Clinical Study Protocol

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: Amendment 2.0 / 23-Oct-2020

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.

A summary of changes to previous protocol versions is appended to the end of the document.

TAKEDA PHARMACEUTICALS

PROTOCOL

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)

Short Title: Efficacy and Safety Evaluation of B-Domain Deleted Recombinant Porcine Factor VIII (rpFVIII, TAK-672) in Japanese Subjects with AHA

Sponsor: Takeda Pharmaceutical Company Limited,
1-1, Doshomachi 4-Chome, Chuo-ku, Osaka-shi, Osaka, Japan

Study Number: TAK-672-3001

IND Number: Not Applicable **EudraCT Number:** Not Applicable

Compound: OBI-1/ BAX801/ TAK-672/ Recombinant Porcine Factor VIII

Date: 23 Oct 2020 **Version/ Amendment Number**: 2.0

Amendment History:

Date	Amendment Number	Amendment Type (for regional Europe purposes only)	Region
23 June 2020	Initial version	Not applicable	Japan
04 September 2020	1.0	Not applicable	Japan
23 October 2020	2.0	Not applicable	Japan

1.0 ADMINISTRATIVE INFORMATION AND PRINCIPLES OF CLINICAL STUDIES

1.1 Contacts and Responsibilities of Study-Related Activities

A separate contact information list will be provided to each site.

TDC sponsored investigators per individual country requirements will be provided with emergency medical contact information cards to be carried by each subject (see the annexes).

General advice on protocol procedures should be obtained through the monitor assigned to the study site.

For protocol- or safety-related questions or concerns, the investigator should contact the CRO medical monitor.

1.2 Approval

INVESTIGATOR AGREEMENT

I confirm that I have read and that I understand this protocol, the Investigator's Brochure and any other product information provided by the sponsor. I agree to conduct this study in accordance with the requirements of this protocol and also to protect the rights, safety, privacy, and well-being of study subjects in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Conference on Harmonisation, E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws and regulations.
- Regulatory requirements for reporting serious adverse events defined in Section 10.2.2 of this protocol.
- Terms outlined in the Clinical Study Site Agreement.
- Responsibilities of the Investigator ([redacted]).

I further authorize that my personal information may be processed and transferred in accordance with the uses contemplated in Appendix C of this protocol.

Signature of Investigator Date

Investigator Name (print or type)

Investigator's Title

Location of Facility (City, State/Province)

Location of Facility (Country)

1.3 Principles of Clinical Studies

This study will be conducted with the highest respect for the individual subjects in accordance with the requirements of this study protocol and also in accordance with the following:

- The ethical principles that have their origin in the Declaration of Helsinki.
- International Council for Harmonisation E6 Good Clinical Practice: Consolidated Guideline.
- All applicable laws and regulations, including, without limitation, data privacy laws, clinical trial disclosure laws, and regulations.

1.4 Summary of Changes in Protocol Amendment 2

This section describes the changes in reference to the Protocol Amendment 2.

The purpose of the changes made in this amendment are intended:

1. To add the protocol signatory section for the investigator.
2. To revise the dose frequency of TAK-672 for subsequent bleeding episodes.
3. To address the footnote definition of "Japanese" patients to be enrolled in this study.
4. To address the addition of the new study analysis set (i.e. pharmacokinetic analysis set, PKS) and its definition.
5. To revise Table A (Schedule of Study Procedures and Assessments for the Qualifying Bleeding Episode) and to its related sections in the body of the text.
6. To describe the investigator consent to use of personal information.

Other changes were also made to clarify the study procedures. In addition, minor revisions (including grammatical and editorial changes) are included for clarification purposes.

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2.0 STUDY SUMMARY

Name of Sponsor(s): Takeda	**Compound:** OBI-1/ BAX801/TAK-672/ Recombinant Porcine Factor VIII	
Title of Protocol: 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)	**IND No.:** Not applicable	**EudraCT No.:** Not applicable
Study Number: TAK-672-3001	**Phase:** 2/3	

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 serious bleeding episodes in Japanese subjects diagnosed with acquired hemophilia A (AHA).

At least 5 subjects are planned to be enrolled and dosed. If a subject is suspected of AHA or has been diagnosed with AHA, the study and the study requirements will be discussed with the subject or his/her legal decision maker. Once the subject provides agreement to be enrolled in the study by signing the informed consent, the study procedures will be initiated. The study will consist of the following evaluation periods:

Screening period (Day -X to Day 0)**:** Subjects who are suspected of AHA and subjects who are diagnosed with AHA will undergo all screening activities after signing an informed consent form. When AHA is confirmed immunosuppressive therapy can be initiated.

Treatment with TAK-672: If the subject demonstrates a qualifying bleeding event, the subject can proceed to treatment with TAK-672. Prior to TAK-672 administration, a blood sample will be drawn for the assessments of hemoglobin (Hgb), hematocrit (Hct), activated partial thromboplastin time (aPTT), factor VIII activity (FVIII:C), and as well as inhibitor titers against human FVIII (hFVIII) and porcine FVIII (pFVIII). TAK-672 will be administrated at an initial dose of 200 U/kg. 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, Hct, aPTT, and FVIII:C. Adverse events (AEs) will also be assessed.

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, this monitoring is to occur every 6 to 12 hours depending on the site and severity of bleeding. Additional doses of TAK-672 may be administered based on clinical status and qualifying bleeding as frequently as every 4 to 12 hours if the investigator determines there is a need. This is to be repeated throughout the management of the bleeding. If the investigator determines, based on clinical status, 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 30 min post-infusion for aPTT and FVIII. aPTT will be assessed as supplementary to FVIII:C level. 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 trough levels of 30 to 40% and a maximum plasma level of FVIII:C not to exceed 200%.

Because subjects are considered to be actively bleeding at the time of the study enrollment, it is considered rational to obtain complete pharmacokinetic (PK) data after the bleeding is controlled and the subject becomes stable. Since there may be an increased immunogenicity risk of administering a dose of TAK-672 to a subject who has not experienced a bleeding episode and for whom treatment is not clinically indicated, assessment of the PK behavior of TAK-672 in a non-bleeding state is most reasonable at the end of treatment of a bleeding episode with TAK-672. Where possible, a final dose of TAK-672 should be provided, and samples should be obtained according to the following schedule relative to the final TAK-672 dose in order to obtain information about the

PK behavior of TAK-672 in the non-bleeding state: pre-infusion dose of 50 U/kg and at 15-20 min, 1, 3, 6, 12, 18, and 24 hrs. post infusion. Pre-PK inhibitor titers against hFVIII and pFVIII will be obtained prior to the final PK infusion of TAK-672. Agreement to participate in the non-bleeding PK part of the study should be obtained at the study enrollment but a subject's participation in the non-bleeding PK part of the study is not mandatory.

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 treatment dose of TAK-672.

Primary Objective:

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

Secondary Objectives:

- To determine the proportion of serious 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 serious bleeding episodes.
- To assess the correlation between response to TAK-672 therapy at specified assessment time points and eventual control of serious bleeding events
- To assess the correlations among the pre-infusion inhibitor titer, the total dose of TAK-672 infused, the post-infusion FVIII:C, 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.

Subject Population: Japanese subjects ≥18 years of age with AHA.

Number of Subjects: At least 5 subjects are planned to be enrolled and dosed.	**Number of Sites:** 5 clinical sites planned, located in Japan
Dose Level(s): TAK-672 will be administered at an initial dose of 200 U/kg. Subsequent doses will be determined based on the post-infusion FVIII:C achieved after the most recent dose given, the target FVIII:C, and pFVIII inhibitor titer (when available)	**Route of Administration:** TAK-672 will be administered as an intravenous infusion at a rate of 1-2 mL/min.
Duration of Treatment: The study duration for each subject will be approximately 3 to 4 months (90 days follow-up after the last dose of TAK-672) for each qualifying bleeding episode.	**Period of Evaluation:** Approximately 1 year

Main Criteria for Inclusion:

1. Male or female Japanese patients of ≥18 years of age
2. Patients who (or their legally authorized representatives) have provided his/her written informed consent form prior to any study-related procedures and study product administration.
3. Patients with a diagnosis of AHA based on clinical evaluation and supportive local laboratory testing as shown below:
   - Presentation with spontaneous bleeding without anatomical cause and without prior known bleeding disorder.
   - Prolonged aPTT without explanation.
   - Abnormal aPTT cross-mixing test consistent with FVIII inhibitors
   - Confirmation of a low FVIII:C
   - Positive FVIII inhibitor (≥0.6 Bethesda Unit [BU]) as measured in either the local or central laboratory
4. Patients with a severe bleeding episode which the investigator finds necessary to treat and whose severe bleeding episode meets at least 1 of the following criteria:
   a. Bleeds that pose a threat to a vital organ that could threaten life (e.g. intracranial bleed, or any site that could obstruct the airway).
   b. Bleeds that pose 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).
   c. Bleeds requiring a blood transfusion to maintain the Hgb level at above-life or organ threatening levels (e.g. post-surgical, gastro-intestinal, retro-peritoneal, and thigh bleeds).
   d. Intramuscular bleeds where muscle viability and/or neurovascular integrity is significantly compromised or at risk of being compromised.
   e. 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).
5. Patients who are taking anti-thrombotics (including anti-platelet agents and anticoagulants) with confirmatory laboratory testing documenting specific FVIII inhibitor titer and with 3 half-lives of the agent elapsed since the last dose.
6. Patients with expected life expectancies of at least 90 days prior to the onset of the hemorrhagic episode.
7. Patients of reproductive age who have agreed to use acceptable methods of contraception during the study and, if female, who have agreed to undergo pregnancy testing as part of the screening process.
8. Patients who are able to and willing to comply with the requirements of the protocol.

Main Criteria for Exclusion:

1. Patients with an established reason for bleeding that is not correctable even with hemostatic therapy.
2. Patients presenting a bleeding episode that is assessed likely to resolve on its own, even if left untreated.
3. Patients with a known major sensitivity (anaphylactoid reactions) to therapeutic products of porcine or hamster origin; examples include therapeutics of porcine origin (e.g. previously marketed porcine FVIII, Hyate:C®) and recombinant therapeutics prepared from hamster cells (e.g. Humira®, Advate®, and Enbrel®).
4. Patients with the use of hemophilia medication prior to the administration of TAK-672 under one of the following conditions: (1) use of "recombinant activated factor VII (rFVIIa)" within 3 hours prior to TAK-672 administration, (2) use of "activated prothrombin complex concentrate (aPCC)" within 6 hours prior to TAK-672 administration, or (3) use of "plasma-derived FX/FVIIa complex concentrate (pd-FX/FVIIa)" within 8 hours prior to TAK-672 administration.
5. Patients with an anticipated need for treatment or device during the study that may interfere with the evaluation of the safety or efficacy of TAK-672, or whose safety or efficacy may be affected by TAK-672.

Main Criteria for Evaluation and Analyses:

The primary efficacy endpoint will be the proportion of serious 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.

PK Evaluation: A routine non-compartmental analysis will be used to estimate, $t_{1/2}$, C_{max}, AUC_{0-t} , AUC_{0-inf}, clearance (CL), and volume of distribution (Vd). Data will be summarized using descriptive statistics.

Statistical Considerations:

Analyses set

Analysis of study data will be based on the following analysis set:

- Full Analysis Set (FAS): All subjects who have received at least 1 dose of TAK-672 (i.e. the main efficacy analysis set used for the efficacy analysis).
- Per-Protocol Set (PPS): A subset of subjects in the FAS population who have no major protocol violations as determined by the sponsor's study clinician (or designee).
- Safety Analysis Set (SAS): all subjects who have received at least 1 dose of TAK-672.
- Pharmacokinetic analysis set (PKS): All subjects who have agreed to undergo a PK assessment for the measurement of plasma FVIII:C and 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).

Primary efficacy endpoint

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 using a well-defined 4-point ordinal scale summarized in the table below:

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.

The proportion of subjects with a positive response to TAK-672 therapy at 24 hours post-treatment and corresponding exact 2-sided Clopper-Pearson 95% confidence interval will be provided using the FAS. Eligible subjects who withdraw from treatment at an earlier time point will be assumed to be non-responders at the 24-hour assessment time point. Subjects who have hemostatic response and stop treatment because bleeding is controlled will be assumed to be responders at the 24-hour assessment time point.

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 assessment time points and eventual control of severe bleeding episodes.
- Correlation among the pre-infusion pFVIII inhibitor 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 assessment time points during treatment or at an early withdrawal, and at the end of the follow-up period (i.e. at 90 days after the last dose of TAK-672).
- 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 the initial dose of TAK-672 until the completion of hemostatic control
- Number of new qualified severe bleeding episodes.

Safety endpoints

- Treatment-emergent AEs and serious adverse events (SAE) 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 assessment time points or visits: at 24 (± 6) hours, at 72 (± 12) hours, during follow-up visits, and at the end of study visit.
- Inhibitors against hFVIII and pFVIII: at Screening and prior to the initial dose of TAK-672 as well as at the following assessment time points or visits after the initial dose of TAK-672: at 72 (± 6) hours, 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 (baby hamster kidney) antibody titer: at Screening and at the end of the study visit or at an early withdrawal.

Sample Size Justification:

The planned total sample size for this study is 5 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

3.0 LIST OF ABBREVIATIONS

AE	adverse event
AHA	acquired hemophilia A
aPCC	activated prothrombin complex concentrate
aPTT	activated partial thromboplastin time
BHK	baby hamster kidney
BU	Bethesda unit
CHA	congenital hemophilia A
ECG	electrocardiogram
eCRF	electronic case report form
FVIII	Factor VIII
FAS	full analysis set
GCP	Good Clinical Practice
Hct	Hematocrit
hFVIII	Human factor VIII
Hgb	hemoglobin
ICH	International Council for Harmonisation
IEC	Independent ethics committee
IMP	Investigational Medicinal Product
IRB	Institutional review board
pFVIII	Porcine factor VIII
PK	Pharmacokinetic
PKS	Pharmacokinetic analysis set
PPS	Per-protocol set
PT	Prothrombin time
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

4.0 INTRODUCTION

4.1 Background

Acquired hemophilia A (AHA) is a very rare bleeding disorder with an incidence of approximately 1.48 individual per million per year [1] and is caused by the development of an auto-antibody to human factor VIII (hFVIII). The clinical manifestation is frequently severe, anatomically diverse, and the mortality rate approaches 20% [2].This disorder occurs more often in subjects aged 70 to 80 years and there appears to be increasing recognition and diagnosis of this auto-immune coagulation disorder. In Japan, 234 cases were reported based on the national survey in 2019. According to 2 studies, the mortality rate in Japan was reported as 13.8% (8/53) and 25% (10/40) respectively [3, 4]. Hemostatic treatment is administered to control the bleeding manifestations. Immunosuppressive therapies are administered concurrently to suppress continued production of the acquired anti- factor VIII (FVIII) antibody. Agents commonly used include corticosteroids and cyclophosphamide.

