Statistical Analysis Plan

NCT Number: NCT04941898

Title: ADYNOVATE SPECIAL DRUG USE RESULT SURVEY (Perioperative Administration)

Study Number: TAK-660-5002

Document Version and Date: Original / 30-Jan-2024

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.

Note; This document was translated into English as the language on original version was Japanese.

Statistical Analysis Plan

(final analysis)

Product name	ADYNOVATE Intravenous KIT
Survey title	ADYNOVATE SPECIAL DRUG USE RESULT SURVEY (perioperative administration)
Protocol No.	TAK660-5002
Sponsor	Takeda Pharmaceutical Company Limited.

Takeda Pharmaceutical Company Limited.
Director, Biostatistics
[redacted]

Year Month Day

Original: Prepared on January 30, 2024

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List of Terms and Abbreviations

- This drug: ADYNOVATE Intravenous Kit is abbreviated as this drug.
- Adverse Event: AE occurred after administration of this drug.
- Adverse reactions: An abbreviation for the term “adverse reactions/infections.” Adverse events other than those assessed as "not related" to this drug by the investigator. This statistical analysis plan uses “adverse drug reactions/infections” in the title and “adverse drug reactions” in the text and tables.
- Serious adverse events: Adverse events assessed as "serious" by the investigator. Events listed in the MedDRA code list (PT code) of the Important Medical Events List will be handled as serious even if the investigator's assessment is “non-serious.”
- "Related" to this drug: Adverse events other than those "not related" to this drug will be handled as "related," and adverse events "not related" to this drug will be handled as "not related."
- Summary statistics: A collective term for sample size, mean, standard deviation, maximum, minimum, and quartiles.
- Patients whose CRFs were not collected: Registered patients whose CRFs were not collected.
- Patients whose CRFs were collected: Registered patients whose CRFs were collected.
- Timing of onset of an adverse event (or adverse drug reaction, etc.): Calculated as the date of onset of the adverse event (or adverse drug reaction, etc.) - the start date of the first dose of this drug +1.
    - If the date of onset of an adverse event (or adverse drug reaction, etc.) is unknown, it will be calculated as January 1. However, if year of initial administration of this drug = year of onset of adverse event (or adverse drug reaction), it will be calculated as month and day of initial administration of this drug.
    - If the start date of an adverse event (or adverse drug reaction) is unknown, it will be counted as day 1. However, if the date of initial administration of this drug = the date of onset of an adverse event (or adverse reaction, etc.), this will be calculated as the date of initial administration of this drug.

Analysis Sets

In this survey, "patients evaluated for safety" and "patients evaluated for efficacy" will be set as analysis sets. This analysis set will be defined as follows:.

- Subjects evaluable for safety

Defined as "Patients receiving this drug who had no major protocol violations and whose safety could be evaluated." Specifically, patients with locked CRFs who meet any of the following criteria will be excluded from the safety analysis set.

- This drug not administered
- Enrollement outside the registration period
- Unknown presence/absence of adverse event

- Patients eligible for efficacy evaluation

Defined as "Patients evaluable for efficacy with no major protocol deviations among patients evaluated for safety." Patients who meet the following conditions among the patients evaluated for safety will be excluded from the patients evaluated for efficacy.

- Other than the target disease

Safety specification (Important identified risks, important potential risks, and important missing information)

- Important identified risks
    - Inhibitor Development: Any of the following:.
        - PT: Factor VIII inhibition
        - PT: Anti Factor VIII antibody positive
        - PT: Antibody test positive
        - PT: Anti factor VIII antibody increased
        - SMQ: Lack of efficacy/effect (Narrow)
    - Shock, anaphylaxis: Events falling under the SMQ of hypersensitivity (Narrow).
- Important potential risks: Not applicable
- Important missing information: Not applicable

1 Number of study sites and patients enrolled and patient composition

1.1 Subject Disposition (Patient Disposition Chart)

Analysis population:	All enrolled patients (patients enrolled)	
Analysis item:	Patients enrolled	
	Number of study sites	
	CRF not collected	
	CRF collected	
	Patients excluded from safety evaluation *	
	Reason for exclusion (multiple counting)	[this drug not administered, enrollment outside the registration period, unknown presence/absence of adverse events]
	Subjects evaluable for safety	
	Patients excluded from efficacy evaluation *	
	Reason for exclusion	[Other than the target disease]
	Patients eligible for efficacy evaluation	

Analytical method:

For the above analytical variables, the following analyses will be performed to prepare the patient composition chart.

