Title: An Open-Label, Single-Dose, Phase 1/2 Study to Evaluate the Pharmacokinetics, Safety, and Tolerability of Human Protein C (TAK-662) for the Treatment of Congenital Protein C Deficiency in Japanese Subjects Followed by an Extension Part

NCT Number: NCT04984889

Statistical analysis plan Approve Date: 28-Oct-2022

Certain information within this statistical analysis plan has been redacted (ie, specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information or company confidential information.

STATISTICAL ANALYSIS PLAN

Study Number: TAK-662-1501

Study Title: An Open-Label, Single-Dose, Phase 1/2 Study to Evaluate the Pharmacokinetic, Safety, and Tolerability of Human Protein C (TAK-662) for the Treatment of Congenital Protein C Deficiency in Japanese Subjects

Phase: Phase 1/2

Version: 4.0

Date: 28 Oct 2022

Prepared by: [redacted]

Based on:

Protocol Version: Amendment 02

Protocol Date: 13 April 2021

REVISION HISTORY

Version	Approval Date	Primary Rationale for Revision
4.0	28 Oct2022	Updates for the analyses of the extension part. • Section 6.1: Corrected the definitions of duration for each treatment types in the extension part. • Section 6.4: Described the definition of calculation for each items. • Section 9.2.4: Specified the type of missing to be handled
3.0	15Sep2022	Updates for the analyses of the extension part. • Section 1.1.2: Added secondary objectives. • Section 1.2.3: Added new section for efficacy endpoints. • Section 5.4 and 5.5: Added new section for the safety analysis set in the extension part and the efficacy analysis set. • Section 6.1: Described the analyses for the PK part and the extension part. • Section 6.2, 6.2.1, 6.2.2, 6.2.4 and 6.3.2: Described the analyses for the extension part. • Section 6.4: Described the efficacy analyses. • Section 6.5, 6.5.1, 6.6, 6.7 and 6.9: Described the analyses for the extension part. • Section 6.11.2: Added new section for the extension part. • Section 6.12: Described the interim analysis for the extension part and the final analysis. • Section 9.2.2: Added the definition of baseline in the extension part. • Section 9.2.3: Added the tables of analysis visits in the extension part. Correction of errors. Section 9.3: WinNonlin version
2.0	11Apr2022	Updates necessary for the interim analysis were made in accordance with the contents of Protocol amendment 2. (but does not include updates for efficacy analysis.) • Updated the ABBREVIATIONS list. • Section 2.0: Study design details updated as per Protocol Amendment 2. • Section 5.1: “Screened Population” was changed to “Screened Set”. • Section 5.3: Updated with Protocol Amendment 2. • Section 6.2.1: Added new section for the analysis of protocol deviations. • Section 6.2.4: Added the handling of an incomplete date in the calculation of “Duration of protein C deficiency” and the method of identifying “Previous treatment with blood products” • Section 6.3.1 : Deleted an erratum in display item (“dosing frequency”).

Version	Approval Date	Primary Rationale for Revision
		• Section 6.3.1 and Section 6.3.2: Modified definitions of "prior" and "concomitant" medications. • Section 6.4: Updated for interim analysis. • Section 6.6: Deleted unnecessary description ("End of Treatment" and "potential clinically significant data"). • Section 6.7: Corrected the examples of analysis items. Deleted unnecessary description ("End of Treatment" and "potential clinically significant data"). • Section 6.10.2: Moved the description to Clinical Pharmacology Analysis Plan. • Section 6.12: Added the description to perform Interim Analysis. • Section 9.2.3: Added tables of analysis visit. • Section 9.2.4: Added new section for the handling of missing severity and relationship for AEs.
1.0	30Apr2021	[Not Applicable]

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LIST OF IN-TEXT TABLES

ABBREVIATIONS

AE	adverse event
AUC	area under the curve
β-hCG	beta human chorionic gonadotropin
BMI	body mass index
CI	confidence interval
CISN	coumarin-induced skin necrosis
C_{max}	maximum concentration
CPAP	Clinical Pharmacology Analysis Plan
CV	coefficient of variation
ECG	Electrocardiogram
eCRF	electronic case report form
ET	early termination
FSH	follicle-stimulating hormone
ICF	Informed Consent Form
IR	incremental recovery
IU	international unit
IVR	in-vivo recovery
MedDRA	Medical Dictionary for Regulatory Activities
NCA	non-compartmental analysis
PF	purpura fulminans
PK	Pharmacokinetic
PT	Preferred Term (MedDRA)
SAE	serious adverse event
SAP	statistical analysis plan
SD	standard deviation
SI	standard international
SOC	System Organ Class (MedDRA)
TEAE	treatment-emergent adverse event
$t_{1/2}$	half-life
t_{max}	time to maximum concentration
US	United States
WHO-DD	World Health Organization Drug Dictionary
WISN	warfarin-induced skin necrosis

