning administration of this drug or safety information could not be reinvestigated will be excluded from the SAS according to the criterion above.

Patients with iatrogenic TTR-FAP in whom TTR-FAP developed after liver transplantation from a donor with TTR-FAP (domino liver transplantation) will be included in this study. Patients registered for a non-target disease (e.g., cardiac amyloidosis) will also be included in the SAS.

5.2. Efficacy Analysis Set

The efficacy analysis set consists of all patients in the SAS in whom at least one of the efficacy endpoints below was evaluated. Patients registered for a non-target disease (e.g., cardiac amyloidosis) will not be included in the efficacy analysis set.

Efficacy endpoints: Neuropathy impairment score (NIS), Norfolk Quality of Life - Diabetic neuropathy (QOL-DN), modified body mass index (mBMI), ambulatory status (walking ability score used in polyneuropathy dysfunction rating scale), neurological assessment scores, and survival time

5.3. Other Analysis Sets

The pharmacokinetics analysis set consists of all patients in the SAS in whom plasma concentration of tafamidis was measured.

5.4. Subgroups

Subgroup analyses for safety and efficacy will be performed with respect to the following factors:

- Patient characteristics
  - Sex [male, female]
  - Age [<15 yrs., ≥15 to <65 yrs., ≥65 yrs.]
  - Body weight [≤50 kg, ≥50 to <60 kg, ≥60 kg]
  - BMI [<18.5, ≥18.5 to <25.0, ≥25]
  - Onset age [≤50 yrs., ≥50 yrs.]
  - Duration of disease [≤5 yrs., ≥5 yrs.]
  - Past treatment with this drug [present, absent]
  - Mutant genotype 2 [with V30M, without V30M]

- Karnofsky performance status [100-80, 70-50, 40-10]
- Family history of TTR-FAP [present, absent]
- Origin of patient [endemic region, non-endemic region]
- Past history of organ transplantation [present, absent]
- Past history of liver transplantation (including for purposes other than the treatment of target disease) [present (including domino liver transplantation), absent] * Only for safety assessment
- Past history of liver transplantation other than domino liver transplantation [present, absent (including domino liver transplantation)] * Only for efficacy assessment
- Hepatic impairment [present, absent]
- Hepatic impairment [absent, mild, moderate, severe]
- Renal impairment [present, absent]
- Baseline total NIS score [≤70, ≥70]
- Baseline NIS-LL score [≤10, >10 to ≤20, >20]
- Baseline total QOL (TQOL) score [≤20, >20 to ≤40, >40]
- Severity of disease [Stage 1 (walking ability score 0-2), Stage 2 (walking ability score 3a/3b), Stage 3 (walking ability score 4)]

  Subgroup analysis for mutant genotype will be performed only in patients with a diagnosis of mutant genotype.

- Others

  - Pretreatment (loperamide) [present, absent]
  - Pretreatment (prednisolone) [present, absent]
  - Pretreatment (rosuvastatin) [present, absent]
  - Pretreatment (NSAIDs) [present, absent]
  - Duration of treatment [≤52 weeks, >52 to ≤104 weeks, >104 to ≤156 weeks, >156 weeks]
  - Concomitant medication (loperamide) [present, absent]
  - Concomitant medication (prednisolone) [present, absent]
  - Concomitant medication (rosuvastatin) [present, absent]
  - Concomitant medication (NSAIDs) [present, absent]

6. ENDPOINTS AND COVARIATES

6.1. Safety Endpoints

- Adverse reactions: AEs related or possibly related to this drug as assessed by the treating physician
- Adverse events
  - All-causality AEs
- Serious adverse events (SAEs) or serious adverse reactions: AEs or adverse reactions considered by the treating physician to be serious

- Major investigation items: Major investigation items include:
  - Hepatotoxicity

Events covered by each major investigation item will be identified according to the latest version of the separately prepared document, Rationale for Setting the Safety Specification Based on Risk Management Plan and Defined Events.

6.2. Efficacy Endpoints

- Neuropathy Impairment Score (NIS)

The NIS will be evaluated at baseline (i.e., before the start of treatment with this drug), at Weeks 78 and 156, and at the end/discontinuation of treatment.

The NIS is a measure of neuropathy that involves 37 assessments of the cranial nerves (items 1 to 5), muscle weakness (items 6 to 24), reflexes (items 25 to 29), and sensation (index finger: items 30 to 33, great toe: items 34 to 37); for items assessed bilaterally, the mean of the right and left is used as the score for the item.

The total NIS score, NIS-lower limbs (NIS-LL) score, and NIS-upper limbs (NIS-UL) score will be determined as a measure of the degree of systemic neuropathy, neuropathy of lower limbs, and neuropathy of upper limbs, respectively.

Subscores assessed include the scores for cranial nerves, muscle weakness, reflexes, and sensation, as well as muscle weakness scores for lower limbs and upper limbs, reflexes scores for lower limbs and upper limbs, and sensation scores for great toe and index finger.

