Clinical Study Protocol

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

Study Number: TAK-660-5002

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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.

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

PROTOCOL FOR SPECIAL DRUG USE RESULT SURVEY
ADYNOVATE SPECIAL DRUG USE RESULT SURVEY
(Perioperative Administration)

Sponsor	**Takeda Pharmaceutical Company Limited**
Protocol No.	**TAK660-5002**
Version No.	**4**
Date of preparation	**23 August 2023**

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1.0 BACKGROUND OF THE SURVEY

This special drug use result survey (hereinafter, "this survey") has been planned to investigate the safety and efficacy of Adynovate Intravenous (hereinafter, "Adynovate") administered perioperatively under actual use conditions in routine clinical practice although no specific safety issues were identified in the phase 3 clinical study (Study 261204) of Adynovate investigating the efficacy and safety of a PEG-rFVIII (pegylated, full-length, recombinant coagulation factor VIII) product (BAX855) when administered perioperatively in patients with severe hemophilia A. This survey will be conducted in compliance with the Good Post-marketing Study Practice Ordinance (GPSP) Ordinance and related regulatory requirements.

2.0 OBJECTIVE

To investigate the safety and efficacy of Adynovate administered in the perioperative period of surgeries or other invasive procedures such as tooth extractions under actual clinical use conditions.

3.0 SAFETY SPECIFICATIONS

Development of inhibitors, shock, and anaphylaxis

4.0 PLANNED SAMPLE SIZE AND RATIONALE

4.1 Planned Sample Size

10 patients (However, 15 surgeries are planned to be included.)

* Patient registration at each site will be continued until the end of the patient registration period even after the target number of patients is reached.

4.2 Rationale

Although there are limited national statistics on the number and details of surgeries performed in patients with hemophilia, the number of surgeries performed in patients with hemophilia A was estimated to be approximately 120 per year using a commercial database. On the basis of the above data and in consideration of the patient registration period as well as the estimated share of Adynovate (approximately 7%) for perioperative administration, the target sample size was set at "10 patients."

In "Advate Special Drug Use Result Survey for Perioperative Administration (Including Tooth Extractions)," data on 74 surgeries in 58 patients were collected, including 11 surgeries in patients aged under 12 years. It is therefore estimated that data on approximately 2 patients aged under 12 years and 15 surgeries (11 major and 4 minor surgeries) can be collected from the planned 10 patients.

5.0 TARGET PATIENTS

Patients with coagulation factor VIII (hereinafter, "FVIII") deficiency who received

Adynovate for surgery/procedure on or after the start date of this survey

6.0 DOSAGE AND ADMINISTRATION

Adynovate to be dissolved in 5 mL of the supplied diluent, and slowly injected intravenously. The infusion rate should not exceed 10 mL/min.

The usual dosage is 10 to 30 IU/kg body weight per dose. The dosage may be adjusted according to the patient's condition.

< Precautions for Dosage and Administration >

For perioperative use, the dose and dosing frequency should be adjusted to maintain FVIII at the required or higher level depending on the surgery/procedure.

Approximate Dose and Dosing Frequency in the Perioperative Period

Type of Surgery	Required FVIII Level (% or IU/dL)	Dose (IU/kg)	Dosing Frequency
Minor Including tooth extractions	30-60	15-30	Repeat every 8-24 hours until the bleeding is resolved
Major Intracranial, intra-abdominal, or intrathoracic surgery, joint replacement surgery	80-100	40-50	Repeat every 8-24 hours until wound healing

Refer to the package insert.

7.0 PLANNED NUMBER OF MEDICAL INSTITUTIONS BY DEPARTMENT

Department of Hematology, Department of Pediatrics, and other departments

Approximately 10 medical institutions

8.0 METHODOLOGY

8.1 Observation Period

From the start to completion of perioperative management, [*1] in principle

[*1] Perioperative management: Management from administration before, during, and after the surgery to completion of the surgical treatment.

8.2 Contract With Medical Institutions

Prior to the conduct of this survey, Takeda Pharmaceutical Company Limited will conclude a written contract with medical institutions.

8.3 Patient Registration Method

Patients will be registered through a “central registration system” by fax.

For patients who were prescribed Adynovate, the investigator/subinvestigator will send the “Patient Registration Form” to the central registration center by fax by Day 30 after

the start of Adynovate administration for perioperative management (with the day of the initial administration of Adynovate defined as “Day 0” and the next day defined as “Day 1”), in principle. Note that a patient may be registered retrospectively if he/she meets the conditions shown in “5.0 Target Patients” even if the patient has received Adynovate for surgery/procedure at a contract medical institution before concluding the contract. If Adynovate is used for a different surgery/procedure in the same patient, the use will be newly registered as a separate episode (1 episode/time).
(For example, if 1 patient undergoes 2 surgeries using Adynovate, 2 episodes will be registered in 1 patient.)