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

To measure the pharmacokinetic (PK) parameters of TAK-662 in asymptomatic subjects with homozygous or double heterozygous congenital protein C deficiency in Japanese subjects.

1.1.2 Secondary Objective(s)

To assess safety profile of TAK-662.

To assess efficacy of TAK-662 in following 1) for on-demand treatment such as purpura fulminans (PF), coumarin-induced skin necrosis (CISN)/ warfarin-induced skin necrosis (WISN), and other vascular thromboembolic events; 2) for short-term thromboembolic prophylaxis during surgical procedures; and 3) for long-term prophylactic treatment of acute thrombotic episodes (Extension part).

1.1.3 Additional Objective(s)

Not applicable.

1.2 Endpoints

1.2.1 Primary Endpoint(s)

- Protein C activity
- PK parameters including but not limited to terminal half-life ($t_{1/2}$), incremental recovery (IR), in-vivo recovery (IVR) , area under the curve (AUC), maximum concentration (C_{max}), and minimum time to reach maximum concentration (t_{max})

1.2.2 Safety Endpoint(s)

- The primary Safety Endpoint

The occurrence of treatment-related adverse experiences.

- Other Safety Endpoint

Body temperature, blood pressure, and pulse rate monitored before and after the investigational product administration, and the last prophylactic treatment (if applicable) prior to the test dose.

1.2.3 Efficacy Endpoint(s)

On-demand treatment

- The treatment of episodes of PF/CISN/WISN and/or other vascular thromboembolic events are rated as effective, effective with complications, or not effective when it is determined that the next infusion is unnecessary according to the efficacy rating scale.

Short-term prophylaxis

- Percentage of surgical episodes during short-term prophylaxis, for which TAK-662 is utilized as short-term prophylaxis, that is free of presentations of PF or thromboembolic complications.

Long-term prophylaxis

Number and rate of episodes of PF and/or thrombotic episodes during long-term prophylaxis.

1.2.4 Exploratory Endpoint(s)

Not applicable.

1.3 Estimand(s)

Not applicable.

2.0 STUDY DESIGN

This is a phase 1/2 open-label, non-randomized, non-controlled, single-dose, multicenter study to evaluate PK, safety, and tolerability of TAK-662 in Japanese subjects with congenital protein C deficiency followed by an extension part.

PK part:

The study is planned to enroll 3 or more subjects in Japan. The subject who has the prophylactic treatment of anticoagulants is allowed to be enrolled. The last prophylactic treatment including protein C ingredient must occur by at least 36 hours before the administration of TAK-662 on Day 1. Other prophylactic treatment such as oral anticoagulants can be administered without any restrictions on period.

Once all screening assessments following informed consent (and assent where applicable) are completed and eligibility is confirmed, the subject will receive a single 80 IU/kg dose of TAK-662 intravenously on Day 1. Prior to the Investigational Product (IP) administration, the subject will be admitted to the study site on Day −1 (One day earlier hospitalization [Day −2] is allowed if applicable). The prophylactic treatment will be given according to the subject's established treatment regimen and at the discretion of the investigator. For the subject with prophylactic treatment including protein C ingredient, the IP for PK will be administered at least after 36 hours of the prophylactic treatment.

From Day 1 to Day 3, the subject will stay in the study site and be followed up for PK and safety before and after the IP administration. The blood sampling for PK will be done immediately prior to infusion and at 30 minutes, and 1, 2, 4, 8, 12, 24, and 36 hours postinfusion; a sampling for the 36 hours postinfusion is allowed to be customized by age, especially for feasibility in children. After 7 days from the IP administration (Day 7), the subject will have the follow-up visit for safety assessment. For the subject who has the prophylactic treatment including protein C ingredient before the administration of the IP for PK, the blood sampling will be additionally done immediately prior to the prophylactic treatment and at 1, 17, and 25 hours post-treatment.

