Statistical Analysis Plan

NCT Number: NCT04580407

Title: A Phase 2/3, Open-Label, Non-controlled Study to Evaluate the Efficacy and Safety of B-Domain Deleted Recombinant Porcine Factor VIII (rpFVIII, TAK-672) in the Treatment of Serious Bleeding Episode in Japanese Subjects with Acquired Hemophilia A (AHA)

Study Number: TAK-672-3001

Document Version and Date: Version 2.0 / 14-Dec-2022

Certain information within this document has been redacted (ie, specific content is masked irreversibly from view) to protect either personally identifiable information or company confidential information.

STATISTICAL ANALYSIS PLAN

Study Number: TAK-672-3001

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Phase: 2/3

Version: 2.0

Date: 14-DEC-2022

Prepared by: [redacted]

Based on:

Protocol Version: Amendment 2.0

Protocol Date: 23 OCT 2020

REVISION HISTORY

The table below captures the revision history. If applicable, a summary of changes to specific sections should be provided in Appendix Section 9.1 of the SAP.

Version	Approval Date	Primary Rationale for Revision
Original version	25-JAN-2021	Not Applicable.
2.0	14-DEC-2022	For various improvements to clarify the contents of the description. Updated the list of ABBREVIATIONS Section 5.2: Deleted unnecessary descriptions Section 6.1: Add definitions of informed consent date Section 6.2.6.1, Section 6.2.6.2 and Section 6.6.1: Corrected categories Section 6.2.7.1: Added definitions of significant protocol deviations Section 6.3.1: Updated analysis variables Section 6.5.2.2-2): Corrected visit Section 6.5.2.2-3): Corrected analysis variables Section 6.5.2.2-4): Corrected visit Section 6.5.2.2-5): Corrected analysis variables and analytical methods Section 6.5.2.2-8): Corrected analysis variables Section 6.5.2.2-9): Corrected analysis variables and deleted the condition of subgroup Section 6.5.4: Corrected unit notation in subgroups Section 6.6.1.2 (13): Moved to 6.6.2 Section 6.6.2: Described the details of analysis Section 6.6.3.1: Corrected visit and deleted unnecessary description in (3) Section 6.6.3.2: Added the description in analytical methods and described classification of the observed value Section 6.6.3.4: Changed analysis methods to frequency distributions to match the data format Section 6.6.6.1: Corrected analysis variables Section 6.6.6.2: Separated sections for each treatment period, described clearly the analysis and deleted the condition of subgroup Section 6.6.6.2.1 and Section 6.6.6.2.2: Corrected analysis variables Section 6.9: Described the details of analysis set Section 9.2.1: Described how to determine the use of specific drugs and how to handle test values containing special characters. Added definitions of calculation and derivation

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ABBREVIATIONS

Abbreviation	Definition
AE	Adverse Event
AESI	Adverse Event of Special Interest
AHA	acquired hemophilia A
ALT	alanine aminotransferase
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
AST	aspartate aminotransferase
AUC	area under the concentration-time curve
BHK	baby hamster kidney
BMI	Body Mass Index
BU	Bethesda unit
CI	Confidence Interval
CL	Clearance
FAS	Full Analysis Set
FVIII	Factor VIII
Hct	hematocrit
hFVIII	human factor VIII
Hgb	hemoglobin
LLN	lower limit of the normal range
MAV	Markedly Abnormal Values
MedDRA	Medical Dictionary for Regulatory Activities
pd-FVIIa/FX	plasma-derived factor VII/factor X complex concentrate
pFVIII	porcine factor VIII
PKS	Pharmacokinetic Analysis Set
PPS	Per-Protocol Set
PT	Preferred Term (MedDRA)
PTE	pretreatment event
rFVIIa	activated recombinant factor VII
rpFVIII	Recombinant porcine factor VIII
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SAS	Safety Analysis Set
SOC	System Organ Class
TEAE	Treatment-Emergent Adverse Event
ULN	upper limit of the normal range
Vd	volume of distribution

1.0 OBJECTIVES, ENDPOINTS AND ESTIMANDS

1.1 Objectives

1.1.1 Primary Objective

The primary objective is to evaluate the efficacy and safety of TAK-672 for the treatment of severe bleeding events in Japanese subjects with AHA.

1.1.2 Secondary Objectives

- *To determine the proportion of severe bleeding episodes that are controlled with TAK-672 therapy*
- *To assess the efficacy of TAK-672 at designated time points after the initiation of therapy*
- *To determine the frequency, total dose, and total number of infusions of TAK-672 required to control all severe bleeding episodes*
- *To assess the correlation between response to TAK-672 therapy at specified assessment time points and eventual control of severe bleeding events*
- *To assess the correlations among the pre-infusion inhibitor titer, the total dose of TAK-672 infused, the post-infusion FVIII activity, the response at 24 hours, and the eventual control of the bleeding event*
- *To assess inhibitor titers against hFVIII and pFVIII at pre-infusion, at specified assessment time points during treatment, and at the end of the follow-up period at 90 days after the final dose of TAK-672*
- *To assess PK in subjects successfully treated with TAK-672 therapy using serial sampling (in a non-bleeding state)*
- *To assess the duration period and total dose from the initial dose of TAK-672 until the completion of hemostasis control*
- *To assess the number of new qualified severe bleeding episodes*

1.1.3 Additional Objective

Not applicable.

1.2 Endpoints

1.2.1 Primary Efficacy Endpoint

The primary efficacy endpoint will be the proportion of severe bleeding episodes with demonstrated response to TAK-672 therapy at 24 hours after the initiation of treatment using a well-defined 4-point ordinal scale summarized in Table 1-A.

Table 1-A Investigator Assessment of Response to TAK-672: Four-Point Ordinal Scale

Assessment of efficacy	*Control of bleeding*	*Clinical Assessment*	*FVIII:C*	*Response*
Effective	*Bleeding stopped*	*Clinical control*	*≥50%*	*positive*
Partially effective	*Bleeding reduced*	*Clinical stabilization or improvement or alternative reason for bleeding*	*≥20%*	*positive*
Poorly effective	*Bleeding slightly reduced or unchanged*	*Not clinically stable*	*<50%*	*negative*
Not effective	*Bleeding worsening*	*Clinically deteriorating*	*<20%*	*negative*

Note: If there is a discrepancy with the FVIII:C, the clinical assessment of bleed control will be the primary determinant of whether the response is positive or negative.

1.2.2 Secondary Efficacy Endpoints

- *The overall proportion of severe bleeding episodes successfully controlled with TAK-672 therapy, as assessed by the investigator.*
- *The proportion of bleeding episodes responsive to TAK-672 therapy at designated assessment time points after the initiation of therapy, as assessed by the investigator.*
- *Frequency, total dose, and total number of infusions of TAK-672 required to successfully control qualifying bleeding episodes.*
- *Correlation between response to TAK-672 therapy at specified time points and eventual control of severe bleeding episodes.*
- *Correlation among the pre-infusion anti-TAK-672 antibody titers, the total dose of TAK-672, the response at 24 hours and the eventual control of the bleeding episode.*
- *Inhibitor titers against hFVIII and pFVIII at pre-infusion, at specified time points during treatment, and at the end of the follow-up period on 90 days post final infusion.*
- *Drug exposure determined by means of non-compartmental methods with the following PK parameters to be estimated: $t_{1/2}$, CL, Vd, area under the concentration-time curve (AUC) and C_{max}/Dose.*
- *Duration period and the total dose from initial dose of TAK-672 until completion of hemostasis control.*
- *Number of new qualified severe bleeding episodes.*

1.2.3 Exploratory Endpoints

Not applicable.

1.2.4 Safety Endpoints

The safety of TAK-672 will be assessed from the following:

- *Treatment emergent AEs and SAEs throughout the study (including the loss of efficacy due to de novo pFVIII inhibitor/anamnestic reaction with an increase of inhibitor titers against pFVIII and/or hFVIII, hypersensitivity, and/or thrombogenicity).*
- *Vital signs throughout the study. Biochemistry, hematology, and urinalyses at Screening and then after the initial dose of TAK-672 at the following time points or visits: at 24 (±6) hours, at 72 (±6) hours, during follow-up visits, and at the end of study visit.*
- *Inhibitor titers against hFVIII and pFVIII at Screening and prior to the initial dose of TAK-672 as well as at the following time points or visits after the initial dose of TAK-672: at 72 (±6) hours and then at an early withdrawal, at PK dose, during follow-up visits (i.e. every 14 (±3) days until complete remission of AHA and then every 28 (±7) days), and at the end of study visit.*
- *Anti-host cell protein (BHK) antibody titer at Screening and at the end of the study visit.*

1.2.5 Other Endpoints

Not applicable.

1.3 Estimand

Definition:

The primary estimand is to evaluate the efficacy of TAK-672 for the treatment of severe bleeding events in Japanese subjects with Acquired Hemophilia A.

Attributes:

- Treatment:

  TAK-672 is administrated at an initial dose of 200 U/kg. If bleeding is effectively controlled by TAK-672, subjects may receive further therapy with TAK-672 to allow healing to take place with the dose designed to maintain the required FVIII:C.

  If a subsequent bleeding occurs and the treatment with TAK-672 for a subsequent bleeding is continued, the subsequent treatment is considered as the initiation of a new treatment and it is not used to assess the efficacy of treatment.

  The dosing of TAK-672 for PK assessment is not used to assess the efficacy of treatment.

  There is no comparison of treatments in this study.

- Population:

  Japanese subjects ≥18 years of age with AHA

- Variable:

  The variable is the response to TAK-672 therapy for the initial bleeding episode at 24 hours after the initiation of treatment.

  The data from 0 to 30 hours and closest to 24 hours will be used.

