Clinical Study Protocol

NCT Number: NCT03169972

Title: ADYNOVATE Drug Use-Results Survey

Study Number: 261601

Document Version and Date: Version 6.0 / 23-Aug-2023

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DRUG USE-RESULTS SURVEY

PRODUCT: ADYNOVATE

PROTOCOL NUMBER: 261601

VERSION 6: 23 Aug 2023

Drug Name	rurioctocog alfa pegol (recombinant)
Marketing Authorization Holder	**Takeda Pharmaceutical Company Limited** 4-1-1 Dosho-machi Chuo-ku, Osaka, Japan
Version	6.0

SUMMARY OF CHANGES

Protocol Versions		
Summary of Change(s) since Last Version of Approved Protocol		
Version Number **6.0**	**Version Date** **21 Dec 2020**	
Description of Change		**Section(s) Affected by Change**
Version number changed		Cover page 1
Added 'Completion date of survey'		Section 3.5 Estimated implementation period of the survey

See Appendix for protocol history, including all versions

TABLE OF CONTENTS

1. PURPOSE

This survey will be conducted to understand the following items in the actual clinical use of ADYNOVATE in patients:

1) Unexpected adverse drug reactions
2) Occurrence of adverse drug reactions in the actual clinical use
3) Factors that may affect safety and efficacy
4) Occurrence of Factor VIII inhibitor development in patients with coagulation factor VIII deficiency (hereinafter hemophilia A)
5) Safety and efficacy for hemophilia A patients who received routine prophylactic therapy and on-demand therapy

2. SAFETY SPECIFICATION

1) Inhibitor development (Factor VIII inhibitor)
2) Shock, anaphylaxis

3. IMPLEMENTATION PLAN FOR THE SURVEY (DRAFT)

3.1 Estimated number of patients in the survey and rationale

Estimated number of patients for the survey:

-Previously treated patients (PTPs) with haemophilia A: 140 patients

-Previously untreated patients (PUPs) with haemophilia A: 25 patients

Rationale:

Of the patients with Haemophilia A in Japan, approximately 4000 receive genetically recombinant blood coagulation factors, of whom approximately 10% are expected to switch from the conventional preparation to ADYNOVATE in the period of 3 years after launching. However, launching and developments of other extended half-life recombinant human coagulation factor VIII (rFVIII) products for Haemophilia A have been progressing. The number of patients who are actually going to receive ADYNOVATE is expected to fall below approximately one-half of the estimated number described above. Therefore, the target patient number was set to 140 PTPs as the number of collectable cases for ADYNOVATE safety examination. For PUPs, statistics show the birthrate of Hemophilia A patients to be 1 out of 5000 males ("Basics and Clinical of Hemophilia", Shirahata) and the number of annual male births to be 515,000 (Demographic Statistics 2015), providing an estimated annual number of births with Hemophilia A of 103. With a percentage of severe and moderate hemophilia A patients of 79.3% (2,137/2,696) (Nationwide Survey on Coagulation Disorders 2015), it is estimated that there are 82 new patients receiving FVIII annually. However, the target number of PUPs for 3 years after approval of SNDA for pediatrics is estimated at approximately 10 % of the above –indicated number of patients treated with ADYNOVATE in view of the progress of clinical development or launch of similar products by competitors nowadays.

3.2 Target patients

Hemophilia A patients who receive ADYNOVATE in the real world clinical setting are eligible for enrollment in this survey. This includes previously treated patients with Factor VIII deficiency (PTPs), and all previously untreated patients with Factor VIII deficiency (PUPs) who are treated with ADYNOVATE at the contracting medical institutions.

ADYNOVATE will be used per the Japan prescribing information (PI).

- Indications: Suppression of bleeding tendency in patients with factor VIII deficiency.

- Administration method and dosage: ADYNOVATE is reconstituted with 5 mL of the attached reconstitution diluent and administered by slow intravenous injection. Do not infuse any faster than 10 mL per minute.

  Normally, administer 10 - 30 international units per kg per body weight per time. Adjust the dose based on the patient's condition.

  For routine dosing, normally, for adults and children ≥ 12 years, administer 40-50 international units per kg body weight per time twice a week. May increase a dose to 60 international units per kg body weight based on the patient's condition. For children < 12 years, administer 40-60 international units per kg body weight per time twice a week. May increase a dose in the range not exceeding 80 international units per kg body weight based on the patient's condition.

3.3 Estimated number of centers (departments)

Approximately 100 departments (or centers) are expected to be involved nationwide, including internal medicine (hematology) department and others.

3.4 Survey Method

This survey is conducted using EDC to collect data based on the following procedures:

1) Request and contract of the survey

Medical representatives in the Company request medical institutions to conduct the surveillance in writing after confirming the list below and conclude a contract.

- There are physicians with experience in hemophilia therapy in the medical institution.
- ADYNOVATE is planned to be used for patients who are targeted in this surveillance in the medical institution.