	Cranial Nerves score	**Muscle Weakness score**	**Reflexes score**	**Sensation score**
Total score [0, 244]	Sum of items 1-37			
NIS-LL score [0, 88]		Sum of items 17-24 (Muscle Weakness for lower limbs)	Sum of items 28-29 (Reflexes for lower limbs)	Sum of items 34-37 (Sensation for great toe)
NIS-UL score [0, 156]	Sum of items 1-5	Sum of items 6-16 (Muscle Weakness for upper limbs)	Sum of items 25-27 (Reflexes for upper limbs)	Sum of items 30-33 (Sensation for index finger)

Each item for cranial nerves and muscle weakness will be graded on the following 8-point scale:

0: Normal
1: 25% Weak

2: 50% Weak
3: 75% Weak
3.25: Move against gravity
3.5: Movement, gravity eliminated
3.75: Muscle flicker, no movement
4: Paralysis

Each item for reflexes and sensation will be graded on the following 3-point scale:

0: Normal
1: Decreased
2: Absent

- Norfolk Quality of Life - Diabetic Neuropathy (QOL-DN)

Quality of life in studied patients will be assessed using Norfolk QOL-DN at baseline, at Weeks 78 and 156, and at the end/discontinuation of treatment.

The QOL-DN questionnaire consists of symptoms part (items 1-7) and activities of daily living part (items 8-35).
The total QOL (TQOL) score as well as subscores for physical function/large nerve fiber disorder, activities of daily living, symptoms, small nerve fiber disorder, and autonomic neuropathy will be determined.

TQOL score [-4, 136]	Sum of all items 1-35
Physical Function/Large Nerve Fiber Disorder score [-4, 56]	Sum of items 8, 11, 13-15, 24, and 27-35
Activities of Daily Living score [0, 20]	Sum of items 12, 22, 23, 25, and 26
Symptoms score [0, 32]	Sum of items 1-7, and 9
Small Nerve Fiber Disorder score [0, 16]	Sum of items 10, and 16-18
Autonomic Neuropathy score [0, 12]	Sum of items 19-21

Items 1-7 will be evaluated by assessing whether the relevant symptom exists in each of the four regions (feet, legs, hands, and arms).

0: None
1: Present in one region
2: Present in two regions
3: Present in three regions

4: Present in all four regions

Items 8-26 will be graded on the following 5-point scale:

0: No difficulty
1: Minimal difficulty
2: Mild difficulty
3: Moderate difficulty
4: Severe difficulty

Items 27-30 and 33-35 will be graded on the following 5-point scale:

0: None at all
1: A little
2: Some
3: Moderately
4: Severely

Item 31 will be graded on the following 5-point scale:

−2: Excellent
−1: Very good
0: Good
1: Ordinary
2: Bad

Item 32 will be graded on the following 5-point scale:

−2: Considerably better
−1: Better to some extent
0: Almost unchanged
1: Worse to some extent
2: Considerably worse

- Modified Body Mass Index (mBMI)

mBMI will be measured at baseline, at Weeks 26, 52, 78, 104, 130, and 156, and at the end/discontinuation of treatment.

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

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

- Ambulatory Status (walking ability rating scale in the polyneuropathy dysfunction score)

Ambulatory status will be assessed at baseline, at Weeks 78 and 156, and at the end/discontinuation of treatment.

Ambulatory status (walking ability) will be graded on the following 6-point scale:

0: Good
1: Able to walk without difficulty despite of sensory disorder in the lower extremities
2: Able to walk without assistance despite of some difficulties
3a: Able to walk with one stick or crutch
3b: Able to walk with two sticks or crutches
4: Unable to walk, restricted to wheelchair or bedridden

- Neurological Assessment

Neurological assessment will be performed at baseline, at Weeks 52 (1 year), 104 (2 years), and 156 (3 years), and at the end/discontinuation of treatment.

The neurological assessments consist of those of motor function, tendon reflexes, light touch, pin prick, vibration, and position sense. Each evaluation item will be evaluated bilaterally except those for the trunk. If a result for the trunk has been recorded for both right and left side, the higher value will be adopted. The total score, motor score, reflexes score, and sensation score will be determined.

Total score [0, 294]	Sum of the motor, reflexes, and sensation scores
Motor score [0, 160]	Sum of the results for motor function grading
Reflexes score [0, 10]	Sum of the results for tendon reflexes grading
Sensation score [0, 124]	Sum of the results for light touch, pin prick, vibration, and position sense

Motor function will be graded on the following 6-point scale:

0: No contraction
1: Flicker contraction
2: Muscle contraction with active motion with gravity eliminated
3: Full range of motion against gravity
4: Full range of motion against gravity with some resistance
5: Full range of motion against gravity with maximum resistance for that muscle

For the purpose of determining the motor score, however, grading should be inverted to read 0 as normal and 5 as abnormal.