  A positive response is defined as "Effective" or "Partially effective" in assessment of efficacy. A negative response is defined as "Poorly effective" or "Not effective".

  Subjects with a positive response are responders, and subjects with a negative response are non-responders.

- Intercurrent events:

  The composite strategy is applied to any intercurrent events which caused early withdrawal.

  Subjects who discontinue prematurely will be considered non-responders. If "Did the patient complete treatment with TAK-672 for successful treatment?" is selected as "Yes" on the eCRF, subjects who discontinue prematurely will be considered as responders.

- Population-level summary:

  The proportion of subjects with a positive response (the percentage of the number of responders divided by the total number of subjects) will be used.

  There is no comparative discussion between specific populations.

2.0 STUDY DESIGN

This is a Phase 2/3, multi-center, prospective, open-label, non-controlled study to evaluate the efficacy and safety of TAK-672 for the treatment of severe bleeding episodes in Japanese subjects diagnosed with AHA.

At least 5 subjects are planned to be enrolled and dosed.

Subjects, after they or their legal representative provide written informed consent, will be screened to determine their eligibility for the study.

A diagnosis of AHA includes the following criteria:

- *Presentation with spontaneous bleeding without anatomical cause and without prior known bleeding disorder*
- *Prolonged activated partial thromboplastin time (aPTT) without explanation*
- *Abnormal aPTT cross mixing study consistent with FVIII inhibitor*
- *Confirmation of a low FVIII:C*
- *Positive FVIII inhibitor (≥0.6 BU) as measured by the Bethesda assay in the local or central laboratory*

If a subject has been diagnosed with AHA, the study and the study requirements will be discussed with the subject or legal decision maker. Once reviewed and questions answered, the subject may be offered the opportunity to enroll in this clinical study. After the subject provides agreement to enroll in the study by signing the informed consent, the study procedures will be initiated.

The study will consist of the following evaluation periods:

Screening:

Subjects who are suspected of AHA or who have been diagnosed with AHA will undergo all screening activities after providing a written informed consent form. When AHA is confirmed, immune-suppressive therapy can be initiated.

A bleeding event is determined to be severe if it meets at least 1 of the following criteria:

- *Bleeds that are a threat to a vital organ that could threaten life (e.g. intracranial bleed, or any site that could obstruct the airway).*
- *Bleeds that are a threat to a vital organ where life is not threatened but the organ function could be impaired (e.g. intraspinal bleed threatening the spinal cord and/or nerve conduction; a continual bleed into the kidney or bladder that could result in an obstructive uropathy, testicular bleed, bleed in and around the eye).*
- *Bleeds requiring a blood transfusion to maintain the hemoglobin (Hgb) level at above-life or organ threatening levels (e.g. post-surgical, gastro-intestinal, retro-peritoneal, and thigh bleeds).*
- *Intramuscular bleeds where muscle viability and/or neurovascular integrity is significantly compromised or at risk of being compromised.*
- *Intra-articular bleeds impacting a major joint associated with severe pain, swelling and severe loss of joint mobility (reduced >70%) or where a bleed could result in joint destruction (e.g. in and around the femoral head).*

Specimens for coagulation testing (FVIII:C), inhibitor assays to hFVIII and pFVIII) will be drawn at Screening for diagnosis and throughout study for ongoing management. These specimens will be collected and processed locally and transported to reference laboratory for confirmatory testing.

Treatment with TAK-672:

Prior to TAK-672 administration, a blood sample will be drawn for the assessments of Hgb, Hct, and coagulation (aPTT and FVIII:C) as well as inhibitor titers against hFVIII and pFVIII.

Approximately 30 minutes post-TAK-672 administration, the subject's vital signs and control of bleeding will be evaluated, and a blood sample will be taken to assess Hgb, hematocrit (Hct), aPTT, and FVIII:C. AE assessment will also be performed.

Subjects will be monitored in a hospital care setting for signs and symptoms of continued bleeding and the investigator will determine the need for laboratory testing and/or further

treatment administration. Based on expert consensus recommendations, monitoring is to occur every 6 to 12 hours depending on the site and severity of bleeding.

Based on clinical status, the study physician will determine if there is a need to administer additional doses of TAK-672; blood samples will be drawn pre-infusion for Hgb, Hct, aPTT, and FVIII:C, and at 30 min post infusion for aPTT and FVIII. Additional doses of TAK-672 may be administered as frequently as every 4 to 12 hours. This is to be repeated throughout the management of the bleeding until the bleeding episode was determined to be controlled.

Subject's clinical status will be evaluated at the following timepoints after the initial dose of TAK-672: at 30 min, at 8 (± 2) hours, at 16 (± 2) hours, at each dose before 24 hours, at 24 hours (± 6), at each dose or every 12 (±6) hours before 72 hours, at each dose or every 24 (±12) hours until last TAK-672 dose or withdrawal, at 24 (+24) hours after last TAK-672 dose, at follow-up visits (i.e. every 14 (± 3) days until complete remission of AHA and then every 28 (±7) days), at the end of study visit (i.e. at 90 (± 7) days after last TAK-672 dose, and at early withdrawal.

At these pre-specified time points, the medications administered for bleed control and immunosuppressive agents given to control the inhibitor titer will be reviewed. Clinical and laboratory assessments will be done to evaluate bleeding site, hemodynamic and hemostatic status including Hgb, Hct, aPTT, FVIII:C, and hFVIII inhibitor titer and pFVIII inhibitor titer.

Immunosuppressive Treatment

Concurrent treatment with immunosuppressive agents will be initiated and determination of specific therapeutic interventions will be at the discretion of the study physician based on standard of care and in consideration of participant co-morbidities and clinical status. Details of these treatments, dosage, frequency, and duration will be recorded in the participant's clinical data collection forms.

Subsequent bleeds:

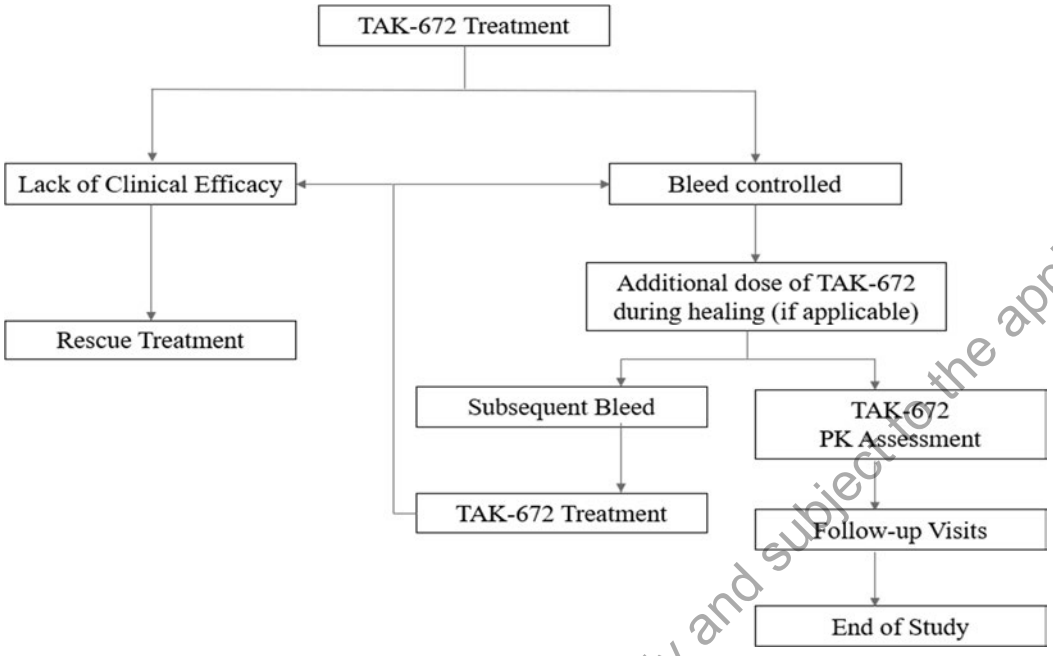
Subjects may be treated either with TAK-672 or bypassing agents at the discretion of the investigator for any subsequent bleeding episodes. The treatment of any subsequent bleeding episodes will not be considered for the purposes of the primary efficacy endpoint.

End of Study:

Subjects will remain in the study unless withdrawn by the investigator or by subject's request. End of study will occur after: (1) a minimum of 5 subjects have been enrolled, (2) each of the subjects has been treated with TAK-672 for at least 1 qualifying severe bleeding episode, and (3) the efficacy of TAK-672 has been evaluated for the treatment of the bleeding episode in each of the subjects. The end of study will be approximately 3 to 4 months (90 days follow-up after the last dose of TAK-672) after the last participant has received the final TAK-672 treatment dose.

A schematic of the study design is included as Figure 6.a.

Figure 6.a Study Schematic diagram



3.0 STATISTICAL HYPOTHESES AND DECISION RULES

3.1 Statistical Hypotheses

Not applicable as no statistical hypothesis is set in this study.

3.2 Statistical Decision Rules

Not applicable.

3.3 Multiplicity Adjustment

Not applicable.

4.0 SAMPLE-SIZE DETERMINATION

The planned total sample size for this study is 5 or more subjects in FAS and is based on feasibility considerations, given the low incidence of AHA in Japan. No formal sample size calculation will be performed for this study.

5.0 ANALYSIS SETS

In this study, 4 kinds of analysis sets are defined: Full analysis set (FAS), Per-protocol set (PPS), Safety analysis set (SAS), and Pharmacokinetic analysis set (PKS).

5.1 Full Analysis Set

The FAS, the main efficacy analysis set, will include all subjects who have received at least 1 dose of the TAK 672 and will be used for the efficacy analyses.