8.4 Preparation and Submission of Survey Forms

Paper survey forms will be used to collect information.
Investigators/subinvestigators will prepare survey forms for all registered patients promptly after necessary observation. If perioperative administration of Adynovate cannot be documented because of prior cancellation of surgery, this should be described. (No entry is required for the subsequent items.)
If an adverse event leads to discontinuation of Adynovate during the observation period, observation should be continued to the extent feasible after discontinuation of administration until resolution of the adverse event, and the survey form should be prepared.
The investigator will sign or affix the name and seal on the survey forms to ensure the accuracy and reliability of the data in the survey forms and promptly submit them to Takeda Pharmaceutical Company Limited.

9.0 PLANNED SURVEY PERIOD

Survey period: June 2021 to 31 December 2023
Patient registration period: June 2021 to 31 August 2023
Survey completion date (final analysis completion date): February 2024 (planned)

10.0 SURVEY ITEMS

Investigators/subinvestigators will enter the following information in the patient registration form and survey form:

10.1 Patient Registration

1) Survey items
Patient identification number (optional), sex, date of birth or age (at the start of perioperative management with Adynovate), (planned) start date of administration of Adynovate for perioperative management, and name of the (planned) surgery

(If the same patient is registered for the second time or later in this survey, the previous patient identification number [optional] or the [planned] start date of administration of Adynovate for the previous perioperative management)

2) Timing of the survey
At the time of patient registration

10.2 Patient Background

1) Survey items
Height, body weight, complications (presence/absence and details), medical history (presence/absence and details), predisposition to hypersensitivity (presence/absence and details), history of surgery (presence/absence and details), pregnancy status (women only), time of diagnosis of hemophilia A, severity of hemophilia A, family history of hemophilia A (presence/absence and details), history of development of FVIII inhibitors, history of administration of Adynovate before the perioperative management, and (latest) hemophilia A treatment before the start of perioperative management (presence/absence and details)

2) Timing of the survey
At the start of perioperative management

10.3 Details of the Treatment

1) Survey items
Status of administration of Adynovate (timing of administration, method of administration, dose, date and time of treatment initiation, and date and time of treatment completion [or discontinuation]), status of administration of FVIII formulations other than Adynovate or bypassing drug products (presence/absence and details), and status of treatment with concomitant drugs (other than FVIII formulations or bypassing drug products; presence/absence, name of drug product, and purpose of treatment)

2) Timing of the survey
From the start of perioperative management to the completion of perioperative management (or discontinuation of treatment)

10.4 Details of the Surgery

1) Survey items
Diagnosis of the disease requiring surgery, operative technique (details of the surgery), type of surgery (major/minor surgery: see Appendix 1), whether or not the surgery is scheduled (emergency/elective surgery), date and time of the surgery, amount of bleeding during surgery, blood transfusion (presence/absence and details), and drainage (presence/absence and details)

2) Timing of the survey
At the time of the surgery

10.5 Efficacy Assessment

1) Survey items
Evaluation of hemostatic efficacy (see Appendix 2)
2) Timing of the survey
During surgery, on postoperative Day 1, and at completion of perioperative management (or at discontinuation of administration)

10.6 Test/Observation Items

Information will be entered in the survey form when each test/observation is performed at each timing of survey under actual use conditions in routine clinical practice.

10.6.1 Laboratory Tests

1) Test items
FVIII activity (FVIII:C), FVIII inhibitors, and FVIII recovery
2) Timing of the survey
Before the start of perioperative management, from the start of perioperative management to the time of testing upon completion of perioperative management (or discontinuation of treatment)

10.6.2 Other Observations

1) Observation items
Date of completion of perioperative management (or discontinuation of treatment) and reason for discontinuation of treatment (in the case of premature discontinuation)
2) Timing of the survey
At the completion of perioperative management (or discontinuation of treatment)

10.7 Adverse Events

1) Survey items
Presence or absence of adverse events (see Table 1), adverse event terms, date of onset, seriousness and the reason for assessing as serious (see Table 2), cause of discontinuation of Adynovate, date of outcome assessment, outcome, causal relationship with Adynovate [*2] (see Table 3)
If the outcome is assessed as not recovered or unknown, a follow-up investigation should be performed to the extent feasible.

[*2] If the event is assessed as unrelated to Adynovate, the rationale for that assessment will be collected.

2) Timing of the survey

From the start of perioperative management to the completion of perioperative management (or discontinuation of treatment)

If the perioperative management period is short (eg, for tooth extractions), the presence/absence of adverse events will be observed until Day 30 after surgery, as a rule.