The most effective approach for treatment of acute bleeding episodes in subjects with hemophilia A is hFVIII replacement therapy [5, 6]. However, the development of antibodies that inhibit FVIII function (inhibitors) in subjects with AHA precludes their treatment with the most effective therapy. Current management of the bleeding episode in AHA is accomplished using the bypassing agents, activated recombinant factor VII (rFVIIa, NovoSeven®), activated prothrombin complex concentrate (aPCC, FEIBA®), and plasma-derived factor VII/factor X complex concentrate (pd-FVIIa/FX, Byclot®). However, there is a potential risk of thrombosis using these agents and that risk increases as subjects grow older and in the presence of underlying disorders that may also be the stimulus to this acquired coagulopathy, such as collagen vascular disorders and malignancy. There is no standard laboratory assay available to monitor the optimal treatment with bypassing agents. Plasma derived porcine factor VIII (pFVIII) (Hyate:C), marketed in the United States of America (USA) was used successfully since the 1980s to achieve hemostasis in the presence of hFVIII inhibitors, as these antibodies generally have low immunological cross-reactivity with pFVIII [7]. Hyate:C was withdrawn from the market in 2004 not because of any safety or efficacy concerns but due to difficult procurement of suitable porcine plasma.

Recombinant pFVIII (TAK-672) is a purified B-domain deleted form of pFVIII that is expressed as a glycoprotein by a well-defined genetically engineered baby hamster kidney (BHK) cell line. The recombinant porcine factor VIII (rpFVIII) is sufficiently similar in structure to hFVIII to temporarily replace the inhibited endogenous FVIII that is needed for effective hemostasis; but is different enough to be less susceptible to inactivation by circulating inhibitory antibodies. The manufacturing process for rpFVIII contains validated viral removal/inactivation steps. The bulk active substance is formulated with excipients containing no animal derived products, filled into glass vials and lyophilized.

Recombinant pFVIII was characterized in terms of hemostatic activity and toxicity using a number of nonclinical in vitro assays and *in vivo* studies in mice, dogs and cynomolgus monkeys [8]. The nonclinical safety profile in the dog, mouse and cynomolgus monkeys was deemed acceptable to proceed with clinical trials.

The safety, efficacy, and pharmacokinetics (PK) of rpFVIII was evaluated by 3 clinical trials prior to marketing approval for treatment of bleeding episodes in AHA.

- A Phase 1 study (OBI-1-101) conducted in subjects with a clinical diagnosis of hemophilia A in the non-bleeding state, who also had anti-hFVIII neutralizing antibody of any measurable level and a current low cross-reacting anti-pFVIII antibody titer ≤20 Bethesda unit (BU), compared with Hyate:C; 9 subjects received either rpFVIII (n=4) or Hyate:C (n=5).[i]
- A Phase 2 open-label, non-comparative study (OBI-1-201) was conducted in 9 subjects with congenital hemophilia A (CHA) and inhibitors to hFVIII who had an uncomplicated joint or soft tissue bleed [9]. A total of 25 non-life/non-limb threatening bleeds were treated in 9 subjects.[ii]
- In the Phase 2/3 prospective, multi-center, open-label study (OBI-1-301), the efficacy and safety of rpFVIII was evaluated in the treatment of serious bleeding episodes in 28 subjects with AHA (median age 70 years) [10].

In addition, a Phase 3 (OBI-1-302) prospective, non-randomized, open-label study was designed to assess treatment of serious bleeding episodes with rpFVIII in subjects with CHA who had developed hFVIII inhibitors. However, this study was terminated by the sponsor after 1 subject was treated; the termination was due to administrative reasons, not due to safety or lack of efficacy concerns. Two non-interventional post-marketing safety surveillance studies are currently ongoing in subjects with AHA (Study 241302 and Study 241501) details of which can be found in the Investigator's Brochure.

In the Phase I study (OBI-1-101), both OBI-1 and Hyate:C were generally well tolerated by subjects. Due to the presence of extraneous proteins, and the much lower concentration of FVIII, a dose of Hyate:C in this study could be administered only over a relatively prolonged time period. Conversely, OBI-1 could be administered more rapidly (approximately 6.7 times as rapidly as Hyate:C). As a result, the shape of the time-concentration curve after administration of the same 100 U/kg dose of each product was quite different, making it appear as though OBI- had a much higher recovery value than did Hyate:C. Thus, the different administration timeframes limit a meaningful comparison of the resulting PK profiles.

If the PK observations of this Phase I study, i.e. higher recovery with OBI-1, reflect a true difference between the 2 products, it is possible that a lower dose of OBI-1 would suffice to treat a subject with a hemophilic bleeding episode. However, this suggestion is speculative given the preliminary nature of the findings and the small number of subjects.

[i] Clinical Study Report: Phase I randomised, parallel-group, blinded comparison study of the safety, tolerance and pharmacokinetics of OBI-1 (B-domain deleted recombinant porcine FVIII) versus Hyate:C (porcine plasma derived FVIII) when administered as a single intravenous injection to subjects with an inhibitor antibody to FVIII, in the nonbleeding state

[ii] Clinical Study Report: Phase II open label study of the hemostatic activity, pharmacokinetics and safety of OBI-1 (B-Domain deleted recombinant porcine FVIII), when administered by intravenous injection, to control non-life and non-limb threatening bleeding episodes in congenital hemophilia A patients with an inhibitor to human FVIII.

In the Phase 2 study (OBI-1-201), the primary efficacy objective was to evaluate the hemostatic efficacy of rpFVIII in the treatment of non-life/non-limb threatening bleeds in subjects with CHA and inhibitors. A total of 25 bleeds in 9 subjects were treated with rpFVIII and all bleeds were successfully controlled with 8 or fewer injections of rpFVIII. The median number of rpFVIII injections administered per bleeding episode was 1.0 (range: 1 to 8) and the median time from bleeding onset to treatment was 5.67 hours (range: 1.5 to 20.0). Across all bleeding episodes the median total dose of rpFVIII per bleeding episode was 224.1 U/kg (range: 50.0 to 1066.4). The median initial treatment dose (including the loading dose if applicable), was 159 U/kg (range: 50 to 576) which resulted in a median increase of 16% in the FVIII plasma level with the one-stage clotting assay (range: 0.5% to 427%) and a median increase of 17% with the chromogenic assay (range: 0% to 248%). Twenty of the 25 (80%) bleeds were controlled within 6 hours after having been administered 1 treatment dose of rpFVIII. For those 20 bleeds controlled with 1 treatment dose (including the loading dose if applicable), the median dose was 200.8 U/kg. The rpFVIII was well tolerated and of the reported adverse events (AEs) (n=61), only 18 AEs were considered treatment emergent. Two subjects reported an AE that was possibly related to the study drug. Three subjects suffered treatment-emergent serious adverse events (SAEs), but none were considered related to the study drug. No reported AE led to treatment interruption, discontinuation from the study, or death. Eight of 9 (8/9, 89%) subjects developed anti-pFVIII antibodies following exposure to rpFVIII. In subjects who received repeated rpFVIII treatment, higher anti-pFVIII titers did not affect efficacy or safety and no increase in AEs or bleeding episodes were reported in the subjects with the highest titers. Regardless of the observed anti-pFVIII titers at pre-treatment or the obtained FVIII recovery levels after treatment initiation, all bleeding episodes were successfully controlled. Analysis of BHK host cell-line antibody levels indicated that no subjects produced detectable levels of antibodies against BHK.

In the prospective, open-label Phase 2/3 study (OBI-1-301), the efficacy of rpFVIII for the treatment of serious bleeding episodes in subjects with AHA was investigated. The study was conducted in subjects who had auto-immune inhibitory antibodies to hFVIII, and experienced serious bleeding episodes that required hospitalization. All subjects had a positive response to treatment for the initial bleeding episodes at 24 hours after dosing. A positive response was observed in 95% (19/20) of subjects evaluated at 8 hours and 100% (18/18) at 16 hours. In addition to response to treatment, the overall treatment success was determined by the investigator based on their ability to discontinue or reduce the dose and/or dosing frequency of rpFVIII. A total of 24/28 subjects (86%) had successful treatment of the initial bleeding episode. Of those subjects treated with rpFVIII as first-line therapy, defined as no immediate previous use of anti-hemorrhagic agents prior to the first rpFVIII treatment, 16/17 subjects (94%) had eventual treatment success reported. Eleven subjects were reported to have received anti-hemorrhagics (e.g. rFVIIa, aPCC, and tranexamic acid) prior to first treatment with rpFVIII. Of these 11 subjects, 8 (73%) subjects had an eventual successful treatment response. No related serious adverse reactions occurred. Non-serious AEs related to treatment were noted and assessed by the investigator in 6/29 subjects (20.7%). All of these adverse effects completely resolved. Two subjects developed pFVIII inhibitors after infusion of study drug (range: 8 to 51 BU) and were discontinued from treatment; however, both subjects had a positive response to treatment at the 24-hour primary endpoint assessment.

An investigation was conducted by the sponsor and, in summary, the 2 incidences of pFVIII inhibitors were considered related to rpFVIII treatment, while the other non-serious treatment-related AEs were considered as unlikely to be related to rpFVIII. The pFVIII inhibitors were detected prior to infusion in 10/29 subjects (range: 0.8 to 29 BU). All of these subjects had a positive response at 24 hours after the first rpFVIII infusion. No anti-BHK antibodies were observed in any of the treated subjects.

4.2 Rationale for the Proposed Study

Subjects with AHA may present with severe bleeding episodes which, if not controlled, will lead to high morbidity or mortality. Because subjects have autoimmune inhibitors to hFVIII, they are typically treated with bypassing agents such as rFVIIa or aPCC or pd-FX/FVIIa (only in Japan). Treatment with such agents is driven solely on clinical observations, including the subject's assessment of symptoms such as pain, as there is no relevant biomarker or monitoring tool. In severe bleeding episodes, monitoring tests to predict hemostatic efficacy are highly desirable, but such assays are only relevant for FVIII products.

Recombinant pFVIII, B-domain deleted rpFVIII glycoprotein (marketed under the tradename OBIZUR®) was approved in other countries for the treatment of bleeding episodes in AHA based on the safety and efficacy data from 28 subjects with AHA treated with B-domain deleted rpFVIII glycoprotein in the Phase 2/3 open-label clinical study OBI-1-301[ii], which showed that hemostatic efficacy of B-domain deleted rpFVIII could be monitored based upon measurement of plasma FVIII activity levels, thus facilitating early determination of clinical benefit and the subject's clinical status.

Moreover, dosing could be tailored based on individual FVIII activity levels ensuring that adequate doses were administered to achieve hemostasis. The safety, hemostatic activity, and PK profile of B-domain deleted rpFVIII glycoprotein were also supported by results of an open-label Phase 2 study in patients with CHA with inhibitors (OBI-1-201) [9] and a randomized Phase 1 study comparing B-domain deleted rpFVIII glycoprotein with a plasma-derived pFVIII (OBI-1-101 [11]).

This study (TAK-672-3001) will evaluate the plasma levels of FVIII:C as well as the safety and efficacy of TAK-672 (B-domain deleted recombinant pFVIII) in subjects with AHA in Japan. It aims to demonstrate an effective control of bleeding manifestations under the monitoring of plasma levels of FVIII:C, which may provide enhanced efficacy and with a lower risk of thromboembolism. The results from this study will extend/support the data obtained from the global phase 2/3 (USA, Canada, European Union, and India) pivotal study for TAK-672 in subjects with AHA (OBI-1-301 [10]) to Japanese subjects with AHA. Data from this study will be used to support regulatory submission for the approval of TAK-672 in Japan.

4.3 Benefit/Risk Profile

Recombinant pFVIII is given for the treatment of bleeding episodes in patients with AHA and was studied in adult and elderly patients with AHA. Patients with AHA are not able to achieve sufficient coagulation with the coagulation factor they produce due to the occurrence of inhibitory antibodies against their endogenously produced hFVIII clotting factor.

Recombinant pFVIII works by providing alternative FVIII, thereby helping the patient's blood to clot naturally in the presence of hFVIII inhibitors, as these antibodies generally have low immunological cross-reactivity with pFVIII [7]. As rpFVIII is produced by genetic engineering (recombinant) technology medicine and is not manufactured or formulated with human or animal components, the risk of transmission of blood borne pathogens is very small.

Treatment-related antibodies against host-cell proteins were not detected in patients treated with rpFVIII in the course of the clinical study OBI-1-301 and no subjects had a reaction to rpFVIII (hypersensitivity or anaphylaxis) in the study. Therefore, the risk for patients to develop antibodies against host-cell proteins following treatment with rpFVIII can be considered to be small.

Development of antibodies against rpFVIII which may reduce the effectiveness of rpFVIII to control bleeding has been observed during the rpFVIII clinical program. High titers against pFVIII may render FVIII replacement with rpFVIII in patients with AHA ineffective, necessitating treatment with agents that promote hemostasis through other mechanisms. The level of pFVIII inhibitor titer (BU) that influences efficacy negatively has not been determined. However, in cases where an anti-porcine titer can be correlated with clinical observation, patients can be considered for alternative therapy with inhibitor bypassing agents (e.g. aPCCs, rFVIIa, and pd-FVIIa/FX) to treat their bleed.

While the development of a high titer of inhibitory rpFVIII antibodies may result in impaired responsiveness to rpFVIII treatment, overall, an effective treatment did not correlate with the presence or absence of pFVIII inhibitory antibodies at baseline or subsequent visits, similar observations have been reported with Hyate:C (plasma derived pFVIII [12]).

Detailed information about the known and expected benefits and risks and reasonably expected AEs of TAK-672 may be found in the Investigator's Brochure.

5.0 STUDY OBJECTIVES AND ENDPOINTS

5.1 Objectives

5.1.1 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.

5.1.2 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

5.2 Endpoints

5.2.1 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 5-A below.

Table 5-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.

5.2.2 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.

5.2.3 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.