5.2 Per-Protocol Set

The PPS is a subset of the FAS population including patients who do not have a major protocol violation as determined by the sponsor's project clinician (or designee).

Major protocol violations listed below:

- Inclusion Criteria:
  - Not applicable
- Exclusion Criteria:

  #3: Known major sensitivity (anaphylactoid reactions) to therapeutic products of porcine or hamster origin

  #4: Use of hemophilia medication

5.3 Safety Analysis Set

The safety analysis set will include all subjects who have received at least 1 dose of TAK-672.

5.4 Pharmacokinetic Analysis Set

The PKS will include all subjects who have agreed to undergo a PK assessment for the measurement of plasma FVIII:C and who have undergone a FVIII measurement for the estimation of its PK parameters, with no major protocol violations as determined by the sponsor's study clinician (or designee).

6.0 STATISTICAL ANALYSIS

6.1 General Considerations

Definitions of Informed Consent Date:

There are two types of informed consent for participation in this study.

1. Informed consent obtained from the subject him/herself
2. Informed consent obtained from the parent/legal guardian

If two types of informed consent are obtained, the earlier date will be treated as the date of informed consent for the analyses of this study.

Definitions of Study Day and Time:

- Study Day (days) and Study Time (hours):

  Study Day and Study Time represent the number of days and hours after the start of treatment. For the number of days after the start of administration, the start day of administration of TAK-672 in each treatment period will be defined as Day 1. For the time after the start of administration, the start date and time of administration will be expressed as Time 0.

- Follow-up Day (days) and Follow-up Time (hours):

  Follow-up Day and Follow-up Time represent the number of days and time after the end of treatment. For the number of days after the end of administration, the end day of administration of TAK-672 in each treatment period is defined as Day 0, and the time after the end of administration is represented as Time 0.

Descriptive Statistics:

Summary tables of data will be provided as appropriate, showing the number of subjects with non-missing data (n), mean, standard deviation, median, minimum, and maximum for continuous variables, and counts and percentage for categorical variables. For categorical variables, the denominator of percentages will be the number of subjects, except for those collected by study visit and/or scheduled time point, in that case the denominator of percentages will be the number of subjects with a non-missing value at the visit and/or the scheduled time point for by-subject summaries or the total number of bleeding episodes for by-event summaries.

Conventions for Decimals:

- Relative to number of decimals in original data, use 1 more decimal for mean, median, and percentiles, 2 more decimals for standard deviation/error, and the same number of decimals for minimum, maximum, and range. Do not exceed 4 decimals.
- Some laboratory parameters or other data may require judicious deviation from this rule.
- Confidence Interval (CI) will be presented using the same number of decimal places as the parameter estimate.
- Display percentages with 1 decimal.

Methods for Handling Dropouts and Missing Data:

In efficacy analyses, eligible subjects who withdraw from treatment at an earlier time point will be assumed to be non-responders. Subjects who had hemostatic response and stopped treatment because the bleeding was controlled, will be assumed to be responders. For analyses using the Safety population, there will be no imputation of missing endpoint values.

Conventions for Calculations and Tabulations:

- In summary displays, AEs are counted only once per subject within MedDRA category (e.g. overall, system organ class, and preferred term).

- When AEs are summarized within levels of another AE assessment (e.g. causality or intensity), AEs are counted once per subject at the worst level of the assessment (e.g. strongest relationship to study drug or greatest intensity). A missing or unknown value for the assessment will be considered worst.
- Treatment-emergent adverse event (TEAE): Adverse events with onset on or after the start of TAK-672 infusion, or medical conditions present prior to the start of TAK-672 infusion but increasing in severity or relationship on or after TAK-672 infusion. If the start date of AE is the same as the date of TAK-672 infusion, but the start time of AE is unknown, it will be treated as a TEAE. A TEAE fulfills any of the following criteria.
  - Is not present before receiving the first infusion of TAK-672.
  - Is present before receiving the first infusion of TAK-672 but the intensity increases on or after receiving.
  - Is present before receiving the first infusion of TAK-672 but the drug relationship becomes related on or after receiving.
- Pretreatment event (PTE): Any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to TAK-672 infusion. If the start date of an event is the same as the date of TAK-672 infusion, but the start time of an event is unknown, it will not be treated as a PTE.

6.1.1 Handling of Treatment Misallocations

Not applicable as it is a non-controlled study.

6.1.2 Analysis Approach for Continuous Variables

No special notes other than Section 6.1.

6.1.3 Analysis Approach for Binary Variables

The exact 2-sided Clopper-Pearson 95% CI will be applied to CIs unless otherwise noted.

6.1.4 Analysis Approach for Time-to-Event Variables

Not applicable as the analysis of time-to-event is not set in this study.

6.2 Disposition of Subjects

6.2.1 Study Information

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Date First Subject Signed Informed Consent Form

Date of Last Subject's Last Visit/Contact

MedDRA Version

WHO Drug Version

SAS Version Used for Creating the Datasets

Analytical Methods:

(1) Study Information

Study information shown in the analysis variables section will be provided.

6.2.2 Screen Failures

Analysis Set:

All Subjects Who Did Not Enter the Treatment Period

Analysis Variables:

Age (years)

Gender [Male, Female]

Analytical Methods:

(1) Screen Failures

Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

6.2.3 Subject Eligibility

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

Eligibility Status

[Eligible for Entrance the Treatment Period, Not Eligible for Entrance the Treatment Period]

Primary Reason for Subject Not Being Eligible

[Adverse Event, Screen Failure, Protocol Deviation, Lost To Follow-up, Withdrawal by Subject, Withdrawal by Parent/Guardian, Study Terminated by Sponsor, Other]

Analytical Methods:

(1) Eligible for Entrance the Treatment Period

Frequency distributions will be provided. When calculating percentages for the primary reasons for subject not being eligible, the total number of ineligible subjects will be used as the denominator.

6.2.4 Number of Subjects Who Entered the Treatment Period by Site

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Status of Entrance into the Treatment Period [Entered]

Stratum:

Site [Site numbers will be used as categories]

Analytical Methods:

(1) Number of Subjects Who Entered the Treatment Period by Site
Frequency distribution will be provided for each stratum.

6.2.5 Disposition of Subjects

6.2.5.1 Disposition of Subjects for the Treatment Period for Initial Qualified Bleeding Episode

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Study Drug Administration Status

[Eligible but Not Treated]

Reason for Not Being Treated

[Adverse Event, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Withdrawal by Parent/Guardian, Study Terminated by Sponsor, Other]

Study Drug Status of the Treatment Period for Initial Qualified Bleeding Episode

[Completion, Prematurely Discontinued Study Drug]

Reason for Discontinuation of Study Drug of the Treatment Period for Initial Qualified Bleeding Episode

[Lack of Efficacy, Adverse Event, Subsequent Bleeding, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Withdrawal by Parent/Guardian, Study Terminated by Sponsor, Other]

Study Status After Study Drug Discontinuation

[Completion, Prematurely Discontinued the Study]

Reason for Discontinuation of the Study

[Lack of Efficacy, Adverse Event, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Withdrawal by Parent/Guardian, Study Terminated by Sponsor, Other]

Analytical Methods:

(1) Disposition of Subjects
Frequency distributions will be provided. When calculating percentages for the reasons for not being treated, the total number of subjects not treated by the study drug will be used as the denominator. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

6.2.5.2 Disposition of Subjects for the Treatment Period for Subsequent Qualified Bleeding Episode

Analysis Set:

All Subjects Who Entered the Treatment Period for Subsequent Qualified Bleeding Episode

Analysis Variables:

Study Drug Status of the Treatment Period for Subsequent Qualified Bleeding Episode

[Completion, Prematurely Discontinued Study Drug]

Reason for Discontinuation of Study Drug of the Treatment Period for Subsequent Qualified Bleeding Episode

[Lack of Efficacy, Adverse Event, Subsequent Bleeding, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Withdrawal by Parent/Guardian, Study Terminated by Sponsor, Other]

Analytical Methods:

(1) Disposition of Subjects
Frequency distributions will be provided. When calculating percentages for the reasons for discontinuation, the total number of subjects who prematurely discontinued will be used as the denominator.

6.2.6 Study Drug Completion Status

6.2.6.1 Study Drug Completion Status of the Treatment Period for Initial Qualified Bleeding Episode

Analysis Set:

All Subjects Who Entered the Treatment Period for Initial Qualified Bleeding Episode

Analysis Variables:

Study Drug Status of the Treatment Period for Initial Qualified Bleeding Episode

[Completion, Prematurely Discontinued Study Drug]

Reason for Discontinuation of Study Drug of the Treatment Period for Initial Qualified Bleeding Episode

[Lack of Efficacy, Adverse Event, Subsequent Bleeding, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Withdrawal by Parent/Guardian, Study Terminated by Sponsor, Other]

Categories:

Duration of Exposure to Study Drug (days) [1-3, 4-6, 7-9, 10-12, 13-15, 16-20, 21-25, 26-30, 31-45, 46-60, 61-90, 91-]

Analytical Methods:

(1) Study Drug Completion Status
Frequency distribution will be provided for each category of duration of exposure to study drug.

6.2.6.2 Study Drug Completion Status of the Treatment Period for Subsequent Qualified Bleeding Episode

Analysis Set:

All Subjects Who Entered the Treatment Period for Subsequent Qualified Bleeding Episode

Analysis Variables:

Study Drug Status of the Treatment Period for Subsequent Qualified Bleeding Episode

[Completion, Prematurely Discontinued Study Drug]

Reason for Discontinuation of Study Drug of the Treatment Period for Subsequent Qualified Bleeding Episode

[Lack of Efficacy, Adverse Event, Subsequent Bleeding, Protocol Deviation, Lost to Follow-up, Withdrawal by Subject, Withdrawal by Parent/Guardian, Study Terminated by Sponsor, Other]

Categories:

Duration of Exposure to Study Drug (days) [1-3, 4-6, 7-9, 10-12, 13-15, 16-20, 21-25, 26-30, 31-45, 46-60, 61-90, 91-]

Analytical Methods:

(1) Study Drug Completion Status
Frequency distribution will be provided for each category of duration of exposure to study drug.