For registered patients, the number of study sites is also shown. The same medical institution with different departments in the survey shall be counted as one medical institution. If there is no subject applicable to the reason for exclusion, 0 subject is displayed. In addition, the number of cases will be displayed for "cases whose CRFs have been collected," "cases whose CRFs have not been collected," "cases subject to safety evaluation," "cases excluded from safety evaluation," "cases subject to efficacy evaluation," and "cases excluded from efficacy evaluation." For patients excluded from the safety evaluation and efficacy evaluation, the number of patients by reason for exclusion will be tabulated and listed.

*"Patients excluded from safety evaluation" refers to locked patients who were excluded from the "patients eligible for safety evaluation." Similarly, "patients excluded from efficacy evaluation" refer to "patients excluded from efficacy evaluation" among the "patients evaluated for safety."

- Frequency tabulations

2 Patient characteristics

2.1 Patient characteristics

Analysis population:	Subjects evaluable for safety	
Analysis item:	Gender	[Male, female]
	Age (years)	[Min<= - <12, 12<= - <18, 18<= - <65, 65<= - <=Max]
	Presence/absence of a history of surgery	[Absent, present, unknown]
	Presence or absence of medical history	[Absent, present, unknown]
	Details of medical history (duplicate counting)	[Hepatitis C, Hepatitis B, and others]
	Complications	[Absent, present]
	Details of complications (duplicate counting)	[Hepatitis C, hepatitis B, chronic hepatitis,
	Liver disease	hepatic cirrhosis]
	Renal disease	[Nephrotic syndrome, glomerulonephritis, chronic renal failure]
	Other diseases	
	Hypersensitivity predisposition	[Absent, present, unknown]
	Height (cm)	[Min<= - <140, 140<= - <150, 150<= - <160, 160<= - <170, 170<= - <=Max, not measured]
	Weight (kg)	[Min<= - <50, 50<= - <65, 65<= - <=Max]
	Age at diagnosis of hemophilia A	[Min<= - <18, 18<= - <65, 65<= - <70, 70<= - <75, 75<= - <80, 80<= - <=Max]
	Severity of Hemophilia A	[Severe, Moderate, Mild]
	Family history of hemophilia A	[Absent, present, unknown]
	Details of family history of hemophilia A (overlapping tabulation)	[Father, mother (Hemophilia A, carrier), brother/sister, grandparent, etc.]
	History of FVIII inhibitor development	[Absent, present, unknown]
	Presence or absence of a history of treatment with this	[Absent, present, unknown]

	drug before perioperative management	
	Before the start of perioperative management (most recent)	[Absent, present, unknown]
	Presence or absence of treatment for hemophilia A	
	Before the start of perioperative management (most recent)	[ADYNOVATE, ADVATE, others]
	Treatment of hemophilia A [Product name] (Multiple counting)	
	Before the start of perioperative management (most recent)	[Prophylaxis, on-demand treatment, others.]
	Treatment of hemophilia A [Administration method] (overlapping tabulation)	
Analytical method:	For the above analytical variables, frequency tabulation of discrete data and summary statistics of continuous data will be calculated.	

3 Details of treatment

3.1 Surgery Performed

Analysis population:	Subjects evaluable for safety	
Analysis item:	Type of Surgery	[Major surgery, Minor surgery]
Analytical method:	Frequency of the number of types of surgery will be tabulated.	

3.2 Intraoperative status

Analysis population:	Subjects evaluable for safety	
Analysis item:	Intraoperative blood loss (mL)	
	Transfusion status	[Absent, present]
	Type of transfusion (duplicate counting)	[Packed red blood cells, packed platelets, fresh frozen plasma]
	Drainage	[Absent, present]
	Drain type (duplicate counting)	[Open, semi-closed and closed drains]
Analytical method:	For the above analytical variables, frequency tabulation of the number of discrete data and summary statistics based on the number of continuous data will be calculated for overall data, major surgery, and minor surgery.	

