Statistical Analysis Plan 2.1

Japanese POEMS syndrome with Thalidomide (J-POST) Trial: multicenter, randomized, double-blind, placebo-controlled, parallel-group, and long-term safety trial of Thalidomide for POEMS syndrome

J-POST Trial (Japanese POEMS Syndrome with Thalidomide Trial)

Phase II/III trial

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11/05/2010	1.0	
10/16/2014	2.0	Full revision including text structure, appearance Changed contract research organization (CRO) company: JGC Pharma Services Co.,⇒EPS Associates Co., Changed statistical analysis supervisor: Hiroyuki Watanabe⇒Yoshikazu Yamabe Deleted one name from persons responsible for statistical analysis
09/28/2015	2.1	Revisions in response to audit (including correction of mistaken and omitted characters, and typographical errors) P2 Revision history - Changed Japanese characters for “Watanabe” P7 Selection criteria (8) - Corrected Japanese characters for “bradycardia” P9 Trial flow – Decadron®⇒Decadron P13 4.2.3 actually administered study drug⇒actually administered study drug P14 4.3.2 number of days from randomization to termination⇒number of days from start of administration to termination P15 4.3.5.1 number of hospital visits⇒number of prescriptions P16 4.3.6.1.3 group period⇒group, period P16 4.3.6.1.3.2 triceps femoris⇒biceps femoris P16 4.3.6.1.3.4 chi-squared test (Fisher’s exact test if necessary)⇒Wilcoxon rank-sum test P18 4.3.7.2 for clinical examination values⇒for clinical examination values and changes P18 4.3.7.2 deleted “, serum VEGF” P18 4.3.7.3 blood pressure (systolic, diastolic) and heart rate⇒blood pressure (systolic, diastolic), heart rate, and body weight P19 4.9 added “total bilirubin” P19 4.9 serum VEGE⇒serum VEGF P19 4.9 vital capacity (VC) units L⇒mL P20 4.10 L1 melphalan-dexamethasone combination therapy⇒melphalan-prednisolone combination therapy

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Summary of Abbreviations

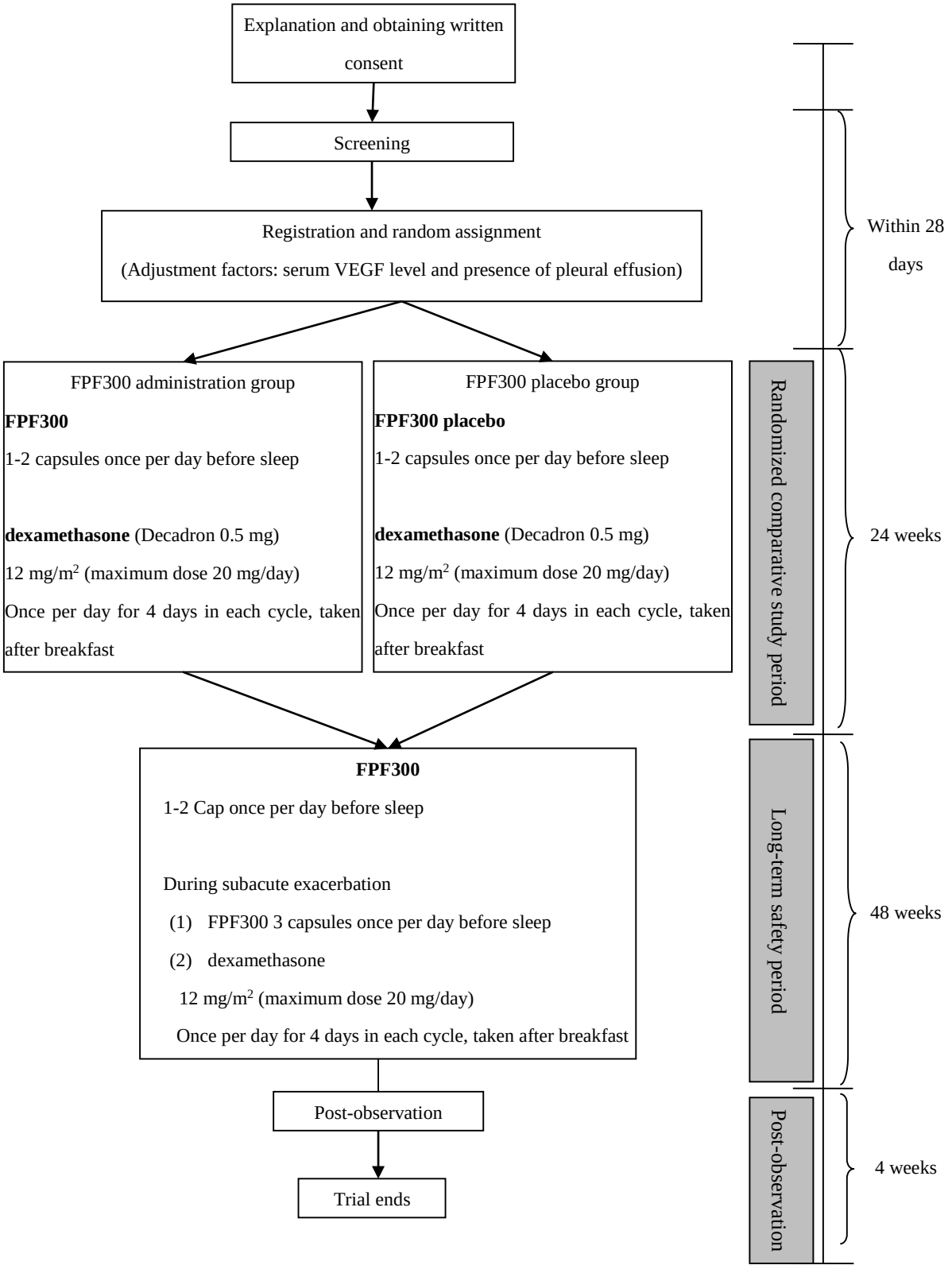
Abbreviation	English
ACTH	Adrenocorticotropic hormone
AST（GOT）	Aspartate aminotransferase (Glutamic oxaloacetic transaminase)
ALT（GPT）	Alanine aminotransferase (Glutamic pyruvic transaminase)
APTT	Activated partial thromboplastin time
BUN	Blood urea nitrogen
Ch-E	Cholinesterase
Cl	Chlorine
CMAP	Compound muscle action potential
CPK	Creatine phosphokinase
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
FDP	Fibrin/fibrinogen degradation products
FSH	Follicle stimulating hormone
FT3	Free triiodothyronine
FT4	Free thyroxine
γ-GTP	γ-Glutamyltranspeptidase
HGH	Human growth hormone (factor)
Ig	Immunoglobulin
K	Potassium
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
LOCF	Last observation carried forward
MMRM	Mixed model repeated measures
Na	Sodium
ONLS	Overall neuropathy limitation scale
PT	Prothrombin time
PS	Performance Status
QOL	Quality of life
TSH	Thyroid stimulating hormone
VC	Vital capacity
VEGF	Vascular endothelial growth factor
WOCF	Worst observation carried forward

1. Summary of the trial

Trial title	Japanese POEMS syndrome with Thalidomide (J-POST) Trial: multicenter, randomized, double-blind, placebo-controlled, parallel-group, and long-term safety trial of Thalidomide for POEMS syndrome - POST Trial (Japanese POEMS Syndrome with Thalidomide Trial)
Trial objective	1) To evaluate the efficacy and safety of thalidomide compared to a placebo in POEMS syndrome. 2) To evaluate the safety and efficacy of long-term administration of thalidomide.
Trial design	A multicenter, randomized, placebo-controlled, double-blind, parallel group, comparative trial (randomized controlled trial [RCT] phase) followed by a long-term safety evaluation trial (long-term open trial period).
Phase	Phase II/III clinical trial
Active product **FPF300**	Generic name: thalidomide (code: FPF 300) Dosage form: No. 2 hard capsules containing thalidomide 100 mg
Placebo **FPF300 placebo**	Placebo capsules that do not contain thalidomide indistinguishable from the active product by their appearance
Inclusion criteria	(1) POEMS syndrome diagnosed according to published diagnostic criteria as 'Probable' and 'Definite' Definite: Three major criteria and at least one minor criterion. Probable: Two major criteria (peripheral neuropathy (polyneuropathy) and elevated serum vascular endothelial growth factor (VEGF)), and at least one minor criterion. Possible: Only one major criteria (peripheral neuropathy (polyneuropathy)), and at least two minor criteria. Major criteria: polyneuropathy (necessary criterion) elevated serum VEGF level (≥1000 pg/mL) M protein (blood M protein-positive). Minor criteria: sclerotic bone lesions, Castleman disease, organomegaly, oedema, pleural effusion, ascites, hydropericardium, endocrinopathy (adrenal, thyroid, pituitary, gonadal, parathyroid, and pancreatic), skin changes (hyperpigmentation, hypertrichosis, plethora, hemangiomata, cyanosis, or white nails), papilledema, and thrombocytosis. *Because of the high prevalence of diabetes mellitus and thyroid abnormalities, this diagnosis alone is not sufficient to meet this minor criterion. (2) Age ≥ 20 years at the time of providing informed consent. (3) Eastern Cooperative Oncology Group (ECOG) Performance Status (PS) of ≤ 3. (4) Overall neuropathy limitation scale (ONLS) total score of ≤ 9. (5) Any of the following laboratory abnormalities: AST (GOT) / ALT (GPT) ≤ 4.0 × upper limit of normal, creatinine < 1.5 × upper limit of normal. (6) Hospitalization at the start of the randomized comparative study period and the long-term safety period. (7) Regular clinic visits every 4 weeks. (8) No clinically significant electrocardiogram (ECG) abnormalities and the absence of advanced bradycardia or bradycardia requiring medical treatment. (9) Written, informed consent from the patient or legal representative. (10) Ineligible for high-dose chemotherapy with peripheral blood stem cell transplantation during the study period. (11) Informed consent to thalidomide education and risk management system