6.2.7 Protocol Deviations and Analysis Sets

6.2.7.1 Protocol Deviations

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Significant Protocol Deviation

[Categories are based on the specifications in Protocol Deviation Management Plan]

Analytical Methods:

(1) Protocol Deviations
Frequency distribution of subjects with significant protocol deviations, as identified by the study team as being major or critical, will be provided for each deviation category. A subject who has several deviations will be counted once in each appropriate category. A subject who has several deviations that can be classified into the same category will be counted only once.

6.2.7.2 Analysis Sets

Analysis Set:

All Subjects Who Entered the Treatment Period

Analysis Variables:

Handling of Subjects [Categories are based on the specifications in Subject Evaluability List]

Analysis Sets	Full Analysis Set	[Included]
	Per-Protocol Set	[Included]
	Safety Analysis Set	[Included]
	Pharmacokinetic Analysis Set	[Included]

Analytical Methods:

(1) Subjects Excluded from Analysis Sets
(2) Analysis Sets
Frequency distributions will be provided. For (1), a subject who has several reasons for exclusion will be counted once in each appropriate category. A subject who has several reasons for exclusion that can be classified into the same category will be counted only once.

6.3 Demographic and Other Baseline Characteristics

6.3.1 Demographics and Other Baseline Characteristics

Analysis Set:

Full Analysis Set

Analysis Variables:

Age (years)

Gender [Male, Female]

Race

[American Indian or Alaska Native, Asian, Black or African American, Native Hawaiian/Other Pacific Islander, White]

Race (Asian)

[Asian Indian, Chinese, Filipino, Japanese, Korean, Vietnamese]

Height (cm)

Weight (kg)

BMI (kg/m^2)

Time since first diagnosis of Acquired Hemophilia A (months)

History of any aPCC, rFVIIa and/or pd-FVIIa/FX use within 6 months prior to obtaining informed consent

[Yes, No]

History of aPCC use within 6 months prior to obtaining informed consent

[Yes, No]

History of rFVIIa use within 6 months prior to obtaining informed consent

[Yes, No]

History of pd-FVIIa/FX use within 6 months prior to obtaining informed consent

[Yes, No]

Hemoglobin at Baseline

Hematocrit at Baseline

APTT Cross Mixing Test

[Inhibitor Pattern, Not Inhibitor Pattern]

Prothrombin Time (sec)

Prothrombin Time (%)

Activated Partial Thromboplastin Time at Baseline

Factor VIII Activity at Baseline

Human Factor VIII Inhibitor at Baseline

Porcine Factor VIII Inhibitor at Baseline

Anti-BHK Antibody at Baseline

[Positive, Negative]

Analytical Methods:

(1) Summary of Demographics and Other Baseline Characteristics
Frequency distributions for categorical variables and descriptive statistics for continuous variables will be provided.

6.3.2 Medical History and Concurrent Medical Conditions

Analysis Set:

Safety Analysis Set

Analysis Variables:

Medical History

Concurrent Medical Conditions

Analytical Methods:

(1) Medical History by System Organ Class and Preferred Term
(2) Concurrent Medical Conditions by System Organ Class and Preferred Term
Frequency distributions will be provided. MedDRA dictionary will be used for coding. Summaries will be provided using SOC and PT, where SOC will be sorted alphabetically and PT will be sorted in decreasing frequency. A subject with multiple occurrences of medical history or concurrent medical condition within a SOC will be counted only once in that SOC. A subject with multiple occurrences of medical history or concurrent medical condition within a PT will be counted only once in that PT.

6.4 Medication History and Concomitant Medications

6.4.1 Prior Medications

Analysis Set:

Safety Analysis Set

Analysis Variables:

Medication History

Analytical Methods:

(1) Medication History by Preferred Medication Name
Frequency distributions will be provided. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names and sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

6.4.2 Concomitant Medications

Analysis Set:

Safety Analysis Set

Analysis Variables:

Concomitant Medications

Analytical Methods:

(1) Concomitant Medications That Started Prior to and Were Ongoing at First Dose of TAK-672 as well as Those That Started After First Dose of TAK-672 by Preferred Medication Name
Frequency distributions will be provided. WHO Drug dictionary will be used for coding. Summaries will be provided using preferred medication names and sorted in decreasing frequency based on the number of reports. A subject who has been administered several medications with the same preferred medication name will be counted only once for that preferred medication name.

6.5 Efficacy Analysis

The FAS will be used for all efficacy analyses, except for the analysis of PK data, where the PKS will be used.

Only initial severe bleeding episodes are qualifying episodes for the efficacy. Subsequent severe bleeding episodes will not be considered as qualifying bleeding episodes for the purposes of the efficacy endpoint.

6.5.1 Primary Endpoint Analysis

The primary efficacy endpoint will be the proportion of severe bleeding episodes with a demonstrated response to TAK-672 therapy at 24 hours after the initiation of treatment.

6.5.1.1 Derivation of Endpoint

The description of variable is shown at Section 1.3.

6.5.1.2 Main Analytical Approach

Analysis Set:

Full Analysis Set

Analysis Variables:

Response to TAK-672 therapy at 24 hours after the initiation of treatment

[Positive, Negative]

Analytical Methods:

(1) The proportion of subjects with a positive response and its CI will be presented. For CI, exact 2-sided Clopper-Pearson 95% CI will be applied.

6.5.1.3 Sensitivity Analysis

The same analysis as the Primary Endpoint Analysis will be performed for PPS.

6.5.1.4 Supplementary Analysis

Not applicable.

6.5.2 Secondary Endpoints Analysis

6.5.2.1 Derivation of Endpoints

- A positive response is defined as "Effective" or "Partially effective" in assessment of efficacy. A negative response is defined as "Poorly effective" or "Not effective".

  Subjects who withdraw from treatment at an earlier time point will be assumed to be non-responders at subsequent time points. If "Completed TAK-672 Therapy for Treatment Success?" in eCRF is selected as "Yes", they will be assumed to be responders at subsequent time points.

- Total dose, total number of infusions, duration, frequency and compliance of TAK-672 infusion will be derived. For more information on derivation, see Section 9.2.1.

6.5.2.2 Main Analytical Approach

The secondary efficacy endpoints are listed below:

1) The overall proportion of severe bleeding episodes successfully controlled with TAK 672 therapy, as assessed by the investigator.

Analysis Set:

Full Analysis Set

Analysis Variables:

Status at end of study treatment for initial treatment period

[Successfully controlled, Uncontrolled]

Analytical Methods:

(1) The proportion of successfully controlled subjects and its CI will be presented.

2) The proportion of bleeding episodes responsive to TAK-672 therapy at designated assessment time points after the initiation of therapy, as assessed by the investigator.

Analysis Set:

Full Analysis Set

Analysis Variables:

Response to TAK-672 therapy at designated assessment time points

[Positive, Negative]

Visit:

during treatment period for initial bleeding episodes; at 30 mins, at 8 hours, at 16 hours, at 24 hours, at 36 hours, at 48 hours, at 60 hours, at 72 hours, at every 24 hours after 72 hours,

during follow-up visits for initial bleeding episodes; at 24 hours, at every 14 days,

end of study.

Analytical Methods:

(1) The Number of subjects with initial severe bleeding episodes at designated assessment time points will be shown. The proportion of subjects with a positive response and its CI will also be presented.

3) Frequency, total dose, and total number of infusions of TAK-672 required to successfully control qualifying bleeding episodes.

Analysis Set:

Subjects of Full Analysis Set Who were Successfully Controlled for Initial Qualified Bleeding Episodes

Analysis Variables:

Total Dose per subject for Initial Treatment Period (U)

Total Dose per subject for Initial Treatment Period (U/kg)

Total number of infusions per subject for Initial Treatment Period

Average number of infusions per day for Initial Treatment Period

Compliance for Initial Treatment Period (%)

Analytical Methods:

(1) Summary of Total Dose, Total number of infusions, Average number of infusions and Compliance
Descriptive statistics will be provided.

4) Correlation between response to TAK-672 therapy at specified time points and eventual control of severe bleeding episodes.

Analysis Set:

Full Analysis Set

Analysis Variables:

Response to TAK-672 therapy at designated assessment time points

[Positive, Negative]

Subgroups:

Status at end of study treatment

[Successfully controlled, Uncontrolled]

Visit:

during treatment period for initial bleeding episodes; at 30 mins, at 8 hours, at 16 hours, at 24 hours, at 36 hours, at 48 hours, at 60 hours, at 72 hours, at every 24 hours after 72 hours,

during follow-up visits for initial bleeding episodes; at 24 hours, at every 14 days,

end of study.

Analytical Methods:

(1) The number of subjects with initial severe bleeding episodes at designated assessment time points by subgroup will be shown. The proportion of subjects with a positive response will be presented.

5) Correlation among the pre-infusion anti-TAK-672 antibody titers, the total dose of TAK-672, the response at 24 hours and the eventual control of the bleeding episode.