3.3 Administration status of this drug

Analysis population:	Subjects evaluable for safety
Analysis item:	Duration of treatment (days) Dose (IU)
Analytical method:	For the above analytical variables, summary statistics based on the number of events will be calculated. One form will be prepared for each preoperative, intraoperative, and postoperative period. At that time, summary statistics will be calculated by administration method (Bolus, continuous infusion) for before and during surgery. For postoperative cases, summary statistics will be calculated by administration method (Prophylaxis, continuous infusion, others).

3.4 Perioperative Management Completion Status

Analysis population:	Subjects evaluable for safety

Analysis item:	Perioperative Management Completion Status	[Disposition]
	Reason for discontinuation of administration (multiple counting)	[Due to the onset of adverse events, the patient did not visit the hospital before the completion of perioperative management, etc., due to insufficient effect, etc.]
Analytical method:	For the above analytical variables, frequency of the number of events will be tabulated.	

4 Matters related to safety

4.1 Status of Occurrence of Adverse Events and Adverse Drug Reactions/Infections

4.1.1 Occurrence of adverse events

Analysis population: Subjects evaluable for safety

Analysis item: Adverse Events

Analytical method: For the above analytical variable, the following analyses should be performed.

（1） Number of subjects with adverse events

（2） Number of AEs

（3） Incidence of adverse events

（4） Type of Adverse Event

The calculation method for each analysis is as follows.

[Number of subjects with adverse events]

- Number of patients with adverse events.

[Number of adverse events]

- Number of AEs that occurred. If the same adverse event occurs more than once in the same patient, the total number of events will be tabulated.

[Incidence of adverse events]

- Calculated as the number of patients with adverse events/number of patients evaluated for safety ×100.

[Type of adverse event]

- AEs will be coded using MedDRA/J. It will be roughly classified by SOC and tabulated by PT. SOC of "investigations" will be summarized by HLGT (Sort in ascending order of HLGT code, but do not output) and PT.
- Within SOC, the number of patients with adverse events and the incidence rate will be described using internationally agreed SOC order. A subject with multiple occurrences of an event within an SOC should be counted only once for that SOC.
- By PT, the number of patients with adverse events and the incidence will be described in ascending order of PT codes. A subject who experienced the same PT more than once should be counted as 1 subject with the PT.

4.1.2 Occurrence status of adverse reactions/infections

Analysis population: Subjects evaluable for safety

Analysis item: Adverse reactions, etc.

Analytical method: For the above analytical variable, the following analyses should be performed.

（1） No. of patients with adverse reactions, etc.

（2） Adverse drug reactions, etc. Number of events

（3） Incidence of adverse drug reactions, etc.

（4） Adverse reactions, etc. type

The calculation method for each analysis is as follows.

[Number of patients with adverse reactions]

- Number of patients with adverse reactions, etc.

[Number of adverse reactions]

- Number of adverse drug reactions, etc. that occurred. If the same adverse drug reaction, etc. occurs multiple times in the same patient, the total number of events will be tabulated.

[Incidence of adverse reactions]

- Number of patients with adverse drug reactions/Number of patients evaluated for safety ×100.

[Types of adverse reactions, etc.]

- Adverse drug reactions will be coded using MedDRA/J. It will be roughly classified by SOC and tabulated by PT. SOC of "investigations" will be summarized by HLGT (Sort in ascending order of HLGT code, but do not output) and PT.
- In SOC, the number of patients with adverse drug reactions, etc. and the incidence will be described in SOC internationally agreed order. A subject with multiple occurrences of an event within an SOC should be counted only once for that SOC.
- By PT, the number of patients with adverse drug reactions, etc. and the incidence will be described in ascending order of PT codes. A subject who experienced the same PT more than once should be counted as 1 subject with the PT.

4.1.3 Incident Status of Adverse Events and Adverse Drug Reactions/Infections Included in Safety Specifications

4.1.3.1 Incidences of adverse events included in the safety specifications (tabulation by risk)

Analysis population: Subjects evaluable for safety

Analysis item: Adverse events corresponding to important identified risks (Inhibitor development, shock/anaphylaxis) in the safety specifications

Stratification item: Total

Seriousness [Serious, non-serious]

Analytical method: For the above analytical variable, the following analyses should be performed for each risk and each stratum of the stratification factor. The risks to be included are defined as described in the Safety Specification (Important Identified Risks).

