16.1.9 Documentation of Statistical Methods

STATISTICAL ANALYSIS PLAN

A Single Arm, Open-label, Long-term Efficacy and Safety Study of Romiplostim in Thrombocytopenic Pediatric Subjects With Immune Thrombocytopenia (ITP)

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Table of Abbreviations

Abbreviation or Term	Definition/Explanation
CI	confidence interval
CSR	Clinical Study Report
CTCAE	Cancer Institute Common Terminology Criteria for Adverse Events
DDT	Data Definition Table
eTPO	endogenous thrombopoietin
IP	investigational product
ITP	immune thrombocytopenia
IVRS	interactive voice response system: telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.
source data	information from an original record or a certified copy of the original record containing patient information for use in clinical research. The information may include, but is not limited to, clinical findings, observations, or other activities in a clinical trial necessary for the reconstruction and evaluation of the trial. Source data are contained in source documents (original records or certified copies, ICH Guideline E6). Examples of source data include subject ID, randomization ID, and stratification value.
TPO	thrombopoietin

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1. Introduction

The purpose of this statistical analysis plan (SAP) is to provide details of the statistical analyses that have been outlined within the protocol for romiplostim Study 20101221 dated 15 January 2014. The scope of this plan includes the interim analysis and the final analyses that are planned and will be executed by the Biostatistics department or designee unless otherwise specified.

2. Objectives

2.1 Primary

The primary objective of the study is to describe the percentage of time that pediatric subjects with ITP have a platelet response in the first 6 months from the start of treatment with romiplostim.

2.2 Secondary

The secondary objectives of the study are:

- To describe the percentage of time that pediatric subjects with ITP have a platelet response over the study duration
- To describe the percentage of time that pediatric subjects with ITP have an increase in platelet count ≥ 20 x 10^9/L above baseline over the study duration
- To describe the use of rescue ITP medications
- To describe the incidence of antibody formation
- To describe the safety of romiplostim as a long-term treatment in pediatric thrombocytopenic subjects with ITP

2.3 Exploratory

The exploratory objectives of the study are:

- To describe the incidence of sustained platelet response
- To describe the incidence of splenectomy
- To describe the subject incidence of romiplostim self-administration

3. Study Overview

3.1 Study Design

This is a phase 3b single arm, open-label, multicenter study evaluating the percentage of time pediatric subjects with ITP have a response while receiving romiplostim, defined as a platelet count ≥ 50 x 109/L and in the absence of ITP rescue medications in the past 4 weeks. This protocol will provide open-label romiplostim to thrombocytopenic pediatric subjects with ITP diagnosed for at least 6 months and who have received at least 1 prior ITP therapy (excluding romiplostim) or are ineligible for other ITP therapies.

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The study design consists of a 4-week screening period, up to a 3-year treatment period, an end of treatment (EOT) visit and an end of study (EOS) visit.

Approximately 200 children with ITP will be enrolled into the study and receive weekly romiplostim until they complete the study, discontinue participation in the study for any reason, or the study ends.

The overall study design is described by a study schema at the end of the protocol synopsis section (refer to the study protocol).

3.2 Sample Size

The sample size for this study is governed by the number of pediatric ITP subjects who meet the eligibility requirements during enrollment period. It is estimated that approximately 200 subjects will enroll into this study. The percentage of time achieving platelet response in the first 6 months of treatment period for ITP subjects with romiplostim (both adults and pediatric) is estimated at 74%. The standard deviation of percentage of time is estimated between 30% and 36% based on previous Nplate data. Given the sample size of 200 subjects, the half width of the 95% confidence interval (CI) for the percentage of time achieving platelet response is estimated to be between 4% and 5%.

4. Study Endpoints and Covariates

4.1 Study Endpoints

4.2 Primary Endpoint

The primary endpoint is the percentage of time with a platelet response, defined as a platelet count of ≥ 50 x 10^9/L without rescue medication use for ITP in the past 4 weeks, starting from Week 2 in the first 6 months of the treatment period.

A rescue-evaluable weekly platelet count is defined as a weekly platelet count without rescue medication use for ITP in the past 4 weeks.

In the first 6 months of treatment period, a monthly platelet response is defined as a the median of rescue-evaluable platelet counts of ≥ 50 x 109/L.

For each subject, the percentage of time with platelet response during the first 6 months is calculated as the number of monthly platelet response divided by the total number of months. If the monthly platelet response is missing , it will be imputed based on the neighboring monthly platelet response status and rescue medication use in the month. If a monthly platelet response is still missing after imputation, it is considered as no response in this month.Subjects who discontinued the treatment early due to lack of

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response (non-responder to romiplostim) before completing 6 months of treatment, the month(s) following their discontinuation of treatment till the 6th month will be imputed as having no monthly platelet response.