5: No contraction
4: Flicker contraction
3: Muscle contraction with active motion with gravity eliminated
2: Full range of motion against gravity
1: Full range of motion against gravity with some resistance
0: Full range of motion against gravity with maximum resistance for that muscle

Tendon reflexes will be graded on the following 2-point scale:

0: Present
1: Absent

Test results for light touch, pin prick, vibration, and position sense will be graded on the following 3-point scale:

0: Normal
1: Decrease
2: Absent

- Evaluation of Survival Time

Survival time will be evaluated by setting death as the event of interest. For patients who complete the study, survival status will be determined on the first follow-up date exceeding 3 years after the start of treatment with this drug at the own site. In the case of death, information on the cause, i.e., whether the death is due to TTR-FAP or to another cause (including unknown) will also be collected. *For patients who started the treatment with this drug after May 2018 (1.5-year observation period), their survival should be confirmed using the attached CRF* on the first follow-up date exceeding *1.5 years after the start of treatment at the own site.*

The following two kinds of event will be evaluated:

– Death from any cause
– FAP-related death (Death from TTR-FAP is set as the event of interest. Death with missing cause will not be regarded as an event of interest.)

Time to event will be evaluated with respect to the following two kinds of time:

– Time from start of treatment to event
– Time from onset of FAP to event

CCI [redacted]

6.4. Covariates

No covariates that may affect the safety and/or efficacy of this drug have been identified from available clinical study and other data.

7. HANDLING OF MISSING DATA

– Adverse Events

  If the severity of, action taken for, or outcome of an AE is missing, their value will be considered "unknown" for data summarizations.

– NIS

  If the evaluation result for the right or left side on the same day is missing, the value for the evaluated side will be adopted as the score for the item.

– QOL-DN

  If the score of an item included in the Physical Function/Large Nerve Fiber Disorder subscale, Activities of Daily Living subscale, Symptoms subscale, Small Nerve Fiber Disorder subscale, or Autonomic Neuropathy subscale is missing, the missing score will be imputed with the mean score from the evaluated items in the relevant subscale as long as ≥60% of the items in the subscale have been evaluated. The score for the subscale will be determined by summing the scores for the evaluated and imputed items.

  The TQOL score will be determined by summing the scores for the evaluated and imputed items if all the 35 items have been evaluated or all missing values imputed by using the aforementioned method. If imputation could not be done by the aforementioned method for some items because of failure of evaluation for ≥60% of all items in a subscale, the TQOL score will be determined as 35 times the mean from the evaluated and imputed items, provided that at least 60% of all items have been evaluated or imputed. If ≥40% of the items in a subscale or the TQOL score are missing, the score for the subscale and the TQOL score will be treated as missing values.

– Neurological Assessment

  If the item toe extension and/or toe flexion in the motor domain have been evaluated and the results are directed to normal, other items in the same domain will be imputed with those directed to normal. If the item triceps surae in the reflexes domain has been evaluated and the result is normal, other items in the same domain will be imputed with normal. If the item toe in the light touch, pin prick, vibration, or position sense domain has been evaluated and the result is normal, other items in the same domain will be imputed with normal.

– Evaluation of Survival Time

  If the cause of death is missing in the record of a death-confirmed patient, the patient will be treated as having died for unknown cause.

8. STATISTICAL METHODS AND ANALYSES

8.1. Statistical Methods

8.1.1. Continuous variables

For continuous variables, summary statistics (n, mean, standard deviation [SD], median, maximum, minimum) will be presented.

8.1.2. Categorical variables

For categorical variables, patients falling into each category will be summarized in terms of frequency (n) and proportion.

8.1.3. Binary variables

For binary variables, patients falling into each binary category will be summarized in terms of n and proportion. When a confidence interval (CI) is determined for a proportion, the two-sided 95% CI (exact method) will be determined.

When a comparison for proportion is made between subgroups, the risk ratio (RR) and its 95% CI will be presented.

8.1.4. Repeatedly measured variables

Mixed effect modeling will be used to analyze repeatedly measured objective variables. The model will include fixed effects of baseline value (included only when the variable represents a change) and time of measurement, and a random effect of patient, with unstructured dispersion being assumed. The least square mean and its standard error at each time of measurement will be determined for each objective variable.

8.1.5. Time (to event) data

For time data containing right-censored data, Kaplan-Meier's method will be used to determine the median, 1st quartile, and 3rd quartile. Kaplan-Meier plots will also be presented, as necessary.

For time data containing interval censored data, the EMICM algorithm will be used to determine the median, 1st quartile, and 3rd quartile. Estimated survival plots will also be presented, as necessary. A reference program is shown in Section 10.3.1.

8.2. Statistical Analyses

8.2.1. Description of patients

Combination clinical practice

Given the nature of this disease as a rare disease, patients may be treated (or receive prescriptions of this drug) at multiple sites during the observation period (combination clinical practice). For possible patients

with combination clinical practice, identification will be determined at a case conference using information on birthdate, sex, mutant genotype, and names of combination practice sites or sites after patient transfer. In principle, data at the site with earlier date of treatment initiation will be adopted for the analysis of patient characteristics. All data after the start of treatment for an identical patient will be combined and handled using this start date of treatment as the origin (data linkage).