The analysis will be performed for PK and safety after all subjects have completed the Day 7 visit.

Extension part:

In the extension part of the current study, sponsor provides 3 different treatment options; on-demand treatment, short-term prophylaxis, and long-term prophylaxis. Based on investigator's careful evaluation on subject's medical condition, subject who completed PK part can continue the administration of TAK-662 until the commercial protein C concentrate is available at each study site or study termination. The 3 different treatment options provide different ways of protein C supplementation.

For on-demand treatment, subjects with PF, CISN/WISN, and/or other acute thromboembolic episode will be enrolled. For short-term prophylaxis, subjects requiring short-term prophylaxis

with protein C concentrate/TAK-662 for surgical procedures will be enrolled. For long-term prophylaxis, subjects requiring long-term prophylaxis with protein C concentrate/TAK-662 will be enrolled.

On-demand treatment and short-term prophylaxis may be carried out more than once depending on the subject's situation. In this case, after the completion of follow-up period, the subject will be re-enrolled and re-start the procedures from pre-dose/pre-surgery period. In addition, subject may transfer to the other treatment. (eg, If a subject who enrolled in long-term prophylaxis requires a surgery, he/she transfers to short-term prophylaxis. Once anticoagulation is initiated and the investigator determines that adequate anticoagulation is achieved, he/she will transfer back to long-term prophylaxis.)

3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Not Applicable.

3.2 Statistical Decision Rules

Not Applicable.

3.3 Multiplicity Adjustment

Not Applicable.

4.0 SAMPLE-SIZE DETERMINATION

The number of patients with congenital protein C deficiency is very few. And the target number of patients is set to 3 or more in consideration of feasibility and inclusion/exclusion criteria in this study based on the opinions of specialist in Japan.

5.0 ANALYSIS SETS

5.1 Screened Set

All subjects who provided a signed Informed Consent Form (ICF) will be included in the Screened Set.

5.2 Safety Analysis Set

The Safety Analysis Set will include all enrolled subjects in the study who take at least 1 dose of TAK-662. A subject will be considered enrolled in the study once the informed consent/assent has been obtained and the subject meets all of the study inclusion criteria.

5.3 Pharmacokinetic Analysis Set

The Pharmacokinetic Analysis Set will include all study participants who take at least 1 dose of TAK-662 and have enough number of quantifiable blood level for TAK-662 collected post-dose without important protocol deviations/violations or events thought to significantly affect the PK.

5.4 Safety Analysis Set in the Extension part

The Safety Analysis Set in the Extension part will include all study participants who take at least 1 dose of TAK-662 in the extension part.

5.5 Efficacy Analysis Set

The Efficacy Analysis Set will include all study participants who take at least 1 dose of TAK-662 in the extension part.

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

The PK part analysis and extension part analysis will be performed separately.

The start date in the extension part is the later date of (1) the date of informed consent for the extension part or (2) the day after the end of study date of PK part.

In addition, the analysis will be performed on subjects who received each treatment type.

There are three treatment types in the extension part.

- On-Demand Treatment
- Short-Term Prophylaxis
- Long-Term Prophylaxis

The duration for each treatment type is from the start date of the first dose of each treatment type to the last assessment day of that treatment.

6.1.1 Analysis Approach for Continuous Variables

Continuous variables will be summarized using the following descriptive statistics: the number of subjects, mean, median, standard deviation, minimum, maximum. 95% confidence interval (CI) of mean value will also be provided where needed.

6.1.2 Analysis Approach for Categorical Variables

Categorical variables will be summarized by the number and percentage of subjects in each category (with a category for missing data as needed). exact 2-sided Clopper-Pearson 95% CI of percentage value will also be provided where needed. Unless otherwise stated, the denominator for percentages is N (the number of subjects in the analysis set).

6.2 Disposition of Subjects

For the PK part:

The number and percent of subjects in each study analysis set (i.e., Screened, Safety and PK) will be presented for the Screened Set.

For the Safety Analysis Set, the number and percentage of subjects who completed or prematurely discontinued the treatment period will be presented. Reasons for premature discontinuation from the treatment period as recorded on the end of treatment page of the electronic case report form (eCRF) will be summarized (number and percentage). A subject data listing will present subject disposition for the Screened Set.