Table 1 Definition of Adverse Events

An adverse event (AE) is any untoward medical occurrence in a patient administered a pharmaceutical product. It need not have a causal relationship with this treatment. An AE can therefore be any unfavorable and unintended sign (including abnormal laboratory findings), symptom, or disease temporally associated with the use of a medicinal product, whether or not considered related to the medicinal product.

AE: adverse event

Table 2 Criteria for Assessment of Seriousness

1. Results in death 2. Is life-threatening The term "life-threatening" refers to an event in which the patient was at risk of death at the time of the event; it does not refer to an event which hypothetically might have caused death if it was more severe 3. Requires inpatient hospitalization or prolongation of existing hospitalization (hospitalization/prolongation of hospitalization) 4. Results in persistent or significant disability/incapacity (disability) 5. Results in congenital anomaly/birth defect (congenital anomaly) 6. May not be immediately life-threatening or result in death or hospitalization but may require intervention to prevent one of the outcomes listed in 1 to 5 above or may jeopardize the patient

* If an AE listed in the "Takeda Medically Significant AE List" is reported, Takeda Pharmaceutical Company Limited will handle it as a serious adverse event.

AE: adverse event

Table 3 Criteria for Assessment of Causal Relationship Between Adverse Events and Adynovate

Assessment	Criteria
Related	An AE that has a temporal correlation to the drug (including the course after discontinuation of the drug) or for which causal relationship to the drug cannot be ruled out because there is at least a reasonable possibility of the involvement of the drug, despite possible contribution of other factors, such as underlying diseases, complications, or concomitant drugs or procedures
Not related	An AE that does not have a temporal correlation to the drug or that can reasonably be explained by other factors, such as underlying disease, complications, or concomitant drugs or procedures

AE: adverse event

11.0 ANALYSIS ITEMS AND METHODS

11.1 Matters Related to Patient Disposition

The number of registered patients, number of patients whose survey forms have been collected, number of patients evaluated for safety and efficacy, number of patients excluded from evaluation, reasons for exclusion, and other information will be tabulated.

11.2 Patient Background

Patient background such as age and complications will be tabulated.

11.3 Details of Treatment

Status of administration of Adynovate will be tabulated.

11.4 Matters Related to Safety

The following analyses will be performed in the patients evaluated for safety. Adverse events will be coded using MedDRA (Medical Dictionary for Regulatory Activities)/J and tabulated and summarized by Preferred Term (PT) and System Organ Class (SOC).

11.4.1 Occurrence of Adverse Events

Frequency tabulation will be performed for adverse events occurring during the observation period by type, seriousness, and causal relationship to Adynovate.

11.4.2 Factors Expected to Affect the Safety

Frequency tabulation will be performed for adverse reactions occurring during the observation period for each stratum of patient background factors (eg, age).

11.5 Matters Related to Efficacy

The following tabulations will be performed in patients evaluated for efficacy.

11.5.1 Hemostatic Efficacy

Assessments of hemostatic efficacy (see Appendix 2) during surgery, after surgery, and on Day 1 and later after surgery (at the completion of perioperative management on Day 1 after surgery or later [or at discontinuation of treatment]) will be tabulated.

12.0 REGISTRATION OF SURVEY INFORMATION

Information about this survey will be registered on the following public websites prior to the start of this survey:

- Japan Registry of Clinical Trials
- Clinical trials registry system of the National Institutes of Health (ClinicalTrials.gov)

13.0 ORGANIZATIONAL STRUCTURE

13.1 Organizational Chart for Operations for Postmarketing Surveillances

See Appendix.

14.0 CONTRACT ORGANIZATIONS

(1) [redacted]

Responsibilities: Operations of the central registration center, data management operations, storage of records, support operations related to postmarketing surveillance, and medical writing operations

(2) [redacted]

Responsibilities: Operations related to monitoring

(3) [redacted]

Responsibilities: Statistical analysis operations

15.0 MILESTONES FOR EVALUATION OF THE SURVEY IMPLEMENTATION STATUS AND RESULTS OBTAINED OR FOR REPORTING TO THE PHARMACEUTICALS AND MEDICAL DEVICES AGENCY AND THEIR RATIONALES

Refer to “2. Summary of Pharmacovigilance Plan” in the risk management plan.

16.0 ADDITIONAL MEASURES THAT MAY BE TAKEN ON THE BASIS OF THE SURVEY RESULTS AND THE CRITERIA FOR THE INITIATION

Refer to “2. Summary of Pharmacovigilance Plan” in the risk management plan.

17.0 OTHER NECESSARY INFORMATION

17.1 Revision of the Protocol

This protocol will be reviewed and revised if necessary as the following information is

collected during the implementation period: progress status, occurrence of adverse reactions and serious adverse reactions that cannot be predicted from the precautions, whether the incidence of specific adverse reactions increases, appropriateness of survey items, and other data. If, for example, partial changes in dosage and administration or indications are approved during the implementation period, the necessity of the revision of this protocol will be discussed as needed and it will be revised if necessary.