Constitution

Using the set of all registered patients, the numbers of registered patients, CRF-collected patients, patients after data linkage, patients included in safety analysis, and patients included in efficacy analysis will be determined. Using the SAS, the number of patients included in the safety analysis will be determined for each planned observation time (Weeks 78 and 156). In addition, CRF-uncollected patients, patients excluded from the safety analysis, and patients excluded from the efficacy analysis will be counted as a total and by reason for exclusion.

Discontinuation and dropouts

Using the SAS, patients who discontinued this study will be summarized in terms of number (n) and proportion by timing of last visit [<52 weeks, ≥52 to <78 weeks, ≥78 to <104 weeks, ≥104 to <156 weeks]. The same summarization will also be performed by reason of discontinuation. Patients who received this drug for ≥156 weeks will be regarded as study completers and will not be counted as those who discontinued this study even if they are recorded as having discontinued at a time point of ≥156 weeks as a result of combination clinical practice.

Patients excluded from analysis

Patients excluded from safety analysis and those excluded from efficacy analysis will be listed in tabular form with their reason for exclusion.

8.2.2. Patient characteristics and treatment history

Patient characteristics and treatment history will be summarized according to Section 8.1 with respect to the following factors:

- Patient Characteristics

For the following factors, summarization will be performed using the SAS and efficacy analysis set:

- Sex [male, female]
- Age (continuous)
- Age [<15 yrs., ≥15 to <65 yrs., ≥65 yrs.]
- Body weight (continuous)
- Body weight [<50 kg, ≥50 to <60 kg, ≥60 kg]
- BMI [<18.5, ≥18.5 to <25.0, ≥25]
- Past treatment with this drug [present, absent, unknown]
- Setting of clinical practice [hospitalization, outpatient]
- History of pregnancy during study period [present, absent, unknown]

- Target disease [TTR-FAP, other (TTR-FAP developing after domino liver transplantation)]
- Duration of disease (continuous)
- Duration of disease [<1 year, ≥1 to <5 yrs., ≥5 to <10 yrs., ≥10 yrs.]
- Onset age (continuous)
- Onset age [<50 yrs., ≥50 yrs.]
- Testing of mutant genotype [performed, not performed/unknown]
- Mutant genotype 1 [only V30M, V30M + non-V30M, only non-V30M, non-V30M + non-V30M, no mutation]
- Karnofsky performance status [100, 90, 80, 70, 60, 50, 40, 30, 20, 10]
- Karnofsky performance status [100-80, 70-50, 40-10]
- Family history of TTR-FAP [present, absent, unknown]
- Origin of patient [endemic region (Nagano Pref., Kumamoto Pref., Ishikawa Pref.), non-endemic region, unknown]
- Past history of organ transplantation [present, absent, unknown]
- Past history of liver transplantation [present (domino liver transplantation, after onset of FAP (incl. onset time unknown)), absent, unknown]
- Timing of liver transplantation (time from onset of FAP) [domino liver transplantation, ≤5 years after onset of FAP, >5 years after onset of FAP, time from onset of FAP to liver transplantation unknown]
- Hepatic impairment [absent, present (mild, moderate, severe, severity unknown), unknown]
- Renal impairment [absent, present (mild, moderate, severe, severity unknown), unknown]
- Baseline total NIS score (continuous)
- Baseline total NIS score [<70, ≥70]
- Baseline NIS-LL score (continuous)
- Baseline NIS-LL score [≤10, >10 to ≤20, >20]
- Baseline TQOL score (continuous)
- Baseline TQOL score [≤20, >20 to ≤40, >40]
- Severity of disease [Stage 1 (walking ability: 0-2), Stage 2 (3a, 3b), Stage 3 (4), undetermined]

For the following factors, summarization will be performed using the SAS:

- Disposition of non-V30M mutations [different non-V30M mutations (multiple counting allowed)]
- Method of diagnosis [clinical symptoms, tissue biopsy (amyloid deposition), tissue biopsy (immunohistological staining), TTR genotype, clinical symptoms + tissue biopsy (amyloid deposition), clinical symptoms + tissue biopsy (immunohistological staining), clinical symptoms + TTR genotype, tissue biopsy (amyloid deposition) + tissue biopsy (immunohistological staining), tissue biopsy (amyloid deposition) + TTR genotype, tissue biopsy (immunohistological staining) + TTR genotype, clinical symptoms + tissue biopsy (amyloid deposition) + tissue biopsy (immunohistological staining), clinical symptoms + tissue biopsy (amyloid deposition) + TTR genotype, clinical symptoms + tissue biopsy (immunohistological staining) + TTR genotype, tissue biopsy (amyloid deposition) + tissue biopsy (immunohistological staining) + TTR genotype, clinical symptoms + tissue biopsy (amyloid

deposition) + tissue biopsy (immunohistological staining)+ TTR genotype, undetermined/unknown]

As for mutant genotype, summarization will be performed only in patients with diagnosis of mutant genotype.