Inclusion and exclusion criteria violations, if any, will be presented in a listing for the Screened Set.

For the Extension part:

For the Safety Analysis Set, the number and percentage of subjects who signed the informed consent form of the extension part, subjects who received TAK-662 infusion in the extension part and subjects who completed or prematurely discontinued study in the extension part will be presented. Reasons for premature discontinuation from study in the extension part as recorded on the end of study page of the eCRF will be summarized (number and percentage). A subject data listing will present subject disposition for all subjects who signed the informed consent form of the extension part.

For all subjects who signed the informed consent form of the extension part, the number and percentage of the Safety Analysis Set in the Extension part and the Efficacy Analysis Set will be presented. For the Safety Analysis Set in the Extension part and the Efficacy Analysis Set, the number and percentage of subjects by treatment type (on-demand treatment, short-term prophylaxis, or long-term prophylaxis) will also be presented.

Also, the listing of inclusion and exclusion criteria violations in the extension part will be output for all subjects who signed the informed consent form of the extension part.

6.2.1 Protocol Deviations

For the PK part:

The number and percent of subjects in each protocol deviation category by severity (critical, major and minor) will be presented for the Screened Set. A listing for protocol deviation will also be provided.

For the Extension part:

The number and percentage of subjects in each protocol deviation category by severity (critical, major and minor) will be presented for the Safety Analysis Set in the Extension part.

Also, the listing for protocol deviation in the extension part will be output for the Safety Analysis Set in the Extension part.

6.2.2 Demographics

For the PK part:

The baseline and demographic characteristics will be summarized for the Safety Analysis Set and PK Analysis Set with descriptive statistics. A listing for demographic characteristics data will also be provided. Demographic and baseline characteristics to be presented include:

- Age (at informed consent date) in years as a continuous parameter
- Sex
- Race
- Ethnicity

- Height (cm) at the Screening visit
- Weight (kg) at the Screening visit
- BMI (kg/m2) at the Screening visit

BMI is calculated as weight (kg)/ [height (m)]^2.

For the Extension part:

The same analysis in the PK part will be performed for the Safety Analysis Set in the Extension part. The values used for analysis are also those of the PK part.

6.2.3 Medical History and Concurrent Medical Conditions

Medical and surgical history will be coded using the Medical Dictionary for Regulatory Activities (MedDRA). Investigator verbatim as well as preferred terms (PT) and system organ class (SOC) will be included in the listings. The medical history will be summarized by SOC and PT within SOC for the Safety Analysis Set, with SOC sorted alphabetically and PT within SOC by descending incidence.

6.2.4 Baseline Characteristics

For the PK part:

The following subject history collected at the Screening visit will be summarized with the descriptive statistics for the Safety Analysis Set and PK Analysis Set:

- Duration of protein C deficiency diagnosed and protein C level at diagnosis
- Current regimen for prophylactic treatment with protein C concentrate or including protein C ingredient (if applicable)
- Thrombotic events and skin necroses
- Previous treatment with blood products

Duration of protein C deficiency will be calculated as (Date of ICF Signed – Date of Diagnosis of protein C deficiency +1)/365.25. If a date of diagnosis of protein C deficiency is incomplete for calculation, the missing day and/or month will be imputed with “01”. If the year is missing, no imputation and calculation is performed.

The identification of previous treatment with blood products will be done by reviewing the actual medication data collected in eCRF.

A listing for subject history data will also be provided.

For the Extension part:

The same analysis in the PK part will be performed for the Safety Analysis Set in the Extension part. The values used for analysis are also those of the PK part.

6.3 Medication History and Concomitant Medications

A listing of all medications, both prior and concomitant, will be presented. The listing will be sorted by subject identifier and will include preferred name, reported name, dose, route of administration, start date, end date, indication, and type of medication (prior only, concomitant only, prior and concomitant).

6.3.1 Prior Medications

Prior medications will be coded using the WHO-DD (World Health Organization Drug Dictionary).

Prior medications are defined as medications with stop date prior to the date of ICF signed.

Prior medication use will be summarized by preferred name using the number and percentage of subjects for the Safety Analysis Set. Medications will be sorted by descending incidence by preferred name. Subjects with multiple occurrences of a medication in preferred name will only be counted once within each preferred name.