Exclusion criteria	(1) Use of thalidomide, melphalan, bortezomib, or lenalidomide within 24 weeks of providing consent. (2) Unstable patients. (3) Oral or intravenous use of steroids within 4 weeks of providing informed consent. (4) Women who are pregnant, may be pregnant, wish to become pregnant, or are breastfeeding. Men who want their partners to become pregnant. (5) Serious complications (heart failure, renal failure, liver failure, peptic ulcer with bleeding, ileus, poorly controlled diabetes, etc.). (6) Other comorbid malignant tumors. (7) Known allergy to thalidomide or dexamethasone. (8) Serious mental disorder. (9) Use of any other experimental drug or therapy within 12 weeks of providing informed consent.. (10) Use of prohibited drugs (other than β-blockers) or therapy within 4 weeks of the baseline. (11) Patients deemed unsuitable for the trial by the principal investigator or sub-investigator for any other reason.
Endpoints	**(Randomized comparative study period)** **Primary endpoint:** (Efficacy) Serum VEGF reduction rate over 24 weeks **Secondary endpoints:** **(1) Secondary efficacy endpoints** Serum VEGF level Achievement of a normal range of serum VEGF level (1000 pg/mL) Motor function (manual muscle testing, grip strength, and ONLS) Median/ulnar nerve conduction velocity, compound muscle action potential amplitude, and F wave latency M protein qualitative test (blood test and immunofixation) Pleural effusion size Vital capacity (VC) Body weight QOL (SF-36) **(2) Secondary safety outcomes** Adverse events **(Long-term safety period)** **Primary endpoint:** (Safety) Adverse events **Secondary endpoints:** (Efficacy) Serum VEGF level Achievement of a normal range of serum VEGF level (1000 pg/mL) Motor function (manual muscle testing, grip strength, and ONLS)

	Median/ulnar nerve conduction velocity, compound muscle action potential amplitude, and F wave latency M protein qualitative test (blood test and immunofixation) Pleural effusion size Vital capacity (VC) Body weight QOL (SF-36)
Target number of participants	24 subjects (12 subjects per group)
Trial period	Trial period: 5 years (September/01/2010–August/31/2015) Registration period: 3.5 years (September/01/2010–February/28/2014)


Explanation and obtaining written consent
Screening
Registration and random assignment
(Adjustment factors: serum VEGF level and presence of pleural effusion)
Within 28 days
FPF300 administration group
FPF300
1-2 capsules once per day before sleep
dexamethasone (Decadron 0.5 mg)
12 mg/m2 (maximum dose 20 mg/day)
Once per day for 4 days in each cycle, taken after breakfast
FPF300 placebo group
FPF300 placebo
1-2 capsules once per day before sleep
dexamethasone (Decadron 0.5 mg)
12 mg/m2 (maximum dose 20 mg/day)
Once per day for 4 days in each cycle, taken after breakfast
Randomized comparative study period
24 weeks
FPF300
1-2 Cap once per day before sleep
During subacute exacerbation
(1) FPF300 3 capsules once per day before sleep
(2) dexamethasone
12 mg/m2 (maximum dose 20 mg/day)
Once per day for 4 days in each cycle, taken after breakfast
Long-term safety period
48 weeks
Post-observation
Trial ends
Post-observation
4 weeks

2. Survey, examinations, and observational parameters

2.1. Participant background

Sex, age, height, body weight, PS, onset of POEMS syndrome, complications, and medical history, prior treatment history, history of allergy and side effects

2.2. Motor function tests

- MMT (left and right)

  deltoids, biceps brachii, wrist and finger extensors, iliopsoas, quadriceps femoris, biceps femoris, tibialis anterior, and gastrocnemius
- Grip (left and right)
- ONLS

  Arm and Leg Scales and Total Score

2.3. Subjective and objective symptoms

Edema and skin abnormalities (pigmentation)

2.4. Vital signs

Systolic and diastolic blood pressure (SBP and DBP, respectively), heart rate, and body weight

2.5. Clinical examinations

- Blood count

  Erythrocytes, hemoglobin, platelets, leukocytes, differential blood count (neutrophils, lymphocytes, monocytes, eosinophils, basophils)
- Coagulation-fibrinolytic system function test

  Fibrinogen, FDP, APTT, PT, PT-INR
- Biochemistry test

  Total protein, albumin, protein fractions (α_1-, α_2-, β-, and γ-globulins), BUN, serum creatinine, CPK, Ch-E, total bilirubin, AST, ALT, ALP, LDH, γ-GTP, CRP, electrolytes (Na, K, and Cl), blood glucose, Ig-G, Ig-A, and Ig-M
- Serum VEGF
- Urine test (qualitative)

  Urinary sugar and protein
- Endocrine test

  ACTH, CS, HGH, somatomedin C, LH, FSH, E2, testosterone, prolactin, TSH, FT3, FT4, and insulin
- Serum free light chains (K, L, and K/L)
- M protein (qualitative and subclass)

2.6. Chest radiography

Pleural effusion (amount)

2.7. Electrocardiography

Assessment results

2.8. Chest, abdominal, and pelvic CT examinations

Quantities of pleural effusion, pericardial fluid, and ascites

2.9. Respiratory function test (spirometer)

VC (%VC)

2.10. Nerve conduction test (median and ulnar nerve)

CMAP amplitude, motor conduction velocity, and F-wave latency

2.11. QOL survey

SF-36v2™ Japanese version

2.12. Adverse events

Adverse event name, date of appearance, Common Terminology Criteria for Adverse Events (CTCAE, version 4.0) grade, severity, causality, exacerbation of primary disease, treatment related to administration of the study drug, other treatment, outcomes, and date of outcome (date outcome is confirmed)

2.13. Study drug adherence status

Duration, dosage, administration method, adherence status (dose instructed or prescribed by investigator, number of capsules taken, and remaining), dose reductions (if due to adverse events, record the code number of event), dose increases, suspensions (if applicable, record duration)

2.14. Concomitant drugs

Name of Drugs, daily dose, administration route, duration of concurrent use, and reason for use

2.15. Completion, early transition, termination

Date of study drug administration completion, or termination and its reason

2.16. Pregnancy test

Test date, assessment results, assessment by obstetrician (if applicable, date of examination and record result as pregnant or not)

3. Assessment variables

3.1. Efficacy assessment variables

3.1.1. Primary assessment variable (randomized comparative study period)

Reduction rate of serum VEGF levels after 24 weeks

The baseline level is the serum VEGF level before administration of the study drug commenced (cycle 1, day 1). The reduction rate of serum VEGF level will be calculated by subtracting the serum VEGF level after 24 weeks from the

baseline level, then dividing this value by the baseline level (see formula below).

$$\text{Reduction rate of serum VEGF} = \frac{(\text{serum VEGF level at the baseline} - \text{serum VEGF level at 24 weeks})}{\text{serum VEGF level at the baseline}}$$

3.1.2. Secondary assessment variables

- Serum VEGF level
- Achievement of serum VEGF target level (1,000 pg/mL)

  Patients whose serum VEGF levels are reduced to less than 1,000 pg/mL are defined as "achieved."
- Motor function (MMT, grip, and ONLS)
- Median, ulnar nerve motor conduction velocity, CMAP amplitude, and F-wave latency
- Qualitative M protein
- Pleural effusion
- VC
- Body weight
- QOL (SF-36)

3.2. Safety assessment variables

3.2.1. Primary assessment variable (long-term safety period)

- Proportion of adverse event incidences
- Proportion of incidence of leukopenia, thrombocytopenia, deep vein thrombosis, bradycardia, peripheral neuropathy, and other serious adverse events thought to be related to the trial

3.2.2. Secondary assessment variables

- Clinical examination values (except serum VEGF and M protein)
- Vital signs

4. Statistical assessments

4.1. Overall items assessed

4.1.1. Handling of missing data

Unless otherwise noted, missing data will not be replaced with substituted values.

4.1.2. Calculation of number of days

The number of days will be calculated as follows with the initial date as day 1.

(1) Number of days: Day = Day (end) – Day (start) + 1 (if end < start, 1 is not added)

(2) Number of weeks: Week = Days/7

(3) Number of months: Month = Days/365.25/12

(4) Number of years: Year = Days/365.25

4.1.3. Baseline values

Values measured before administration of the study drug will be used as the baseline values. If measurements for either blood pressure, heart rate, blood, urine or serum VEGF have been performed several times before administration of the study drug, the measurement closest to the start of administration will be used as the baseline value.

4.1.4. Significance and confidence levels

Unless otherwise noted, a 2-sided significance level of 5% will be used for all tests. For calculating confidence intervals (CIs), a 2-sided confidence level of 95% will be used.

4.1.5. Descriptive statistics

Unless otherwise noted, the following descriptive statistics are included in the analysis plan.

Nominal and ordinal variables: category frequency and proportion

Continuous variables: number of cases (n), mean, standard deviation (SD), minimum (min.), median, and maximum (max).

4.2. Analysis sets

4.2.1. Full analysis set (FAS)

Subjects, who are registered in this trial and have been administered at least one dose of the study drug will be included in the FAS. However, subjects whose cases contain major violations of the protocol (such as no consent obtaining or early registration before the trial) will be excluded.

4.2.2. Per protocol set (PPS)

The PPS population subjects will exclude all subjects in the FAS population who meet any of the following major violations of the protocol.

- Inclusion criteria violation
- Exclusion criteria violation
- Prohibited concomitant drug use violation
- Prohibited concomitant therapy violation
- Adherence rate less than 75% during the randomized comparative study or the long-term safety periods

4.2.3. Safety analysis set (SAF)

Safety analyses will be performed on the SAF population subjects who are registered in the trial and received the assigned study drug at least once for each treatment group.

4.2.4. Handling of trial patients (cases)

The coordinating investigator and principal investigators will decide how to handle registered patients. If unforeseen problems occur, handling of the cases will be decided based on discussions with statistical advisers or members of the efficacy and safety assessment committee if necessary.

4.2.5. Central review for nerve conduction velocity and pleural effusion

Efficacy of nerve conduction velocity and pleural effusion will be evaluated in accordance with criteria determined

independently by the efficacy and safety assessment committee. The central review of the evaluation will be analyzed for the secondary endpoints.

4.3. Statistical analysis items and plan

The primary analysis for all efficacy endpoints will be performed on the FAS while the analyses on the PPS will be treated as reference data. Safety analyses will be performed on the SAF.