- **Others**

Summarization will be performed according to Section 8.1 for the following aspects:

- Disposition of concomitant medications (Concomitant medications are defined as drugs recorded in Concomitant Drug Therapies or Pretreatments Used for Target Disease [including NSAIDs etc.] that were used in the period from the start of the treatment with this drug to the discontinuation/end of the treatment. If the treatment with this drug continued exceeding the end of observation, drugs used by the last visit should be eligible.)
- Disposition of concomitant non-drug therapies (Concomitant non-drug therapies are defined as therapies recorded in Concomitant Non-Drug Therapies that were used in the period from the start of the treatment with this drug to the discontinuation/end of the treatment. If the treatment with this drug continued exceeding the end of observation, therapies used by the last visit should be eligible.)
- Disposition of pretreatments (Pretreatments are defined as pretreatments used for target disease [including NSAIDs etc.] or drugs recorded in Concomitant Drug Therapies that were administered before the start of the treatment with this drug.)

Using the SAS, the following aspects of patients will be summarized in terms of n and proportion by system organ class (SOC) and by preferred term (PT):

- Past medical history (diseases or syndromes recorded as “past history” in the medical history)
- Complications (diseases or syndromes recorded as “current history” in the medical history)

Exposure of this drug

Using the SAS, exposure of this drug will be summarized with respect to the following aspects:

- Duration of treatment [<52 weeks, ≥52 to <78 weeks, ≥78 to <104 weeks, ≥104 to <156 weeks, ≥156 weeks]
- Initial daily dose [<20 mg, 20mg, ≥20 mg]
- Total number of treatment weeks (continuous, non-dosing periods excluded, unit: weeks)
- Total dose administered (continuous)

The duration of treatment is defined as the length of the time from the date of first dose to the last dose in this study, including non-dosing periods. If the patient remains on the treatment at the end of observation period, the duration of treatment will have the value “>156 weeks”.

8.2.3. Safety analysis

Using the SAS, the following safety analyses will be performed:

8.2.3.1. Adverse reactions

All adverse reactions

Adverse reactions will be summarized by SOC and PT in terms of n and proportion.

In particular, important potential risks, i.e., events related to hepatotoxicity, hypersensitivity reaction, developmental and reproductive toxicity, and infections will be summarized for each event in terms of n and proportion; when n is very small for each event, however, only a listing will be presented in tabular form.

In addition, each of events related to pain in extremity, myalgia, gastrointestinal symptoms, skin, central nervous system, fall, suicide, hepatopathy, thyroid function, vitamin A deficiency, and increased blood glucose will be summarized separately in terms of n and proportion, as necessary.

Serious adverse reactions

Serious adverse reactions will be summarized by SOC and PT in terms of n and proportion.

Details of adverse reactions

Adverse reactions will be summarized in terms of n and proportion by each of the following factors:

- Seriousness [serious, non-serious]
- Known/unknown [known, unknown]
- Action taken [permanent discontinuation, temporary discontinuation or dose reduction, dose increase or no change]
- Outcome [not recovered, recovered with sequelae, improved, resolved/recovered, unknown]

Multiple adverse reactions of the same PT occurring in the same patient will be handled as follows:

- Seriousness: If both serious and non-serious reactions of the same PT occurred in the same patient, the patient will be counted as one with serious reaction.
- Known/unknown: If both known and unknown reactions of the same PT occurred in the same patient, the patient will be counted as one with unknown reaction.
- Action taken: If multiple actions were taken for adverse reactions of the same PT, only one category of action will be adopted with “permanent discontinuation”, “temporary discontinuation or dose reduction”, and “dose increase or no change” being given priority in this order.
- Outcome: The outcome for the last event will be adopted.

Major investigation items

For each of the following major investigation items, patients who experienced relevant events will be summarized in terms of n and proportion:

- Hepatotoxicity

In addition, patients who experienced each major investigation item will be summarized by action taken and outcome for each SOC and PT.

Onset timing of adverse reactions

Adverse reactions will be summarized by timing of first onset [<26 weeks, ≥26 to <52 weeks, ≥52 to <78 weeks, ≥78 to <104 weeks, ≥104 to <156 weeks, ≥156 weeks] for each SOC and PT in terms of n and proportion. When calculating the proportion, the denominator will be the number of patients in each category of onset time who received at least one dose.

Association between pretreatment and adverse reactions

To examine the association between a pretreatment and adverse reactions, patients with any adverse reaction will be summarized by pretreatment in terms of n.

Association between concomitant medication and adverse reactions

To examine the association between a concomitant medication and adverse reactions, patients with any adverse reaction will be summarized by concomitant medication in terms of n. For each patient, concomitant medications used after the last dose should be excluded from consideration.

Adverse reactions in patients excluded from the SAS

Using the set of all CRF-collected patients, adverse reactions in patients excluded from the SAS will be tabulated. In addition, patients with an adverse reaction will be counted for each SOC and PT.

8.2.3.2. Adverse events

All adverse events

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

Adverse events by serious/non-serious

The number and proportion of patients with serious adverse events will be tabulated by SOC and PT by causal relationship. Non-serious adverse events will also be tabulated in the same manner.