6.0 STUDY DESIGN AND DESCRIPTION

6.1 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 [13], 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:

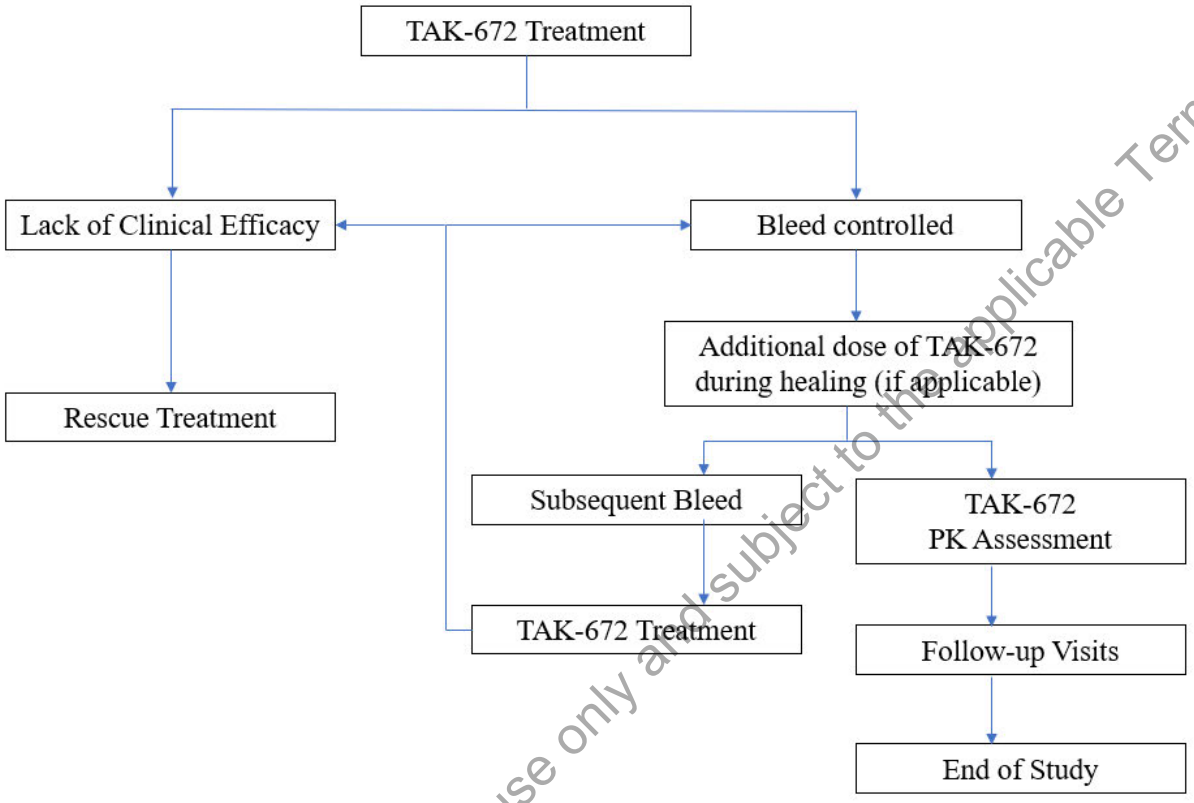
Subjects may be treated either with TAK-672 or bypassing agents at the discretion of the investigator for any subsequent bleeding episodes. The treatment of any subsequent bleeding episodes will not be considered for the purposes of the primary efficacy endpoint (Section 9.3.5).

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. A schedule of assessments is listed in [redacted]

Figure 6.a Study Schematic diagram



6.2 Justification for Study Design, Dose, and Endpoints

This is an open-label, single cohort prospective bridging study to confirm equivalent efficacy and safety of TAK-672 for the treatment of severe bleeding episodes in Japanese subjects diagnosed with AHA. The study design, dosing, and endpoints are based on the Phase 2/3 OBI-1-301 Clinical Study Protocol which demonstrated that rpFVIII was safe and well-tolerated and demonstrated a positive response in the treatment of severe bleeding events in subjects with AHA. Five or more subjects are planned to be enrolled and dosed with rpFVIII in accordance with the guidelines from the Phase 2/3 Clinical Study. Bleed control endpoints and safety assessments are also consistent so to confirm uniformity of treatment response.

Rationale of dose regimen:

Dose regimen of OBI-1-301 was established based on the results of OBI-1-201. The results are summarized below:

OBI-1 (now designated as TAK-672) was investigated in subjects with CHA with inhibitors to hFVIII in Study OBI-1-201. Nine subjects were treated for a total of 25 non-life, non-limb threatening bleeding events. A bolus dose was administered in 17/25 (68%) of the bleeding episodes. All bleeding episodes were determined to be successfully controlled with 8 or fewer infusions of OBI-1; twenty (80%) bleeding episodes were controlled with 1 infusion; 5 (20%) bleeding episodes required 2 to 8 infusions. Across all bleeds, the total doses given to control a single bleeding episode ranged between 50 U/kg and 1066.4 U/kg (bolus dose and treatment dose) for a median total dose of 224.1 U/kg. For those 20 bleeds controlled with 1 treatment dose (including the bolus dose if applicable), the median dose was 200.8 U/kg. The Data Safety Monitoring Committee agreed that the data presented supported the safety and efficacy of OBI-1 in the treatment of non-life-threatening bleeds in patients with congenital hemophilia. It was decided to close the study OBI-1-201 early and to select a fixed initial dose of 200 U/kg of OBI-1 for future studies.

In the prospective, open-label, pivotal phase 2/3 study (OBI-1-301), the fix initial dose of 200 U/kg resulted in positive response in all 28 subjects and control of the primary bleed at the time of final treatment dosing was achieved in 24 of 28 (85.7%). Regarding safety, no related serious AEs occurred. Positive anti-pFVIII inhibitor test results led to study discontinuation in two subjects and were considered to be non-serious AEs related to OBI-1 in accordance with predefined criteria. No thrombotic events, thrombocytopenia or hypersensitivity reactions related to OBI-1 were observed. Overall results suggest that OBI-1 had good tolerability, justifying the initial dose of 200 U/kg.

Rationale of primary and secondary endpoints:

In OBI-1-301 study, all 28 subjects with AHA had a positive response to treatment of initial dose of 200 U/kg rpFVIII assessed at 24 hour-time point regardless of baseline inhibitor titers and cross-reactivity to pFVIII. And the bleed control was successfully achieved in 86% of the subjects. The early primary assessment of hemostatic response at 24 hours after initial dose of 200 U/kg rpFVIII appears to be a good predictor for the overall control of bleeding. Accordingly, the same primary endpoint as in OBI-1-301 study, a response at 24 hours after initiation of TAK-672 using a well-defined 4-point ordinal scale will also be used in TAK-672-3001 study.

Six secondary efficacy endpoints assessed in the OBI-1-301 study will also be assessed in the TAK-672-3001 study, allowing the comparison of the results between the 2 studies. In addition, 2 other efficacy endpoints will be included in the TAK-672-3001 to support the analyses of the study results: (1) the duration period and the total dose from the initial dose of TAK-672 until the completion of hemostatic control and (2) the number of new qualified severe bleeding episodes

6.3 Premature Termination or Suspension of Study or Study Site

6.3.1 Criteria for Premature Termination or Suspension of the Study

The study will be completed as planned unless 1 or more of the following criteria are satisfied that require temporary suspension or early termination of the study.

- New information or other evaluation regarding the safety or efficacy of the study drug that indicates a change in the known risk/benefit profile for TAK-672, such that the risk/benefit profile is no longer acceptable for subjects participating in the study.
- Significant violation of Good Clinical Practice (GCP) that compromises the ability to achieve the primary study objectives or compromises subject safety.
- Study-specific criteria for terminating the study.

6.3.2 Criteria for Premature Termination or Suspension of Study Sites

A study site may be terminated prematurely or suspended if the site (including the investigator) is found in significant violation of GCP, protocol, or contractual agreement, is unable to ensure adequate performance of the study, or as otherwise permitted by the contractual agreement.

6.3.3 Procedures for Premature Termination or Suspension of the Study or the Participation of Study Site(s)

In the event that the sponsor or regulatory authority elects to terminate or suspend the study or the participation of a study site, a study-specific procedure for early termination or suspension will be provided by the sponsor; the procedure will be followed by applicable study sites during the course of termination or study suspension.

7.0 SELECTION AND DISCONTINUATION/WITHDRAWAL OF SUBJECTS

It is planned to recruit 5 or more subjects at approximately 5 centers.

Subjects who are screened but fail to fulfill 1 or more entry criteria (as defined in Section 7.1 and Section 7.2) can be rescreened if a subsequent bleeding episode should occur after resolution of the initial bleeding episode for which the subject was not deemed a suitable candidate for the study at that time.

7.1 Inclusion Criteria

Patients with AHA who meet all of the following criteria will qualify for entry into the study:

1. Male or female Japanese[iii] patients of ≥18 years of age.
2. Patients who (or their legally authorized representatives) have provided his/her written informed consent form prior to any study-related procedures and study product administration.
3. Patients with a diagnosis of AHA based on clinical evaluation and supportive local laboratory testing as shown below:
    - Presentation with spontaneous bleeding without anatomical cause and without prior known bleeding disorder.
    - Prolonged aPTT without explanation.
    - Abnormal aPTT cross mixing test consistent with FVIII inhibitors
    - Confirmation of a low FVIII:C.
    - Positive FVIII inhibitor (≥ 0.6 BU) as measured either in the local or central laboratory
4. Patients with a severe bleeding episode which the investigator finds necessary to treat and whose severe bleeding episode meets at least 1 of the following criteria:
    - Bleeds that pose a threat to a vital organ that could threaten life (e.g. intracranial bleed, or any site that could obstruct the airway).
    - Bleeds that pose 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 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.

[iii] Japanese is defined as those who are in Japan, are born in Japan and have Japanese parents and Japanese maternal and paternal grandparents.

- 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).

5. Patients who are taking anti-thrombotics (including anti-platelet agents and anticoagulants) with confirmatory laboratory testing documenting specific FVIII inhibitor titer and with 3 half-lives of the agent elapsed since the last dose.
6. Patients with expected life expectancies of at least 90 days prior to the onset of the hemorrhagic episode.
7. Patients of reproductive age who have agreed to use acceptable methods of contraception during the study and, if female, who have agreed to undergo pregnancy testing as part of the screening process.
8. Patients who are able to and willing to comply with the requirements of the protocol.

7.2 Exclusion Criteria

Any patient who meets any of the following criteria will not qualify for entry into the study:

1. Patients with an established reason for bleeding that is not correctable even with hemostatic therapy.
2. Patients with a bleeding episode that is assessed likely to resolve on its own, even if left untreated.
3. Patients with a known major sensitivity (anaphylactoid reactions) to therapeutic products of porcine or hamster origin; examples include therapeutics of porcine origin (e.g. previously marketed porcine FVIII, Hyate:C®) and recombinant therapeutics prepared from hamster cells (e.g. Humira®, Advate®, and Enbrel®).
4. Patients with the use of hemophilia medication prior to the administration of TAK-672 under one of the following conditions: (1) use of rFVIIa within 3 hours prior to TAK-672 administration, (2) use of aPCC within 6 hours prior to TAK-672 administration, (3) use of pd-FX/FVIIa within 8 hours prior to TAK-672 administration.
5. Patients with an anticipated need for treatment or device during the study that may interfere with the evaluation of the safety or efficacy of TAK-672, or whose safety or efficacy may be affected by TAK-672.
6. Patients who are currently pregnant or breastfeeding, or planning to become pregnant or father a child during the study
7. Patients who have participated in another clinical study and has been exposed to an investigational product or device within 30 days prior to the study enrollment.
8. Patients who are scheduled to participate in another non-observational (interventional) clinical study involving an investigational product or device during the course of the study.
9. Patients who are unable to or unwilling to comply with the study design, protocol requirements, and/or the follow-up procedures.

10. Patients whose majority of age are under legal protection.
11. Patients who are an immediate family member, study site employee, or are in a dependent relationship with a study site employee who is involved in the conduct of this study (e.g. spouse, parent, child, sibling) or may consent under duress.
12. Patients who are judged by the investigator as being ineligible for any other reason.

7.3 Excluded Medications

Subjects must be instructed not to take any medications including over-the-counter products, without first consulting with the investigator.

The following concomitant medications are not permitted during this study:

- Hemophilia medication (rFVIIa within 3 hours or aPCC within 6 hours or pd-FX/FVIIa within 8 hours prior to TAK-672 administration).
- Hemophilia medication other than TAK-672 at any time during the study unless required for use as rescue medication after failure/study withdrawal.

The management of a serious thromboembolic event may require anticoagulation, and this may need to be administered concurrent with the use of TAK-672 to ensure that another bleeding episode or continuing severe hemorrhage does not occur on withdrawal of TAK-672. In such instances medical monitor should be consulted.

7.4 Criteria for Discontinuation or Withdrawal of a Subject

The primary reason for discontinuation or withdrawal of the subject from the study or study drug should be recorded in the electronic case report form (eCRF) using the following categories. For screen failure subjects, refer to Section 9.1.11.

1. Lack of efficacy: If FVIII activity of >50% is not obtained, even after administration of 2 or more additional doses of TAK-672 after the initial TAK-672 infusion, or a clinical response has not been observed, the decision to discontinue TAK-672 therapy and switch to an alternative "rescue" therapy should be considered by the investigator. If FVIII:C of >50% are obtained, but a clinical response has not been observed, consideration should be given to the need for additional interventions (such as surgery) to address uncontrolled bleeding that is not associated with the FVIII acquired inhibitor.
2. Pretreatment event (PTE) or AE: The subject has experienced a PTE that requires early study termination or AE that requires early study drug discontinuation because continued participation/exposure imposes an unacceptable risk to the subject's health, or the subject is unwilling to continue because of the PTE or AE.
3. Significant protocol deviation: The discovery after the first dose of study drug that the subject failed to meet protocol entry criteria or did not adhere to protocol requirements, and continued administration of TAK-672 poses an unacceptable risk to the subject's health. In this setting, study drug should be discontinued but an attempt should be made to continue the subject on study for safety follow-up.

4. Lost to follow-up: The subject did not return to the clinic and attempts to contact the subject were unsuccessful. Attempts to contact the subject must be documented in the subject's source documents.
5. Voluntary withdrawal: The subject (or subject's legally acceptable representative) wishes to withdraw from the study. The reason for withdrawal, if provided, should be recorded in the eCRF.
6. Note: All attempts should be made to determine the underlying reason for the withdrawal and, where possible, the primary underlying reason should be recorded (i.e. withdrawal due to an AE should not be recorded in the "voluntary withdrawal" category. Similarly, lack of efficacy should not be recorded in the "voluntary withdrawal" category).
7. Study termination: The sponsor, institutional review board (IRB), or regulatory agency terminates the study.
8. Other: Note: The specific reasons should be recorded in the "specify" field of the eCRF.