[Number of subjects with adverse events]

- Number of patients with adverse events.

[Number of adverse events]

- Number of AEs that occurred. If the same adverse event occurs more than once in the same patient, the total number of events will be tabulated.

[Incidence of adverse events]

- Calculated as the number of patients with adverse events/number of patients evaluated for safety ×100.

[Type of adverse event]

- AEs will be coded using MedDRA/J. It will be roughly classified by SOC and tabulated by PT. SOC of "investigations" will be summarized by HLGT (Sort in ascending order of HLGT code, but do not output) and PT.
- Within SOC, the number of patients with adverse events and the incidence rate will be described using internationally agreed SOC order. A subject with multiple occurrences of an event within an SOC should be counted only once for that SOC. However, if there are differences in the category of each stratification item, the subject will be counted as 1 subject in each category. For the last stratification item, 1 will be adopted according to the priority.
- By PT, the number of patients with adverse events and the incidence will be described in ascending order of PT codes. A subject who experienced the same PT more than once should be counted as 1 subject with the PT. However, if there are differences in the category of each stratification item, the subject will be counted as 1 subject in each category. For the following stratification items, 1 item will be adopted in accordance with the priority order.

Seriousness: Serious → Non-serious

4.1.3.2 Incident Status of Adverse Reactions/Infections Included in Safety Specifications (Tabulation by Risk)

Analysis population: Subjects evaluable for safety

Analysis item: Adverse drug reactions, etc. corresponding to important identified risks (Inhibitor development, shock/anaphylaxis) in the safety specifications

Stratification item: Total

Seriousness [Serious, non-serious]

Analytical method: For the above analytical variable, the following analyses should be performed for each risk and each stratum of the stratification factor. The risks to be included are defined as described in the Safety Specification (Important Identified Risks).

[Number of patients with adverse reactions]

- Number of patients with adverse reactions, etc..

[Number of adverse reactions]

- Number of adverse drug reactions, etc. that occurred. If the same adverse drug reaction, etc. occurred multiple times in the same patient, the total number of events will be tabulated.

[Incidence of adverse reactions]

- Number of patients with adverse drug reactions/Number of patients evaluated for safety ×100.

[Type of adverse reactions, etc.]

- Adverse drug reactions will be coded using MedDRA/J. It will be roughly classified by SOC and tabulated by PT. SOC of "investigations" will be summarized by HLGT (Sort in ascending order of HLGT code, but do not output) and PT.
- In SOC, the number of patients with adverse drug reactions, etc. and the incidence will be described in SOC internationally agreed order. A subject with multiple occurrences of an event within an SOC should be counted only once for that SOC. However, if there are differences in the category of each stratification item, the subject will be counted as 1 subject in each category. For the last stratification item, 1 will be adopted according to the priority.
- By PT, the number of patients with adverse drug reactions, etc. and the incidence will be described in ascending order of PT codes. A subject who experienced the same PT more than once

should be counted as 1 subject with the PT. However, if there are differences in the category of each stratification item, the subject will be counted as 1 subject in each category. For the following stratification items, 1 item will be adopted in accordance with the priority order.

Seriousness: Serious → Non-serious

4.2 Status of occurrence of adverse events, adverse drug reactions, and infections in patients excluded from safety evaluation

4.2.1 Status of adverse events in patients excluded from safety evaluation

Analysis population: Patients excluded from safety evaluation

Analysis item: Adverse Events

Analytical method: For the above analytical variable, analyses should be performed in the same manner as in Section 4.1.1.

4.2.2 Occurrence Status of Adverse Reactions/Infections in Patients Excluded from Safety Evaluation

Analysis population: Patients excluded from safety evaluation

Analysis item: Adverse reactions, etc.

Analytical method: For the above analytical variable, analyses should be performed in the same manner as in Section 4.1.2.