Deaths

For patients recorded as "death," date of registration, age at the time of registration, experience of treatment with this drug, target disease and onset timing, mutant genotype, Karnofsky performance status, classification of accumulated cases/non-accumulated cases, presence or absence of liver transplant, NIS at baseline, QOL-DN, ambulatory status, name of adverse event, date of onset of adverse event, and causal

relationship of adverse event to this drug will be shown in a list. The number and proportion of patients will be tabulated for the grade of serious adverse events.

Adverse events leading to discontinuation

Adverse events leading to treatment discontinuation will be tabulated by SOC and PT.

8.2.3.3. Subgroup analyses

The number and proportion of patients who experienced at least 1 adverse reaction will be tabulated by factor specified in Section 5.4. The evaluation specified in Section 8.1.3 will be performed to evaluate the relationship between patient characteristics and the onset of adverse reactions. In the calculation of risk ratio, the categories to be used as the reference are underlined.

Hepatotoxicity will also be evaluated in the same manner as above if it occurs at a sufficient incidence in the evaluation.

The evaluation specified in Section 8.1.3 will be performed for infection with the presence or absence of liver transplant as a factor.

The number and proportion of patients with adverse reactions will be tabulated by SOC and PT by history of liver transplant. Events related to blood disorder in particular will be examined based on the tabulation results

The number and proportion of patients with adverse reactions will be tabulated by SOC and PT for each category of age [< 15 years, ≥ 15 to < 65 years, ≥ 65 years], hepatic impairment [Yes, No], and renal impairment [Yes, No]. The number and proportion of patients with adverse reactions in the subgroup of hepatic impairment [severe] will also be tabulated by SOC and PT.

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8.2.4. Efficacy analyses

8.2.4.1. Time course of NIS

For each of the total score, NIS-LL score, and NIS-UL score, the following analyses will be performed:

1. Summary statistics at each evaluation time point (see A1.1) will be calculated.

2. Summary statistics of the change from before the start of treatment with this drug to each evaluation time point after the start of treatment with this drug will be calculated.

8.2.4.2. Time course of QOL-DN

The following analyses will be performed for TQOL score, physical function/large nerve fiber disorder score, activities of daily living score, symptom score, small nerve fiber disorder score, and autonomic neuropathy score:

1. Summary statistics at each evaluation time point (see A1.1) will be calculated.

2. Summary statistics of the change from before the start of treatment with this drug to each evaluation time point after the start of treatment with this drug will be calculated.

8.2.4.3. Time course of mBMI

Summary statistics of mBMI at each evaluation time point (See A1.2) will be calculated.

Summary statistics of the change from before the start of treatment with this drug to each evaluation time point after the start of treatment with this drug will be calculated in the same manner.

8.2.4.4. Time course of ambulatory status (ambulatory ability scale in polyneuropathy disability score)

The number and proportion of patients will be calculated with ambulatory status before the start of treatment with this drug on the side of the table and ambulatory status at each evaluation time point after the start of treatment with this drug (see A1.1) on the top of the table.

8.2.4.5. Time course of neurological assessment

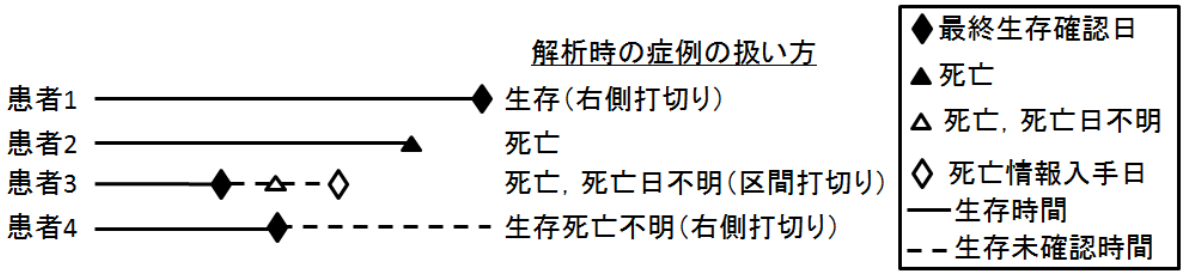
Summary statistics of the measured values of the total score, motor function score, tendon reflex score, and sensation score at each evaluation time point (see A1.3) will be calculated.

Summary statistics of the change from before the start of treatment with this drug to each evaluation time point after the start of treatment with this drug will be calculated in the same manner.

8.2.4.6. Evaluation of survival time

Each time to each event (2 x 2) noted in the evaluation of survival time in Section 6.2 will be analyzed as described in Section 8.1.5. Survival rates will also be calculated at 1.5 and 3 years for the time from the start of treatment to the event and at 10 and 20 years for the time from FAP onset to the event (enter NA if not estimable). When death related to FAP is an event, other deaths will be right-censored.

The outline of how to handle cases at the time of analysis in the evaluation of survival time is shown below.



8.2.4.7. Subgroup analyses

For the measured values of NIS-LL score and TQOL and the changes from the baseline at each time point in A1.1, summary statistics will be calculated for each factor specified in Section 5.4. For prior treatments and concomitant medications, whether to perform subgroup analysis for which treatment/medication will be examined prior to analysis and recorded in order to perform more appropriate evaluation.