7.5 Procedures for Discontinuation or Withdrawal of a Subject

The investigator may discontinue a subject's study participation at any time during the study when the subject meets the study termination criteria described in Section 7.4. In addition, a subject may discontinue his or her participation without giving a reason at any time during the study. Should a subject's participation be discontinued, the primary criterion for termination must be recorded by the investigator in the eCRF. In addition, efforts should be made to perform all procedures scheduled for the Early Termination Visit.

In case of a subject discontinuation or withdrawal from study treatment, he/she will be encouraged to continue the study and complete all the relevant study visits and assessments.

8.0 CLINICAL STUDY MATERIAL MANAGEMENT

8.1 Study Drug and Materials

8.1.1 Dosage Form, Manufacturing, Packaging, and Labeling

In this protocol, the term study drug refers to TAK-672.

8.1.1.1 Study Drug

Recombinant pFVIII (TAK-672) is a purified B-domain deleted form of pFVIII that is expressed as a glycoprotein by a genetically engineered BHK cell line. The molecular weight of rpFVIII is approximately 175 kDa (based on its 1448 amino acid sequence). Porcine FVIII has 86% pair-wise sequence homology with hFVIII.

TAK-672 will be supplied as white lyophilized powder filled into 3 mL vials. Each vial of rpFVIII contains a 500 U of FVIII activity for reconstitution with 1.0 mL of sterile water for injection.

Recombinant pFVIII is formulated for intravenous infusion. The reconstituted solution of rpFVIII should be clear and colorless in appearance and administered intravenously (IV) at room temperature no later than 3 hours after reconstitution.

8.1.1.2 Rescue Medication

If after administration of 2 or more additional doses of TAK-672 after the initial TAK-672 infusion adequate FVIII activity is not obtained, or a clinical response has not been observed, the decision to discontinue TAK-672 therapy and switch to an alternative "rescue" therapy should be considered by the investigator.

8.1.2 Storage and handling

TAK-672 must be kept in an appropriate, limited-access, secure place until it is used or returned to the sponsor or designee for destruction. TAK-672 must be stored under the conditions specified on the label and remain in the original container until dispensed. A daily temperature log of the drug storage area must be maintained every working day.

Lyophilized vials of rpFVIII should be kept refrigerated prior to use at 2°C to 8°C (36°F to 46°F). Additionally, the following precautions should be taken when handling rpFVIII:

- Should not be kept in freezing conditions.
- Should not be used if frozen, even if it has been thawed.
- Should not be used beyond the expiration date printed on the carton or vial.
- Once reconstituted, to be use within 3 hours or should be discarded.

Recombinant pFVIII is to be reconstituted in sterile water for injection United States Pharmacopeia (unit). The potency of the reconstituted product is the same as the number of units indicated on the vial. Reconstituted solution is clear and colorless, is essentially free of particulate material and has a pH of 6.8 to 7.2. Once reconstituted, the vial of rpFVIII should be used within 3 hours or discarded. Recombinant pFVIII should not be mixed with other medicinal products for infusions. Any unused product should be discarded. The reconstitution procedures for rpFVIII are detailed in the Pharmacy Manual.

8.1.3 Dose and Regimen

TAK-672 will be administered at an initial dose 200 U/kg and will be administered as an intravenous infusion at a rate of 1 to 2 mL/min.

For subjects with bleeding episodes of particular clinical concern (e.g. severe mucosal, intracranial, retro- or intraabdominal, genitourinary, neck, traumatic, postoperative), the dose and frequency of TAK-672 doses will be titrated to target post-infusion and trough FVIII:C of at least 80% for the first 24 hours. For all other severe bleeding episodes (e.g. joint, muscle, soft tissue) in the first 24 hours and all bleeding episodes after the first 24 hours, the TAK-672 dose will be titrated to target post-infusion and trough FVIII:C of ≥50%. aPTT concurrently measured with FVIII:C will be assessed as supplementary to FVIII:C level. If FVIII:C is not optimal (>80% for bleeds of particular concern and >50% for muscle and joint bleeds), then infusions may be repeated; however, the dose of TAK-672 administered should not exceed 800 U/kg every 4 hours, and the plasma levels of FVIII:C should not exceed 200%. FVIII:C needs to be carefully monitored during ongoing TAK-672 therapy to maintain or decrease therapeutic levels as necessary and to discontinue treatment when the inhibitor is eradicated by the concurrent immunosuppressive therapy. Patients will be clinically monitored for complications of their co-morbid conditions that include measurement of molecular markers of thrombosis, imaging study, electrocardiogram (ECG), etc. Vital signs including blood pressure, heart rate, respiratory rate, and temperature will be routinely monitored during treatment, minimally at each assessment, with additional monitoring in cases of continued or excessive bleeding. Additional monitoring by clinical means and, where appropriate, via other approaches such as imaging, will be required for each specific bleeding site, which will include frequent monitoring of Hgb levels if there is external or extensive internal bleeding.

TAK-672 treatment will continue until bleeding is successfully controlled, until the lack of efficacy is judged by the investigator, or until the subject withdraws from the study, whichever occurs first. If FVIII:C of >50% is not obtained, even after 2 or more additional doses of TAK-672 are administered after the initial dose of TAK-672 with no clinical response observed, and when the initial pFVIII inhibitor titer is found to be high or the inhibitor increases as anamnestic response during the treatment, decision to discontinue TAK-672 therapy and switch to an alternative therapy (bypass therapy) should be considered by the investigator without delay. If FVIII:C of >50% is obtained with no clinical response observed, consideration should be given to the need for additional interventions (such as surgery) to address uncontrolled bleeding that is not associated with the acquired FVIII inhibitor.

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 trough levels (30-40%) and a maximum plasma level of FVIII:C not to exceed 200%. FVIII:C will be monitored while the subject is on treatment with TAK-672 during the healing phase. The monitoring of FVIII:C will be discontinued when the TAK-672 therapy is discontinued. and healing process is determined as completed by the investigator.

8.1.4 Overdose

In the Phase II study (OBI-1-201), cumulative doses of up to 137,404 U of OBI-1 were given over 8 days without any drug-related SAEs being reported.

Appropriate treatment of an overdose of TAK-672 will be determined by the investigator according to the clinical and laboratory characteristics of the events and will be recorded in the subject's CRF/eCRF. An event resulting from an overdose of the study medication is not considered as serious unless it meets the definition of an SAE and consequently should be reported on the SAE form.

8.2 Study Drug Assignment and Dispensing Procedures

Subjects will receive treatment according to the study schedule. The Enrollment Number will be entered onto the eCRF.

When a subject has a qualifying bleeding event, he/she will be assigned to receive TAK-672. The medication identification Number will be entered onto the eCRF.

8.3 Accountability and Destruction of Sponsor-Supplied Drugs

The on-site pharmacist (site designee) will receive the pharmacy manual created by the sponsor, according to which the site designee will appropriately manage the sponsor-supplied TAK-672. The investigator will also receive those procedures from the sponsor. The procedures include those for ensuring appropriate receipt, handling, storage, management, dispensation of the sponsor-supplied TAK-672.

All remaining partially used and/or unused TAK-672 vials will be returned to the sponsor or sponsor's representative after study completion/termination or destroyed with the permission of the sponsor in accordance with applicable laws and study site procedures.

If TAK-672 vials are to be destroyed, the on-site pharmacist (site designee) will provide documentation in accordance with sponsor's specifications.

9.0 STUDY PLAN

9.1 Study Procedures

The following sections describe the study procedures and data to be collected. For each procedure, subjects are to be assessed by the same investigator or site personnel whenever possible. The Schedule of Study Procedures is located in [redacted].

9.1.1 Informed Consent Procedure

The requirements of the informed consent are described in Section 15.2.

Informed consent must be obtained prior to the subject entering into the study.

A unique subject identification number (subject number) will be assigned to each subject at the time signed informed consent is obtained; this subject number will be used throughout the study.

9.1.2 Demographics, Medical History, and Medication History Procedure

Demographic information to be obtained will include date of birth, sex, and race of the subject at Screening.

At Screening, the subject's medical history will be described for the following body systems including severity or surgery and start and end dates, if known: eyes, ears, nose, and throat; respiratory; cardiovascular; gastrointestinal; musculoskeletal; neurological; endocrine; hematopoietic/lymphatic; dermatological; and genitourinary.

Medical history will include the collection of acquired hemophilia history, bleeding episode history, and history of aPCC or rFVIIa or pd-FVIIa/FX usage for 6 months prior to Screening. Relevant medical and surgical history and all medications taken 3 months prior to Screening will also be collected.

All medications taken and non-drug therapies received within 3 months before providing informed consent until completion/termination will be recorded on the concomitant medications and non-drug therapies eCRFs.

9.1.3 Physical Examination Procedure

A baseline physical examination defined as the assessment prior to first dose of study drug will consist of the following body systems: (1) eyes; (2) ears, nose, throat; (3) cardiovascular system; (4) respiratory system; (5) gastrointestinal system; (6) dermatologic system; (7) extremities; (8) musculoskeletal system; (9) nervous system; (10) lymph nodes; and (11) other. All subsequent physical examinations should assess clinically significant changes from the assessment prior to first dose examination.

(Note: Abbreviated physical examination should not be used).

9.1.4 Weight and Height

Height (cm) and weight (kg) will be measured at Screening as described in [redacted].

9.1.5 Vital Sign Procedure

Vital signs include body temperature (°C), respiratory rate (breaths/min), pulse rate (beats/min), and systolic and diastolic blood pressure (mmHg).

All vital signs will be measured at Screening and at 30 minutes of administration of TAK-672 and as per schedule mentioned in [redacted]. Blood pressure will be measured when subjects are in the supine position and resting for more than 5 minutes.

Vital sign values are to be recorded on the eCRF. For each abnormal vital sign value, the investigator will determine whether or not to report an AE (see definition in Section 10.1.2) and record the medical diagnosis, symptom, or sign on the AE eCRF. When vital signs are scheduled at the same time as blood draws, the blood draw will take priority and vital signs will be obtained within 0.5 hour before or after the scheduled blood draw.

Additional tests and other evaluations required to establish the significance or etiology of an abnormal value, or to monitor the course of an AE should be obtained when clinically indicated. Any abnormal value that persists should be followed at the discretion of the investigator.

9.1.6 Efficacy Measurement

9.1.6.1 Primary Efficacy Endpoint and Evaluation

The primary efficacy outcome is 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 the table below. A positive response is defined as effective or partially effective control of bleeding. The investigator assessment of bleeding is the most important factor in assessing the response to TAK-672 therapy. Thus, if there appears to be inconsistency between the clinical assessment and the FVIII:C (e.g. clinical response with undetectable FVIII:C), the clinical assessment will determine the outcome.

Table 9-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

The tools that may be used to assess the control of bleeding will vary depending upon the site of bleeding. These may include but are not limited to:

- Obvious blood loss (external blood loss and bodily fluids).
- Hematology results (Hgb and other hematological parameters).
- Blood transfusion and blood component requirements.
- Physical or technological examination of the bleeding site, including measurement of hematoma and swelling, limb circumference where applicable, assessment of tenderness, spirometry for respiratory tract bleeds.
- Neurological examination, including mental status, cranial nerves, sensory, strength, deep tendon reflexes, gait and coordination.
- Imaging studies to assess the size of the bleeding site where this cannot be assessed by visually.

A summary of the assessments that may be considered as evidence that bleeding is effectively controlled (stopped or significantly reduced), by body system of anticipated sites of bleeding, is provided in Table 9-B. Some or all of these may be used in any particular bleeding episode. The summary should not be considered exhaustive. The type of assessment(s) and outcome of assessment(s) will be documented in the eCRFs.

Table 9-B Investigator Assessment of Control of Bleeding

Assessment results*	Muscle	Joint	Abdominal				Severe mucosal	Intra-cranial	GU		Neck	Post-operative	Traumatic	Chest		Bone fracture
			GI	Intra-peritoneal	Visceral	Retro-peritoneal			Genital	Urinary	Retro-pharyngeal			Pulmonary	Pleural	
External blood loss stopped or quantitatively reduced	N/A	N/A	N/A	N/A	N/A	N/A		N/A			N/A				N/A	
Blood in bodily fluids no longer present or decreased**	N/A					N/A	N/A				N/A					N/A
Hematoma size decreased or stabilized				N/A	N/A	N/A	N/A			N/A	N/A					
Swelling and/or limb circumference decreased or stabilized				N/A	N/A	N/A	N/A	N/A		N/A				N/A	N/A	
Neurological symptoms stabilized or improved	N/A	N/A	N/A	N/A	N/A		N/A	X	N/A	N/A	N/A			N/A	N/A	N/A
Pain decreased or gone							N/A	N/A						N/A		
Range of motion improved			N/A	N/A	N/A		N/A	N/A	N/A	N/A				N/A		
Tenderness decreased or gone							N/A	N/A						N/A		

Table 9-B Investigator Assessment of Control of Bleeding

Assessment results*	Muscle	Joint	Abdominal				Severe mucosal	Intra-cranial	GU		Neck	Post-operative	Traumatic	Chest		Bone fracture
			GI	Intra-peritoneal	Visceral	Retro-peritoneal			Genital	Urinary	Retro-pharyngeal			Pulmonary	Pleural	
Breathing stabilized or improved (spirometry)	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A			N/A
RBC transfusions decreased or stopped																
Hemoglobin levels stabilized or improved (without transfusion)	N/A	N/A						N/A								
Volume of bleed stabilized or reduced as assessed by imaging			N/A				N/A									

*Each assessment is a yet/no result. Actual values/measurements/assessments should be documented and provide with the CRF.
**For GI bleeds, endoscopy, hematemesis, melena; for intraperitoneal or retroperitoneal bleeds, refers to ascites.
Abbreviations: eCRF = electronic Case Report Form, GI = Gastrointestinal; GU = Genitourinary; NA = Not applicable, RBC = Red Blood Cell

9.1.6.2 Secondary Efficacy Endpoints and Evaluations

Assessments of FVIII:C will be conducted every 4 to 12 hours for the first 24 hours after the initial dose of TAK-672 except where slow decline is documented. Following the first 24 hours, FVIII:C should be conducted with each subsequent dose of TAK-672 throughout treatment

Assessment of efficacy response will be evaluated at the following time points 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 (± 6) hours, 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 at an early withdrawal, at follow-up visits (i.e. at 24 (+24) hours after last dose of TAK-672 as well as at 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 the last dose of TAK-672). The timing of these assessments is relative to the administration of the first dose of TAK-672 until the resolution of the bleeding episode, failure of therapy is concluded, or withdrawal of the subject, whichever occurs first. The investigator will make a decision about further TAK-672 treatment based on the assessment and available information on pFVIII inhibitor.

The total dose and total number of TAK-672 infusions, and the exact time of each infusion will be recorded.

