Statistical Analysis Plan

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Study Number: 261601

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STATISTICAL ANALYSIS PLAN

PRODUCT: ADYNOVATE

DRUG USE-RESULT SURVEY

PROTOCOL IDENTIFIER: 261601

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1. INTRODUCTION

This statistical analysis plan (SAP) describes the rules and details for analysis of effectiveness and safety data as described in Protocol 261601.

This SAP is based on final protocol (English version 5.0 dated 21 Dec 2020; Japanese version 7.0 dated 12 May 2022).

1.1 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 effectiveness
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

1.2 Safety specification

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

2. STUDY DESIGN

This is a Drug Use - Result Survey (DURS) of ADYNOVATE in the Post Marketing Surveillance in patients diagnosed with hemophilia A.

2.1 Targeted 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.

2.2 Estimated number of patients in the survey and the rational

Estimated number of patients for the survey:

- Previously treated patients (PTPs) with haemophilia A: 140 patients
- Previously untreated patients (PUPs) with haemophilia A: 25 patientsRational:

Of the patients with Haemophilia A in Japan, approximately 4000 receive genetically recombinant blood coagulation factors, of which approximately 10% are optimistically 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.

2.3 Randomization and Blinding

N/A

2.4 Estimated number of centers (departments)

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

2.5 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, 2021

2.6 Survey Method

The survey is conducted using EDC system via internet, the data will be collected every 6-months. The observation periods for each patient are 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. ANALYSIS ITEMS

3.1 Subject 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

3.2 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).

3.3 Items related to Effectiveness

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

4. ANALYSIS SETS

4.1 Registered population

All subjects who are enrolled in this survey.

4.2 Case Report Form(CRF) collected population

4.3 All subjects for which enrollment has been completed and CRF have been collected.Safety analysis set

CRF collected population excluding the subjects who meet the following criteria:

- ADYNOVATE unused
- Patient no-visit after the first visit
- AE presence/absence is unknown
- Out of contract period
- Others

4.4 Effectiveness analysis set

Safety population excluding the subjects who meet the following criteria:

- Off-label use
- Effectiveness is unknown (Missing)

5. STATISTICAL CONSIDERATIONS

5.1 Descriptive statistics

Descriptive statistics consists of the number of observations, mean, standard deviation, median, interquartile range, and the minimum and maximum values.

As a general rule, the number of digits displayed for statistics is as follows.

Item	Display digits
Case number	Integer
Rate	Rounded to 3 decimal places and displayed to 2 decimal places.
Summary statistics (mean, median, 1st /3rd quartile)	Rounds down two significant digits of the target data and displays up to one digit down.
Summary Statistics (Standard Deviation)	Rounds down to 3 significant digits of the target data and displays up to 2 digits below.
Summary Statistics (Min, Max)	Significant digits of the target data.

5.2 Handling of Missing, Unused, and Spurious Data

If there are missing data in a continuous variable, exclude the missing data from the analysis without interpolating. If there is a missing data in a discrete variable, it is classified as unknown or missing and aggregated. (The definitions of unknown and missing are specified in the Derived Dataset Specification and Table Specification.)

6. CHANGES FROM THE PLANNED STATISTICAL ANALYSIS IN PROTOCOL

N/A

7. STATISTICAL ANALYSIS

7.1 Disposition of Subjects

The disposition of subjects will be presented for the Registered population. The number of subjects included in each subject population (4.1～4.4) will be summarized. In addition, the number of subjects who were excluded from each population will be summarized by reason of exclusion.

Discontinuations will be summarized with details of the reason for discontinuations.

7.2 Demographic and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented for the Safety analysis set. Aggregated by total, PTPs and PUPs.

1. The items are below and details will be defined in TFL Shells.Patient backgrounds at the start of administration
   age, gender, pregnant, inpatient/outpatient status, race

2. Patient backgrounds (Complication/ Past history)
   past history of serious bleeding episode, hemophilic arthropathy, target joint, past surgical history, other past history, complication (including renal and hepatic complications), allergy

3. Patient backgrounds (related to Hemophilia)
   Previous history of factor VIII products administration[Eds], age of diagnosis (age), congenital/acquired disease, family history of hemophilia, clinical severity of hemophilia (residual factor VIII activity), annualized bleeding rate (ABR), history of factor VIII inhibitor measurement, family history of inhibitor development, previous administration of other factor VIII products [product name, regimens (prophylaxis, on-demand, prophylaxis/on-demand, others)].

7.3 Extent of Exposure

Exposure to ADYNOVATE will be summarized for the safety population in terms of following items.

The items are below and details will be defined in TFL Shells.