4.3.1. Summary data of population

The data will be collected and evaluated according to treatment group and the results will be presented using tables and figures. Frequencies will be calculated for all of the following population criteria. Other than the number of randomized cases themselves, the proportion of each population against the number of randomized cases will also be calculated. The populations are described below. Diagrams will be created to show the frequencies of each group and the relationships between groups.

- Number of randomized cases
- Number of cases with no study drug administration
- Randomized comparative study period
  - SAF population
  - Number of study completion cases, termination cases, early transition to long-term open trial period cases
  - FAS population
  - PPS population
- Long-term safety period
  - SAF population
  - Number of study completion cases, termination cases
  - FAS population
  - PPS population

4.3.2. Handling of termination and deviation cases

All termination cases will be classified by treatment group and the reason for termination and analyzed by frequency and proportion. Each population frequency and proportion will be divided against the number of randomized cases. In addition, a summary table will be created for all relevant cases, which will contain the following items.

- Subject identification code
- Name of study site
- Assigned trial group
- Number of days from start of administration to termination
- Primary reason for termination

All deviation cases will be classified by treatment group and the reason for deviation and analyzed by frequency and proportion. Reasons for deviation may include: violation of inclusion criteria, exclusion criteria, dosage and admimnistration method (such as dose escalation, dose maintenance, dose reduction, re-administration/reincrease, early

transition or planned transition from the randomized comparative trial (RCT) period to the long-term safety trial period, prohibited medications or therapies from RCT period to the long-term safety trial period, thalidomide dose escalation or dexamethasone administration after dose maintenance of thalidomide and etc.). Each population frequency and proportion will be divided against the number of randomized cases. In addition, a summary table will be created for all relevant cases, which will contain the following items.

- Subject identification code
- Name of study sites
- Assigned trial group
- Primary reason for deviation

4.3.3. Data sets for analysis

The number of participants assigned to each analysis population is shown in section 4.3.1. A summary table will be created for the excluded cases, and will contain the following items.

- Subject identification code
- Name of study sites
- Assigned trial group
- Inclusion or exclusion in each analysis set (FAS, PPS, and SAF)
- Reason for exclusion

4.3.4. Demographic and baseline characteristics

The descriptive statistics of patient background data and baseline values of the survey examination and observational items will be calculated according to treatment group for each analysis population. A chi-squared test (and if necessary, Fisher's exact test) will be used for nominal variables, Wilcoxon's rank-sum test for ordinal variables, and a *t*-test for continuous variables (significance level: 2-sided 10%).

Complications as well as medical, prior treatment, allergy, and side effect histories will be compiled individually after converting replacement readings, if necessary. For replacement readings, a summary table showing the readings before and after conversion will be created, which will be approved by the coordinating investigator and the statistical analysis supervisor. A summary table of replacement readings of the complications is attached as Appendix 1.

4.3.5. Trial compliance

4.3.5.1. Study drug adherence status

The SAF will be classified by treatment group and analyzed by frequency and proportion of study drug adherence, and the following items will be analyzed.

- Dosage and administration method
- Administration Period
- Total dose
- Proportion of administration (dose taken/dose prescribed by investigators)
- Temporary drug cessation (yes or no)

- Reason for temporary cessation
- Number of prescription times

In addition, a summary table will be created for the adherence status of the study drug.

4.3.6. Analysis of efficacy

The analyses will be performed on the endpoints described below. A chronological case summary table will be created for each endpoint.

4.3.6.1. Randomized comparative trial (RCT) period

After the primary endpoint data has been obtained and all the data has been fixed for all cases in the RCT period, the efficacy analyses will be performed on the cases obtained up until the end of the RCT period (after 24 weeks, at early transition to the long-term safety period or termination).

4.3.6.1.1. Primary endpoints

The primary endpoint of this trial is to verify whether thalidomide causes a significant reduction in the rate of VEGF after 24 weeks compared with a placebo. The main analysis will test the null hypothesis that the reduction rate of VEGF will be equivalent in both groups. To achieve this, analyses of covariance will be performed with pre-trial VEGF and the presence of pleural effusion as the covariates. The reduction rates of VEGF for each group, point estimates of the difference between the groups, and CIs will be calculated.

In this analysis, missing serum VEGF measurements from after 24 weeks will be supplemented with the LOCF for the primary analysis, and data supplemented by the WOCF as a sensitivity analysis will be analyzed in the same way as the primary analysis.

As a separate sensitivity analysis, data that has not been supplemented will be used to perform the MMRM. In this case, the correlation structure will be unstructured and compound symmetry will be used when convergence is not obtained.

In addition, changes in the mean reduction rate of VEGF over time will be illustrated in a figure.

4.3.6.1.2. Secondary efficacy endpoints

The analyses of the secondary efficacy endpoints will be performed to support the discussion on the results of the primary analysis in this trial. Group comparisons will be performed as deemed necessary.

4.3.6.1.3. Change in serum VEGF over time

Changes in VEGF over time for each group will be shown as descriptive statistics. In addition, data measured over time will be analyzed using a linear mixed effect model. To achieve this, a logarithmic transformation (base 10) will be performed on the VEGF levels. The factors will be the VEGF level before administration, presence of pleural effusion, group, duration, and interaction between group and duration. The correlation structure will be assumed to be unstructured while autoregressive and compound symmetry (in that order) will be used when convergence is not obtained.

4.3.6.1.3.1. Achievement of serum VEGF target level (1,000 pg/mL)

To test the null hypothesis that the proportion of patients who achieve the target serum VEGF level (1,000 pg/mL) after 24 weeks is equal in both treatment groups, logistic regression analysis will be performed and evaluated using

Wald chi-square statistics.

The covariates for this will be pre-trial VEGF level and presence of pleural effusion. Changes in the proportion of patients who achieve the target serum VEGV level (1,000 pg/mL) over time will be shown for each group and data measured over time will be analyzed using a generalized linear mixed effect model. The factors for this will be VEGF level before administration, presence of pleural effusion, group, duration, and interaction between group and duration. The correlation structure will be assumed to be unstructured, and autoregressive and compound symmetry (in that order) will be used when convergence is not obtained.

4.3.6.1.3.2. Motor function indices (MMT, grip, and ONLS)

Descriptive statistics for the items listed below will be calculated together according to treatment group and visit. A chi-squared test (and, if necessary, Fisher's exact test) will be used for nominal variables, Wilcoxon's rank-sum test for ordinal variables, and a *t*-test for continuous variables (significance level: 2-sided 10%). The items to be calculated together are as follows.

- MMT (left and right mean values):

  Deltoid, wrist and finger extensors, biceps brachii, biceps femoris, quadriceps femoris, iliopsoas, tibialis anterior, and gastrocnemius
- Grip (left and right mean values)
- ONLS

  Arm and leg scales and total Score

4.3.6.1.3.3. Median and ulnar nerve motor conduction velocity, CMAP amplitude, and F-wave latency

Descriptive statistics for median and ulnar nerve motor conduction velocity, CMAP amplitude, and F-wave latency will be calculated together according to the treatment group and visit. A 2-sample *t*-test will be used to examine the differences in mean values between the groups.

To test the null hypothesis that the median and ulnar nerve motor conduction velocity, CMAP amplitude, and F-wave latency after 24 weeks is equal, the MMRM will be compared with age and sex as the covariables.

4.3.6.1.3.4. Qualitative M protein (serum and immunofixation)

Qualitative M protein data will be calculated together according to treatment group and visit, and the frequency and proportion of the categories will be presented according to treatment group. Wilcoxon's rank-sum test will be performed.

4.3.6.1.3.5. Pleural effusion, ascites, and pericardial fluid

The data will be calculated together according to treatment group and visit, and the frequency and proportion of the categories will be presented according to treatment group. Wilcoxon's rank-sum test will be performed. The scores for the variables will be 1: none, 2: small amount, 3: moderate amount, and 4: large amount.

4.3.6.1.3.6. Vital capacity

The descriptive statistics for the VC will be calculated together according to treatment group and visit. A 2-sample *t*-test will be used to examine the differences in mean values between the groups.

4.3.6.1.3.7. Body weight

The descriptive statistics for body weight will be calculated according to treatment group and visit. A 2-sample *t*-test will be used to examine the differences in mean values between the groups.

4.3.6.1.3.8. QOL (SF-36)

The descriptive statistics for the SF-36 subscale will be calculated according to treatment group and visit. Wilcoxon's rank-sum test will be used to compare the scores between the groups.

4.3.6.2. Long-term safety period

The final analysis of the long-term safety period will be performed after all patients have completed the study drug administration and the data becomes fixed.

Since the primary endpoint for the long-term open trial period is safety, all efficacy endpoints will be treated as secondary ones. The efficacy endpoints for the long-term open trial period will be analyzed using the same tests that were used in the RCT. All subjects in the long-term safety period will be treated as though they were allocated into the active product administered group.

4.3.7. Safety analysis

Safety analysis will be performed in both the RCT and long-term open trial period.

The safety endpoints will be the proportion of adverse event occurences and occurence of serious adverse events thought to be related to the treatment, such as leukopenia, thrombocytopenia, deep vein thrombosis, bradycardia, and peripheral neuropathy. Tabulation tables will be created for each outcome. Exact 2-sided 95% CIs for binomial distributions will be calculated for each group for interval estimates of the proportions. If necessary, Fisher's exact test will be performed to compare the groups. Summary tables of the cases over time will be created for each outcome.

4.3.7.1. Adverse events (AEs)

Adverse events will be collected, graded with CTCAE, and coded using MedDRA/J SOC and PT.

A summary table for converting adverse event names to MedDRA/J will be created.

4.3.7.1.1. Analysis of adverse events

The number of cases that experience adverse events and their proportion will be presented. The number of cases with associated AEs, the incidence rate, and the number of occurrences will be recorded in the analytical tables. In addition, exact 2-sided 95% CIs for binomial distributions will be calculated for each group. If the same adverse event occurs two or more times in a particular patient, the worst grade will be adopted when the number of cases is totaled. In principle, one adverse event will be coded as one item.