9.1.6.3 Safety Endpoints and Evaluations

Adverse Event

Subjects will be monitored for AEs after the initial dose of TAK-672 until the end of the study (i.e. until 90 (±7) days after the last dose of TAK-672) or 30 days after subject's withdrawal, whichever occurs first). AEs will be elicited by direct, nonleading questioning or will be recorded if offered voluntarily by the subject. Further details for AE reporting can be found in Section 10.1.2.

Nonqualifying Bleeding Episodes

All nonqualifying concurrent bleeding episodes will be recorded on the eCRF as AEs. These nontarget concurrent bleeding episodes represent the nontarget bleeding episodes described in Section 6.1.

Vital Signs

Blood pressure and heart rate, body temperature and respiratory rate will be recorded at time points indicated in study schedule.

Clinical Laboratory Tests

Blood samples for clinical laboratory tests will be taken as indicated in [redacted].

Refer to Table 9-C for list of tests to be performed.

Pregnancy

A urine sample will be collected for a pregnancy test at Screening for female subjects of childbearing potential to test for pregnancy. If this is found to be positive, it will be followed up with a serum pregnancy test. Further details on handling pregnancy can be found in Section 9.1.10.

9.1.6.4 Pharmacokinetic endpoints and evaluations

Non-bleeding state: Blood for FVIII:C to assess the PK of TAK-672 will be collected at pre-infusion of PK dose and at 15-20 min, 1, 3, 6, 12, 18, and 24 hours post infusion. These samples will be tested at a central laboratory for pre-infusion and all post-infusion PK time points.

9.1.7 Documentation of Concomitant Medications

Concomitant medication is any drug given in addition to the study drug. These may be prescribed by a physician or obtained by the subject over the counter. Concomitant medication is not provided by the sponsor. Medications administered for treatment of the auto-antibody with start date (versus treatments administered for control of bleeding) and treatments administered for bleed control (other than TAK-672) will be reviewed and confirmed as per study schedule described in [redacted]. Subjects will be asked whether they have taken any medication other than the study drug (used from signing of informed consent through the end of the study), and all medication including vitamin supplements, over-the-counter medications, and oral herbal preparations, must be recorded in the eCRF. Concomitant medication will be coded by using the World Health Organization Drug Dictionary and will be summarized with the number and percentage of subjects receiving concomitant medication by drug class and preferred drug name.

9.1.8 Documentation of Concurrent Medical Conditions

Concurrent medical conditions are those significant ongoing conditions or diseases that are present at signing of informed consent. This includes clinically significant laboratory, ECG, or physical examination abnormalities noted at the screening examination, according the judgment of the investigator. The condition (i.e. diagnosis) should be described.

9.1.9 Procedures for Clinical Laboratory Samples

Blood samples will be collected for the assay of hFVIII inhibitors, pFVIII inhibitors, and BHK antibodies at the time points indicated in [redacted].

All FVIII and aPTT assays related to subject management decisions by the investigator will be performed at the investigator's local laboratory.

A central reference laboratory will perform assays (FVIII, pFVIII inhibitor, hFVIII inhibitor, and anti-BHK) on each subject's initial pretreatment sample (before the first TAK-672 infusion) and on each subject's samples collected at the follow-up visits as per study schedule. Anti-BHK will only be tested pretreatment and at the final visit. The assessment of inhibitors to porcine and human FVIII will be determined based on the one-stage coagulation assay. Further details on blood collection, tube preparation and shipment will be provided in the Study Manual.

Table 9-C lists the test results that will be obtained for each laboratory specimen.

Table 9-C Clinical Laboratory Tests

Hematology	Serum Chemistry	Urinalysis
RBC count, Hemoglobin Hematocrit Mean cell volume Mean cell hemoglobin Mean corpuscular hemoglobin concentration WBC count with differential and platelet count Neutrophils Lymphocytes Monocytes Eosinophils Basophils	ALT AST Alkaline phosphatase Total bilirubin Blood urea nitrogen Glucose Uric acid Creatinine	pH, protein, ketones, glucose, bilirubin, blood, urobilinogen, specific gravity by dipstick and microscopy if any findings are abnormal. Complete urinalysis will be conducted if dipstick is positive .
Other:		
Plasma	Urine	
Coagulation: aPTT, PT, APTT cross-mixing test, FVIII:C, inhibitor titers against hFVIII and pFVIII	Female subjects of childbearing potential only: hCG (for pregnancy)	

Abbreviations: ALT = alanine aminotransferase, aPTT = activated partial thromboplastin time, AST = aspartate aminotransferase, FVIII = factor VIII, hCG = human chorionic gonadotropin, PT = prothrombin time, RBC = Red blood cell, WBC = White blood cell

The investigator (or designee) is responsible for transcribing or attaching laboratory results to the eCRF. The investigator will maintain a copy of the laboratory accreditation and the reference ranges for the laboratory used.

9.1.10 Pregnancy

Pregnancy itself is not regarded as an AE unless there is a suspicion that the Investigational Medicinal Product (IMP) has interfered with a contraceptive method. If pregnancy occurs during the study, the outcome of the pregnancy will then need to be collected post-study and it may be necessary to discontinue treatment with the IMP. Investigators must inform all female subjects of child-bearing potential that it is currently unknown whether TAK-672-3001 poses any risk to an unborn child and should instruct subjects to use appropriate methods of contraception. Subjects should also be instructed to inform the investigator immediately should they become pregnant during the study. The investigator should counsel the subject, discuss the risks of continuing with the pregnancy and the possible effects on the fetus. The investigator should also recommend that the subject be closely monitored by her personal physician until conclusion of the pregnancy, and once concluded, that both the subject and her infant be carefully monitored throughout the puerperium. Breast feeding is not recommended as there is no data regarding the safety of a nursing child either during or following TAK-672-3001 administration to the mother. All AEs will be communicated to the investigator by the subject. Pregnancies with a conception date within 90 days after subject's last dose of IMP or completion of the study should also be reported to the investigator by the subject for onward reporting to the Sponsor.

9.1.11 Documentation of Screen Failure

Investigators must account for all subjects who have provided a written informed consent.

If the subject is withdrawn at the screening visit, the investigator should complete the eCRF.

The primary reason for screen failure is recorded in the eCRF using the following categories:

- PTE/AE.
- Not meeting all of the inclusion criteria or meeting any of the exclusion criteria; reason(s) should be specified
- Significant protocol deviation.
- Lost to follow-up.
- Voluntary withdrawal .
- Study termination.

Subject identification numbers assigned to subjects who fail screening should not be reused.

9.1.12 Documentation of Study Entrance

Only subjects who meet all of the inclusion criteria and none of the exclusion criteria are eligible for entrance into the treatment phase.

If the subject is found to be not eligible for treatment phase, the investigator should record the primary reason for failure on the applicable eCRF.

9.2 Monitoring Subject Treatment Compliance

The investigator or designee will administer TAK-672 to the subjects. Subject compliance to study treatment will be calculated as the total dose administered (U) divided by total dose planned (U). The administration of each dose of TAK-672 will be documented in the eCRF.

9.3 Schedule of Observations and Procedures

Subjects will be screened in accordance with predefined inclusion and exclusion criteria as described in Section 7.0.

The schedule of assessments during the study (screening, treatment phase, follow-up, and end of the study visit) are summarized in Table A.

9.3.1 Screening (Day -X to Day 0)

A written informed consent from the subject or subject's legal representative should be obtained prior to screening. At Screening, potential subjects will be allocated a unique subject number. Additional details for allocation of subject numbers are available in the Study Manual.

If a potential participant is in a non-bleeding or non-qualified bleeding state, he/she may be prequalified for study eligibility; a determination of FVIII:C, hFVIII inhibitor and pFVIII inhibitor titre will be assessed. The hFVIII inhibitor titer must be known. Eligible prequalified subjects will only be enrolled at the time a qualified severe bleeding episode occurs.

The following screening criteria can be determined during prequalification, if applicable, and should be updated if any apparent change is seen at time of study entry.

- Subject's acquired hemophilia history
- Demographic information
- Significant medical or surgical history
- Prior and concomitant medication
- Physical examination.
- Weight and height
- Vital signs
- Eligibility checks
- Hematology, biochemistry, and urinalysis as listed in Table 9-C.
- Review of treatments administered for bleeding control other than TAK-672.
- Inhibitor titers against hFVIII and pFVIII
- Blood collection for coagulation tests (including aPTT), prothrombin (PT), aPTT cross-mixing test, and FVIII:C.

The following screening criteria can be determined during prequalification and do not need to be re-evaluated if prescreened within 7 days prior to subject enrollment:

- Anti-BHK antibody titers.
- Blood or urine pregnancy test on females of childbearing potential.

9.3.2 Treatment Period

9.3.2.1 Initial TAK-672 Administration

All subjects who demonstrate a qualified bleeding event will receive an intravenous infusion of TAK-672 at an initial dose of 200 U/kg body weight at a rate of 1 to 2 mL/min. Prior to TAK-672 infusion, 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. Other assessments to be performed are:

- Review of treatments administered for bleeding control other than TAK-672
- Review of previous and concomitant medications
- Vital signs
- AEs

9.3.2.2 Assessments at 30 Minutes post dose of TAK-672

- Vital signs
- Assessment of Efficacy: evaluation of bleeding site, available laboratory results (Hgb, Hct, aPTT, and FVIII:C) and clinical status.
- AEs

9.3.2.3 Evaluation of Subject's Clinical Status After the Initial Dose of TAK-672 Until the End of Study Visit or Early Withdrawal

At the pre-specified time points described in Table A (Schedule of Activities), the medications administered for bleed control and immunosuppressive agents administered to control the inhibitor titer will be reviewed. Clinical and laboratory assessments will be performed to evaluate bleeding site, hemodynamic, and hemostatic status including Hgb, Hct, aPTT, PT, and FVIII:C as per the Schedule of Activities. Specimens for inhibitor titers against hFVIII and pFVIII will be drawn at the following time points after the initial dose of TAK-672: at 72 (±12) hours, at PK dose, at every 14(± 3) days until complete remission of AHA and then every 28 (±7) days, and at 90 (±7) days after last TAK-672 dose. TAK-672 treatment will continue until bleeding is successfully controlled, until TAK-672 treatment is discontinued due to lack of efficacy as judged by the investigator or until the subject withdraws from the study, whichever occurs first. In addition, the assessments mentioned below will be performed: 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 trough levels (30 to 40%) based on the clinical presentation and a maximum plasma level of FVIII:C not to exceed 200%. In addition, the following assessments will be performed:

- Review of previous and concomitant medications
- Vital signs
- AEs
- TAK-672 infusion
- Efficacy of TAK-672 by evaluating hemodynamic and hemostatic status including Hgb, Hct, aPTT, and FVIII:C

9.3.3 TAK-672 PK Assessment

Because subjects are considered to be actively bleeding at the time of the study enrollment, it is considered rational to obtain complete PK data after the bleeding is controlled and the subject is stable. Since there may be an increased immunogenicity risk of administering a dose of TAK-672 to a subject who has not experienced a bleeding episode and for whom treatment is not clinically indicated, assessment of the PK behavior in the non-bleeding state is most reasonable at the end of treatment of a bleeding episode with TAK-672. For subjects who have agreed to undergo a PK assessment, blood samples will be collected for FVIII:C at pre infusion, at 15 to 20 minutes as well as at 1, 3, 6, 12, 18 and 24 hours post infusion more than 48 hours after the last treatment dose of TAK-672 is administered at 50 U/kg. Inhibitor titers for hFVIII and pFVIII will be assessed prior to the PK dose of TAK-672.

Agreement to participate in the non-bleeding PK part of the study should be obtained at the study enrollment but a subject's participation in the non-bleeding PK part of the study is not mandatory.

If the subject has successfully responded to TAK-672, the subject will be administered at 50 U/kg of TAK-672 and will then undergo a serial blood sampling for the PK analysis (FVIII:C) at the following time points:

- Prior to administration
- At 15-20 min as well as 1, 3, 6, 12, 18, and 24 hours post infusion

9.3.4 Follow-up

Subjects will be followed-up at the following time points: (1) For those subjects who have not agreed to undergo a PK assessment: at 24 (+ 24) hours after the last treatment dose of TAK-672 (2) For those subjects who have agreed to undergo a PK assessment: at 24 (+ 24) hours after the PK dose of TAK-672 (3) at every 14 (± 3) days until complete remission of AHA, and (4) every 28 (± 7) days after complete remission of AHA.

Complete remission will be defined as undetectable inhibitor titer with more than 70% of FVIII:C obtained and with immune-suppression stopped [14]. Subjects who withdraw from the study should be followed for at least 30 days after the last dose of TAK-672 to assess AEs. Following assessments should be performed at the follow-up visits:

- Review of treatments administered for bleeding control other than TAK-672
- Review of previous and concomitant medications
- Vital signs
- Hematology, biochemistry, and urinalysis
- Efficacy of TAK-672 by evaluating bleeding site, available laboratory results (Hgb, Hct, aPTT, and FVIII:C), and clinical status
- Inhibitor titers against hFVIII and pFVIII, and
- AEs

End of the study assessment will be performed on a subject at the final study site visit if 90 (± 7) days have elapsed since the last treatment dose or the PK dose of TAK-672 is administered to the subject for the initial qualified bleeding episode. If there is any subsequent bleeding episode to which TAK-672 is administered, end of the study assessment will be performed at the subject's final study site visit with the originally planned schedule if 90 days have not elapsed since the last treatment dose or the PK dose of TAK-672 is administered to the subject for the initial bleeding episode. If more than 90 days have elapsed since the last treatment dose or the PK dose of TAK-672 is administered to the subject, end of treatment with TAK-672 and end of the study assessment will occur simultaneously.

For those subjects who prematurely withdraw from the study or those who have any additional severe bleeding episode requiring a treatment with TAK-672, which will result in having less than 30 days between the last treatment dose of TAK-672 and the final study site visit, subjects will be asked to visit his or her study site or will be contacted via e-mail or telephone call during the 30-days follow-up period for any AEs after the last treatment dose of TAK-672.

9.3.5 Subsequent bleeds

For subjects who have positive responses to TAK-672, subsequent severe bleeding episodes (treated as in-patient) are eligible for treatment with TAK-672 but will not be considered as qualifying bleeding episodes for the purposes of primary efficacy analysis. Bleeding that occurs at the same site of the qualifying bleed after initially successful hemostasis and prior to 2 weeks following the last TAK-672 dose, will be considered a continuation of the same bleeding episode. These will be recorded as AEs with all treatments, assessments and outcomes appropriately documented.