6.3.2 Concomitant Medications

Concomitant medications will also be coded using the WHO-DD.

For the PK part:

Concomitant medications are defined as medications with onset dates on or after the date of ICF signed, medications with onset dates prior to the date of ICF signed without a stop date, or medications with a stop date after the date of ICF signed.

Concomitant medications will be summarized in the same way as prior medications (refer to Section 6.3.1).

For the Extension part:

For concomitant medications after the start date of the extension part, the same analysis in the PK part will be performed for the Safety Analysis Set in the Extension part.

Also, the listing of concomitant medications in the extension part will be output for the Safety Analysis Set in the Extension part.

6.4 Efficacy Analysis

For the Extension part:

Efficacy analyses will be performed for the Efficacy Analysis Set by treatment type.

- Efficacy Analysis Set in On-Demand Treatment
- Efficacy Analysis Set in Short-Term Prophylaxis

- Efficacy Analysis Set in Long-Term Prophylaxis

The efficacy analyses by treatment type are as follows.

- On-Demand Treatment

  The treatment of episodes of PF/CISN/WISN and/or other vascular thromboembolic events will be rated as "effective", "effective with complications", or "not effective" according to the efficacy rating scale. The rating of treatment effect in Efficacy Analysis Set in On-Demand Treatment will be summarized by number of treatments (overall, first, second and subsequent) using descriptive statistics.

- Short-Term Prophylaxis

  Percentage of surgical episodes for which TAK-662 will be utilized as short-term prophylaxis, that is free of presentations of PF or thromboembolic complications will be calculated. PF or thromboembolic complications in Efficacy Analysis Set in Short-Term Prophylaxis will be summarized using descriptive statistics.

- Long-Term Prophylaxis

  Number of episodes of PF and/or thrombotic episodes while receiving long-term prophylaxis and rate of episodes of PF and/or thrombotic episodes per month (defined as 30.4375 days) will be calculated. Episodes of PF and/or thrombotic episodes in Efficacy Analysis Set in Long-Term Prophylaxis will be summarized using descriptive statistics.

Time to resolution and total dose received until resolution of episodes of PF/CISN/WISN and/or other vascular thromboembolic events will be summarized using descriptive statistics for the Efficacy Analysis Set in On-Demand Treatment.

- Time to Resolution of Episode (number of days): (date of last assessment - date of first dose + 1) for each On-Demand Treatment period
- Total Dose Received until Resolution of Episode (IU/mL) : Total amount of actual dose (IU/ml) for each On-Demand Treatment period

Duration of treatment periods will be summarized using descriptive statistics for the Efficacy Analysis Set in Short-Term Prophylaxis and Efficacy Analysis Set in Long-Term Prophylaxis.

- Duration of treatment periods of Short-Term Prophylaxis (number of days) : (date of last dose – date of first dose + 1) for each Short-Term Prophylaxis period
- Duration of treatment periods of Long-Term Prophylaxis (number of days) : (date of last dose – date of first dose + 1) for each Long-Term Prophylaxis period

A listing for efficacy analysis data will also be provided for the Efficacy Analysis Set.

In addition, a listing for skin lesions of acute episodes of PF/CISN/WISN will be provided for the Efficacy Analysis Set.

6.5 Safety Analysis

The safety analysis will be performed using the Safety Analysis Set. Safety variables include AEs, clinical laboratory variables, vital signs, ECG variables and physical examination. For each safety variable, the last value collected before the first dose of the investigational product will be used as the baseline for all analyses of that safety variable.

For the extension part, safety analyses will be performed for the following.

- Safety Analysis Set in the Extension part
- Safety Analysis Set in the Extension part in On-Demand Treatment
- Safety Analysis Set in the Extension part in Short-Term Prophylaxis
- Safety Analysis Set in the Extension part in Long-Term Prophylaxis

6.5.1 Adverse Events

AEs will be coded using MedDRA. Investigator verbatim as well as PT and SOC will be included in the listings.

For the PK part:

Treatment emergent AEs (TEAEs) are defined as AEs whose onset occurs, severity worsens, or intensity increases after receiving the study medication. AEs with an unknown date of onset and a stop date after the start of the study treatment or unknown stop date will be included as TEAEs. Any AE with a start date equal to the date of first dose, where the time of the AE cannot definitively place the start of the AE prior to the first dose, will be considered treatment emergent. AEs which are not treatment emergent will be flagged in listings.

