Title: RIXUBIS Drug Use-Result Survey (Japan)

NCT Number: NCT02937831

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Certain information within this statistical analysis plan has been redacted (ie, specific content is masked irreversibly from view with a black bar) to protect either personally identifiable information or company confidential information.

STATISTICAL ANALYSIS PLAN

PRODUCT:RIXUBIS

DRUG USE-RESULT SURVEY

PROTOCOL IDENTIFIER: 251601

Study Sponsor(s): Shire Japan KK

1-8-2 Marunouchi, Chiyoda-ku, Tokyo
Japan

Author: [redacted]

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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 251601.

This SAP is based on final protocol (English version dated 20 May 2016; Japanese version 1.0 dated 27 May 2016).

1.1 Purpose

This survey will be conducted to understand the following items observed in the actual clinical use of RIXUBIS 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 IX inhibitor development in patients with coagulation factor IX deficiency (hereinafter hemophilia B)
5. Safety and effectiveness for hemophilia B patients who received routine prophylactic therapy, on-demand therapy and perioperative therapy

1.2 Safety specification

1. Inhibitor development (Factor IX inhibitor)
2. Shock, anaphylaxis
3. Thromboembolism

2. STUDY DESIGN

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

2.1 Targeted patients

All patients with hemophilia B receiving RIXUBIS after its launching at medical institutions which contracted this investigation.

2.2 Estimated number of patients in the survey and the rational

Estimated number of subjects for the survey: 30

Rational: There are currently about 250 hemophilia B patients who receive recombinant formulation of Factor IX in Japan. The expectation of the number of patients switching from current products to RIXUBIS is supposed to be limited while other new products

are under development, resulting in the determining of the collectible subject number of 30. Of note, the number is considered enough to retain 95% reliability for detecting unexpected adverse reactions with incidence of 10%.

2.3 Randomization and Blinding

N/A

2.4 Estimated number of centers (departments)

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

2.5 Estimated implementation period of the survey

The surveillance period is as follows:
Period of survey: June 2016 - May 2021
Period of registration: June 2016 - May 2019
Of note, if 30 subjects are successfully registered before the end of registration period, registration should be sustained as long as possible until the registration period ends.

2.6 Survey Method

This survey is conducted using paper-based case report forms (CRFs).
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 more than 4 previous exposure days to other products): One year after the beginning of RIXUBIS administration
- PUPs (Previously untreated patients who had 3 or less previous exposure days to other products: Two years or 100 EDs after the beginning of RIXUBIS administration whichever comes first

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

For All patients of safety analysis set, PTPs/PUPs, Adverse Reactions by demographic and baseline characteristics

3.3 Items related to Efficacy

- Prophylaxis therapy: Annualized Bleeding Rate (ABR)
- On-demand replacement therapy: hemostatic effectiveness*, number of doses to treat a bleed
- Perioperative therapy: In- and post-surgery hemostatic effectiveness*

*Effectiveness physician rated is consisting of 4 grades ,“none”, “moderate”, “good”, or “excellent” (defined in Protocol Appendix).

4. ANALYSIS SETS

4.1 Registered population

All subjects who are enrolled in this survey.

4.2 Completed CRF population

All Collected CRF population that their CRFs are completed.

4.3 Safety analysis set

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

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

The details of definition is following to “Exclusion Criteria for safety” that is created by Data Management.

4.4 Effectiveness analysis set

Safety population excluding the subjects who meet the following criteria:

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

The details of definition is following to “Exclusion Criteria for effectiveness” that is created by Data Management.

5. STATISTICAL CONSIDERATIONS

5.1 Statistical Test

In each analysis, unless otherwise specified, significance level is based on two-sided 5% and $p<0.05$ is considered statistically significant. No adjustments for multiplicity are being made.

For continuous variables, appropriate statistical tests will be applied (paired t-test, Student’s t-test, Wilcoxon signed-rank test, Wilcoxon rank-sum test, etc.).
For categorical variables, Fisher’s exact tests will be applied for 2 x 2 categories and Chi-squared tests will be applied for variables with 3 or more categories.

5.2 Descriptive statistics

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

5.3 Interim Analyses

Once information for 30 subjects is collected, an interim analysis will be conducted including comparison with the results of clinical trials. Then, necessity for continuing further CRF collection will be examined, the conclusion of which is to be reported to PMDA by attaching analysis results obtained at the completion of collecting 30-subject information or in other ways.

5.4 Handling of Missing, Unused, and Spurious Data

If there is “Missing” in continuous variables, not to be supplemented, to be excluded from analysis object. If there is “Missing” in discrete variables, treat it as “Missing” (not to be categorized within “Unknown”) and to be tabulated.

5.5 Changes from the Planned Statistical Analysis in Protocol

6. TBDSTUDY SUBJECTS

6.1 Disposition of Subjects

Disposition of subjects will be presented for the Registered population..

The number of subjects included in each subject population (4.1～4.5) 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.

6.2 Demographic and Baseline Characteristics

Descriptive summaries of demographic and baseline characteristics will be presented for the Safety analysis set and Effectiveness analysis set by total and therapeutic regimens (Prophylaxis therapy only, On-demand replacement therapy only, On-demand replacement therapy to Prophylaxis therapy, others).