Bleeding episodes that are not considered a continuation of the initial bleeding episode (e.g. bleeding episodes that occur at other sites or more than 2 weeks after the last dose of TAK-672) will be considered AEs with all treatments, assessments and outcomes appropriately documented. The treatment and data collection approach for subsequent bleeds should be as described for the initial bleeding episode but these data will not be considered for the purposes of the primary efficacy endpoint.

Subjects may be treated either with TAK-672 or bypassing agents at the discretion of the investigator for any subsequent bleeding episode. Other study visits will be repeated as described for the initial bleeding episode and as mentioned in [redacted]. The treatment of any subsequent bleeding episodes will not be considered for the purposes of the primary efficacy endpoint.

9.3.6 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. 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 treatment dose of TAK-672. The procedure will be performed as discussed Section 9.3.4.

9.3.7 Post Study Care

Post study care is not provided for this study.

10.0 PRETREATMENT EVENTS AND ADVERSE EVENTS

10.1 Definitions

10.1.1 Pretreatment Events

A PTE is defined as any untoward medical occurrence in a clinical investigation subject who has signed informed consent to participate in a study but prior to administration of any study drug; it does not necessarily have to have a causal relationship with study participation.

10.1.2 Adverse Events

An AE is defined as any untoward medical occurrence in a clinical investigation subject administered a drug; it does not necessarily have to have a causal relationship with this treatment.

An AE can therefore be any unfavorable and unintended sign (e.g. a clinically significant abnormal laboratory value), symptom, or disease temporally associated with the use of a drug whether or not it is considered related to the drug.

In addition, drug-device AEs related to quality or malfunction will be collected.

10.1.3 Additional Points to Consider for PTEs and AEs

An untoward finding generally may:

- Indicate a new diagnosis or unexpected worsening of a pre-existing condition. (Intermittent events for pre-existing conditions or underlying disease should not be considered PTEs or AEs).
- Necessitate therapeutic intervention.
- Require an invasive diagnostic procedure.
- Require discontinuation or a change in dose of study drug or a concomitant medication.
- Be considered unfavorable by the investigator for any reason.

  PTEs/AEs caused by a study procedure (e.g. a bruise after blood draw) should be recorded as a PTE/AE.

Diagnoses vs. signs and symptoms:

- Each event should be recorded to represent a single diagnosis. Accompanying signs (including abnormal laboratory values or ECG findings) or symptoms should NOT be recorded as additional AEs. If a diagnosis is unknown, sign(s) or symptom(s) should be recorded appropriately as a PTE(s) or as an AE(s).

Laboratory values and ECG findings:

- Changes in laboratory values or ECG findings are only considered to be PTEs or AEs if they are judged to be clinically significant (i.e. if some action or intervention is required or if the investigator judges the change to be beyond the range of normal physiologic fluctuation). A laboratory or ECG re-test and/or continued monitoring of an abnormal value or finding are not considered an intervention. In addition, repeated or additional noninvasive testing for verification, evaluation or monitoring of an abnormality is not considered an intervention.
- If abnormal laboratory values or ECG findings are the result of pathology for which there is an overall diagnosis (e.g. increased creatinine in renal failure), the diagnosis only should be reported appropriately as a PTE or as an AE.

Pre-existing conditions:

- Pre-existing conditions (present at the time of signing of informed consent) are considered concurrent medical conditions and should NOT be recorded as PTEs or AEs. Baseline evaluations (e.g. laboratory tests, ECG, X-rays etc.) should NOT be recorded as PTEs unless related to study procedures. However, if the subject experiences a worsening or complication of such a concurrent medical condition, the worsening or complication should be recorded appropriately as a PTE (worsening or complication occurs before start of study drug) or an AE (worsening or complication occurs after start of study drug). Investigators should ensure that the event term recorded captures the change in the condition (e.g. "worsening of…").
- If a subject has a pre-existing episodic concurrent medical condition (e.g. asthma, epilepsy) any occurrence of an episode should only be captured as a PTE/AE if the condition becomes more frequent, serious or severe in nature. Investigators should ensure that the AE term recorded captures the change in the condition from Baseline (e.g. "worsening of…").
- If a subject has a degenerative concurrent medical condition (e.g. cataracts, rheumatoid arthritis), worsening of the condition should only be recorded as a PTE/AE if occurring to a greater extent to that which would be expected. Investigators should ensure that the AE term recorded captures the change in the condition (e.g. "worsening of…").

Worsening of PTEs or AEs:

- If the subject experiences a worsening or complication of a PTE after the start of study drug, the worsening or complication should be recorded as an AE. Investigators should ensure that the AE term recorded captures the change in the PTE (e.g. "worsening of…").
- If the subject experiences a worsening or complication of an AE after any change in study drug, the worsening or complication should be recorded as a new AE. Investigators should ensure that the AE term recorded captures the change in the condition (e.g. "worsening of…").

Changes in intensity of AEs/Serious PTEs:

- If the subject experiences changes in intensity of an AE/serious PTE, the event should be captured once with the maximum intensity recorded.

Preplanned procedures (surgeries or interventions):

- Preplanned procedures (surgeries or therapies) that were scheduled prior to signing of informed consent are not considered PTEs or AEs. However, if a preplanned procedure is performed early (e.g. as an emergency) due to a worsening of the pre-existing condition, the worsening of the condition should be recorded as a PTE or an AE. Complications resulting from any planned surgery should be reported as AEs.

Elective surgeries or procedures:

- Elective procedures performed where there is no change in the subject's medical condition should not be recorded as PTEs or AEs but should be documented in the subject's source documents. Complications resulting from an elective surgery should be reported as AEs.

Insufficient clinical response (lack of efficacy):

- Insufficient clinical response, efficacy, or pharmacologic action should NOT be recorded as an AE. The investigator must make the distinction between exacerbation of pre-existing illness and lack of therapeutic efficacy.

Overdose:

- Cases of overdose with any medication without manifested side effects are NOT considered PTEs or AEs, but instead will be documented on an Overdose page of the eCRF. Any manifested side effects will be considered PTEs or AEs and will be recorded on the AE page of the eCRF.

10.1.4 Serious Adverse Events

An SAE is defined as any untoward medical occurrence after the initial dose of TAK-672 at any dose that:

1. Results in DEATH.
2. Is LIFE-THREATENING.
    - The term "life-threatening" refers to an event in which the subject was at risk of death at the time of the event; it does not refer to an event that hypothetically might have caused death if it were more severe.
3. Requires inpatient HOSPITALIZATION or prolongation of existing hospitalization.
4. Results in persistent or significant DISABILITY/INCAPACITY.
5. Leads to a CONGENITAL ANOMALY/BIRTH DEFECT.
6. Is an IMPORTANT MEDICAL EVENT that satisfies any of the following:
    - May require intervention to prevent items 1 through 5 above.
    - May expose the subject to danger, even though the event is not immediately life threatening or fatal or does not result in hospitalization.

- Includes any event or synonym described in the Takeda Medically Significant AE List (Table 10-A).

Table 10-A List of Takeda Medically Significant Adverse Events

Term	
Acute respiratory failure/acute respiratory distress syndrome	Hepatic necrosis
Torsade de pointes/ventricular fibrillation / ventricular tachycardia	Acute liver failure
	Anaphylactic shock
Malignant hypertension	Acute renal failure
Convulsive seizure (including seizure and epilepsy)	Pulmonary hypertension
Agranulocytosis	Pulmonary fibrosis including interstitial lung disease
Aplastic anemia	Confirmed or suspected endotoxin shock
Toxic epidermal necrolysis/Stevens-Johnson syndrome	Confirmed or suspected transmission of infectious agent by a medicinal product
COVID-19 related disease	Neuroleptic malignant syndrome/malignant hyperthermia
COVID-19 pneumonia	Spontaneous abortion/stillbirth and fetal death

Abbreviation: AE = Adverse event; SAE = Serious adverse events
Note: Terms identified on the Medically Significant AE List represent the broad medical concepts to be considered as "Important Medical Events" satisfying SAE reporting requirements.

PTEs that fulfill 1 or more of the serious criteria above are also to be considered SAEs and should be reported and followed up in the same manner (Sections 10.2.2 and 10.3).

10.1.5 AEs of Special Interest

An AE of Special Interest is one of scientific and medical concern specific to the compound or program, for which ongoing monitoring and rapid communication by the investigator to Takeda may be appropriate. Such events may require further investigation in order to characterize and understand them and would be described in protocols and instructions provided for investigators as to how and when they should be reported to Takeda.

The AE requiring special monitoring for this study are hypersensitivity reactions, including anaphylaxis, that may occur following rpFVIII infusion; *de novo* inhibitor to porcine FVIII/anamnestic reaction with increase of inhibitor titer to pFVIII and/or hFVIII. Early signs of allergic reactions, which can progress to anaphylaxis, include angioedema, chest-tightness, dyspnea, hypotension, wheezing, urticaria, pruritus, and thromboembolic events.

AE of Special Interest occurring during the treatment period or the follow-up period should be reported by the investigator to the sponsor immediately or within 1 business day of/after the first onset or subject's notification of the event.

An AE of Special Interest Form or an SAE form should be completed, signed, or signed and sealed by the investigator and reported to the sponsor within 10 business days.

The investigator should submit the original copy of the AE of Special Interest Form or the SAE form to the sponsor.

AEs of special interest have to be recorded as AEs in the eCRF. An evaluation form along with all other required documentation must be submitted to the sponsor.

10.1.6 Intensity of PTEs and AEs

The different categories of intensity (severity) are characterized as follows:

Mild:	The event is transient and easily tolerated by the subject.
Moderate:	The event causes the subject discomfort and interrupts the subject's usual activities.
Severe:	The event causes considerable interference with the subject's usual activities.

10.1.7 Causality of AEs

The relationship of each AE to study drug(s) will be assessed using the following categories:

Related:	An AE that follows a reasonable temporal sequence from administration of a drug (including the course after withdrawal of the drug), or for which possible involvement of the drug cannot be ruled out, although factors other than the drug, such as underlying diseases, complications, concomitant medications and concurrent treatments, may also be responsible.
Not Related:	An AE that does not follow a reasonable temporal sequence from administration of a drug and/or that can reasonably be explained by other factors, such as underlying diseases, complications, concomitant medications and concurrent treatments.

10.1.8 Relationship to Study Procedures

Relationship (causality) to study procedures should be determined for all PTEs and AEs.

The relationship should be assessed as Related if the investigator considers that there is reasonable possibility that an event is due to a study procedure. Otherwise, the relationship should be assessed as Not Related.

10.1.9 Start Date

The start date of the AE/PTE is the date that the first signs/symptoms were noted by the subject and/or investigator.

The start date of PTEs/AEs will be determined using the following criteria;

Table 10-B Criteria for Determining Start Date of PTEs/AEs

PTEs/AEs	Start Date
Any signs/symptoms/diseases (diagnosis)	The date that the first signs/symptoms/diseases were noted by the subject and/or the investigator should be recorded.
Asymptomatic diseases	The date when examination was performed for diagnosis and diagnosis was confirmed should be recorded. The date when diagnosis was confirmed should also be recorded even when values or findings showed previous values or findings or the onset time can be estimated.
Worsening or complication of concurrent medical conditions or any signs/symptoms /diseases before treatment	The date that a worsening or complication of the condition was noted first by the subject and/or the investigator should be recorded.
The examination after start of the study drug showed abnormal values/findings.	The date of examination when an abnormal value or findings that was judged to be clinically significant was noted should be recorded.
The examination at the start of the study drug showed abnormal values/ findings and the subsequent examinations showed worsening of the symptoms.	The date of examination when apparent elevation, reduction, increase or decrease was confirmed in judgment according to the trends in those values or findings should be recorded.

10.1.10 Stop Date

The stop date of the AE/PTE is the date at which the subject recovered, the event resolved but with sequelae or the subject died.

10.1.11 Frequency

Episodic AEs/PTE (e.g. vomiting) or those which occur repeatedly over a period of consecutive days are intermittent. All other events are continuous.

10.1.12 Action Concerning Study Drug

- Drug withdrawn – a study drug is stopped due to the particular AE.
- Dose not changed – the particular AE did not require stopping a study drug.
- Unknown – only to be used if it has not been possible to determine what action has been taken.
- Not Applicable – a study drug was stopped for a reason other than the particular AE, e.g. the study has been terminated, the subject died, dosing with study drug was already stopped before the onset of the AE.
- Dose Reduced – the dose was reduced due to the particular AE.
- Dose Increased – the dose was increased due to the particular AE.
- Dose Interrupted – the dose was interrupted due to the particular AE.

10.1.13 Outcomes of Adverse Events and Pretreatment Adverse Events

The types and definitions of the outcomes of AE/PTE are explained below:

- Recovered/Resolved – Subject returned to first assessment status with respect to the AE/PTE.
- Recovering/Resolving – the intensity is lowered by 1 or more stages: the diagnosis or signs/symptoms has almost disappeared; the abnormal laboratory value improved but has not returned to the normal range or to baseline; the subject died from a cause other than the particular AE/PTE with the condition remaining "recovering/resolving".
- Not recovered/not resolved – there is no change in the diagnosis, signs or symptoms; the intensity of the diagnosis, signs/symptoms or laboratory value on the last day of the observed study period has got worse than when it started; is an irreversible congenital anomaly; the subject died from another cause with the particular AE/PTE state remaining "Not recovered/not resolved".
- Resolved with sequelae – the subject recovered from an acute AE/PTE but was left with permanent/significant impairment (e.g. recovered from a cardiovascular accident but with some persisting paresis).
- Fatal – the AEs/PTEs which are considered as the cause of death.
- Unknown – the course of the AE/PTE cannot be followed up due to hospital change or residence change at the end of the subject's participation in the study.

10.2 Procedures

10.2.1 Collection and Reporting of AEs

10.2.1.1 PTE and AE Collection Period

Subjects will be monitored for AEs from the time the subject presents with the initial bleeding episode until the end of the follow-up period. Collection of PTEs will commence from the time the subject signs the informed consent to participate in the study and continue until the subject is first administered TAK-672 or until screen failure. For subjects who discontinue prior to study drug administration, PTEs are collected until the subject discontinues study participation.

Collection of AEs will commence from the time when the subject is first administered TAK-672. Routine collection of AEs will continue until 30 days after early withdrawal/termination/end of study visit.

10.2.1.2 PTE and AE Reporting

AEs will be elicited by direct, nonleading questioning or will be recorded if offered voluntarily by the subject. At each study visit, the investigator will assess whether any subjective AEs have occurred. A neutral question, such as "How have you been feeling since your last visit?" may be asked. Subjects may report AEs occurring at any other time during the study.