AEs will be summarized overall using descriptive statistics (e.g., number and percent of subjects). The number of events will also be presented. Categories summarized will include any TEAEs, severity of TEAEs, relationship of TEAEs to study treatment, treatment emergent serious AEs (TESAEs), severity of TESAEs, relationship of TESAEs to study treatment and TEAEs leading to death.

TEAEs will be summarized using number and percentage of subjects. Subject incidence for AEs within each SOC and PT will be presented, unless otherwise specified. The number of events will also be presented. Categories summarized are as follows:

TEAEs,

- Severity of TEAEs,
- Relationship of TEAEs to study treatment,
- TESAEs.

Presentation by SOC and PT will present SOC sorted alphabetically and PT within SOC by descending incidence. Listings will be provided for serious adverse events (SAEs) and AEs leading to death. The listings will be sorted by subject identifier and will include SOC, PT,

reported term, start date/time, end date/time, frequency, severity, relationship, action taken, and outcome.

For the Extension part:

The same analysis in the PK part will be performed for the Safety Analysis Set in the Extension part, Safety Analysis Set in the Extension part in On-Demand Treatment, Safety Analysis Set in the Extension part in Short-Term Prophylaxis and Safety Analysis Set in the Extension part in Long-Term Prophylaxis.

Also, the listing of the extension part, which is the same as the PK part, will be output for the Safety Analysis Set in the Extension part.

6.6 Clinical Laboratory Data

For the PK part:

Clinical laboratory tests are to be performed at site visits with results processed by a central laboratory. Laboratory tests include the following (Table 1):

Table 1 List of Laboratory Tests

Hematology: • Hematocrit • Hemoglobin • Platelet count • Red blood cell count • White blood cell count • White blood cell count with differential	**Biochemistry:** • Alanine aminotransferase **Pregnancy tests** (females of childbearing potential): • Urine β-HCG • FSH

Laboratory parameters will be presented in standard international (SI) units. The summaries will be based on central lab results only.

Quantitative results will be summarized for hematology and serum chemistry at each scheduled visit. Both actual values and change from baseline will be summarized. Laboratory results data will be presented in a listing for each lab panel (chemistry and hematology) by subject, visit, and parameter. Laboratory values outside of the normal range will be flagged. Urine pregnancy results will be presented in a listing only.

For the Extension part:

The same analysis in the PK part will be performed. For the Safety Analysis Set in the Extension part in On-Demand Treatment, Safety Analysis Set in the Extension part in Short-Term Prophylaxis and Safety Analysis Set in the Extension part in Long-Term Prophylaxis, quantitative results will be summarized for hematology and serum chemistry at each scheduled

visit. However, only actual values will be summarized in On-Demand Treatment (change from baseline will not be included).

Also, the listing of the extension part, which is the same as the PK part, will be output for the Safety Analysis Set in the Extension part.

6.7 Vital Signs, Body Weight and BMI

For the PK part:

Descriptive statistics will be used to summarize the vital signs (i.e., systolic blood pressure, diastolic blood pressure, pulse rate, respiratory rate, and body temperature) by scheduled visit for the Safety Analysis Set. Both actual values and changes from baseline will be summarized.

A listing for vital signs data will also be provided.

For the Extension part:

The same analysis in the PK part will be performed. For the Safety Analysis Set in the Extension part in On-Demand Treatment, Safety Analysis Set in the Extension part in Short-Term Prophylaxis and Safety Analysis Set in the Extension part in Long-Term Prophylaxis, descriptive statistics will be used to summarize the vital signs by scheduled visit. However, only actual values will be summarized in On-Demand Treatment (change from baseline will not be included).

Also, the listing of the extension part, which is the same as the PK part, will be output for the Safety Analysis Set in the Extension part.

6.8 Electrocardiogram

The number and percentage of subjects with each type of ECG finding (Normal/Abnormal, Not Clinically Significant/Abnormal, Clinically Significant) will be presented for the Safety Analysis Set. All ECG data will be listed.

6.9 Extent of Exposure and Compliance

For the PK part:

All exposure data will be listed.

For the Extension part:

The listing of the extension part, which is the same as the PK part, will be output for the Safety Analysis Set in the Extension part.