4.3 Occurrence Status of Adverse Events and Adverse Drug Reactions/Infections by Seriousness, Time to Onset, Outcome, and Causal Relationship with this drug

4.3.1 Occurrence of adverse events by seriousness, time of onset, and outcome

Analysis population: Subjects evaluable for safety

Analysis item: Adverse Events

Stratification item: Total

Seriousness	[Serious, non-serious]
Timing of onset (day)	[1<= - <=5, 6<= - <=10, 11<= - <=20, 21<= - <=30, 31<= - <=Max]
Outcome	[Recovered/resolved, resolving, not recovered, recovered with sequelae, fatal (due to this event), unknown]

Analytical method: For the above analysis set, the following analyses should be performed for each stratum of the stratification factor.

（1） Number of subjects with adverse events

（2） Number of AEs

（3） Incidence of adverse events

（4） Type of Adverse Event

The calculation method for each analysis is as follows.

[Number of subjects with adverse events]

- Number of patients with adverse events.

[Number of adverse events]

- Number of AEs that occurred. If the same adverse event occurs more than once in the same patient, the total number of events will be tabulated.

[Incidence of adverse events]

- Calculated as the number of patients with adverse events/number of patients evaluated for safety ×100.

[Type of adverse event]

- AEs will be coded using MedDRA/J. It will be roughly classified by SOC and tabulated by PT. SOC of "investigations" will be summarized by HLGT (Sort in ascending order of HLGT code, but do not output) and PT.
- Within SOC, the number of patients with adverse events and the incidence rate will be described using internationally agreed SOC order. A subject with multiple occurrences of an event within an SOC should be counted only once for that SOC. However, for the same SOC, 1 case shall be adopted according to the order of priority at the end.
- By PT, adverse events The number of patients with adverse events and the incidence will be described in ascending order of PT codes. A subject who experienced the same PT more than once should be counted as 1 subject with the PT. However, for the same PT, adopt 1 case in the following order of priority.

  Seriousness: Serious → Non-serious

  Time of onset: 1-5 days → 6-10 days →11 to 20 days →21 to 30 days → ≥ 31 days

  Outcome: Death (due to this event) → recovered with sequelae → not recovered → recovering → recovered → unknown

4.3.2 Occurrence Status of Adverse Reactions/Infections by Seriousness, Onset Timing, and Outcome

Analysis population:	Subjects evaluable for safety	
Analysis item:	Adverse reactions, etc.	
Stratification item:	Total	
	Seriousness	[Serious, non-serious]
	Timing of onset (day)	[1<= - <=5, 6<= - <=10, 11<= - <=20, 21<= - <=30, 31<= - <=Max]
	Outcome	[Recovered/resolved, resolving, not recovered, recovered with sequelae, fatal (due to this event), unknown]

Analytical method: For the above analysis set, the following analyses should be performed for each stratum of the stratification factor.

（1） No. of patients with adverse reactions, etc.

（2） Adverse drug reactions, etc. Number of events

（3） Incidence of adverse drug reactions, etc.

（4） Adverse reactions, etc. type

The calculation method for each analysis is as follows.

[Number of patients with adverse reactions]

- Number of patients with adverse reactions, etc..

[Number of adverse reactions]

- Number of adverse drug reactions, etc. that occurred. If the same adverse drug reaction, etc. occurred multiple times in the same patient, the total number of events will be tabulated.

[Incidence of adverse reactions]

- Number of patients with adverse drug reactions/Number of patients evaluated for safety ×100.

[Type of adverse reactions, etc.]

- Adverse drug reactions will be coded using MedDRA/J. It will be roughly classified by SOC and tabulated by PT. SOC of "investigations" will be summarized by HLGT (Sort in ascending order of HLGT code, but do not output) and PT.
- In SOC, the number of patients with adverse drug reactions, etc. and the incidence will be described in SOC internationally agreed order. A subject with multiple occurrences of an event within an SOC should be counted only once for that SOC. However, for the

same SOC, 1 case shall be adopted according to the order of priority at the end.