Subjects experiencing a serious PTE must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or there is a satisfactory explanation for the change. Non-serious PTEs, related or unrelated to the study procedure, need not to be followed up for the purposes of the protocol.

All subjects experiencing AEs, whether considered associated with the use of the study drug or not, must be monitored until the symptoms subside and any clinically relevant changes in laboratory values have returned to baseline or until there is a satisfactory explanation for the changes observed. All PTEs and AEs will be documented in the PTE/AE page of the eCRF, whether or not the investigator concludes that the event is related to the drug treatment. The following information will be documented for each event:

1. Event term
2. Start and stop date and time
3. Frequency
4. Intensity
5. Investigator's opinion of the causal relationship between the event and administration of study drug(s) (i.e. "related" or "not related")
6. Investigator's opinion of the causal relationship to study procedure(s), including the details of the suspected procedure
7. Action concerning study drug (not applicable for PTEs)
8. Outcome of event
9. Seriousness

10.2.2 Collection and Reporting of SAEs

When an SAE occurs through the AE collection period it should be reported according to the following procedure:

An SAE should be reported by the investigator to the sponsor/the Emergency Reception Center for Safety Information (see annex) within 1 business day of the SAE occurrence, along with any relevant information. The investigator should submit the detailed SAE form to the sponsor/the Emergency Reception Center for Safety Information appropriate personnel (see annex) within 10 calendar days. The information should be completed as fully as possible but contain, at a minimum:

- A short description of the event and the reason why the event is categorized as serious.
- Subject identification number
- Investigator's name
- Name of the study drug(s)
- Causality assessment

The investigator should submit the original copy of the SAE form to the sponsor

Any SAE spontaneously reported to the investigator following the AE collection period should be reported to the sponsor if considered related to study participation

Reporting of Serious PTEs will follow the procedure described for SAEs.

10.3 Follow-up of SAEs

If information not available at the time of the first report becomes available at a later date, the investigator should complete a follow-up SAE form or provide other written documentation and fax it immediately. Copies of any relevant data from the hospital notes (e.g. laboratory tests, discharge summary, postmortem results) should be sent to the addressee, if requested.

All SAEs should be followed up until resolution or permanent outcome of the event. The timelines and procedure for follow-up reports are the same as those for the initial report.

10.3.1 Safety Reporting to Investigators, IRBs, and Regulatory Authorities

The sponsor will be responsible for reporting all suspected unexpected serious adverse reactions (SUSARs) and any other applicable SAEs to regulatory authorities, investigators and IRBs, the head of the study site, as applicable, in accordance with national regulations in the countries where the study is conducted. Relative to the first awareness of the event by/or further provision to the sponsor or sponsor's designee, SUSARs will be submitted to the regulatory authorities as expedited report within 7 days for fatal and life-threatening events and 15 days for other serious events, unless otherwise required by national regulations. The sponsor will also prepare an expedited report for other safety issues where these might materially alter the current benefit-risk assessment of a study drug/sponsor-supplied drug or that would be sufficient to consider changes in the study drug/sponsor-supplied drug administration or in the overall conduct of the trial. The study site also will forward a copy of all expedited reports to his or her IRB.

11.0 STUDY-SPECIFIC COMMITTEES

No Steering Committee, Data Safety Monitoring Committee, or Clinical Endpoint Committee will be used in this study

12.0 DATA HANDLING AND RECORDKEEPING

The full details of procedures for data handling will be documented in the Data Management Plan. AEs, PTEs, medical history, and concurrent medical conditions will be coded using the Medical Dictionary for Regulatory Activities. Drugs will be coded using the World Health Organization (WHO) Drug Dictionary.

12.1 Electronic Case Report Forms

Completed eCRFs are required for each subject who signs an informed consent.

The sponsor or its designee will supply study sites with access to eCRFs. The sponsor will make arrangements to train appropriate site staff in the use of the eCRF. These forms are used to transmit the information collected in the performance of this study to the sponsor and regulatory authorities. eCRFs must be completed in English.

After completion of the entry process, computer logic checks will be run to identify items, such as inconsistent dates, missing data, and questionable values.

Corrections are recorded in an audit trail that captures the old information, the new information, identification of the person making the correction, the date the correction was made, and the reason for change. Reasons for significant corrections should additionally be included.

The principal investigator must review the eCRFs for completeness and accuracy and must e-sign the appropriate eCRFs as indicated. Furthermore, the investigator must retain full responsibility for the accuracy and authenticity of all data entered on the eCRFs; in this study, however, FVIII:C and Anti-hFVIII as well as Anti-pFVIII, Anti-BHK titer, and clinical laboratory tests will not be recorded directly into the eCRF.

After the lock of the study database, any change of, modification of or addition to the data on the eCRFs should be made by the investigator with use of change and modification records of the eCRFs/eCRFs (Data Clarification Form) provided by the sponsor. The principal investigator must review the data change for completeness and accuracy, and must sign, or sign and seal, and date.

eCRFs will be reviewed for completeness and acceptability at the study site during periodic visits by the sponsor or its designee. The sponsor or its designee will be permitted to review the subject's medical and hospital records pertinent to the study to ensure accuracy of the eCRFs. The completed eCRFs are the sole property of the sponsor and should not be made available in any form to third parties, except for authorized representatives of appropriate governmental health or regulatory authorities, without written permission of the sponsor.

12.2 Record Retention

The investigator and the head of the study site agree to keep the records stipulated in Section 12.1 and those documents that include (but are not limited to) the study-specific documents, the identification log of all participating subjects, medical records, all original signed and dated informed consent forms, electronic copy of eCRFs, including the audit trail, and detailed records of drug disposition to enable evaluations or audits from regulatory authorities, the sponsor or its designees.

The investigator and the head of the study site are required to retain essential relevant documents until the day specified as 1) or 2) below, whichever comes later. However, if the sponsor requests a longer time period for retention, the head of the study site should discuss how long and how to retain those documents with the sponsor.

1. The day on which marketing approval of the study drug is obtained (or the day 20 years after the date of notification in the case that the investigation is discontinued).
2. The day 20 years after the date of early termination or completion of the study.

In addition, the investigator and the head of the study site should retain the essential relevant documents until the receipt of a sponsor-issued notification to state the retention is no longer required.

13.0 STATISTICAL METHODS

13.1 Statistical and Analytical Plans

A Statistical Analysis Plan (SAP) will be prepared and finalized prior to database lock. This document will provide further details regarding the definition of analysis variables and analysis methodology to address all study objectives.

13.1.1 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).

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

The definition of each analysis set will be described in more details in the SAP. The sponsor will verify the validity of the definitions of the analysis sets as well as the rules for handling data, with consulting a medical expert as needed. If necessary, the SAP will be supplemented with new handling rules that were not discussed at the planning stage. The SAP must be finalized prior to database lock.

13.1.2 Analysis of Demographics and Other Baseline Characteristics

Descriptive summary statistics (number, mean, standard deviation, median, minimum, and maximum) or frequency counts of demographic and baseline characteristics data will be presented for the FAS.

13.1.3 Efficacy Analysis

13.1.3.1 Primary Efficacy 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 initial dose of TAK-672 using a well-defined 4-point ordinal scale summarized in Section 5.2.1.

The proportion of subjects with a positive response to TAK-672 therapy at 24 hours post-treatment and corresponding exact 2-sided Clopper-Pearson 95% confidence interval (CI) will be provided using the FAS. Eligible subjects who withdraw from treatment at an earlier time point will be assumed to be non-responders at the 24-hour assessment time point.

Subjects, who have hemostatic response and stop treatment because bleeding is controlled, will be assumed to be responders at the 24-hour assessment time point.

13.1.3.2 Secondary Efficacy Analysis

The secondary efficacy endpoints are:

- 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 as mentioned in [redacted] 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 the specified time points during treatment and eventual control of severe bleeding episodes.
- Correlation between the pre-infusion pFVIII inhibitor 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 the specified time points during treatment: i.e. at 72 (±6) hours, at PK dose of TAK-672, at every 14 (± 3) days until complete remission of AHA and then every 28 (±7) days, and at the end of the follow-up period (i.e. 90 (±7) days after the last dose of TAK-672).
- Duration period and the total dose from initial dose of rpFVIII until completion of hemostasis control.
- Number of new qualified severe bleeding episodes.

In particular, the proportion of subjects with a positive response to TAK-672 therapy and corresponding exact 2-sided Clopper-Pearson 95% CI will be summarized at specified response assessment time points as defined in Section 9.1.6.2. Eligible subjects who withdraw from treatment at an earlier time point will be assumed to be non-responders at the subsequent time points. Subjects who had hemostatic response and stopped treatment because of the control at an earlier time point will be assumed to be responders at subsequent time points.

13.1.4 PK Analysis

Plasma levels of FVIII will be summarized using descriptive statistics according to nominal (scheduled) time post-dose and day. In addition, the following PK parameters will be estimated using non-compartmental methods for the data obtained from the non-bleeding state: C_{max}, AUC, CL, $t_{1/2}$, and C_{max}/Dose, or the peak level C_{max} (U/mL) normalized by dose (U/kg).

13.1.5 Safety Analysis

The safety of TAK-672 will be assessed from the following at the designated time points:

- Treatment-emergent AEs and SAEs
- Vital signs
- Biochemistry, hematology, and urinalyses
- Inhibitor titers against hFVIII and pFVIII
- Anti-host-cell protein (BHK) antibody titer

All safety analyses will be based on the safety analysis set.

Treatment-emergent AEs are defined as AEs (including loss of efficacy due to anamnestic reaction with increase of inhibitor titer to porcine FVIII and/or human FVIII, hypersensitivity, thrombogenicity) with onset on or after the start of study treatment, or medical conditions present prior to the start of study treatment but increasing in severity or relationship on or after the start of study treatment.

All AEs will be coded using Medical Dictionary for Regulatory Activities. Data will be summarized using preferred term and primary system organ class.

Descriptive summary statistics will be presented for absolute value and change from baseline at each scheduled assessment time point for clinical laboratory tests, vital signs and hFVIII/-rpFVIII inhibitor titers.

Descriptive summary statistics for BHK antibody titer at Screening and at the end of study will be presented.

13.2 Interim Analysis and Criteria for Early Termination

No interim analysis is planned.

13.3 Determination of Sample Size

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.

14.0 QUALITY CONTROL AND QUALITY ASSURANCE

14.1 Study-Site Monitoring Visits

Monitoring visits to the study site will be made periodically during the study to ensure that all aspects of the protocol are followed. Source documents will be reviewed for verification of data recorded on the eCRFs. Source documents are defined as original documents, data, and records. The investigator and the study site/head of the study site guarantee access to source documents by the sponsor or its designee (Contract Research Organization) and by the IRB or independent ethics committee (IEC).

All aspects of the study and its documentation will be subject to review by the sponsor or sponsor's designee, including but not limited to the Investigator's Binder, study drug, subject medical records, informed consent documentation, documentation of subject authorization to use personal health information, and review of eCRFs and associated source documents. It is important that the investigator and other study personnel are available during the monitoring visits and that sufficient time is devoted to the process.

14.2 Protocol Deviations

The investigator can deviate and change from the protocol for any medically unavoidable reason, for example, to eliminate an immediate hazard to subjects, without a prior written agreement with the sponsor or a prior approval from IRB. In the event of a deviation or change, the principal investigator should notify the sponsor and the head of the study site of the deviation or change as well as its reason in a written form, and then retain a copy of the written form. When necessary, the principal investigator may consult and agree with the sponsor on a protocol amendment. If the protocol amendment is appropriate, the amendment proposal should be submitted to the head of the study site as soon as possible and an approval from IRB should be obtained.

The investigator should document all protocol deviations.

14.3 Quality Assurance Audits and Regulatory Agency Inspections

The study site also may be subject to quality assurance audits by the sponsor or designees. In this circumstance, the sponsor-designated auditor will contact the site in advance to arrange an auditing visit. The auditor may ask to visit the facilities where laboratory samples are collected, where the medication is stored and prepared, and any other facility used during the study. In addition, there is the possibility that this study may be inspected by regulatory agencies, including those of foreign governments (e.g. the Food and Drug Administration, the United Kingdom Medicines and Healthcare products Regulatory Agency, the Pharmaceuticals and Medical Devices Agency of Japan). If the study site is contacted for an inspection by a regulatory body, the sponsor should be notified immediately. The investigator and study site/head of the study site guarantee access for quality assurance auditors to all study documents as described in Section 14.1.

15.0 ETHICAL ASPECTS OF THE STUDY

This study will be conducted with the highest respect for the individual subjects (i.e. subjects) according to the protocol, the ethical principles that have their origin in the Declaration of Helsinki, and the International Council for Harmonisation (ICH) Harmonized Tripartite Guideline for GCP. Each investigator will conduct the study according to applicable local or regional regulatory requirements and align his or her conduct in accordance with the "Responsibilities of the investigator" that are listed in [redacted]. The principles of Helsinki are addressed through the protocol and through appendices containing requirements for informed consent and investigator responsibilities.

15.1 IRB and/or IEC Approval

The IRBs and IECs must be constituted according to the applicable requirements of each participating region. The sponsor or designee will require documentation noting all names and titles of members who make up the respective IRB or IEC. If any member of the IRB or IEC has direct participation in this study, written notification regarding his or her abstinence from voting must also be obtained.

The sponsor or designee will supply relevant documents for submission to the respective IRB or IEC for the protocol's review and approval. This protocol, the Investigator's Brochure, a copy of the informed consent form, and, if applicable, subject recruitment materials and/or advertisements and other documents required by all applicable laws and regulations, must be submitted to a central or local IRB or IEC for approval. The IRB's or IEC's written approval of the protocol and subject informed consent must be obtained and submitted to the sponsor or designee before commencement of the study (i.e. before shipment of the sponsor-supplied drug or study-specific screening activity/signing a contract for the clinical study). The IRB or IEC approval must refer to the study by exact protocol title, number, and version date; identify versions of other documents (e.g. informed consent form) reviewed; and state the approval date. Until the site receives full IRB/IEC approval no protocol activities, including screening may occur.

Study sites must adhere to all requirements stipulated by their respective IRB or IEC. This may include notification to the IRB or IEC regarding protocol amendments, updates to the informed consent form, recruitment materials intended for viewing by subjects, local safety reporting requirements, reports and updates regarding the ongoing review of the study at intervals specified by the respective IRB or IEC, and submission of the investigator's final status report to IRB or IEC. All IRB and IEC approvals and relevant documentation for these items must be provided to the sponsor or its designee.

Subject incentives should not exert undue influence for participation. Payments to subjects must be approved by the IRB or IEC and sponsor.