4.3.7.1.2. Analysis of adverse events of Grade 3 or higher

For AEs graded CTCAE Grade 3 or higher, the number of cases that experience these events and their proportion will be presented. The number of cases with AEs, the incidence rate, and the number of AEs will be recorded in the analytical tables. In addition, exact 2-sided 95% CIs for the binomial distributions will be calculated for each group.

4.3.7.1.3. Analysis of adverse events for which causality cannot be ruled out

For adverse events for which causal relationship with the study drug cannot be ruled out, the number of cases that experience these events and the proportion of their occurrence will be totaled. The number of cases with associated adverse events, the incidence rate, and the number of occurrences will be recorded in the analytical tables. In addition, exact 2-sided 95% CIs for binomial distributions will be calculated for each group.

4.3.7.1.4. Analysis of adverse events observed in at least 20% of each trial group

For adverse events observed in at least 20% of each trial group, the number of cases these events occur in and their incidence proportions will be totaled. The number of cases with an associated adverse event, the incidence rate, and the number of occurrences will be recorded in the analytical tables. In addition, exact 2-sided 95% CIs for the binomial distributions will be calculated for each group.

4.3.7.1.5. Calculation of adverse events that required dose changes or termination of drug administration

For adverse events that required dose changes or termination of administration as stated in "Treatments related to study drug" under "Adverse events" in the case reports, the number of cases these events occur in and their incidence proportions will be calculated together. The number of cases with an associated adverse event, the incidence rate, and the number of occurrences will be recorded on the analytical tables. In addition, exact 2-sided 95% CIs for the binomial distributions will be calculated for each group.

4.3.7.1.6. Death and other serious adverse events

For incidences of death and other serious adverse events, the number of cases these occur in, and their incidence proportions will be totaled. The number of cases with an associated adverse event, the incidence rate, and the number of occurrences will be recorded on the analytical tables. In addition, exact 2-sided 95% CIs for the binomial distributions will be calculated for each group.

4.3.7.2. Assessment of clinical examination values

The descriptive statistics for each clinical examination value and degree of change will be calculated together according to treatment group and visit for the SAF. In addition, figures showing the changes in mean values will be created for each parameter examined (except endocrine and urine tests). Please note that blood counts, as well as biochemistry, coagulation-fibrinolytic system function, urine, and endocrine tests, and serum free light chains will be treated as groups.

4.3.7.2.1. Deviations from clinical examination reference values

The frequency and proportion of deviations from reference values will be calculated for each clinical examination for the SAF.

4.3.7.3. Vital signs

The descriptive statistics for SBP and DBP, heart rate, and body weight will be calculated together according to treatment group and visit for the SAF. In addition, figures showing the changes in mean values will be created for each examination item.

4.3.7.4. Blood drug concentration (trough level)

The descriptive statistics for blood drug concentration (trough level) will be calculated using the usage method and amount for the cases in the long-term safety period. The quantification limit for thalidomide is 0.5 μg/mL.

4.3.8. Other analyses

4.3.8.1. Dexamethasone adherence status

The SAF's adherence status for dexamethasone will be calculated together according to group. The following items will be calculated together.

- Number of days drug was administered for each usage amount and method
- Total duration administered
- Total amount administered

4.3.8.2. Concomitant drugs (including dexamethasone) and therapies

The data of concomitant drugs (including dexamethasone) and therapies used will not be calculated toegther, although a summary table showing the following items will be prepared.

Group, participant identification number, name of drug/therapy, (administration route and dose of drugs), duration of administration/therapy, number of days of administration/therapy, and reason for use

4.4. Interim analysis

An interim analysis will not be performed during the randomized comparative study period.

While there will be no interim analysis, an unblinded analysis after the randomized comparative study period and final analysis after the long-term safety period are planned.

4.5. "Randomized comparative study period analysis report" and "Final analysis report"

The data will be analyzed after it becomes fixed in all cases for which the primary endpoint data is obtained in the randomized comparative study period. Then, a final analysis will be performed after all patients have completed the study drug administration and the data becomes fixed. The statistical analysis supervisor will prepare a "Randomized comparative study period analysis report" and "Final analysis report" to be submitted to the coordinating investigators and the physicians supervising the trial.

4.6. Multicenter trial

Due to the small number of cases in this trial, the data will not be calculated according to institution.

4.7. Adjustment of redundancy

Redundancy adjustments will not be performed.

4.8. Partial populations

Due to the small number of cases in this trial, the data will not be calculated for partial populations.

4.9. Units and number of digits

In the summary tables, the units and the number of digits are shown exactly as they are in the input values but in the

tabulation tables, the following rules govern the standard units and the number of digits.

In addition, one digit after the decimal point is used when expressing percentages.

Min and Max: standard number of digits

Mean, Median, and Lsmean: standard number of digits + 1

SD, CI, and SE: standard number of digits + 2

Please note that the number of digits in the derived variables will not be rounded up during calculations, but rounding off will be performed according to the stipulated number of digits before the results are displayed in the tabulation or summary tables.

Standard units and number of digits

Item	Unit	No. of digits		Item	Unit	No. of digits
Height	cm	1		LDH	U/L	1
Body weight	kg	0.1		γ-GTP	U/L	1
PS	-	1		CRP	mg/dL	0.1
Grip	kg	0.1		Na	mmol/L	1
SBP	mmHg	1		K	mmol/L	0.1
DBP	mmHg	1		Cl	mmol/L	1
PR	times/min	1		Blood glucose	mg/dL	1
Erythrocyte count	10^6/μL	0.01		Ig G	mg/dL	1
Hemoglobin	g/dL	0.1		Ig A	mg/dL	1
Platelets	10^3/μL	1		Ig M	mg/dL	1
Leukocyte count	10^3/μL	0.1		ACTH	pg/mL	0.1
Neutrophils	%	0.1		CS	μg/dL	0.1
Lymphocytes	%	0.1		HGH	ng/mL	0.01
Monocytes	%	0.1		Somatomedin C	ng/mL	0.1
Eosinophils	%	0.1		LH	mIU/mL	0.01
Basophils	%	0.1		FSH	mIU/mL	0.01
Fibrinogen	mg/dL	1		E2	pg/mL	1
FDP	μg/mL	0.1		Testosterone	ng/mL	0.01
APTT	seconds (s)	0.1		Prolactin	ng/mL	0.01
PT	%	1		TSH	μIU/mL	0.001
PT-INR	-	0.01		FT3	pg/mL	0.01
Total protein	g/dL	0.1		FT4	ng/dL	0.01
Albumin	g/dL	0.1		Insulin	μIU/mL	0.1
α_1-globulin	%	0.1		Vital capacity	mL	1
α_2-globulin	%	0.1		%VC	%	0.1
β-globulin	%	0.1		Serum VEGF	pg/mL	1
γ-globulin	%	0.1		Serum free light chain (K)	mg/dL	0.01
BUN	mg/dL	1		Serum free light chain (L)	mg/dL	0.01
Serum creatinine	mg/dL	0.01		Serum free light chain (K/L)	-	0.01
CPK	U/L	1		Serum free light chain	mg/dL	0.01
Ch-E	U/L	1		CMAP amplitude	mV	0.1
Total bilirubin	mg/dL	0.1		Nerve conduction velocity	m/s	1
AST	U/L	1		F-wave latency	ms	0.1
ALT	U/L	1		Thalidomide concentration	μg/mL	0.0001
ALP	U/L	1				

4.10. Basis for setting target number of participants

Although no standard therapy has been established, combination therapy with melphalan and prednisolone has often been selected for use in previous POEMS syndrome groups. An epidemiological study by the Chiba University Hospital found that the reduction rate of VEGF after 24 weeks was 0.35 ± 0.20 and 0.55 ± 0.25 with melphalan-prednisolone and thalidomide-dexamethasone combination therapies, respectively. While the results of therapy with dexamethasone alone have not been reported, the reduction rate of VEGF after 24 weeks is expected to be about 0.1 to 0.2. We hypothesize that in POEMS syndrome, the reduction rate of VEGF after 24 weeks with dexamethasone as the base therapy would be 0.2 in the case of the placebo and 0.55 (SD=0.25) in the case of thalidomide. Using a 2-sided significance level of 5% and 80% detection power, the *t*-statistics showed that there should be 10 cases in each group. When dropouts and other related events are considered, we determined that each group should have 12 cases for a total of 24 cases.

5. Notes

5.1. Software used for statistical analysis, totaling, and creating figures and tables

・SAS (version 9.2 and later)

・Microsoft Excel (2010 and later)

5.2. Program development and validation

Program development and validation will be performed according to the statistical analysis procedure manual and validation plan.

6. Personnel and description of duties

The personnel that will be involved in this trial and their duties are as follows.

Duty	Supervisor
Statistical analysis supervisor	Yoshikazu Yamabe, EPS Associates Co.
Statistical analysis supervisor	Yuji Watanabe, EPS Associates Co.

Any personnel changes that occur will be recorded in a history of changes as an additional document.