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[redacted]

[redacted]

[redacted]

8.2.6. Pharmacokinetics

8.2.6.1. Measurement of plasma tafamidis concentrations in patients with severe hepatic impairment

If plasma tafamidis concentrations were measured in patients with severe hepatic impairment, they will be listed and compared with those previously obtained in healthy adults and subjects with moderate hepatic impairment (Study Fx1A-105).

9. Listings

The following listings will be prepared:

- Patient listing
- List of mutant genotypes (patients diagnosed with mutant genotypes)
- List of patients with adverse reactions
- List of patients with adverse reactions excluded from safety analysis
- List of patients with serious adverse reactions
- List of patients with adverse reactions among patients with hepatic impairment
- List of patients with adverse reactions among patients with renal impairment
- List of elderly patients with adverse reactions
- List of pediatric patients with adverse reactions
- List of patients with adverse reactions among patients who became pregnant during the period from the start date of treatment to the end of the observation period (or the end date of the study)
- List of events corresponding to major investigation items
- List of patients with adverse reactions of major investigation items
- List of deaths

- List of adverse reactions in pregnant and parturient women
- List of adverse reactions of diseases other than the target disease of the study (cardiac amyloidosis, etc.)
- List of patients with liver transplant
- List of efficacy endpoints
  - NIS
  - QOL-DN
  - mBMI
  - Ambulatory status
  - Neurological assessment
  - Survival time
- List of medical evaluations of physical symptoms

In addition, the following tables corresponding to the attached forms will be prepared at the time of periodic safety update report and reexamination:

- Attached Form 1-2 (Status of occurrence of adverse reactions/infections up to the time of approval): Equivalent to Attached Form 2 for reexamination application materials
- Attached Form 2 (Status of occurrence of adverse reactions/infections in post-marketing surveillance, etc.): Attached Form 15 for reexamination application materials
- Attached Form 16 (List of outline of subjects)

10. Appendices

10.1. Appendix 1: Details of Data Extraction

If there are multiple records within the acceptable window, the record closer to the target visit will be adopted.

A1.1 Definition of Visit Timing 1

Endpoint	Visit (target)	Definition [acceptable window]
NIS QOL-DN Ambulatory status Medical assessment of physical symptoms	Before the start of treatment (BL; Base line)	[Before the start of treatment with this drug, Week 4]
	Week 78	[Weeks 4, Week 104]
	Week 156	(> Week 104, ∞]

A1.2 Definition of Visit Timing 2

Endpoint	Visit (target)	Definition [acceptable window]
mBMI	Before the start of treatment (BL)	[Before the start of treatment with this drug, Week 4]
	Week 26	[Week 4, Week 39]
	Week 52	[Week 40, Week 65]
	Week 78	[Week 66, Week 91]
	Week 104	[Week 92, Week 117]
	Week 130	[Week 118, Week 143]
	Week 156	[Week 144, Week 169]

A1.3 Definition of Visit Timing 3

Endpoint	Visit (target)	Definition [acceptable window]
Neurological assessment	Before the start of treatment (BL)	[Before the start of treatment with this drug, Week 4]
	Week 52	[Week 4, Week 78]
	Week 104	[Week 79, Week 130]
	Week 156	[Week 131, Week 182]

10.2. Appendix 2: Details of Efficacy Endpoints

10.2.1. Neuropathy Impairment Score (NIS)

1	Cranial Nerves	3rd Nerve
2	Cranial Nerves	6th Nerve
3	Cranial Nerves	Facial Weakness
4	Cranial Nerves	Palate Weakness
5	Cranial Nerves	Tongue Weakness
6	Muscle Weakness	Respiratory
7	Muscle Weakness	Neck Flexion
8	Muscle Weakness	Shoulder Abduction
9	Muscle Weakness	Elbow Flexion
10	Muscle Weakness	Brachio-radialis
11	Muscle Weakness	Elbow Extension
12	Muscle Weakness	Wrist Flexion
13	Muscle Weakness	Wrist Extension
14	Muscle Weakness	Finger Flexion
15	Muscle Weakness	Finger Spread
16	Muscle Weakness	Thumb Abduction
17	Muscle Weakness	Hip Flexion
18	Muscle Weakness	Hip Extension
19	Muscle Weakness	Knee Flexion
20	Muscle Weakness	Knee Extension
21	Muscle Weakness	Ankle Dorsiflexors
22	Muscle Weakness	Ankle Plantar Flexors
23	Muscle Weakness	Toe Extensors
24	Muscle Weakness	Toe Flexors
25	Reflexes	Biceps Brachii
26	Reflexes	Triceps Brachii
27	Reflexes	Brachioradialis
28	Reflexes	Quadriceps Femoris
29	Reflexes	Triceps Surae
30	Sensation－I. Finger	Touch Pressure
31	Sensation－I. Finger	Pin Prick
32	Sensation－I. Finger	Vibration
33	Sensation－I. Finger	Joint Position
34	Sensation－G.Toe	Touch Pressure
35	Sensation－G.Toe	Pin Prick
36	Sensation－G.Toe	Vibration
37	Sensation－G.Toe	Joint Position