For Prophylaxis therapy:
Administration period, Dose (IU/kg), Frequency of administration (times/week), Total dose during the observation

In case that Administration for Breakthrough bleeding during the Prophylaxis therapy is present:
Administration period, Dose (IU/kg), Total dose during the observation, Bleeding details (bleeding site, severity, kind of bleeding:traumatic or spontaneous), Total number of administrations

For On-demand replacement therapy:
Administration period, Dose (IU/kg), Total dose during the observation, Bleeding details (bleeding site, severity, kind of bleeding:traumatic or spontaneous)Total number of administrations

7.4 Concomitant Medications

Concomitant drugs/therapies will be listed. In addition, the concomitant drug is listed in Re-examination form “Bessiyoushiki 16”.

7.5 EFECTIVENESS Evaluation

All efectiveness analysis will be performed for effectiveness analysis set.

7.5.1 Annualized Bleeding Rate (ABR)

For Prophylaxis therapy and On-demand replacement therapy, calculate summary statistics for annualized bleeedingd rate (ABR). Summary statistics are calculated for each ppopulation that Tatal, PTPs and PUPs.The calculation of ABR is below.

ABR (times/case・year) = (Number of spontaneous bleeding during each administration period / each administration period) * 365.2425

7.5.2 Hemostatic effectiveness

For Prophylaxis therapy and On-demand replacement therapy, calculate the number of bleeding and the number of administartion for hemostatic.

Hemostatic effectiveness consists of 4 grades (“none”, “moderate”, “good”, or “excellent”) (defined in Protocol Appendix).

7.6 Safety Evaluation

Unless otherwise specified, all safety analysis will be performed for safety analysis set.

7.6.1 Adverse Events

Adverse Events (AEs) will be coded using Medical Dictionary for Regulatory Activities (MedDRA) (appropriate version).

7.6.2 Summary of Adverse Reactions/infections

Adverse reactions/infections are defined as Adverse events if a causal relationship with a medicinal product is suspected. Unless the causality is defined as ‘Unrelated’, treat it as ‘suspected’.

Adverse reactions/infections will be summarized by SOC and PT (SOC: internationally agreed order, PT: PT code order). In addition, this is aggregated by PTP and PUP, respectively.

The details of items are below:

Number of patients who had at least one Adverse Reaction, Number of Adverse Reactions, Rate of Adverse Reaction, Number and Rate of Adverse reactions by SOC and PT.

Number of patients subject to analysis, number of patients with adverse reactions, number of adverse reactions, incidence rate of adverse reactions, number of incidence cases and incidence ratio by SOC and PT.

7.6.3 OCCURRENCE OF ADVERSE DRUG REACTION BY PATIENT BACKGROUND AND THERAPY

The number of cases of adverse reactions will be tabulated by patient background factors. In addition, aggregation is performed by PTPs/PUPs. Details of patient background factors are specified in TLF-Shells.

As for age, the incidence status of SOC and PT will be tabulated by age.

7.6.4 OCCURRENCE OF ADVERSE DRUG REACTION FOR SEVIRITY, TITME OF ONSET AND OUTCOME

The number of adverse reactions by sivrity, time of onset, and outcome will be tabulated by SOC and PT.

7.6.5 OCCURRENCE OF ADVERSE DRUG REACTION IN PATIENTS EXCLUDED FROM SAFETY ANALYSIS SET

For patients excluded from safety evaluation, the number of ppatients with adverse reactions by severity and PTPs/PUPs will be tabulated by SOC and PT.

7.6.6 OCCURRENCE OF ADVERSE EVENT

All adverse events will be tabulated by SOC and PT. The aggregation method is the same as for adverse drug reactions and infections.

7.7 Safety Specification

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

About the above items, aggregate the number of patients that incident the event. Aggregation will be done by severity, PTPs and PUPs. The extraction conditions for safety specifications are specified in the Derived Dataset Specification.

7.8 Form

The ruled form for Re-examination(Form 12, 15, and 16), prepared based on the latest version of the notice of the Ministry of Health, Labour and Welfare and the Japan Pharmaceutical Manufacturers Association's "Guide to Application for Reexamination".

8. ANALYSIS SOFTWARE

Statistical analysis will be performed using SAS Version 9.4 or later and SAS Enterprise Guide (SAS Institute Japan) 8.2 or later.

9. GUIDANCE DOCUMENTS

- TLF Shells
- Table Specification
- Derived Dataset Specification

10. REFERENCE

- Guide to Application for Reexamination"（Ver Oct 2021）

11. REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	2018Mar01	New
2.0	2023June05	Update for final analysis