End

Appendix 1 Summary of replacement readings for complications

Complications to be totaled	**Complications recorded by physicians**
Hyperuricemia	Hyperuricemia, gout
Hypertension	Hypertensive condition, hypertension
Diabetes	Diabetes
Abnormal lipid metabolism	Abnormal lipid metabolism, lipid abnormality, hyperlipidemia, hypertriglyceridemia

Appendix 2 Summary of reports

Section name	**SAP Chapter No.**	**Generated report title**
Participant background	4.3.1	
Participant background	4.3.1	Table 10_1_1_1 Participant breakdown totals (randomized cases)
Participant background	4.3.1	Table 10_1_1_2 Participant breakdown figures (randomized cases)
Participant background	4.3.2	Table 10_1_2_1 Totals of cases terminated from the trial (randomized cases)
Participant background	4.3.2	List 16_2_1 Summary table of cases terminated from the trial (randomized cases)
Participant background	4.3.2	Table 10_1_3_1 Totals of cases of deviations (randomized cases)
Participant background	4.3.2	List 16_2_2 Summary table of cases of deviations (randomized cases)
Participant background	4.3.3	List 16_2_3 Summary table of cases excluded from the analyses (randomized cases)
Participant background	4.3.4	Table 10_2_1_1 Demographic characteristics (SAF)
Participant background	4.3.4	Table 10_2_1_2 Demographic characteristics (FAS)
Participant background	4.3.4	Table 10_2_1_3 Demographic characteristics (PPS)
Participant background	4.3.4	List 16_2_4 Summary table of demographic data (SAF)

Section name	**SAP Chapter No.**	**Generated report title**
Participant background	4.3.4	Table 10_2_2_1 Reference value characteristics 1: serum VEGF level, free light chains, M protein, subjective and objective symptoms (SAF)
Participant background	4.3.4	Table 10_2_2_2 Reference value characteristics 1: serum VEGF level, free light chains, M protein, subjective and objective symptoms (FAS)
Participant background	4.3.4	Table 10_2_2_3 Reference value characteristics 1: serum VEGF level, free light chains, M protein, subjective and objective symptoms (PPS)
Participant background	4.3.4	Table 10_2_3_1 Reference value characteristics 2: manual muscle test (MMT, SAF)
Participant background	4.3.4	Table 10_2_3_2 Reference value characteristics 2: manual muscle test (MMT, FAS)
Participant background	4.3.4	Table 10_2_3_3 Reference value characteristics 2: manual muscle test (MMT, PPS)
Participant background	4.3.4	Table 10_2_4_1 Reference value characteristics 3: grip, ONLS, chest radiography, ECG, chest/abdominal/pelvic CT (SAF)
Participant background	4.3.4	Table 10_2_4_2 Reference value characteristics 3: grip, ONLS, chest radiography, ECG, chest/abdominal/pelvic CT (FAS)
Participant background	4.3.4	Table 10_2_4_3 Reference value characteristics 3：grip, ONLS, chest radiography, ECG, chest/abdominal/pelvic CT (PPS)
Participant background	4.3.4	Table 10_2_5_1 Reference value characteristics 4: nerve conduction velocity test, respiratory function test, vital signs (SAF)
Participant background	4.3.4	Table 10_2_5_2 Reference value characteristics 4: nerve conduction velocity test, respiratory function test, vital signs (FAS)
Participant background	4.3.4	Table 10_2_5_3 Reference value characteristics 4: nerve conduction velocity test, respiratory function test, vital signs (PPS)
Participant background	4.3.4	Table 10_2_6_1 Reference value characteristics 5: blood test, coagulation system test (SAF)
Participant background	4.3.4	Table 10_2_6_2 Reference value characteristics 5: blood test, coagulation system test (FAS)
Participant background	4.3.4	Table 10_2_6_3 Reference value characteristics 5: blood test, coagulation system test (PPS)
Participant background	4.3.4	Table 10_2_7_1 Reference value characteristics 6: blood chemistry test (SAF)
Participant background	4.3.4	Table 10_2_7_2 Reference value characteristics 6: blood chemistry test (FAS)

Section name	SAP Chapter No.	Generated report title
Participant background	4.3.4	Table 10_2_7_3 Reference value characteristics 6: blood chemistry test (PPS)
Participant background	4.3.4	Table 10_2_8_1 Reference value characteristics 7: urine test, endocrine test, pregnancy test (SAF)
Participant background	4.3.4	Table 10_2_8_2 Reference value characteristics 7: urine test, endocrine test, pregnancy test (FAS)
Participant background	4.3.4	Table 10_2_8_3 Reference value characteristics 7: urine test, endocrine test, pregnancy test (PPS)
Participant background	4.3.5.1	Table 12_1_1 Study drug adherence status (SAF)
Participant background	4.3.5.1	List 16_2_5_1 Summary of study drug adherence status (SAF)
Efficacy	4.3.6	
Efficacy	4.3.6.1.1	Table 11_4_1_1 Changes in reduction rate of serum VEGF (FAS)
Efficacy	4.3.6.1.1	Table 11_4_1_1_1 Changes in reduction rate of serum VEGF (PPS)
Efficacy	4.3.6.1.1	Figure 11_4_1_1 Changes in reduction rate of serum VEGF (FAS)
Efficacy	4.3.6.1.1	Figure 11_4_1_1_1 Changes in reduction rate of serum VEGF (PPS)
Efficacy	4.3.6.1.1	List 16_2_6_1 VEGF summary table (FAS)
Efficacy	4.3.6.1.2.1	Table 11_4_1_2 Changes in serum VEGF (FAS)
Efficacy	4.3.6.1.2.1	Table 11_4_1_2_1 Changes in serum VEGF (PPS)
Efficacy	4.3.6.1.2.2	Table 11_4_1_3 Changes in achievement of VEGF target level (1,000 pg/mL, FAS)
Efficacy	4.3.6.1.2.2	Table 11_4_1_3_1 Changes in achievement of VEGF target level (1,000 pg/mL, PPS)
Efficacy	4.3.6.1.2.3	Table 11_4_1_4 Changes in motor function indices (FAS)
Efficacy	4.3.6.1.2.3	Table 11_4_1_4_1 Changes in motor function indices (PPS)
Efficacy	4.3.6.1.2.4	Table 11_4_1_5 Changes in nerve conduction test results (FAS)
Efficacy	4.3.6.1.2.4	Table 11_4_1_5_1 Changes in nerve conduction test results (PPS)
Efficacy	4.3.6.1.2.5	Table 11_4_1_6 Changes in M protein quantitative test results (FAS)
Efficacy	4.3.6.1.2.5	Table 11_4_1_6_1 M Changes in M protein quantitative test results (PPS)
Efficacy	4.3.6.1.2.5	List 16_2_6_4 Summary table of M quantitative protein, pleural effusion, ascites, and pericardial fluid (FAS)
Efficacy	4.3.6.1.2.6	Table 11_4_1_7 Changes in amount of pleural effusion, ascites, and pericardial fluid (FAS)
Efficacy	4.3.6.1.2.6	Table 11_4_1_7_1 Changes in amount of pleural effusion, ascites, and pericardial fluid (PPS)
Efficacy	4.3.6.1.2.7	Table 11_4_1_8 Changes in vital capacity (VC, FAS)
Efficacy	4.3.6.1.2.7	Table 11_4_1_8_1 Changes in vital capacity (VC, PPS)

Section name	SAP Chapter No.	Generated report title
Efficacy	4.3.6.1.2.7	List 16_2_8_9 Vital capacity (VC) summary table (FAS)
Efficacy	4.3.6.1.2.8	Table 11_4_1_9 Changes in body weight (FAS)
Efficacy	4.3.6.1.2.8	Table 11_4_1_9_1 Changes in body weight (PPS)
Efficacy	4.3.6.1.2.9	Table 11_4_1_10 Changes in QOL (SF-36, FAS)
Efficacy	4.3.6.1.2.9	Table 11_4_1_10_1 Changes in QOL (SF-36, PPS)
Efficacy	4.3.6.1.2.9	List 16_2_8_10 QOL (SF-36) summary table (FAS)
Efficacy	4.3.6.1.3.2	List 16_2_6_2 Motor function index summary table (FAS)
Efficacy	4.3.6.1.3.3	List 16_2_6_3 Nerve conduction test result summary table (FAS)
Safety	4.3.7	
Safety	4.3.7.1	Table 14_3_1 Summary table of alternate readings for adverse events (SAF)
Safety	4.3.7.1.1	Table 12_2_1 Adverse events (SAF)
Safety	4.3.7.1.1	List 16_2_7 Summary table of cases in which adverse events occurred (SAF)
Safety	4.3.7.1.2	Table 12_2_3_1 Adverse events of Grade 3 or higher (SAF)
Safety	4.3.7.1.2	List 14_3_1_2 Summary table of adverse events of Grade 3 or higher (SAF)
Safety	4.3.7.1.3	Table 12_2_3_2 Adverse events for which causality cannot be ruled out (SAF)
Safety	4.3.7.1.3	List 14_3_1_3 Summary table of adverse events for which causality cannot be ruled out (SAF)
Safety	4.3.7.1.4	Table 12_2_3_3 Adverse events that occurred in at least 20% of cases (SAF)
Safety	4.3.7.1.5	Table 12_2_3_4 Adverse events that required dose changes/termination of administration (SAF)
Safety	4.3.7.1.6	Table 12_3_1_1 Death or other serious adverse events (SAF)
Safety	4.3.7.1.6	List 12_3_1_2 Summary table of death or other serious adverse events (SAF)
Safety	4.3.7.2	Table 12_4_2_1 Totals of time-series changes in clinical examination values (SAF)
Safety	4.3.7.2	Figure 12_4_2_1 Totals of time-series changes in clinical examination values (SAF)
Safety	4.3.7.2	Table 12_4_2_2 Totals of time-series changes in clinical examination values (semi-quantitative, quantitative tests, SAF)
Safety	4.3.7.2	List 16_2_8_1 Summary table of clinical examination values (blood count, SAF)
Safety	4.3.7.2	List 16_2_8_2 Summary table of clinical examination values (coagulation-fibrinolytic system) (SAF)
Safety	4.3.7.2	List 16_2_8_3 Summary table of clinical examination values (biochemistry 1, SAF)
Safety	4.3.7.2	List 16_2_8_4 Summary table of clinical examination values (biochemistry 2, SAF)
Safety	4.3.7.2	List 16_2_8_5 Summary table of clinical examination values (endocrine, SAF)
Safety	4.3.7.2	List 16_2_8_6 Summary table of clinical examination values (serum free light chains, SAF)
Safety	4.3.7.2	List 16_2_8_7 Summary table of clinical examination values (urine test, SAF)
Safety	4.3.7.2.1	Table 12_4_2_3 Totals of time-series changes in the amounts of clinical examination value change (SAF)

Section name	**SAP Chapter No.**	**Generated report title**
Safety	4.3.7.2.2	Table 12_4_2_4 Totals of deviations from clinical examination reference values (SAF)
Safety	4.3.7.3	Table 12_5 Totals of time-series changes in vital signs (SAF)
Safety	4.3.7.3	Figure 12_5 Totals of time-series changes in vital signs (SAF)
Safety	4.3.7.3	List 16_2_8_8 Summary table of vital signs (SAF)
Safety	4.3.7.4	Table 12_6 Trough blood levels of thalidomide (SAF)
Safety	4.3.7.4	List 12_6_1 Summary of trough blood levels of thalidomide (SAF)
Safety	4.3.8.1	Table 12_1_2 Adherence status of base study drug (SAF)
Safety	4.3.8.2	List 16_2_5_2 Summary table of concomitant drugs, therapies (SAF)