10.2.2. Norfolk Quality of Life-Diabetic neuropathy (QOL-DN)

1	Symptoms	Numbness
2	Symptoms	Tingling sensation, prickling sensation with a pin, prickling sensation with a needle
3	Symptoms	Electrical sensation
4	Symptoms	Other abnormal sensations
5	Symptoms	Surface pain
6	Symptoms	Deep pain
7	Symptoms	Muscle weakness
8	Activities of daily living	During the past 4 weeks, have you had difficulty falling asleep at night due to pain?
9	Activities of daily living	During the past 4 weeks, have you felt painful to touch sheets or clothes or put on your shoes?
10	Activities of daily living	During the past 4 weeks, have you failed to feel any burns or injuries?
11	Activities of daily living	During the past 4 weeks, have you noticed any symptoms that interfered with your normal activities?
12	Activities of daily living	During the past 4 weeks, have you felt difficulty performing fine hand or finger tasks such as clicking on a button of clothing, flipping on a book page, or pinching a coin from a table?
13	Activities of daily living	During the past 4 weeks, have you noticed unsteadiness of your feet when walking?
14	Activities of daily living	During the past 4 weeks, have you had any problems with standing up from the chair without using your hands?
15	Activities of daily living	During the past 4 weeks, have you had problems going down stairs?
16	Activities of daily living	During the past 4 weeks, have you had no sensation in your feet while walking?
17	Activities of daily living	During the past 4 weeks, have you been unable to distinguish between hot and cold water by hand?
18	Activities of daily living	During the past 4 weeks, have you been unable to distinguish between hot and cold water by foot?
19	Activities of daily living	During the past 4 weeks, have you vomited particularly after meals (except vomiting associated with a cold or other illness)?
20	Activities of daily living	During the past 4 weeks, have you had diarrhea or problems with your intestines?
21	Activities of daily living	During the past 4 weeks, have you had fainting or dizziness when you stand up?
22	Activities of daily living	Bathing/showering?

23	Activities of daily living	Clothing?
24	Activities of daily living	Walking?
25	Activities of daily living	Sitting or standing from the toilet?
26	Activities of daily living	Using tableware?
27	Activities of daily living	Have you experience any reduction in the time of work or other activities?
28	Activities of daily living	Have you experienced less completion than you expected?
29	Activities of daily living	Have you had fewer types of work or other activities?
30	Activities of daily living	Have you had difficulty performing work or other activities (extra effort needed)?
31	Activities of daily living	How is your general health now?
32	Activities of daily living	Compared to 3 months ago, how would you rate your health now?
33	Activities of daily living	During the past 4 weeks, how much has your physical health interfered with your normal interactions with family, friends, neighbors, or other peers?
34	Activities of daily living	Over the past 4 weeks, how much has your pain interfered with your normal work (including work in and outside your home)?
35	Activities of daily living	During the past 4 weeks, how much has muscle weakness or instability interfered with your normal work (including work in and outside your home)?

10.2.3. Neurological Assessment

1	Motor	Elbow flexion
2	Motor	Brachioradialis
3	Motor	Elbow extension
4	Motor	Wrist flexion
5	Motor	Wrist extension
6	Motor	Finger flexion
7	Motor	Finger spread
8	Motor	Thumb abduction
9	Motor	Hip flexion
10	Motor	Hip extension
11	Motor	Knee flexion
12	Motor	Knee extension
13	Motor	Ankle dorsiflexors
14	Motor	Ankle plantar flexors
15	Motor	Toe extension
16	Motor	Toe flexors
1	Reflexes	Biceps brachii

2	Reflexes	Triceps brachii
3	Reflexes	Brachioradialis
4	Reflexes	Quadriceps femoris
5	Reflexes	Triceps surae
1	Light Touch	Fingers
2	Light Touch	Hand
3	Light Touch	Lower arm
4	Light Touch	Upper arm
5	Light Touch	Thigh
6	Light Touch	Knee
7	Light Touch	Mid-calf
8	Light Touch	Lower-calf
9	Light Touch	Mid-foot
10	Light Touch	Toe
11	Light Touch	Trunk
1	Pin Prick	Fingers
2	Pin Prick	Hand
3	Pin Prick	Lower arm
4	Pin Prick	Upper arm
5	Pin Prick	Thigh
6	Pin Prick	Knee
7	Pin Prick	Mid-calf
8	Pin Prick	Lower-calf
9	Pin Prick	Mid-foot
10	Pin Prick	Toe
11	Pin Prick	Trunk
1	Vibration	Wrist
2	Vibration	Thumb
3	Vibration	Hip
4	Vibration	Knee
5	Vibration	Ankle
6	Vibration	Toe
1	Position Sense	Wrist
2	Position Sense	Fingers
3	Position Sense	Ankle
4	Position Sense	Toe

CCI [redacted]

[redacted]

Proc Iclifetest Data=data Method= EMICM Plots=survival Outsurv=out;

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[redacted]