6.10 Pharmacokinetic Analyses

6.10.1 Pharmacokinetic Parameters

The PK parameters will be derived and estimated based on measured Protein C activity in plasma using non-compartmental analysis (NCA) in accordance with the Clinical Pharmacology Analysis Plan (CPAP) generated separately.

6.10.2 Statistical Analysis of Pharmacokinetic Data

Details will be provided in the CPAP.

6.11 Other Analyses

6.11.1 Physical Examination

The physical examination data will be listed for all subjects in the Safety Analysis Set.

6.11.2 Protein C activity

For the Extension part:

The protein C activity data will be listed for all subjects in the Safety Analysis Set in the Extension part.

6.12 Interim Analyses

For the PK part:

Interim analyses of study data will be undertaken as described below. No adaptive design or data monitoring committee is planned for this study. One formal interim data analyses to support the Japanese New Drug Application submission will be completed. It will summarize safety and PK of treatment with TAK-662 in Japanese subjects with homozygous or double heterozygous congenital protein C deficiency. The first interim analysis will be conducted when all enrolled subjects have reached last visit of PK part. The target data is all data obtained at this point in PK part. An interim clinical study report summarizing data will be prepared.

For the Extension part:

An interim analysis for the Extension part will be performed using the cut-off data of September 30, 2022. The required analyses are all tables and listings for the Safety Analysis Set in the Extension part or the Efficacy Analysis Set. (These are indicated in "For the Extension part:" of Section 6.2, Section 6.2.1, Section 6.2.2, Section 6.2.4, Section 6.3.2, Section 6.4, Section 6.5.1, Section 6.6, Section 6.7, and Section 6.9.) Analysis by treatment type will be performed only for the treatment type that occurred.

7.0 REFERENCES

No references used in this SAP.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

There is no change of analysis from protocol.

9.0 APPENDIX

9.1 Changes from the Previous Version of the SAP

Not Applicable.

9.2 Data Handling Conventions

9.2.1 General Data Reporting Conventions

The small sample size resulting from the small study population requires the use of descriptive statistics with a goal of summarizing the sample and thus discourages the use of inferential statistics.

Descriptive statistics will be presented as follows:

The following rules will be followed for decimal places and rounding:

- Unless otherwise specified, means (arithmetic and geometric) and medians will be rounded and presented to 1 decimal place more than the raw data and standard deviations to 2 decimal places more than the raw data. Minimum and maximum values will be presented to the same number of decimal places as the raw data.
- Unless otherwise specified, percentages should be presented to one decimal place. Less than signs (i.e., '<') should be presented as appropriate (e.g., 0.04% should be presented as < 0.1%, not 0.0%). This rule also applies to CV (%).
- BMI and duration of protein C deficiency diagnosed should be rounded to 1 decimal place for reporting.

Study day will be calculated as follows;

- If the evaluation date is on or after the date of first day of study medication:
  Study day = date of evaluation – first day of study medication + 1
- If the evaluation date is before the date of first day of study medication:
  Study day = date of evaluation – first day of study medication

9.2.2 Definition of Baseline

For the PK part:

For summary purposes, the baseline value will be defined as the last available pre-dose value.

For the Extension part:

The baseline value in Short-Term Prophylaxis will be defined as the last available pre-surgery value in the extension part before the first dose of TAK-662 in the extension part.

The baseline value in Long-Term Prophylaxis will be defined as the last available predose value in the extension part before the first dose of TAK-662 in the extension part.

9.2.3 Definition of Visit Windows

Nominal visits will be used for the per-visit analyses. Therefore, no windowing of visits by actual study day will be done for data obtained at the scheduled visits. However, the analysis visit of baseline data (identified according to Section 9.2.2) should be "Baseline". For subjects who withdraw from the study pre-maturely, if the early termination (ET) visit falls into the window of a scheduled visit as defined in the protocol, the ET visit is also summarized for that scheduled visit, unless the scheduled visit already took place.