SAF: Safety Analysis Set; FAS: Full Analysis Set; PPS: Per Protocol Set

Statistical Analysis Plan – Supplement 1 version 1.1

Japanese POEMS syndrome with Thalidomide (J-POST) Trial: multicenter, randomized, double-blind, placebo-controlled, parallel-group, and long-term safety trial of Thalidomide for POEMS syndrome

J-POST Trial (Japanese POEMS Syndrome with Thalidomide Trial)

Phase II/III trial

Coordinating Investigator:

Chiba University Hospital, Department of Neurology

Satoshi Kuwabara (personal seal)

Approval date: 2/10/2015

Statistical Analysis Supervisor:

EPS Associates Co., Project Development Headquarters

Yoshikazu Yamabe (personal seal)

Approval date:9/28/2015

Revision history:

Date created	Revision No.	Content of revision
April 28, 2015	1.0	Newly created
September 28, 2015	1.1	Revisions in response to audit P5 4.1, pre-trial vascular endothelial growth factor (VEGF) level (≥ and < 3,000)⇒pre-trial VEGF level (≥ and < 3,000 pg/mL) P6 4.3.2, vital capacity (VC and VC%) actual values and change from baseline⇒vital capacity (VC and VC%) actual values, change from baseline, and rate of change P7 4.6, Changed Japanese characters for “sinus bradycardia” P9 6, Vital capacity units L⇒mL P9 6, serum VEGE⇒serum VEGF P9 6, added “total bilirubin”

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Summary of Abbreviations

Abbreviation	English
ACTH	Adrenocorticotropic hormone
AST (GOT)	Aspartate aminotransferase (Glutamic oxaloacetic transaminase)
ALT (GPT)	Alanine aminotransferase (Glutamic pyruvic transaminase)
APTT	Activated partial thromboplastin time
BUN	Blood urea nitrogen
Ch-E	Cholinesterase
Cl	Chlorine
CMAP	Compound muscle action potential
CPK	Creatine phosphokinase
CRP	C-reactive protein
CT	Computed tomography
CTCAE	Common Terminology Criteria for Adverse Events
ECOG	Eastern Cooperative Oncology Group
FDP	Fibrin/fibrinogen degradation products
FSH	Follicle stimulating hormone
FT3	Free triiodothyronine
FT4	Free thyroxine
γ-GTP	γ-Glutamyltranspeptidase
HGH	Human growth hormone (factor)
Ig	Immunoglobulin
K	Potassium
LDH	Lactate dehydrogenase
LH	Luteinizing hormone
LOCF	Last observation carried forward
Lsmean	Least square mean
Max, max	Maximum
Min, min	Minimum
MMRM	Mixed model repeated measures
MMT	Manual muscle testing
N, n	Number
Na	Sodium
ONLS	Overall neuropathy limitation scale
PT	Prothrombin time
PS	Performance status

Abbreviation	English
QOL	Quality of life
SD, Sd, sd	Standard deviation
SE, Se, se	Standard error
TSH	Thyroid stimulating hormone
VC	Vital capacity
VEGF	Vascular endothelial growth factor
WOCF	Worst observation carried forward

1. Introduction

This document describes the additional statistical analysis plan in detail after unblinding to this Japanese POEMS syndrome with Thalidomide (J-POST) Trial: multicenter, randomized, double-blind, placebo-controlled, parallel-group, and long-term safety trial of Thalidomide for POEMS syndrome

2. Objective of additional analyses

The analysis of the results based solely on the Statistical Analysis Plan (version 2.0) for Japanese POEMS syndrome with Thalidomide (J-POST) Trial: multicenter, randomized, double-blind, placebo-controlled, parallel-group, and long-term safety trial of Thalidomide for POEMS syndrome exhibited some insufficiencies in the explanations and interpretations. Therefore, additional analyses of efficacy and safety were planned.

3. Data for analysis

The data set to be analyzed for this plan will be used for the one created based on the Statistical Analysis Plan (version 2.0) for Japanese POEMS syndrome with Thalidomide (J-POST) Trial: multicenter, randomized, double-blind, placebo-controlled, parallel-group, and long-term safety trial of Thalidomide for POEMS syndrome.

4. Content of additional analysis

The following additional analyses will be performed.

4.1. Vascular endothelial growth factor (VEGF)

1). A difference was observed between the groups in the performance status (PS) and, therefore, this will be included as a covariate in the planned primary analysis, which is an analysis of covariance with the last observation carried forward (LOCF) data on the reduction rate of VEGF from baseline. Thus, the covariates are pre-trial VEGF (≥ and < 3,000 pg/mL), the presence of pleural effusion, and PS (1, 2, and 3). A similar covariance analysis using the worst observation carried forward (WOCF) data will be performed as a sensitivity analysis. For a separate sensitivity analysis, unsupplemented data will be used for the mixed model repeated measures (MMRM), and the

PS will be included in the model. The least squares mean (Lsmean) estimates for each group at the end of the randomized period, Lsmean estimates and 95% confidence intervals (CIs) for differences between the groups, and *t*-test p-values will be calculated. Compound symmetry will be used for the correlation structure.

2). Changes in the VEGF measurements as well as the reduction and reduction rate from baseline over time will be illustrated in figures for each group and each participant. Changes in the mean values and standard deviations over time will also be illustrated in figures for each group. Non-LOCF data of reduction rates will be used for the figures.

Changes in the rate of VEGF target level achievement and 95% CIs over time will be illustrated in figures base on groups.

3). The standard error (SE) and 95% CIs will be shown for the MMRM results using log 10 transformed VEGF levels in Table 11_4_1_2, which shows Lsmean and p-values for differences from the placebo group.

4.2. Nerve conduction test

Median nerve (right and left): Compound muscle action potential (CMAP) amplitude, nerve conduction velocity, and F-wave latency.

Ulnar nerve (right and left): CMAP amplitude, nerve conduction velocity, and F-wave latency.

The following analyses will be performed for actual measurements, change from baseline, and rate of change of the 12 parameters of the F-wave latency, which will be corrected for height (165 cm conversion).

$$\text{F}-\text{wave latency (height corrected value)} = \frac{165}{height\ (cm)} \times \text{F wave latency (actual value)}$$

4). Descriptive statistics (n, mean, standard deviation [SD], minimum [min], median, and maximum [max]) will be shown in a table by observation period (baseline, at the end of cycle 3, and end of the random period) and by group.

5). Lsmean estimates for each group, Lsmean estimates and 95% CIs for differences between the groups, and *t*-test p-values will be calculated using covariance analysis with sex, age, and baseline values as the covariates using LOCF data from the end of the random period. Sex will be treated as a categorical variable while age and baseline values are the continuous variables.

6). Lsmean estimates for each group at the end of the random period, Lsmean estimates and 95% CIs for differences between the groups and *t*-test p-values will be calculated using MMRM based on the observation period data. The factors for MMRM will be sex, age, baseline values, group, visit, and the interaction between group and visit. The correlation structure will be assumed to be compound symmetry.

7). Changes over time will be illustrated in figures for each examination item, group, and participant. Changes over time for mean values and SDs for each group will also be shown in figures.

4.3. Grip strength, vital capacity, and body weight

1). Grip strength

Descriptive statistics (n, mean, SD, min, median, and max) and p-values for *t*-tests between the groups will be illustrated in a table for the actual grip measurements (right, left, and left-right mean), change from baseline, and rate of change by observation period (baseline; end of cycles 1, 2, 3, 4, and 5; and end of random period) and by

group. In addition, as a reference, Lsmean estimates for each group, Lsmean estimates and 95% CIs for differences between the groups, and *t*-test p-values will be calculated using covariance analysis with baseline values of the LOCF data as the covariate.

2). Vital capacity

Descriptive statistics (n, mean, SD, min, median, and max) and p-values for *t*-tests between the groups will be illustrated in a table for the LOCF data on actual vital capacity measurements (VC and VC%), change from baseline, and rate of change by observation period (baseline and end of random period) and by group. Lsmean estimates for each group, Lsmean estimates and 95% CIs for differences between the groups, and *t*-test p-values will be calculated using covariance analysis with baseline values from LOCF data at the end of the random period as the covariate. Baseline values will be treated as continuous variables.

3). Body weight

Descriptive statistics (n, mean, SD, min, median, and max) and p-values for *t*-tests between the groups will be illustrated in a table for data of actual body weight values, change from baseline, and rate of change by observation period (baseline; end of cycles 1, 2, 3, 4, and 5, and end of random period) and by group.

4). Changes over time will be illustrated in figures by examination item, group, and participant. Changes over time for mean values and SDs will also be illustrated in figures for each group.

4.4. Pleural effusion, ascites, and pericardial fluid

Distributions of the change from baseline in the evaluated values of each variable and the scores for each variable (1: none, 2: low, 3: moderate, and 4: high amounts) will be illustrated in a table based on observation period (baseline; end of cycle 3, and end of random period) and by group. Differences in the distributions between the groups at each time point will be evaluated using a 2-sample Wilcoxon test, and p-values will be shown. P-values will be 1-sided and obtained with the exact calculation method. In addition, a shift table for baseline values will be shown.

Distributions of the amount of pleural effusion will be illustrated in a bar graph for each group.

A summary table for pleural effusion, serum VEGF levels, the rate of VEGF change, and the number of days administered by the end of the random period/early transition/termination will be created based on the group, participant, and observation period.

4.5. Manual muscle testing (MMT)

Total scores will be determined from the manual muscle testing (MMT). The following analyses will also be performed to determine the change in total score from baseline and the rate of change

Descriptive statistics (n, mean, SD, min, median, and max) and p-values for *t*-tests between the groups will be shown in a table based on the observation period (baseline; end of cycles 1, 2, 3, 4, and 5; and end of random period) and the group.