- By PT, adverse drug reactions, etc. The number of patients with adverse drug reactions and the incidence shall be described in ascending order of PT codes. A subject who experienced the same PT more than once should be counted as 1 subject with the PT. However, for the same PT, adopt 1 case in the following order of priority.
  Seriousness: Serious → Non-serious
  Time of onset: 1-5 days → 6-10 days →11 to 20 days →21 to 30 days → ≥ 31 days
  Outcome: Death (due to this event) → recovered with sequelae → not recovered → recovering → recovered → unknown

4.4 Factors that may affect the safety

4.4.1 Onset status of adverse reactions/infections by patient background and treatment factors

Analysis population:	Subjects evaluable for safety	
Analysis item:	Adverse reactions, etc.	
Stratification item:	Gender	[Male, female]
	Age (years)	[Min<= - <12, 12<= - <18, 18<= - <65, 65<= - <=Max]
	Presence/absence of a history of surgery	[Absent, present, unknown]
	Presence or absence of medical history	[Absent, present, unknown]
	Complications	[Absent, present]
	Hypersensitivity predisposition	[Absent, present, unknown]
	Severity of Hemophilia A	[Severe, Moderate, Mild]
	History of FVIII inhibitor development	[Absent, present, unknown]
	Presence or absence of a history of treatment with this drug before perioperative management	[Absent, present, unknown]
	Before the start of perioperative management (most recent)	[Absent, present, unknown]

Presence or absence of treatment
for hemophilia A

Analytical method: For the above analysis set, the following analyses should be performed for each stratum of the stratification factor.

（1） Number of patients with adverse reactions, etc.

（2） Incidence of adverse drug reactions

The calculation method for each analysis is as follows.

[Number of patients with adverse reactions]

- Number of patients with adverse reactions, etc.

[Incidence of adverse reactions]

Number of patients with adverse drug reactions/Number of patients evaluated for safety ×100.

4.4.2 Occurrence Status of Adverse Reactions/Infections by Age

Analysis population:	Subjects evaluable for safety	
Analysis item:	Adverse reactions, etc.	
Stratification item:	Age (years)	[Min<= - <18, 18<= - <65, 65<= - <70, 70<= - <75, 75<= - <80, 80<= - <=Max]

Analytical method: For the above analytical variable, the same analyses as those in Section 4.1.2 will be performed for each stratum of the stratification factor.

5 Efficacy

5.1 hemostatic effect

Analysis population:	Patients eligible for efficacy evaluation
Analysis item:	hemostatic effect
At evaluation point:	During surgery, on postoperative Day 1, and at the time of completion (or discontinuation) of postoperative perioperative management
Evaluation Category:	[Markedly effective, effective, slightly effective, ineffective]
Analytical method:	For the above analytical variables, frequency will be tabulated for the number of patients evaluated and the number of events at each evaluation time point.

6 Occurrence Status of Adverse Reactions/Infections in Additional Pharmacovigilance Plan

6.1 Incidences of ADRs and infections included in additional pharmacovigilance plan (Attached Form 12)

Analysis population:	Subjects evaluable for safety
Analysis item:	Adverse reactions, etc. corresponding to safety specifications (Important identified risks, important potential risks, and important missing information)
Stratification item:	Seriousness [Serious, non-serious]
Analytical method:	For the above analytical variables, the following analyses should be performed for each of the subgroups of the stratification factors in accordance with (Note) 1~4 in Attached Form 12 to PSEHB/PED Notification No. 0325-10 dated March 25, 2020. （1） Number of patients with events and incidence The order of description of risk names and risk names shall follow the definitions described in the Safety Specification (Important identified risks, important potential risks, and important missing information).

7 Case Summary for Post-marketing Surveillance, etc.

7.1 Case summary in post-marketing surveillance, etc. (Attached Form 16)

Analysis population:	Subjects evaluable for safety
Analysis item:	Case No. Name of medical institution Gender Age Reason for use (Disease code, disease name) Comorbidity (Disease code, disease name) Route of administration Maximum dose Mean dose Unit Duration of use (duration of this drug treatment) Concomitant medications (Drug code, drug name) Degree of effect Adverse reactions (Disease code, disease name, outcome) CRF No. Dropout Reason for dropout
Analytical method:	A list of the above analysis items will be prepared in accordance with the reexamination data entry file preparation guideline specified in the Notification No. 1119 (3) of the Pharmaceutical Evaluation Division, PSEHB dated November 19, 2020.

Preparation history (version control)

Version	Date	Author/Reporter	Comments
Original Version	2024.1.30	[redacted]	Preparation of initial version

[Appendix 1] Comparison table of changes

Page	Before amendment	After amendment	Reason for change