Table 2 Analysis Visit of Vital Signs in the PK part

Analysis Visit	Analysis Timepoint
Baseline	Predose
Day 1	30 Min Postdose
Day 1	2 Hours Postdose
Day 1	4 Hours Postdose
Day 2	24 Hours Postdose

Table 3 Analysis Visit of Vital Signs in the Extension part (On-Demand Treatment)

EPOCH	VS.VISIT	VS.TPT	Analysis Visit	Analysis Timepoint
EXTENSION	On-Demand Treatment - First Acute Episode	Predose	On-Demand Treatment - First Acute Episode	Predose
EXTENSION	On-Demand Treatment - First Acute Episode	Follow-up	On-Demand Treatment - First Acute Episode	Follow-up
EXTENSION	On-Demand Treatment - Second and Subsequent Acute Episodes	Follow-up	On-Demand Treatment - Second Acute Episodes	Follow-up 2
EXTENSION	On-Demand Treatment - Second and Subsequent Acute Episodes	Follow-up	On-Demand Treatment - Subsequent Acute Episodes	Follow-up 3

Table 4 Analysis Visit of Vital Signs in the Extension part (Short-Term Prophylaxis)

EPOCH	VS.VISIT	VS.TPT	Analysis Visit	Analysis Timepoint
EXTENSION	Short-Term Prophylaxis	Pre-surgery	Short-Term Prophylaxis	Pre-surgery
EXTENSION	Short-Term Prophylaxis	Day E2	Short-Term Prophylaxis	Day E2
EXTENSION	Short-Term Prophylaxis	End of Treatment	Short-Term Prophylaxis	End of Treatment

Table 5 Analysis Visit of Clinical Laboratory Evaluations -Hematology- in the PK part

Analysis Visit
Baseline
Day 2
Day 7/Follow-Up

Table 6 Analysis Visit of Clinical Laboratory Evaluations -Hematology- in the Extension part (On-Demand Treatment)

EPOCH	VS.VISIT	VS.TPT	Analysis Visit	Analysis Timepoint
EXTENSION	On-Demand Treatment - First Acute Episode	Predose	On-Demand Treatment - First Acute Episode	Predose
EXTENSION	On-Demand Treatment - First Acute Episode	Follow-up	On-Demand Treatment - First Acute Episode	Follow-up
EXTENSION	On-Demand Treatment - Second and Subsequent Acute Episodes	Follow-up	On-Demand Treatment - Second Acute Episodes	Follow-up 2
EXTENSION	On-Demand Treatment - Second and Subsequent Acute Episodes	Follow-up	On-Demand Treatment - Subsequent Acute Episodes	Follow-up 3

Table 7 Analysis Visit of Clinical Laboratory Evaluations -Hematology- in the Extension part (Short-Term Prophylaxis)

EPOCH	VS.VISIT	VS.TPT	Analysis Visit	Analysis Timepoint
EXTENSION	Short-Term Prophylaxis	Pre-surgery	Short-Term Prophylaxis	Pre-surgery
EXTENSION	Short-Term Prophylaxis	End of Treatment	Short-Term Prophylaxis	End of Treatment

Table 8 Analysis Visit of Clinical Laboratory Evaluations -Hematology- in the Extension part (Long-Term Prophylaxis)

EPOCH	VS.VISIT	VS.TPT	Analysis Visit	Analysis Timepoint
EXTENSION	Long-Term Prophylaxis	Predose	Long-Term Prophylaxis	Predose
EXTENSION	Long-Term Prophylaxis	Treatment Period Month Y *	Long-Term Prophylaxis	Treatment Period Month Y*

*: Y represents the number of Months, which should be an integer. (Y=1, 2, 3, ...)

Table 9 Analysis Visit of Clinical Laboratory Evaluations - Chemistry- in the PK part

Analysis Visit
Baseline

9.2.4 Handling of Missing Severity Assessment and Relatedness

If the severity is missing for an AE, then a severity of "Severe" will be assigned. Also, if the relationship is missing for an AE, then a severity of "Related" will be assigned.

The imputed values for severity assessment and relationship will be used for incidence summaries, while both the actual and the imputed values will be presented in data listings.

9.3 Analysis Software

Statistical analyses will be performed using Version 9.4 (or newer) of SAS® (SAS Institute, Cary, North Carolina , US) on a suitably qualified environment.

Pharmacokinetic parameters will be derived using noncompartmental methods with Phoenix® WinNonlin® Version 8.1 or higher (Certara, L.P. Princeton, New Jersey, US) and/or SAS® Version 9.4 or higher (SAS Institute, Inc., Cary, North Carolina, US).