Lsmean estimates for each group at the end of the random period, Lsmean estimates and 95% CIs for differences between the groups and *t*-test p-values will be calculated using the MMRM. Baseline values, group, visit, and interaction between group and visit will be the factors for the MMRM. The correlation structure will be assumed to be compound symmetry.

Changes over time will be illustrated in figures by group and participant. Changes over time for mean values and

SDs will also be illustrated in figures for each group.

4.6. Sinus bradycardia

The influence of the following factors on sinus bradycardia incidence will be examined in subjects in the safety analysis set (SAF), who were administered the active product. The items listed under demographic characteristics and reference value characteristics in Table 10_2_1, 2, 4, 5, 6, 7, and 8 (baseline data will be used for all items) and the presence or absence of subacute exacerbation. Cases that transitioned early to the long-term safety trial were considered to have exhibited subacute exacerbation.

Reports will be created for the drugs (active product and placebo) in the Table 10_2 series above for the presence and absence of onset.

4.7. Subacute exacerbation

The influence of the following factors on presence or absence of subacute exacerbation will be examined in subjects in the SAF, who were administered the study drug. The items listed under demographic characteristics and reference value characteristics in Table 10_2_1, 2, 3, 4, 5, 6, 7, and 8 (baseline data will be used for all items).

Reports will be created for the drugs (active product and placebo) in the Table 10_2 series above for the presence and absence of subacute exacerbation. A case summary table will be created for cases of subjects with subacute exacerbation (that transitioned early to the long-term safety trial). The items to be shown are the name of the clinical trial site, subject identification code number, drug treatment group, and final day of study drug administration (number of days since administration commenced).

5. Definitions

5.1. LOCF

If data from the final evaluation (end of the random period) is missing, and there are evaluations from regular visits before the final evaluation (baseline, end of cycles 1, 2, 3, 4, and 5), the missing value will be replaced with the substituted measurement taken closest to the end of the randomized period. If evaluation was conducted only at the baseline before the final evaluation,, the baseline value will be used as the replacement.

5.2. WOCF

If data from the final evaluation (end of the randomized period) is missing and there are evaluations from regular visits before the final evaluation (baseline, end of cycles 1, 2, 3, 4, and 5), the missing value will be replaced with the worst of those values. If evaluation was conducted only at the baseline before the final evaluation,, the baseline value will be used as the replacement.

6. Units and number of digits

In the summary tables, the units and number of digits are shown exactly as they are in the input values but in the tabulated tables, the following rules govern the standard units and number of digits.

In addition, 1 digit after the decimal point is shown for percentages.

Min and Max: standard number of digits

Mean, Median, and Lsmean: standard number of digits + 1

SD, xx% CI, SE: standard number of digits + 2

Please note that the number of digits of the derived variables will not be rounded during calculations, but rounding will be performed based on the stipulated number of digits before the data is displayed in the tabulated or summary tables.

The following are the standard units and number of digits.

Item	Unit	No. of digits		Item	Unit	No. of digits
Height	cm	1		LDH	U/L	1
Body weight	kg	0.1		γ-GTP	U/L	1
PS	-	1		CRP	mg/dL	0.1
Grip	kg	0.1		Na	mmol/L	1
SBP	mmHg	1		K	mmol/L	0.1
DBP	mmHg	1		Cl	mmol/L	1
PR	time/min	1		Blood glucose	mg/dL	1
Erythrocyte count	10^6/μL	0.01		Ig G	mg/dL	1
Hemoglobin	g/dL	0.1		Ig A	mg/dL	1
Platelets	10^3/μL	1		Ig M	mg/dL	1
Leukocyte count	10^3/μL	0.1		ACTH	pg/mL	0.1
Neutrophils	%	0.1		CS	μg/dL	0.1
Lymphocytes	%	0.1		HGH	ng/mL	0.01
Monocytes	%	0.1		Somatomedin C	ng/mL	0.1
Eosinophils	%	0.1		LH	mIU/mL	0.01
Basophils	%	0.1		FSH	mIU/mL	0.01
Fibrinogen	mg/dL	1		E2	pg/mL	1
FDP	μg/mL	0.1		Testosterone	ng/mL	0.01
APTT	seconds	0.1		Prolactin	ng/mL	0.01
PT	%	1		TSH	μIU/mL	0.001
PT-INR	-	0.01		FT3	pg/mL	0.01
Total protein	g/dL	0.1		FT4	ng/dL	0.01
Albumin	g/dL	0.1		Insulin	μIU/mL	0.1
α_1-globulin	%	0.1		VC	mL	1
α_2-globulin	%	0.1		%VC	%	0.1
β-globulin	%	0.1		Serum VEGF	pg/mL	1
γ-globulin	%	0.1		Serum free light chain (K)	mg/dL	0.01
BUN	mg/dL	1		Serum free light chain (L)	mg/dL	0.01
Serum creatinine	mg/dL	0.01		Serum free light chain (K/L)	-	0.01
CPK	U/L	1		Serum free light chain	mg/dL	0.01
Ch-E	U/L	1		CMAP amplitude	mV	0.1
Total bilirubin	mg/dL	0.1		Nerve conduction velocity	m/s	1
AST	U/L	1		F-wave latency	ms	0.1
ALT	U/L	1		Thalidomide concentration	μg/mL	0.0001
ALP	U/L	1		MMT total score	-	1

Please refer to the summary of abbreviations on page 4 for definitions of abbreviations used here.

7. Summary of reports

Section name	SAP Chapter No.	Generated report title
1	4.1	Table AD_11_4_1_2 Change in serum VEGF (FAS/PPS)
2	4.1	Table AD_11_4_1_11 Change in reduction rate of serum VEGF (LOCF, FAS/PPS)
3	4.2	Table AD_11_4_1_12_1_1 Change in actual nerve conduction measurements 1 (LOCF/身長補正) (FAS/PPS)
4	4.2	Table AD_11_4_1_12_1_2 Covariance analysis of actual nerve conduction measurements (LOCF/height corrected, FAS/PPS)
5	4.2	Table AD_11_4_1_12_2_1 Time series analysis of variance of actual nerve conduction measurements (MMRM/height corrected, FAS/PPS)
6	4.2	Table AD_11_4_1_13_1_1 Changes in amount of nerve conduction test result change 1 (LOCF/height corrected, FAS/PPS)
7	4.2	Table AD_11_4_1_13_1_2 Covariance analysis of nerve conduction test results (LOCF/height corrected, FAS/PPS)
8	4.2	Table AD_11_4_1_13_2_1 Time series analysis of variance of nerve conduction test results (MMRM/ height corrected, FAS/PPS)
9	4.2	Table AD_11_4_1_14_1_1 Changes in rate of nerve conduction test result change 1 (LOCF/ height corrected, FAS/PPS)
10	4.2	Table AD_11_4_1_14_1_2 Covariance analysis of rate of nerve conduction test result change (LOCF/height corrected, FAS/PPS)
11	4.2	Table AD_11_4_1_14_2_1 Time series analysis of variance of rate of nerve conduction test result change (MMRM/height corrected, FAS/PPS)
12	4.3	Table AD_11_4_1_15_1 Changes in grip (right, FAS/PPS)
13	4.3	Table AD_11_4_1_15_2 Changes in grip (left, FAS/PPS)
14	4.3	Table AD_11_4_1_15_3 Changes in grip (left-right mean, FAS/PPS)
15	4.3	Table AD_11_4_1_16_1 Covariance analysis of and changes in vital capacity (VC, LOCF, FAS/PPS)
16	4.3	Table AD_11_4_1_16_2 Covariance analysis of and changes in percentage VC (VC%, LOCF, FAS/PPS)
17	4.3	Table AD_11_4_1_17_1 Changes in actual body weight measurements (FAS/PPS)
18	4.3	Table AD_11_4_1_17_2 Changes in body weight change (FAS/PPS)
19	4.3	Table AD_11_4_1_17_3 Changes in rate of body weight change (FAS/PPS)
20	4.4	Table AD_11_4_1_18 Changes in amounts of pleural effusion, ascites, and pericardial fluid change (FAS/PPS)
21	4.4	Table AD_11_4_1_19 Shift table from baseline for amounts of pleural effusion, ascites, and pericardial fluid (FAS/PPS)
22	4.5	Table AD_11_4_1_20 Changes in manual muscle testing (MMT) total score (FAS/PPS)

Section name	SAP Chapter No.	Generated report title
23	4.6	Table AD_12_2_3_5_1 Demographic characteristics based on presence/absence of sinus bradycardia (active treatment group, SAF/FAS/PPS)
24	4.6	Table AD_12_2_3_5_2 Reference value characteristics based on presence/absence of sinus bradycardia 1: serum VEGF, free light chains, M protein, and subjective/objective symptoms (active treatment group, SAF/FAS/PPS)
25	4.6	Table AD_12_2_3_5_3 Reference value characteristics based on presence/absence of sinus bradycardia 3: grip, overall neuropathy limitation scale (ONLS), chest radiography, electrocardiography (ECG), chest/abdominal/pelvic computed tomography (CT, active treatment group, SAF/FAS/PPS)
26	4.6	Table AD_12_2_3_5_4 Reference value characteristics based on presence/absence of sinus bradycardia 4: nerve conduction tests, respiratory function tests, and vital signs (active treatment group, SAF/FAS/PPS)
27	4.6	Table AD_12_2_3_5_5 Reference value characteristics based on presence/absence of sinus bradycardia 5: blood and coagulation system tests (active treatment group, SAF/FAS/PPS)
28	4.6	Table AD_12_2_3_5_6 Reference value characteristics based on presence/absence of sinus bradycardia 6: blood biochemistry tests (active treatment group, SAF/FAS/PPS)
29	4.6	Table AD_12_2_3_5_7 Reference value characteristics based on presence/absence of sinus bradycardia 7: urine, endocrine, and pregnancy tests (active treatment group, SAF/FAS/PPS)
30	4.7	Table AD_12_2_3_6_1 Demographic characteristics based on presence/absence of subacute exacerbation (SAF/FAS/PPS)
31	4.7	Table AD_12_2_3_6_2 Reference value characteristics based on presence/absence of subacute exacerbation 1: serum VEGF, free light chains, M protein, and subjective/objective symptoms (SAF/FAS/PPS)
32	4.7	Table AD_12_2_3_6_3 Reference value characteristics based on presence/absence of subacute exacerbation 2: MMT (SAF/FAS/PPS)
33	4.7	Table AD_12_2_3_6_4 Reference value characteristics based on presence/absence of subacute exacerbation 3: grip, ONLS, chest radiography, ECG, and chest/abdominal/pelvic CT (SAF/FAS/PPS)
34	4.7	Table AD_12_2_3_6_5 Reference value characteristics based on presence/absence of subacute exacerbation 4: nerve conduction and respiratory function tests, as well as vital signs (SAF/FAS/PPS)
35	4.7	Table AD_12_2_3_6_6 Reference value characteristics based on presence/absence of subacute exacerbation 5: blood and coagulation system tests (SAF/FAS/PPS)
36	4.7	Table AD_12_2_3_6_7 Reference value characteristics based on presence/absence of subacute exacerbation 6: blood biochemistry tests (SAF/FAS/PPS)
37	4.7	Table AD_12_2_3_6_8 Reference value characteristics based on presence/absence of subacute exacerbation 7: urine, endocrine, and pregnancy tests (SAF/FAS/PPS)
38	4.1	Figure AD_11_4_1_11_1_1_1F Changes in serum VEGF (SAF/FAS/PPS)
39	4.1	Figure AD_11_4_1_11_2_1_1F Changes in amount of serum reduction of VEGF (SAF/FAS/PPS)
40	4.1	Figure AD_11_4_1_11_3_1_1F Changes in serum VEGF reduction rate (SAF/FAS/PPS)