17.2 Measures to Be Taken in Case of Any Problem or Question

If case of any problem in the safety or efficacy, the data will be closely examined and appropriate measures will be considered.

APPENDIX 1 DEFINITIONS OF TYPES OF SURGERY

Surgical procedures are deemed as major or minor on the basis of the following definitions and examples:

Table 4 Definitions and Examples of Types of Surgery

Type	Definition	Example
Major	• A surgery that is expected to take more than 3 days from the surgery/intervention to hemostasis or recovery • A surgery requiring moderate or deep sedation, general anesthesia, or major conduction block to ensure patient comfort	• Major orthopedic surgery (eg, joint replacement) • Major abdominal surgery • Intracranial surgery • Cardiovascular surgery • Other surgeries including those with a high risk of major blood loss or blood influx into anatomically closed zones
Minor	• A surgery that is expected to take not more than 3 days from the surgery/intervention to hemostasis or recovery • A surgery that can be safely and comfortably performed with minimal preoperative medication or intraoperative sedation for patients under local or surface anesthesia	• Skin lesion removal • Arthroscopy and arthroscopic surgery (eg, synovectomy) • Simple dental procedures or tooth extractions • Placement and/or removal of central venous catheter • Synoviorthesis and arthrocentesis

APPENDIX 2 CRITERIA FOR EFFICACY ASSESSMENT

Intraoperative hemostatic efficacy (see Table 5), postoperative hemostatic efficacy (see Table 6), and hemostatic efficacy at the completion of perioperative management on postoperative Day 1 and later (see Table 7) will be evaluated.

Table 5 Rating Scale for Intraoperative Hemostatic Efficacy

Rating	Criteria
Excellent	Intraoperative blood loss is equal to or less than (≤100%) the values expected for a non-hemophilic patient population undergoing the same type of procedure.
Good	Intraoperative blood loss is increased by up to 50% (101%-150%) compared with the values expected for a non-hemophilic patient population undergoing the same type of procedure.
Fair	Intraoperative blood loss is increased by more than 50% (>150%) compared with the values expected for a non-hemophilic patient population undergoing the same type of procedure.
Poor	Proper administration of the product fails to provide sufficient therapeutic effect, and bleeding does not stop. Rescue therapy with Advate *3 or other replacement therapy is required.

*3 Administration of FVIII products other than Adynovate or bypassing agents required for adequate hemostasis.

Table 6 Rating Scale for Postoperative Hemostatic Efficacy (Postoperative Day 1)

Rating	Criteria
Excellent	Postoperative hemostatic efficacy of Adynovate is at least as good as that expected for a non-hemophilic patient population undergoing the same type of surgical procedure.
Good	Postoperative hemostatic efficacy of Adynovate is probably as good as that expected for a non-hemophilic patient population undergoing the same type of surgical procedure.
Fair	Postoperative hemostatic efficacy of Adynovate is apparently inadequate compared with comparable procedures, although postoperative hemostasis is maintained. Rescue therapy with Advate or other replacement therapy is not required.
Poor	Proper administration of the product fails to provide sufficient therapeutic effect, and bleeding does not stop. Rescue therapy with Advate or other replacement therapy is required.

Table 7 Rating Scale for Postoperative Hemostatic Efficacy (Upon Completion of Perioperative Management [or Discontinuation of Treatment])

Rating	Criteria
Excellent	Hemostatic efficacy of Adynovate on postoperative Day 1 and later is at least as good as that expected for a non-hemophilic patient population undergoing the same type of surgical procedure.
Good	Hemostatic efficacy of Adynovate on postoperative Day 1 and later is probably as good as that expected for a non-hemophilic patient population undergoing the same type of surgical procedure.
Fair	Hemostatic efficacy of Adynovate on postoperative Day 1 and later is apparently inadequate compared with comparable procedures, although postoperative hemostasis is maintained. Rescue therapy with Advate or other replacement therapy is not required.
Poor	Proper administration of the product fails to provide sufficient therapeutic effect, and bleeding did not stop on postoperative Day 1 and later. Rescue therapy with Advate or other replacement therapy is required.

Document History

Version	Date	Comments
original version	2021/06/30	New document
2nd version	2021/07/21	Minor changes to “10.1 Patient Registration”
3rd version	2023/05/15	Minor changes to “13.0 ORGANIZATION STRUCTURE,” addition to “14.0 CONTRACT ORGANIZATIONS,” and the attachment of Appendix 2
4th version	2023/08/23	The addition of the survey completion date (final analysis completion date) to “9.0 PLANNED SURVEY PERIOD” and minor changes to “14.0 CONTRACT ORGANIZATIONS”