Upon agreement of implementation of the drug use surveillance, the MAH will enter into agreement with the medical institution using a designated contract document.

2) Registration of patient

The central registration procedure will be used in EDC system.
The investigators register PTPs receiving ADYNOVATE within approximately 3 months after the administration (in principle), and all PUPs receiving ADYNOVATE after its

launching at participating medical institutions.
The investigators will access to their designated sites of EDC system and complete the required information for registration.
The registration form includes the following information;

- site management patient number
- gender
- date of birth
- starting date of administration
- EDs of other factor VIII products before ADYNOVATE administration (0-3, 4-50, 51-150, or >150 days)

3) CRF collection and observation period duration of the survey

The survey is conducted using multiple CRFs in parts with 6-month observation period per CRF. The total observation period per subject is as follows.

- PTPs (Previously treated patients who had 4 or more days to other products): One year after the beginning of ADYNOVATE administration
- PUPs (Previously untreated or minimally treated patients who had 3 or less previous exposure days to other products): Two years after the beginning of ADYNOVATE administration

3.5 Estimated implementation period of the survey

The surveillance period is as follows:

- Estimated Period of survey: February 1st, 2017 to January 31st, 2023
- Estimated period of registration: February 1st , 2017 to January 31st, 2022

3.6 Items for investigation

1) Patient demographics at the start of administration

Pregnancy status (in case of female), body height, body weight, inpatient/outpatient status, race, past history of serious bleeding episode (date, hemorrhage intracranial, gastrointestinal hemorrhage, bleeding into the iliopsoas muscle and others), past surgical history (surgery name, surgery date), other past history(HCV etc.), hemophilic arthropathy, target joint, complication (including renal and hepatic complications), allergy, date of diagnosis (age), congenital/acquired disease, family history of hemophilia, clinical severity of hemophilia (residual factor VIII activity, date of measurement), annualized bleeding rate (ABR)[i], history of factor VIII inhibitor measurement (date, value and result of measurement, date and value of peak inhibitor record), family history of inhibitor development, previous administration of other factor VIII products (product name, regimens (prophylaxis, on-demand, prophylaxis/on-demand)

[i] Patient diary and medical records will be used for the calculation of ABR.

2) Concomitant drugs and concomitant therapies

3) Administration status of ADYNOVATE

In terms of the treatment during surveillance period of ADYNOVATE, administration status and number of bleeding events will be investigated for regular replacement (prophylaxis) therapy, and on-demand replacement therapy.

Prophylaxis therapy:

Administration period for prophylaxis, body weight and date of measurement, dosage, frequency of administration, total number of doses, purpose of prophylaxis*
In case of bleeding during the prophylaxis therapy: number[ii] of bleeding events(site and date), dosage, number of doses to treat a bleed.

*Purpose of prophylaxis:

- Long-term prophylaxis: Therapy for the purpose of long term (at least 6 months of duration) prevention of bleeding with dosing interval of more than once a week. Less than 2 weeks of untreated periods may be allowed during 6 months.
- Short-term prophylaxis: Therapy for the purpose of relatively short term (less than 6 months of duration) prevention of bleeding with dosing interval of more than once a week.
- Preventive treatment: dosing before events; sports, physical activities, rehabilitations, etc. that may cause bleeding.

On-demand replacement therapy:

Administration period for on-demand, body weight and date of measurement, dosage, number of doses to treat a bleed, number of bleeding events (site and date).

4) Factor VIII inhibitor titer, plasma factor VIII levels
Date of measurement, measured value, and others as well as inhibitor development and plasma factor VIII levels during the surveillance period are investigated routinely.

5) Discontinuations/withdrawals
The timing and reasons for discontinuation/withdrawal will be investigated, if any.

6) Efficacy of ADYNOVATE
The hemostatic effectiveness of ADYNOVATE for bleeding during prophylactic therapy and on-demand replacement therapy is assessed in reference to Outcome measures of Treatment Response are shown in the Attached Form. The number and the amount of given doses before hemostasis was achieved. Change of target joints.

7) Laboratory tests

[ii] To enable the calculation of ABR, please record information about bleeding in a patient's diary, etc. . if breakthrough bleeding occurs during the prophylaxis therapy.

Review values which were voluntarily measured in any medical institution before the start of, and during ADYNOVATE administration. In addition, review clinically significant abnormal fluctuation of the laboratory values that were measured in any medical institution at the end of any X-month observation period or at the time of discontinuation/withdrawal during the maximum X-year of a total observation period, if any.

8) Adverse Events
Adverse event name, onset date, seriousness, severity, presence of treatment, treatment details, outcome, outcome date, causal relationship to ADYNOVATE, presence of autopsy in death case.