Analysis Set:

Full Analysis Set

Analysis Variables:

Pre-Infusion Anti-TAK-672 Antibody Titers

Total Dose per subject for Initial Treatment Period (U)

Total Dose per subject for Initial Treatment Period (U/kg)

Response to TAK-672 therapy at 24 hours after the initiation of treatment

[Positive, Negative]

Subgroups:

Status at end of study treatment

[Successfully controlled, Uncontrolled]

Analytical Methods:

(1) Summary of Pre-Infusion Anti-TAK-672 Antibody Titers, Total Dose per subject for Initial Treatment Period and Response to TAK-672 therapy at 24 hours
Descriptive statistics will be provided by subgroup. The proportion of subjects with a positive response will be presented.

6) Inhibitor titers against hFVIII and pFVIII at pre-infusion, at specified time points during treatment, and at the end of the follow-up period on 90 days post final infusion.

Analysis Set:

Full Analysis Set

Analysis Variables:

Human Factor VIII Inhibitor

Porcine Factor VIII Inhibitor

Visit:

baseline,

during treatment period for initial bleeding episodes; at 72 hours,

during follow-up visits for initial bleeding episodes; at every 14 days,

end of study.

Analytical Methods:

(1) Summary of hFVIII and pFVIII Inhibitor Titers

Descriptive statistics for observed values and changes from baseline will be provided at designated assessment time points.

(2) Mean and Standard Deviation Plots
Mean observed values and changes from baseline will be plotted with standard deviation bars at designated assessment time points.

7) *Drug exposure determined by means of non-compartmental methods with the following PK parameters to be estimated: $t_{1/2}$, CL, Vd, area under the concentration-time curve (AUC) and C_{max}/Dose.*

See Section 6.7.1.

8) Duration period and the total dose from initial dose of TAK-672 until completion of hemostasis control.

Analysis Set:

Subjects of Full Analysis Set Who were Successfully Controlled for Initial Qualified Bleeding Episodes

Analysis Variables:

Total Dose per subject for Initial Treatment Period (U)

Total Dose per subject for Initial Treatment Period (U/kg)

Duration of Initial Treatment Period (days)

Analytical Methods:

(1) Summary of Duration and the Total Dose of TAK-672
Descriptive statistics will be provided.

9) Number of new qualified severe bleeding episodes.

Analysis Set:

Full Analysis Set

Analysis Variables:

Qualified bleeding episodes?

[Yes, No]

Analytical Methods:

(1) The number of subjects with at least one Subsequent Qualified Bleeding Episodes will be shown.

6.5.2.3 Sensitivity Analysis

Not applicable.

6.5.2.4 Supplementary Analysis

Not applicable.

6.5.3 Other Secondary Endpoints Analysis

Not applicable.

6.5.4 Subgroup Analysis

The subgroup analysis is the same as the primary efficacy endpoint analysis except for analysis set.

Analysis Set:

Full Analysis Set

Subgroups:

Anti-pFVIII inhibitor titer prior to initiation of treatment

[≤20 BU/mL, >20 BU/mL]

Analysis Variables:

Response to TAK-672 therapy at 24 hours after the initiation of treatment

[Positive, Negative]

Analytical Methods:

(1) The proportion of subjects with a positive response and its CI will be presented

6.6 Safety Analysis

6.6.1 Adverse Events

6.6.1.1 Overview of Treatment-Emergent Adverse Events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

Severity/Intensity	[Mild, Moderate, Severe]
Relationship to Study Drug	[Related, Not Related]

Analytical Methods:

The following summaries will be provided.

(1) Overview of Treatment-Emergent Adverse Events
   1) All Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
   2) Intensity of Treatment-Emergent Adverse Events (number of events, number and percentage of subjects).
   3) Relationship of Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)
   4) Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
   5) Serious Treatment-Emergent Adverse Events (number of events, number and percentage of subjects)
   6) Relationship of serious Treatment-Emergent Adverse Events to study drug (number of events, number and percentage of subjects)
   7) Serious Treatment-Emergent Adverse Events leading to study drug discontinuation (number of events, number and percentage of subjects)
   8) Treatment-Emergent Adverse Events resulting in death (number of events, number and percentage of subjects)

TEAEs will be counted according to the rules below.

Number of subjects

- Summaries for 3) and 6).

  A subject with occurrences of TEAE in both categories (i.e. Related and Not Related) will be counted once in the Related category.

- Summary for 2).

  A subject with multiple occurrences of TEAE will be counted once for the TEAE with the maximum intensity.

- Summaries other than 2), 3) and 6).

  A subject with multiple occurrences of TEAE will be counted only once.

Number of events

- For each summary, the total number of events will be calculated.

6.6.1.2 Displays of Treatment-Emergent Adverse events

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE

Categories:

Severity/Intensity [Mild, Moderate, Severe]

Time of Onset (day) [1-3, 4-6, 7-9, 10-12, 13-15, 16-20, 21-25, 26-30, 31-45, 46-60, 61-90, 91-]

Analytical Methods:

The following summaries will be provided using frequency distribution.

TEAEs will be coded using the MedDRA and will be summarized using SOC and PT.

SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by System Organ Class only or PT only.

(1) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(2) Treatment-Emergent Adverse Events by System Organ Class
(3) Treatment-Emergent Adverse Events by Preferred Term
(4) Intensity of Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(5) Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(6) Intensity of Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(7) Treatment-Emergent Adverse Events Leading to Study Drug Discontinuation by System Organ Class and Preferred Term
(8) Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(9) Intensity of Serious Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(10) Serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(11) Intensity of Serious Drug-Related Treatment-Emergent Adverse Events by System Organ Class and Preferred Term
(12) Treatment-Emergent Adverse Events by System Organ Class and Preferred Term Over Time

The frequency distribution will be provided according to the rules below.

Number of subjects

- Summary tables other than (4), (6), (9), (11) and (12).

  A subject with multiple occurrences of TEAE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAE within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set.

- Summary tables for (4), (6), (9) and (11).

  A subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once for the TEAE with the maximum intensity. Percentages will be based on the number of subjects in the safety analysis set.

- Summary tables for (12).

  A subject with a TEAE that occurs in more than one interval is counted in all the intervals that the TEAE occurs. For each time interval, a subject with multiple occurrences of TEAE within a SOC or a PT will be counted only once in that SOC or PT.

  When calculating percentages for each time interval, the number of subjects at risk (i.e. subjects who either have an exposure or have an occurrence of TEAE, during or after the corresponding time interval) will be used as the denominator. The number of subjects whose onset of any one of the TEAEs is within the time interval will be used as the numerator.

Number of events

- For each summary, the total number of events will be calculated.

6.6.1.3 Displays of Pretreatment Events

Analysis Set:

All Subjects Who Signed the Informed Consent Form

Analysis Variables:

PTE

Analytical Methods:

The following summaries will be provided using frequency distribution.

PTEs will be coded using the MedDRA and will be summarized using SOC and PT. SOC will be sorted alphabetically and PT will be sorted in decreasing frequency.

(1) Pretreatment Events by System Organ Class and Preferred Term
(2) Serious Pretreatment Events by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

Number of subjects

- A subject with multiple occurrences of PTE within a SOC will be counted only once in that SOC. A subject with multiple occurrences of PTE within a PT will be counted only once in that PT.

Number of events

- For each summary, the total number of events will be calculated.

6.6.2 Adverse Events of Special Interest

Analysis Set:

Safety Analysis Set

Analysis Variables:

TEAE of Special Interest (TEAESI)

Analytical Methods:

The following summaries will be provided using frequency distribution.

There are 4 types of TEAESIs, each identified as below.

1. Hypersensitivity reactions:
   SMQs (broad): Hypersensitivity
2. *de novo* inhibitor to porcine FVIII:
   PTs: Anti factor VIII antibody increased, Anti factor VIII antibody positive, Anti factor VIII antibody test, Antibody test positive, Coagulation factor VIII level abnormal, Coagulation factor VIII level decreased, Condition aggravated, Inhibiting antibodies, Inhibiting antibodies positive, Cross sensitivity reaction, Factor VIII inhibition
3. Anamnestic reaction with increase of inhibitor titer to pFVIII and/or hFVIII:
   SMQ (broad): Lack of efficacy/effect and PTs (Anamnestic reaction, Anti factor VIII antibody increased, Anti factor VIII antibody positive, Anti factor VIII antibody test, Antibody test positive, Coagulation factor VIII level increased, Factor VIII inhibition)
4. Thromboembolic events:
   SMQ (broad): Embolic and thrombotic events

TEAESIs will be coded using the MedDRA and will be summarized using SOC and PT.

SOC will be sorted alphabetically and PT will be sorted in decreasing frequency for tables provided by SOC and PT. SOC and PT will be sorted in decreasing frequency for tables provided by System Organ Class only or PT only.

(1) Treatment-Emergent Adverse Events of Special Interest (hypersensitivity reactions) by System Organ Class and Preferred Term
(2) Treatment-Emergent Adverse Events of Special Interest (de novo inhibitor to porcine FVIII) by System Organ Class and Preferred Term
(3) Treatment-Emergent Adverse Events of Special Interest (anamnestic reaction with increase of inhibitor titer to pFVIII and/or hFVIII) by System Organ Class and Preferred Term
(4) Treatment-Emergent Adverse Events of Special Interest (thromboembolic events) by System Organ Class and Preferred Term

The frequency distribution will be provided according to the rules below.

Number of subjects

- Summary tables for (1), (2), (3) and (4).

  A subject with multiple occurrences of TEAESI within a SOC will be counted only once in that SOC. A subject with multiple occurrences of TEAESI within a PT will be counted only once in that PT. Percentages will be based on the number of subjects in the safety analysis set.

Number of events

- For each summary, the total number of events will be calculated.