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

1. Patient backgrounds at the start of administration
   age, gender, pregnant, body weight, inpatient/outpatient status, race

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

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

6.3 Extent of Exposure

Exposure to RIXUBIS will be summarized for the safety population in terms of following items. Descriptive statistics consisting of the number of observations, the mean, the standard deviation, the median, and the minimum, and maximum values will be summarized.

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

For Prophylaxis therapy:

Term of administration, Dose (IU/kg), Total dose during the observation, Total number of administrations, Number of administrations per week

In case that Administration for Breakthrough bleeding during the Prophylaxis therapy is Presence:

Term of administration, Dose (IU/kg), Total dose during the observation, Total number of administrations

Additionally for the whole Prophylaxis therapy including for Breakthrough bleeding, the same items (Term of administration, Dose(IU/kg), Total dose during observation, Total number of administrations, Number of administrations per week) will be summarized.

For On-demand replacement therapy:

Term of administration, Dose (IU/kg), Total dose during the observation, Total number of administrations

For Perioperative therapy:

Term of administration, Dose (IU/kg), Total dose during the observation by Pre-Intraoperative, Post operative, and total.

6.4 Concomitant Medications

Concomitant drugs/therapies will be listed.

7. EFFICACY EVALUATION

All efficacy analysis will be performed for effectiveness analysis set.

7.1 Annualized Bleeding Rate (ABR)

For Prophylaxis therapy and On-demand replacement therapy, ABR will be calculated.

Descriptive statistics, consisting of the number of observations, the mean, the standard deviation, the median, and the minimum, and maximum values, interquartile range will be summarized by total and demographic and baseline characteristics.

The calculation of ABR is below.

ABR (times/year) = Total number of bleedings of
Breakthrough bleeding during the Prophylaxis therapy
(or/and On-demand replacement therapy)
÷ Duration of observation (days)
× 365.25

7.2 Hemostatic effectiveness

For Bleeding episode (On-demand replacement therapy) and Breakthrough bleeding episode (During the Prophylaxis therapy), hemostatic effectiveness and number of administrations to treat a bleed will be summarized.

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

For Perioperative therapy, In- and post-surgery hemostatic effectiveness are defined as effectiveness variable.

Effectiveness is consisting of 4 grade (“none”, “moderate”, “good”, or “excellent”) (defined in Protocol Appendix).

Regarding In- and post-surgery hemostatic effectiveness, frequency and percentage will be summarized by event.

7.3 Transition of Target joint

The transition of target joint is evaluated by the number of cases with one or more improved, unchanged or newly recognized target joint from the start of administration at the end of observation period.

8. SAFETY EVALUATION

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

8.1 Adverse Events

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

8.1.1 Summary of Adverse Reactions/infections

Adverse reactions/infections are defined as Adverse events if a causal relationship with a medical 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).

The details of items are below.

Number of centers, Number of patients, 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

8.1.2 Summary of Serious Adverse Events/infections

If the seriousness of an Adverse Event/infection differs between Investigator and Sponsor, the serious one will be adopted.

Serious adverse events/infections will be summarized by SOC and PT (SOC: internationally agreed order, PT:PT code order).

The details of items are below:

Number of centers, Number of patients, Number of patients who had at least one Serious Adverse Event, Number of Serious Adverse Events, Rate of Serious Adverse Event, Number and Rate of Serious Adverse Events by SOC and PT.

8.1.3 Summary of Adverse Reactions by demographic and baseline characteristics

The frequency and percentage of subjects who experience adverse reactions at least once will be summarized overall and by demographic and baseline characteristics for the safety analysis set and for PTPs/PUPs. Demographic and baseline characteristics will be defined in TFL Shells.

8.1.4 Summary of all Adverse Events

All AEs are summarized by severity, SOC and PT. All AEs will be listed.

8.2 Safety Specification

1. Inhibitor development (Factor IX inhibitor)
2. Shock, anaphylaxis
3. Thromboembolism

For the safety specification items listed above, the frequency and percentage of the subjects who experienced them at least once will be summarized by total and demographic and baseline characteristics. Demographic and baseline characteristics items will be defined in TFL Shells.

Additionally, exposure days from start date of administration to occurrence of inhibitor development will be reported.

8.3 Clinical Laboratory Evaluations

Except for Factor IX inhibitor, a laboratory test is not mandatory for this survey and data will be collected optionally for the parameters related to adverse events.

8.4 Inhibitor/Antibody Development

Refer to **8.3.**

9. ANALYSIS SOFTWARE

Statistical analysis will be performed using SAS Version 9.4 32bit (or higher).

10. GUIDANCE DOCUMENTS

- TFL Shells
- Exclusion cases

11. REFERENCES

- Greenbook：Guide to creating “Periodic Safety Update Reports” RMP compatible version (Ver.September 2014)
  [「安全性定期報告書」作成の手引き―RMP 対応版―（平成 26 年 9 月版）]
- Greenbook：Guide of “Re-examination” (Ver.March 2010)
  [再審査申請の手引き （平成 22 年 3 月版）]

12. REVISION HISTORY

Version	Issue Date	Summary of Changes
1.0	2018Mar01	New Document