- Inhibitor to FVIII
  Date(s) of inhibitor detection
  Date(s) of inhibitor disappearance
  FVIII inhibitor titer(s)

- Other adverse events
  Event
  Onset Date
  Stop Date
  Seriousness (and seriousness criteria)
  Severity
  Disease progression (if applicable)
  Outcome
  Action Taken
  Date of death (if applicable)
  Cause of death (if applicable)
  Causality assessment by Investigator

9) Additional investigation items at the onset of adverse events
Upon the occurrence of inhibitor development or events such as anaphylactic shock, or anaphylaxis additional investigation will be conducted for the following items:
Lot number of ADYNOVATE, administration rate of ADYNOVATE, status of concomitant drugs administration (concomitant drug name, whether suspected drug or not, administration route, dosage form, dose, number of doses per day, administration period, reason for use), concomitant therapies, re-administration of suspected drugs, clinical course of the case, etc., laboratory tests (if performed, including abnormal values with clinical significance)

3.7 Statistical Analysis and Analysis Method

1. Analysis items

   a. Patient population

   Number of registered subjects, number of subjects whose CRFs are collected, number of subjects in safety analysis set, number of subjects in the effectiveness analysis set, number of withdrawal/discontinuation, reasons for and details of withdrawal/discontinuation, and others.

b. Items related to safety

All patients, PTP/PUP

- Occurrence of SAEs and ADRs/infections (type, severity of ADRs and incidence etc.)
- Factors that may affect safety (type and incidence of ADRs according to patient background)

c. Items related to efficacy

- Prophylaxis: ABR
- On-demand: hemostatic effectiveness, number of doses to treat a bleed
  Physician rated effectiveness ("poor", "fair", "good", or "excellent")

2. Analysis method

Mainly, frequency tabulation is performed for classified data and summarization based on mean values and standard deviation is for sequential data. The detail is described in Statistics Analysis Plan.

3.8 Organization Structure for Surveillance

Same as described in the Risk Management Plan.

3.9 Outsource Details

Contractor for the operations 1

[redacted]

Scope of the contract

EDC management, progress management, data management, tabulation analysis, and others.

Contractor for the operations 2

[redacted]

Scope of the contract
Records retention management and medical writing for the survey.

Contractor for the operations 3

[redacted]

Scope of the contract
Monitoring activities and its management for the survey.

4. ADDITIONAL MEASURES TO BE POSSIBLY TAKEN BASED ON THE RESULTS OF THE SURVEY AND DECISION CRITERIA FOR THE INITIATION

The Risk Management Plan will be reviewed at appropriate timepoints in consideration of the following:

- Necessity to modify risk minimization activities for the current safety investigation items
- Necessity to modify the protocol (such as continuation of the surveillance and implementation of additional surveillances), including necessity to add another safety investigation item
- Necessity to develop risk minimization measures for added safety investigation items, if any

5. MILESTONES FOR THE IMPLEMENTATION STATUS OF THE SURVEY AND THE ASSESSMENT OF THE RESULTS, OR ANTICIPATED TIMING FOR REPORTING TO PMDA AND THE JUSTIFICATION

Milestones were set at the time of creating periodic safety update report and at application for re-examination to assess comprehensive safety data.

The milestones are the time points when the interim report and the final report are created. To conduct safety evaluation including the comparison with the clinical study results, as well as to consider whether any amendments are needed including the addition of the number of investigated cases to examine the safety of ADYNOVATE.

6. OTHER NECESSARY MATTERS

1. Revision of the protocol
   Based on new findings that may be obtained as the survey proceeds, the protocol will be revised as necessary after considering whether or not amendment is needed.

2. Actions to be taken if issues or questions are found
   A hypothesis will be established, and an implementation of specific use result survey will be considered in order to verify that hypothesis when the occurrence of serious unexpected adverse drug reaction is indicated, or a significant increase in frequency of adverse drug reaction is found, or any issues in efficacy and safety are found as compared with the period prior to the approval, or the occurrence of heterogeneous adverse drug reaction is indicated.

Attached Form

Outcome Measure of Treatment Response

Outcome is measured based on the following criteria by the physician

Table: Hemostatic Effectiveness	
Excellent	Full relief of pain and cessation of objective signs of bleeding (e.g., swelling, tenderness, and decreased range of motion in the case of musculoskeletal hemorrhage) after a single infusion. No additional infusion is required for the control of bleeding. Administration of further infusions to maintain hemostasis would not affect this scoring.
Good	Definite pain relief and/or improvement in signs of bleeding after a single infusion. Possibly requires more than 1 infusion for complete resolution.
Fair	Probable and/or slight relief of pain and slight improvement in signs of bleeding after a single infusion. Required more than 1 infusion for complete resolution.
Poor	No improvement or condition worsens

APPENDIX: PROTOCOL HISTORY

Document	Date	Comment
Original Protocol/ Version 1.0	07 DEC 2016	
Version 2.0	07 DEC 2017	Approved
Version 3.0	05 APR 2018	Administrative changes to the protocol
Version 4.0	20 MAR 2019	Additional outsource
Version 5.0	21 DEC 2020	Prolonged 'Estimated period of registration' Changed in the outsourced operations
Version 6.0	23 AUG 2023	Added 'Completion date of survey'