6.6.3 Clinical Laboratory Evaluations

6.6.3.1 Hematology and Serum Chemistry

Analysis Set:

Safety Analysis Set

Analysis Variables:

Hematology

Erythrocytes, Hemoglobin, Hematocrit, Ery. Mean Corpuscular Volume, Ery. Mean Corpuscular Hemoglobin, Ery. Mean Corpuscular HGB Concentration, Platelets, Leukocytes, Leukocytes differentials (Neutrophils, Lymphocytes, Monocytes, Eosinophils, Basophils)

Serum Chemistry

Alkaline phosphatase, Alanine Aminotransferase, Aspartate Aminotransferase, Bilirubin, Urea Nitrogen, Glucose, Urate, Creatinine

Visit:

Other than Hemoglobin and Hematocrit:

baseline,

during treatment period; at 24 hours, at 72 hours,

during follow-up visits; at 24 hours, at every 14 days,

end of study.

For Hemoglobin and Hematocrit:

baseline,

during treatment period; at 30 min, at 8 hours, at 16 hours, at 24 hours, at 36 hours, at 48 hours, at 60 hours, at 72 hours, at every 24 hours after 72 hours,

during follow-up visits; at 24 hours, at every 14 days,

end of study.

Analytical Methods:

For each variable, summaries (1) to (2) will be provided.

For applicable variables, summaries (3) will be provided.

(1) Summary of Laboratory Test Results and Change from Baseline by Visit
Descriptive statistics for observed values for each visit and changes from baseline will be provided.
(2) Case Plots
Plots over time for each subject will be presented.
(3) Number and Percentage of Subjects with Markedly Abnormal Values of Laboratory Parameters
Overall frequency distributions of MAV as well as frequency distributions of MAV for each post-baseline visit will be provided. If a laboratory parameter has both lower and upper MAV criteria, analysis will be performed for each. Further details are given in Appendix (refer to Section 9.4).

6.6.3.2 Urinalysis

Analysis Set:

Safety Analysis Set

Analysis Variables:

pH

Specific gravity

Protein [Negative, Positive]

Ketones	[Negative, Positive]
Glucose	[Negative, Positive]
Bilirubin	[Negative, Positive]
Occult blood	[Negative, Positive]
Urobilinogen	[Negative, Positive]
Leukocytes	[Absent, Present]
Erythrocytes	[Absent, Present]
Bacteria	[Absent, Present]
Casts	[Absent, Present]
Crystals	[Absent, Present]

Visit:

baseline,

during treatment period; at 24 hours, at 72 hours,

during follow-up visits; at 24 hours, at every 14 days,

end of study.

Analytical Methods:

For pH and specific gravity, summaries (1) and (2) will be provided.

For other analysis variables, summaries (3) will be provided.

(1) Summary of Urine Laboratory Test Results and Change from Baseline by Visit
Descriptive statistics for observed values for each visit and changes from baseline will be provided.
(2) Case Plots
Plots over time for each subject will be presented.
(3) Number of Subjects in Categories of Urine Laboratory Test Results by Visit
Shift tables showing the number of subjects in each category at baseline and each postdose visit will be provided. In analysis variables of Protein, Ketones, Glucose, Bilirubin, Occult blood or Urobilinogen, observed values other than "Negative" (or "-") are treated as "Positive".

6.6.3.3 Inhibitor titers against hFVIII and pFVIII

Analysis Set:

Safety Analysis Set

Analysis Variables:

Human Factor VIII Inhibitor

Porcine Factor VIII Inhibitor

Visit:

baseline,

during treatment period; at 72 hours,

during follow-up visits; at every 14 days,

end of study.

Analytical Methods:

For each variable, summaries (1) and (2) will be provided.

(1) Summary of hFVIII and pFVIII Inhibitor Titers Results and Change from Baseline by Visit
Descriptive statistics for observed values for each visit and changes from baseline will be provided.
(2) Case Plots
Plots over time for each subject will be presented.

6.6.3.4 Anti-BHK antibody titer

Analysis Set:

Safety Analysis Set

Analysis Variables:

Anti-BHK Antibody

[Positive, Negative]

Visit:

baseline,

end of study.

Analytical Methods:

(1) Number of Subjects in Categories of Anti-BHK Antibody Results by Visit
Frequency distributions for each visit will be provided.

6.6.4 Vital Signs

Analysis Set:

Safety Analysis Set

Analysis Variables:

Temperature

Systolic Blood Pressure

Diastolic Blood Pressure

Pulse Rate

Respiratory Rate

Visit:

baseline,

during treatment period; at 30 mins, at 8 hours, at 16 hours, at 24 hours, at 36 hours, at 48 hours, at 60 hours, at 72 hours, at every 24 hours after 72 hours,

during follow-up visits; at 24 hours, at every 14 days,

end of study.

Analytical Methods:

For each variable, summaries (1) and (2) will be provided.

(1) Summary of Vital Signs Results and Change from Baseline by Visit
Descriptive statistics for observed values for each visit and changes from baseline will be provided.
(2) Case Plots
Plots over time for each subject will be presented.

6.6.5 Other Safety Analysis

Not applicable.

6.6.6 Extent of Exposure and Compliance

6.6.6.1 Extent of Exposure and Compliance throughout the Study

Analysis Set:

Safety Analysis Set

Analysis Variables:

Total Dose per subject throughout the Study (U)

Total Dose per subject throughout the Study (U/kg)

Total number of infusions per subject throughout the Study

Average number of infusions per day throughout the Study

Compliance throughout the Study (%)

Analytical Methods:

(1) Summary of Total Dose, Total number of infusions, Average number of infusions and Compliance
Descriptive statistics will be provided.

6.6.6.2 Extent of Exposure and Compliance for each Treatment Period

6.6.6.2.1 Extent of Exposure and Compliance for Initial Treatment Period

Analysis Set:

Safety Analysis Set

Analysis Variables:

Total Dose per subject for Initial Treatment Period (U)

Total Dose per subject for Initial Treatment Period (U/kg)

Total number of infusions per subject for Initial Treatment Period

Average number of infusions per day for Initial Treatment Period

Compliance for Initial Treatment Period (%)

Analytical Methods:

(1) Summary of Total Dose, Total number of infusions, Average number of infusions and Compliance
Descriptive statistics will be provided.

6.6.6.2.2 Extent of Exposure and Compliance for Subsequent Treatment Period

Analysis Set:

Subjects of Safety Analysis Set who entered the Treatment Period for Subsequent Qualified Bleeding Episode

Analysis Variables:

Total Dose per subject for Subsequent Treatment Period (U)

Total Dose per subject for Subsequent Treatment Period (U/kg)

Total number of infusions per subject for Subsequent Treatment Period

Average number of infusions per day for Subsequent Treatment Period

Compliance for Subsequent Treatment Period (%)

Analytical Methods:

(1) Summary of Total Dose, Total number of infusions, Average number of infusions and Compliance
Descriptive statistics will be provided.

6.7 Pharmacokinetic, Pharmacodynamic, and Biomarker Analysis

6.7.1 Pharmacokinetic Analysis

6.7.1.1 Plasma Concentrations

Analysis Set:

Pharmacokinetic Analysis Set

Analysis Variables:

Plasma Concentrations of FVIII:C

Visit:

PK at pre-infusion, at 15 -20 min, at 1 hour, at 3 hours, at 6 hours, at 12 hours, at 18 hours, at 24 hours.

Analytical Methods:

(1) Summary of Plasma levels of FVIII:C
Descriptive statistics will be provided at designated assessment time points.

6.7.1.2 Pharmacokinetic Parameters

Analysis Set:

Pharmacokinetic Analysis Set

Analysis Variables:

Pharmacokinetic parameters of FVIII:C

C_{max}, AUC, CL, $t_{1/2}$, and C_{max}/Dose, or the peak level C_{max} (U/mL) normalized by dose (U/kg)

Analytical Methods:

(1) Summary of Pharmacokinetic Parameters of FVIII:C
Descriptive statistics will be provided.

6.7.2 Pharmacodynamic Analysis

Not applicable.

6.7.3 Biomarker Analysis

Not applicable.

6.8 Patient Reported Outcomes (PROs) and Health Care Utilization Endpoints Analysis

6.8.1 PRO Analysis

Not applicable.

6.8.2 Health Care Utilization Analysis

Not applicable.

6.9 Other Analysis

1) The same analysis as the Primary Endpoint Analysis will be performed regarding responses of subsequent bleeding episodes at 24 hours.

Analysis Set:

Subjects of Full Analysis Set who entered the Treatment Period for Subsequent Qualified Bleeding Episode

Analysis Variables:

Response to TAK-672 therapy at 24 hours after the initiation of treatment for subsequent treatment period

[Positive, Negative]

Analytical Methods:

(1) The proportion of subjects with a positive response and its CI will be presented.

2) Subject plots of FVIII:C and aPTT over time.

Analysis Set:

Safety Analysis Set

Analysis Variables:

FVIII:C

aPTT

Analytical Methods:

(1) Case Plots
Plots over time for each subject will be presented.

6.10 Interim Analysis

No interim analysis is planned.

6.11 Data Monitoring Committee/Internal Review Committee/ [Other Data Review Committees]

Not applicable.

7.0 REFERENCES

Not applicable.

8.0 CHANGES TO PROTOCOL PLANNED ANALYSES

Not applicable.

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

- Dates and times will not be imputed unless needed for a specific calculation.
- Age is calculated as an integer in years as the difference between the subject's date of informed consent and the date of birth.
- Body Mass Index (BMI) will be calculated as following:
  BMI (kg/m^2) = weight (kg)/ (height (m))^2
- "Time since first diagnosis of Acquired Hemophilia A (months)" is defined as the duration from the date of initial diagnosis to the date of TAK-672 infusion. If the day of diagnosis is unknown, it is imputed as "01".