15.2 Subject Information, Informed Consent, and Subject Authorization

Written consent documents will embody the elements of informed consent as described in the Declaration of Helsinki and the ICH Guidelines for GCP and will be in accordance with all applicable laws and regulations. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) describe the planned and permitted uses, transfers, and disclosures of the subject's personal and personal health information for purposes of conducting the study. The informed consent form and the subject information sheet (if applicable) further explain the nature of the study, its objectives, and potential risks and benefits, as well as the date informed consent is given. The informed consent form will detail the requirements of the participant and the fact that he or she is free to withdraw at any time without giving a reason and without prejudice to his or her further medical care.

The investigator is responsible for the preparation, content, and IRB or IEC approval of the informed consent form and if applicable, the subject authorization form. The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be approved by both the IRB or IEC and the sponsor prior to use.

The informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) must be written in a language fully comprehensible to the prospective subject. It is the responsibility of the investigator to explain the detailed elements of the informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) to the subject. Information should be given in both oral and written form whenever possible and in the manner deemed appropriate by the IRB or IEC. In the event the subject is not capable of rendering adequate written informed consent, then the subject's legally acceptable representative may provide such consent for the subject in accordance with applicable laws and regulations.

The subject, or the subject's legally acceptable representative, must be given ample opportunity to: (1) inquire about details of the study and (2) decide whether or not to participate in the study. If the subject, or the subject's legally acceptable representative, determines he or she will participate in the study, then the informed consent form and subject authorization form (if applicable) must be signed and dated by the subject, or the subject's legally acceptable representative, at the time of consent and prior to the subject entering into the study. The subject or the subject's legally acceptable representative should be instructed to sign using their legal names, not nicknames, using blue or black ballpoint ink. The investigator must also sign and date the informed consent form and subject authorization (if applicable) at the time of consent and prior to subject entering into the study.

Once signed, the original informed consent form, subject authorization form (if applicable), and subject information sheet (if applicable) will be stored in the investigator's site file. The investigator must document the date the subject signs the informed consent in the subject's medical record. Copies of the signed informed consent form, the signed subject authorization form (if applicable), and subject information sheet (if applicable) shall be given to the subject.

All revised informed consent forms must be reviewed and signed by relevant subjects or the relevant subject's legally acceptable representative in the same manner as the original informed consent. The date the revised consent was obtained should be recorded in the subject's medical record, and the subject should receive a copy of the revised informed consent form.

15.3 Subject Confidentiality

The sponsor and designees affirm and uphold the principle of the subject's right to protection against invasion of privacy. Throughout this study, a subject's source data will only be linked to the sponsor's clinical trial database or documentation via a subject identification number. As permitted by all applicable laws and regulations, limited subject attributes, such as sex, age, or date of birth may be used to verify the subject and accuracy of the subject's unique identification number.

To comply with ICH Guidelines for GCP and to verify compliance with this protocol, the sponsor requires the investigator to permit the monitor or the sponsor's designee, representatives from any regulatory authority (e.g. Food and Drug Administration, Medicines and Healthcare products Regulatory Agency, Pharmaceuticals and Medical Devices Agency), the sponsor's designated auditors, and the appropriate IRBs and IECs to review the subject's original medical records (source data or documents), including, but not limited to, laboratory test result reports, ECG reports, admission and discharge summaries for hospital admissions occurring during a subject's study participation, and autopsy reports. Access to a subject's original medical records requires the specific authorization of the subject as part of the informed consent process (Section 15.2).

Copies of any subject source documents that are provided to the sponsor must have certain personally identifiable information removed (i.e. subject name, address, and other identifier fields not collected on the subject's eCRF).

15.4 Publication, Disclosure, and Clinical Trial Registration Policy

15.4.1 Publication and Disclosure

The investigator is obliged to provide the sponsor with complete test results and all data derived by the investigator from the study. During and after the study, only the sponsor may make study information available to other study investigators or to regulatory agencies, except as required by law or regulation. Except as otherwise allowable in the study site agreement, any public disclosure (including publicly accessible websites) related to the protocol or study results (other than study recruitment materials and/or advertisements), is the sole responsibility of the sponsor.

The sponsor may publish any data and information from the study (including data and information generated by the investigator) without the consent of the investigator. Manuscript authorship for any peer-reviewed publication will appropriately reflect contributions to the production and review of the document. All publications and presentations must be prepared in accordance with this section and the study site agreement. In the event of any discrepancy between the protocol and the study site agreement, the study site agreement will prevail.

The investigator needs to obtain a prior written approval from the sponsor to publish any information from the study externally such as to a professional association.

15.4.2 Clinical Trial Registration

In order to ensure that information on clinical trials reaches the public in a timely manner and to comply with applicable laws, regulations and guidance, Takeda will, at a minimum register all interventional clinical trials it sponsors anywhere in the world on ClinicalTrials.gov and/or other publicly accessible websites before start of study, as defined in Takeda Policy/Standard. Takeda contact information, along with investigator's city, state (for Americas investigators), country, and recruiting status will be registered and available for public viewing.

For some registries, Takeda will assist callers in locating study sites closest to their homes by providing the investigator name, address, and phone number to the callers requesting trial information. Once subjects receive investigator contact information, they may call the site requesting enrollment into the trial. The investigative sites are encouraged to handle the trial inquiries according to their established subject screening process. If the caller asks additional questions beyond the topic of trial enrollment, they should be referred to the sponsor.

Any investigator who objects to the sponsor providing this information to callers must provide the sponsor with a written notice requesting that their information not be listed on the registry site.

15.4.3 Clinical Trial Results Disclosure

Takeda will post the results of clinical trials on ClinicalTrials.gov and/or other publicly accessible websites, as required by Takeda Policy/Standard, applicable laws and/or regulations.

15.5 Insurance and Compensation for Injury

Each subject in the study must be insured in accordance with the regulations applicable to the site where the subject is participating. If a local underwriter is required, then the sponsor or sponsor's designee will obtain clinical study insurance against the risk of injury to subjects. Refer to the study site agreement regarding the sponsor's policy on subject compensation and treatment for injury. If the investigator has questions regarding this policy, he or she should contact the sponsor or sponsor's designee.

16.0 REFERENCES

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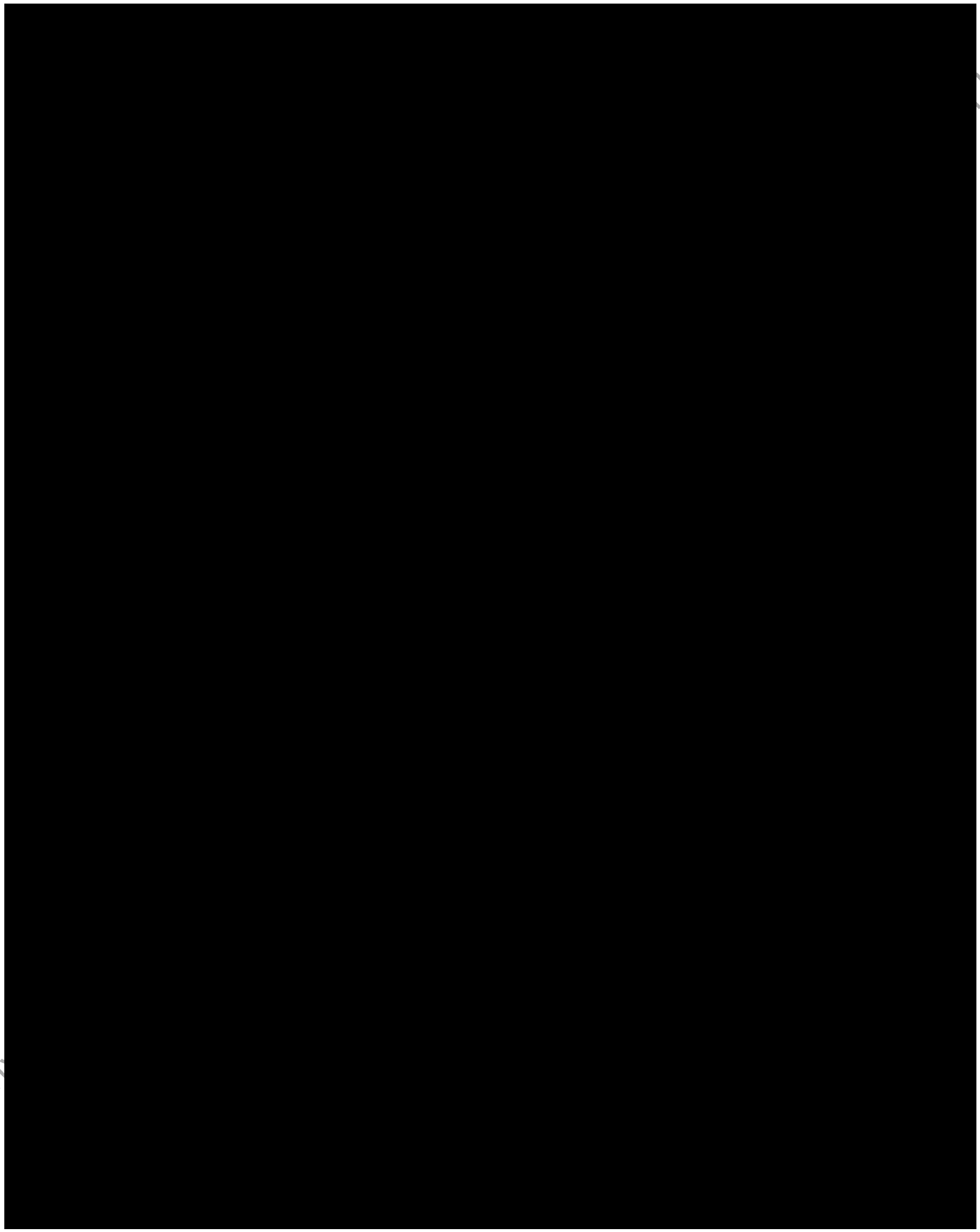

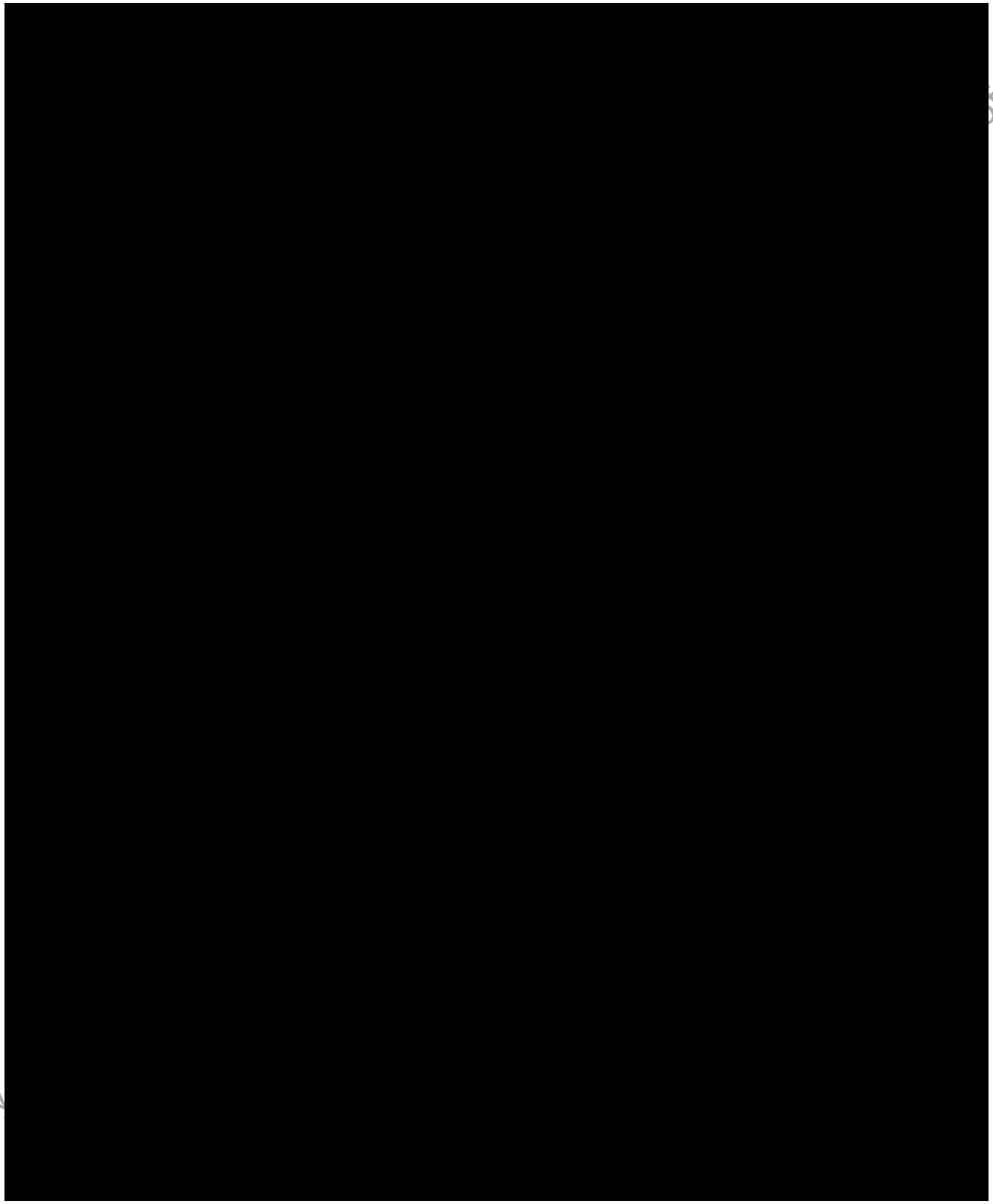

Document History

Version	Date	Comments
Initial version	2020/06/23	New document
Amendment 1.0	2020/09/04	The purpose of the changes made in this amendment are intended: 1. To address the correct information on the blood coagulation tests conducted prior to the treatment with TAK-672 2. To address the correct information on the timing and frequency of TAK-672 administration 3. To address the correct timing of blood collection and vital sign measurements 4. To address the correct information on the record retention period 5. To address the correct information on clinical laboratory tests 6. To address the correct information on screening criteria 7. To improve the readability of the paragraph
Amendment 2.0	2020/10/23	The purpose of the changes made in this amendment are intended: 1. To add the protocol signatory section for the investigator. 2. To revise the dose frequency of TAK-672 for subsequent bleeding episodes. 3. To address the footnote definition of "Japanese" patients to be enrolled in this study. 4. To address the addition of the new study analysis set (i.e. pharmacokinetic analysis set, PKS) and its definition. 5. To revise Table A (Schedule of Study Procedures and Assessments for the Qualifying Bleeding Episode) and to its related sections in the body of the text. 6. To describe the investigator consent to use of personal information.