Section name	SAP Chapter No.	Generated report title
41	4.1	Figure AD_11_4_1_11_4F Changes in rate of target serum VEGF level achievement and 95% confidence intervals (CIs, SAF/FAS/PPS)
42	4.2	Figure AD_11_4_1_12_1_1F Changes in median nerve compound muscle action potential (CMAP) amplitude (right, SAF/FAS/PPS)
43	4.2	Figure AD_11_4_1_12_1_2F Changes in median nerve conduction velocity (right, SAF/FAS/PPS)
44	4.2	Figure AD_11_4_1_12_1_3F Changes in median nerve F wave latency (right, SAF/FAS/PPS)
45	4.2	Figure AD_11_4_1_12_1_4F Changes in ulnar nerve CMAP amplitude (right, SAF/FAS/PPS)
46	4.2	Figure AD_11_4_1_12_1_5F Changes in ulnar nerve conduction velocity (right, SAF/FAS/PPS)
47	4.2	Figure AD_11_4_1_12_1_6F Changes in ulnar nerve F wave latency (right, SAF/FAS/PPS)
48	4.2	Figure AD_11_4_1_12_1_7F Changes in median nerve CMAP amplitude (left, SAF/FAS/PPS)
49	4.2	Figure AD_11_4_1_12_1_8F Changes in median nerve conduction velocity (left, SAF/FAS/PPS)
50	4.2	Figure AD_11_4_1_12_1_9F Changes in median nerve F wave latency (left, SAF/FAS/PPS)
51	4.2	Figure AD_11_4_1_12_1_10F Changes in ulnar nerve CMAP amplitude (left, SAF/FAS/PPS)
52	4.2	Figure AD_11_4_1_12_1_11F Changes in ulnar nerve conduction velocity (left, SAF/FAS/PPS)
53	4.2	Figure AD_11_4_1_12_1_12F Changes in ulnar nerve F wave latency (left, SAF/FAS/PPS)
54	4.2	Figure AD_11_4_1_12_2_1F Changes in median nerve CMAP amplitude change (right, SAF/FAS/PPS)
55	4.2	Figure AD_11_4_1_12_2_2F Changes in median nerve conduction velocity change (right, SAF/FAS/PPS)
56	4.2	Figure AD_11_4_1_12_2_3F Changes in median nerve F wave latency change (right, SAF/FAS/PPS)
57	4.2	Figure AD_11_4_1_12_2_4F Changes in ulnar nerve CMAP amplitude change (right, SAF/FAS/PPS)
58	4.2	Figure AD_11_4_1_12_2_5F Changes in ulnar nerve conduction velocity change (right, SAF/FAS/PPS)
59	4.2	Figure AD_11_4_1_12_2_6F Changes in ulnar nerve F wave latency change (right, SAF/FAS/PPS)
60	4.2	Figure AD_11_4_1_12_2_7F Changes in median nerve CMAP amplitude change (left, SAF/FAS/PPS)
61	4.2	Figure AD_11_4_1_12_2_8F Changes in median nerve conduction velocity change (left, SAF/FAS/PPS)
62	4.2	Figure AD_11_4_1_12_2_9F Changes in median nerve F wave latency change (left, SAF/FAS/PPS)
63	4.2	Figure AD_11_4_1_12_2_10F Changes in ulnar nerve CMAP amplitude change (left, SAF/FAS/PPS)
64	4.2	Figure AD_11_4_1_12_2_11F Changes in ulnar nerve conduction velocity change (left, SAF/FAS/PPS)
65	4.2	Figure AD_11_4_1_12_2_12F Changes in ulnar nerve F wave latency change (left, SAF/FAS/PPS)
66	4.2	Figure AD_11_4_1_12_3_1F Changes in rate of median nerve CMAP amplitude change (right, SAF/FAS/PPS)
67	4.2	Figure AD_11_4_1_12_3_2F Changes in rate of median nerve conduction velocity change (right, SAF/FAS/PPS)
68	4.2	Figure AD_11_4_1_12_3_3F Changes in rate of median nerve F-wave latency change (right, SAF/FAS/PPS)
69	4.2	Figure AD_11_4_1_12_3_4F Changes in rate of ulnar nerve CMAP amplitude change (right, SAF/FAS/PPS)
70	4.2	Figure AD_11_4_1_12_3_5F Changes in rate of ulnar nerve conduction velocity change (right, SAF/FAS/PPS)

Section name	SAP Chapter No.	Generated report title
71	4.2	Figure AD_11_4_1_12_3_6F Changes in rate of ulnar nerve F-wave latency change (right, SAF/FAS/PPS)
72	4.2	Figure AD_11_4_1_12_3_7F Changes in rate of median nerve CMAP amplitude change (left, SAF/FAS/PPS)
73	4.2	Figure AD_11_4_1_12_3_8F Changes in rate of median nerve conduction velocity change (left, SAF/FAS/PPS)
74	4.2	Figure AD_11_4_1_12_3_9F Changes in rate of median nerve F-wave latency change (left, SAF/FAS/PPS)
75	4.2	Figure AD_11_4_1_12_3_10F Changes in rate of ulnar nerve CMAP amplitude change (left, SAF/FAS/PPS)
76	4.2	Figure AD_11_4_1_12_3_11F Changes in rate of ulnar nerve conduction velocity change (left, SAF/FAS/PPS)
77	4.2	Figure AD_11_4_1_12_3_12F Changes in rate of ulnar nerve F wave latency change (left, SAF/FAS/PPS)
78	4.3	Figure AD_11_4_1_15_1_1_1F Grip: changes in actual measurements (right, SAF/FAS/PPS)
79	4.3	Figure AD_11_4_1_15_1_1_2F Grip: changes in amount of change (right, SAF/FAS/PPS)
80	4.3	Figure AD_11_4_1_15_1_1_3F Grip: changes in rate of change (right, SAF/FAS/PPS)
81	4.3	Figure AD_11_4_1_15_1_2_1F Grip: changes in actual measurements (left, SAF/FAS/PPS)
82	4.3	Figure AD_11_4_1_15_1_2_2F Grip: changes in amount of change (left, SAF/FAS/PPS)
83	4.3	Figure AD_11_4_1_15_1_2_3F Grip: changes in rate of change (left, SAF/FAS/PPS)
84	4.3	Figure AD_11_4_1_15_1_3_1F Grip: changes in actual measurements (left-right mean, SAF/FAS/PPS)
85	4.3	Figure AD_11_4_1_15_1_3_2F Grip: changes in amount of change (left-right mean, SAF/FAS/PPS)
86	4.3	Figure AD_11_4_1_15_1_3_3F Grip: changes in rate of change (left-right mean, SAF/FAS/PPS)
87	4.3	Figure AD_11_4_1_16_1_1F Changes in VC (SAF/FAS/PPS)
88	4.3	Figure AD_11_4_1_16_1_2F Changes in amount of VC change (SAF/FAS/PPS)
89	4.3	Figure AD_11_4_1_16_1_3F Changes in rate of VC change (SAF/FAS/PPS)
90	4.3	Figure AD_11_4_1_16_2_1F Changes in VC% (SAF/FAS/PPS)
91	4.3	Figure AD_11_4_1_16_2_2F Changes in VC% change (SAF/FAS/PPS)
92	4.3	Figure AD_11_4_1_16_2_3F Changes in rate of VC% change (SAF/FAS/PPS)
93	4.3	Figure AD_11_4_1_17_1_1F Body weight: changes in actual measurements (SAF/FAS/PPS)
94	4.3	Figure AD_11_4_1_17_1_2F Body weight: changes in amount of change (SAF/FAS/PPS)
95	4.3	Figure AD_11_4_1_17_1_3F Body weight: changes in rate of change (SAF/FAS/PPS)
96	4.4	Figure AD_11_4_1_18F Changes in amount of pleural effusion (SAF/FAS/PPS)
97	4.5	Figure AD_11_4_1_20_1F MMT total score: changes in actual measurements (SAF/FAS/PPS)
98	4.5	Figure AD_11_4_1_20_2F MMT total score: changes in amount of change (SAF/FAS/PPS)
99	4.5	Figure AD_11_4_1_20_3F MMT total score: changes in rate of change (SAF/FAS/PPS)
100	4.7	List AD_16_2_2 Summary of cases that transitioned early to the long-term safety trial (SAF/FAS/PPS)
101	4.5	ListAD_16_2_3 Summary of correlation between VEGF levels and amount of pleural effusion (SAF/FAS/PPS)

SAF, Safety Analysis Set; FAS, Full Analysis Set; PPS, Per Protocol Set