  Time since first diagnosis (months)= (date of TAK-672 infusion − date of diagnosis + 1) / 30.42.
- In "History of XXX use within 6 months prior to obtaining informed consent" (XXX: "aPCC", "rFVIIa" or "pd-FVIIa/FX"), for the period "within 6 months (6 × 30.42) prior to obtaining informed consent", if (a) "the period includes a start or end date of XXX" or (b) "the start date of XXX is before informed consent and the end date of XXX is after informed consent", then "Yes" is given.
- The final results of "Anti-BHK Antibody" are obtained after two assessments, "Screening" and "Confirmatory". If results of both "Screening" and "Confirmatory" are "Positive", the final result is "Positive". If either result of "Screening" or "Confirmatory" is "Negative", the final result is "Negative".

- Values below the lower limit of quantification (including "ND") will be treated as 0 value when calculating the descriptive statistics. Values above the upper limit of quantification will be treated as the upper limit value.
- Total dose, total number of infusions, duration, frequency and compliance of TAK-672 infusion will be derived as follow. These derived values do not include values for PK assessment.
  - Total Dose per subject for each Treatment Period (U): Total amount of actual dose (U) for each treatment period.
  - Total Dose per subject for each Treatment Period (U/kg): Total Dose per subject for each Treatment Period (U) / Weight (kg).
  - Total Dose per subject throughout the Study (U): Sum of total doses for each treatment period.
  - Total Dose per subject throughout the Study (U/kg): Total Dose per subject throughout the Study (U) / Weight (kg).
  - Total number of infusions per subject for each Treatment Period: Total number of infusions for each treatment period.
  - Total number of infusions per subject throughout the Study: Sum of total infusions for each treatment period.
  - Duration of each treatment period (days): For each treatment period, the date of last dose for treatment − the date of initial dose +1.
  - Duration throughout the study (days): Sum of duration of each treatment period.
  - Average number of infusions per day for each Treatment Period: Total number of infusions for each Treatment Period / duration of each treatment period.
  - Average number of infusions per day throughout the Study: Total number of infusions throughout the Study / duration throughout the study.
  - Compliance for each Treatment Period (%): For each treatment period, 100 × (sum of (Actual Dose (U)) / sum of (Planned Dose (U))).
  - Compliance throughout the Study (%): Throughout the study, 100 × (sum of (actual dose (U)) / sum of (planned dose (U))).

9.2.2 Definition of Baseline

- For all analyses, unless otherwise noted, the baseline value will be defined as the last available pre-dose value.
- If pre-dose central lab data is missing, then the (or latest) available pre-dose local lab value will be used.

9.2.3 Definition of Visit Windows

All evaluable data (i.e. non-missing data) will be handled according to the following rules.

Data collected as End of Study Visit data in the eCRF will be used as End of Study data at the time of analysis visit.

For analysis visits other than the End of Study, the following procedures will be performed.

With the exception of data collected in the eCRF as End of Study Visit data, observation obtained in the corresponding time interval listed in the table below will be used.

Data collected as treatment period data in the eCRF, even if they fall within the corresponding time interval of the follow-up period, will not be adopted as data at the analysis visit of the follow-up period, they will be adopted only as data at the analysis visit of the treatment period.

Data collected as follow-up period data in the eCRF, even if they fall within the corresponding time interval of the treatment period, will not be adopted as data at the analysis visit of the treatment period, they will be adopted only as data at the analysis visit of the follow-up period.

If there are multiple observations within the same scheduled Study Time, the observation with closest Study Time to the scheduled Study Time will be used. If there are two observations equidistant to the scheduled Study Time, the later observation will be used. The difference from the scheduled Study Time will be determined based on Study Time/Day or Follow-up Time/Day.

Period indicates which Bleeding Episode the treatment or follow-up period data are for. Data from the treatment or follow-up period for the initial Bleeding Episode will be presented as Period 1, and data from the treatment or follow-up period for the subsequent Bleeding Episode will be presented as Period 2. Period 2 data will not be used as follow-up period data for Period 1.

Table 9.2.a Visit Window of Assessment of Efficacy

Period	Analysis Visit	Scheduled Study Time (hours)/Day (days)		Time Interval		
				Study Time (hours)	Follow-up Time (hours)	Follow-up Day (days)
1	At 30 mins	Study Time:	0.5	0 – <4		
1	At 8 hours	Study Time:	8	4 – <12		
1	At 16 hours	Study Time:	16	12 – <18		
1	At 24 hours	Study Time:	24	0 – <30 *		
1	At 36 hours	Study Time:	36	30 – <42		
1	At 48 hours	Study Time:	48	42 – <54		
1	At 60 hours	Study Time:	60	54 – <66		
1	At 72 hours	Study Time:	72	66 – <84		
1	At every 24 hours after 72 hours	Study Time:	24 n (n≥4) **	24 n − 12 – <24 n + 12 (n≥4) **		

Table 9.2.a Visit Window of Assessment of Efficacy

Period	Analysis Visit	Scheduled Study Time (hours)/Day (days)		Time Interval		
				Study Time (hours)	Follow-up Time (hours)	Follow-up Day (days)
1	Follow-up at 24 hours	Follow-up Time:	24		0 – <168	
1	Follow-up at 14 days	Follow-up Day:	14			7 – <21
1	Follow-up at 28 days	Follow-up Day:	28			21 – <35
1	Follow-up at 42 days	Follow-up Day:	42			35 – <49
1	Follow-up at 56 days	Follow-up Day:	56			49 – <63
1	Follow-up at 70 days	Follow-up Day:	70			63 – <77
1	Follow-up at 84 days	Follow-up Day:	84			77 – 91
2	At 30 mins	Study Time:	0.5	0 – <4		
2	At 8 hours	Study Time:	8	4 – <12		
2	At 16 hours	Study Time:	16	12 – <18		
2	At 24 hours	Study Time:	24	18 – <30		
2	At 36 hours	Study Time:	36	30 – <42		
2	At 48 hours	Study Time:	48	42 – <54		
2	At 60 hours	Study Time:	60	54 – <66		
2	At 72 hours	Study Time:	72	66 – <84		
2	At every 24 hours after 72 hours	Study Time:	24 n (n ≥4) **	24 n − 12 – <24 n + 12 (n ≥4) **		
2	Follow-up at 24 hours	Follow-up Time:	24		0 – <168	
2	Follow-up at 14 days	Follow-up Day:	14			7 – <21
2	Follow-up at 28 days	Follow-up Day:	28			21 – <35
2	Follow-up at 42 days	Follow-up Day:	42			35 – <49
2	Follow-up at 56 days	Follow-up Day:	56			49 – <63
2	Follow-up at 70 days	Follow-up Day:	70			63 – 77
	End of Study	- ***			-	

*: If there is a record that could be used for both "At 24 hours" and previous analysis visit, the record will be duplicated and become each analysis visit data.
For subjects who discontinue treatment with TAK-672 by 18 hours, a record for the assessment at 24 hours will be generated newly. If "Completed TAK-672 Therapy for Treatment Success?" on the eCRF is selected as "Yes", the record of positive response will be generated. If "No", the record of negative response will be generated.
**: n represents the Study Day, which should be an integer not less than 4.
***: For the analysis visit of End of Study, the data collected as End of Study Visit data in the eCRF will be used.

For FVIII:C data collected for PK assessment, observation obtained in the corresponding time interval listed in the table below will be used.

Table 9.2.b Visit Window of FVIII: C for PK Assessment

Period	Analysis Visit	Scheduled Study Time (hours)		Time Interval Follow-up Time (hours)
1	PK at pre-infusion	Follow-up Time:	0	<0
1	PK at 15 -20 min	Follow-up Time:	0.25	0 – <0.5
1	PK at 1 hour	Follow-up Time:	1	0.5 – <2
1	PK at 3 hours	Follow-up Time:	3	2 – <4.5
1	PK at 6 hours	Follow-up Time:	6	4.5 – <9
1	PK at 12 hours	Follow-up Time:	12	9 – <15
1	PK at 18 hours	Follow-up Time:	18	15 – <21
1	PK at 24 hours	Follow-up Time:	24	21 – 27

Table 9.2.c Visit Window of Vital Signs

Period	Analysis Visit	Scheduled Study Time (hours)/Day (days)		Time Interval Study Time (hours)	Time Interval Follow-up Time (hours)	Time Interval Follow-up Day (days)
1	Baseline	Study Time:	0	<0		
1	At 30 mins	Study Time:	0.5	0 – <4		
1	At 8 hours	Study Time:	8	4 – <12		
1	At 16 hours	Study Time:	16	12 – <18		
1	At 24 hours	Study Time:	24	18 – <30		
1	At 36 hours	Study Time:	36	30 – <42		
1	At 48 hours	Study Time:	48	42 – <54		
1	At 60 hours	Study Time:	60	54 – <66		
1	At 72 hours	Study Time:	72	66 – <84		
1	At every 24 hours after 72 hours	Study Time:	24 n (n≥4) *	24 n − 12 – <24 n + 12 (n≥4) *		
1	Follow-up at 24 hours	Follow-up Time:	24		0 – <168	
1	Follow-up at 14 days	Follow-up Day:	14			7 – <21
1	Follow-up at 28 days	Follow-up Day:	28			21 – <35
1	Follow-up at 42 days	Follow-up Day:	42			35 – <49
1	Follow-up at 56 days	Follow-up Day:	56			49 – <63
1	Follow-up at 70 days	Follow-up Day:	70			63 – <77
1	Follow-up at 84 days	Follow-up Day:	84			77 – 91

Table 9.2.c Visit Window of Vital Signs

Period	Analysis Visit	Scheduled Study Time (hours)/Day (days)		Time Interval		
				Study Time (hours)	Follow-up Time (hours)	Follow-up Day (days)
2	At 0 min	Study Time:	0	<0		
2	At 30 mins	Study Time:	0.5	0 – <4		
2	At 8 hours	Study Time:	8	4 – <12		
2	At 16 hours	Study Time:	16	12 – <18		
2	At 24 hours	Study Time:	24	18 – <30		
2	At 36 hours	Study Time:	36	30 – <42		
2	At 48 hours	Study Time:	48	42 – <54		
2	At 60 hours	Study Time:	60	54 – <66		
2	At 72 hours	Study Time:	72	66 – <84		
2	At every 24 hours after 72 hours	Study Time:	24 n (n≥4) *	24 n − 12 – <24 n + 12 (n≥4) *		
2	Follow-up at 24 hours	Follow-up Time:	24		0 – <168	
2	Follow-up at 14 days	Follow-up Day:	14			7 – <21
2	Follow-up at 28 days	Follow-up Day:	28			21 – <35
2	Follow-up at 42 days	Follow-up Day:	42			35 – <49
2	Follow-up at 56 days	Follow-up Day:	56			49 – <63
2	Follow-up at 70 days	Follow-up Day:	70			63 – 77
	End of Study	- **			-	

*: n represents the Study Day, which should be an integer not less than 4.

**: For the analysis visit of End of Study, the data collected as End of Study Visit data in the eCRF will be used.

For hematology, biochemistry, and urinalysis data other than Hgb and Hct, observation obtained in the corresponding time interval listed in the table below will be used.

Table 9.2.d Visit Window of Hematology, biochemistry and urinalysis

Period	Analysis Visit	Scheduled Study Time (hours)/Day (days)		Time Interval		
				Study Time (hours)	Follow-up Time (hours)	Follow-up Day (days)
1	Baseline	Study Time:	0	<0		
1	At 24 hours	Study Time:	24	0 – <48		
1	At 72 hours	Study Time:	72	48 –		
1	Follow-up at 24 hours	Follow-up Time:	24		0 – <168	
1	Follow-up at 14 days	Follow-up Day:	14			7 – <21

Table 9.2.d Visit Window of Hematology, biochemistry and urinalysis

Period	Analysis Visit	Scheduled Study Time (hours)/Day (days)		Time Interval		
				Study Time (hours)	Follow-up Time (hours)	Follow-up Day (days)
1	Follow-up at 28 days	Follow-up Day:	28			21 – <35
1	Follow-up at 42 days	Follow-up Day:	42			35 – <49
1	Follow-up at 56 days	Follow-up Day:	56			49 – <63
1	Follow-up at 70 days	Follow-up Day:	70			63 – <77
1	Follow-up at 84 days	Follow-up Day:	84			77 – 91
2	At 24 hours	Study Time:	24	0 – <48		
2	At 72 hours	Study Time:	72	48 –		
2	Follow-up at 24 hours	Follow-up Time:	24		0 – <168	
2	Follow-up at 14 days	Follow-up Day:	14			7 – <21
2	Follow-up at 28 days	Follow-up Day:	28			21 – <35
2	Follow-up at 42 days	Follow-up Day:	42			35 – <49
2	Follow-up at 56 days	Follow-up Day:	56			49 – <63
2	Follow-up at 70 days	Follow-up Day:	70			63 – 77
	End of Study	- *			-	

*: For the analysis visit of End of Study, the data collected as End of Study Visit data in the eCRF will be used.

Table 9.2.e Visit Window of Hgb, Hct

Period	Analysis Visit	Scheduled Study Time (hours)/Day (days)		Time Interval		
				Study Time (hours)	Follow-up Time (hours)	Follow-up Day (days)
1	Baseline	Study Time:	0	<0		
1	At 30 mins	Study Time:	0.5	0 – <4		
1	At 8 hours	Study Time:	8	4 – <12		
1	At 16 hours	Study Time:	16	12 – <18		
1	At 24 hours	Study Time:	24	18 – <30		
1	At 36 hours	Study Time:	36	30 – <42		
1	At 48 hours	Study Time:	48	42 – <54		
1	At 60 hours	Study Time:	60	54 – <66		
1	At 72 hours	Study Time:	72	66 – <84		
1	At every 24 hours after 72 hours	Study Time:	24 n (n ≥4) *	24 n − 12 – <24 n + 12 (n ≥4) *		
1	Follow-up at 24 hours	Follow-up Time:	24		0 – <168	

Table 9.2.e Visit Window of Hgb, Hct

Period	Analysis Visit	Scheduled Study Time (hours)/Day (days)		Time Interval		
				Study Time (hours)	Follow-up Time (hours)	Follow-up Day (days)
1	Follow-up at 14 days	Follow-up Day:	14			7 – <21
1	Follow-up at 28 days	Follow-up Day:	28			21 – <35
1	Follow-up at 42 days	Follow-up Day:	42			35 – <49
1	Follow-up at 56 days	Follow-up Day:	56			49 – <63
1	Follow-up at 70 days	Follow-up Day:	70			63 – <77
1	Follow-up at 84 days	Follow-up Day:	84			77 – 91
2	At 0 min	Study Time:	0	<0		
2	At 30 mins	Study Time:	0.5	0 – <4		
2	At 8 hours	Study Time:	8	4 – <12		
2	At 16 hours	Study Time:	16	12 – <18		
2	At 24 hours	Study Time:	24	18 – <30		
2	At 36 hours	Study Time:	36	30 – <42		
2	At 48 hours	Study Time:	48	42 – <54		
2	At 60 hours	Study Time:	60	54 – <66		
2	At 72 hours	Study Time:	72	66 – <84		
2	At every 24 hours after 72 hours	Study Time:	24 n (n≥4) *	24 n − 12 – <24 n + 12 (n≥4) *		
2	Follow-up at 24 hours	Follow-up Time:	24		0 – <168	
2	Follow-up at 14 days	Follow-up Day:	14			7 – <21
2	Follow-up at 28 days	Follow-up Day:	28			21 – <35
2	Follow-up at 42 days	Follow-up Day:	42			35 – <49
2	Follow-up at 56 days	Follow-up Day:	56			49 – <63
2	Follow-up at 70 days	Follow-up Day:	70			63 – 77
	End of Study	- **			-	

*: n represents the Study Day, which should be an integer not less than 4.

**: For the analysis visit of End of Study, the data collected as End of Study Visit data in the eCRF will be used.

Table 9.2.f Visit Window of hFVIII inhibitor titer and pFVIII inhibitor titer

Period	Analysis Visit	Scheduled Study Time (hours)/Day (days)		Time Interval		
				Study Time (hours)	Follow-up Time (hours)	Follow-up Day (days)
1	Baseline	Study Time:	0	<0		
1	At 72 hours	Study Time:	72	0 –		
1	Follow-up at 14 days	Follow-up Day:	14			0 – <21
1	Follow-up at 28 days	Follow-up Day:	28			21 – <35
1	Follow-up at 42 days	Follow-up Day:	42			35 – <49
1	Follow-up at 56 days	Follow-up Day:	56			49 – <63
1	Follow-up at 70 days	Follow-up Day:	70			63 – <77
1	Follow-up at 84 days	Follow-up Day:	84			77 – 91
2	At 0 min	Study Time:	0	<0		
2	At 72 hours	Study Time:	72	0 –		
2	Follow-up at 14 days	Follow-up Day:	14			0 – <21
2	Follow-up at 28 days	Follow-up Day:	28			21 – <35
2	Follow-up at 42 days	Follow-up Day:	42			35 – <49
2	Follow-up at 56 days	Follow-up Day:	56			49 – <63
2	Follow-up at 70 days	Follow-up Day:	70			63 – 77
	End of Study	- *			-	

*: For the analysis visit of End of Study, the data collected as End of Study Visit data in the eCRF will be used.

For the anti-BHK titer, data collected in the eCRF as End of Study Visit data or Withdrawal data will be used as End of Study data at the time of analysis visit. For other data to be collected, observation obtained in the corresponding time interval listed in the table below will be used.

Table 9.2.g Visit Window of Anti-BHK Titer

Period	Analysis Visit	Scheduled Study Time (hours)		Time Interval		
				Study Time (hours)	Follow-up Time (hours)	Follow-up Day (days)
1	Baseline	Study Time:	0	<0		
	End of Study	- *			-	

*: For the analysis visit of End of Study, the data collected as End of Study Visit data or Withdrawal data in the eCRF will be used.

9.3 Analysis Software

All statistical analyses will be conducted using SAS® Version 9.4, or later.

9.4 Criteria for Markedly Abnormal Values

(1) Hematology and Serum Chemistry

For each parameter, all evaluable data (i.e. non-missing) will be classified as a MAV or not. The criteria in the table below will be used. The lower limit of the normal range and the upper limit of the normal range are abbreviated as LLN and ULN.

Table 9.4.a MAV Criteria of Hematology

Parameter	Gender	Age	MAV Criteria	
			Lower Criteria	Upper Criteria
RBC ($\times 10^6/\mu L$)	-	-	<0.8×LLN	>1.2×ULN
Hemoglobin (g/dL)	-	-	<0.8×LLN	>1.2×ULN
Hematocrit (%)	-	-	<0.8×LLN	>1.2×ULN
Platelets ($\times 10^3/\mu L$)	-	-	<75	>600
WBC ($\times 10^3/\mu L$)	-	-	<0.5×LLN	>1.5×ULN

Table 9.4.b MAV Criteria of Serum Chemistry

Parameter	Gender	Age	MAV Criteria	
			Lower Criteria	Upper Criteria
ALT (GPT) (IU/L)	-	-	-	>3×ULN
AST (GOT) (IU/L)	-	-	-	>3×ULN
Alkaline Phosphatase (IU/L)	-	-	-	>3×ULN
Total Bilirubin (mg/dL)	-	-	-	>2.0
Creatinine (mg/dL)	-	-	-	>2.0