The primary endpoint is summarized by descriptive statistics (n, mean, standard deviation, median, Q1 [25th percentile], Q3 [75th percentile], minimum, and maximum) of this percentage of time with platelet response averaging across subjects.

4.3 Secondary Endpoints

- The percentage of time with platelet response starting from Week 2 until the end of the treatment (EOT) period.
- For each subject, the percentage of time with a platelet response from Week 2 till EOT is calculated as the number of weeks with a platelet response divided by the total number of weeks. Weekly platelet counts are imputed by last observation carry forward using rescue-evaluable weekly platelet counts during the treatment period.
- Descriptive statistics (n, mean, standard deviation, median, Q1 [25th percentile], Q3 [75th percentile], minimum, and maximum) are provided for the average percentage of time across subjects.
- The percentage of time with an increase in platelet count ≥ 20 x 109/L above baseline starting from Week 2 until the end of the treatment period without rescue medication use for ITP in the past 4 weeks.
- For each subject, the percentage of time with an increase in platelet count ≥ 20 x 109/L above baseline from Week 2 till EOT is calculated as the number of weeks with an increase in platelet count ≥ 20 x 109/L above baseline divided by the total number of weeks. Weekly platelet counts are imputed by last observation carry forward using rescue-evaluable weekly platelet counts during the treatment period.
- Descriptive statistics (n, mean, standard deviation, median, Q1 [25th percentile], Q3 [75th percentile], minimum, and maximum) are provided for the average percentage of time across subjects.
- Subject incidence of rescue ITP medications used.
- Total number and percentage of subjects who reported any usage of rescue medications for ITP are calculated with a sub-categorization by preferred terms.
- The incidence of anti-romiplostim neutralizing antibodies and cross reactive antibodies to TPO at any time during the study.
- Number and percentage of subjects who developed anti-romiplostim neutralizing antibodies and/or cross reactive antibodies to TPO by study visits are calculated.
- The incidence of adverse events, including clinically significant changes in laboratory values.
- The summary for adverse events will be performed for the categories of all adverse events, romiplostim-related adverse events, serious adverse events, adverse events leading to withdrawal from the study, adverse events of interest (hemorrhage events, etc.). Both subject incidence and duration-adjusted rates of adverse events are calculated for overall study duration and by study period at every 6 months. Subject listings for all adverse events, serious adverse events, adverse events leading to study withdrawal, and fatal adverse events are provided.

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- Summary statistics are calculated for blood chemistry and CBC at each visit. Shift tables between the worst post-baseline and baseline values are provided based on the National Cancer Institute CTCAE, version 3.0.

4.4 Exploratory Endpoints

- The subject incidence with a sustained platelet count of ≥ 50 x 109/L for 6 months or greater without any use of ITP medications (concomitant, rescue, or romiplostim)
- An onset of a sustained platelet response is defined as consecutive platelet counts
- ≥ 50 x 109/L in the absence of any ITP medications (including romiplostim and other concomitant or rescue medications for ITP). Number and percentage of subjects who have an onset of a sustained platelet response and maintained for at least 24 weeks are summarized.
- The incidence of splenectomy during the treatment period for subjects entering the study pre-splenectomy
- Number and percentage of subjects who did not undergo a splenectomy before study enrollment and had a splenectomy during treatment period are summarized.
- The subject incidence of romiplostim self-administration
- Number and percentage of subjects who initiated self-administration during treatment period are summarized.

5. Hypotheses and/or Estimations

The statistical analysis in this open-label study will be descriptive in nature and no hypothesis testing is intended. The percentage of time with a platelet response in the first 6 months of the study will be estimated. Categorical data will be presented in the form of number and percentage. Continuous data will be provided with the descriptive statistics (n, mean, standard deviation, median, Q1 [25th percentile], Q3 [75th percentile], minimum, and maximum).

6. Definitions

Term	Definition/Explanation
End of study for individual subject (EOS)	Defined as the last day that protocol-specified procedures are conducted for an individual subject
End of treatment (EOT)	Defined as the last assessment for the protocol-specified treatment phase of the study for an individual subject
End of study (primary completion)	Defined as the time when the last subject is assessed or receives an intervention for the purposes of final collection of data for the primary outcome. This will occur once the last subject participating has completed the EOS visit.
Interactive Voice Response System (IVRS)	Telecommunication technology that is linked to a central computer in real time as an interface to collect and process information.

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Term	Definition/Explanation
Study Day 1	Defined as the first day that romiplostim is administered to the subject
Study Week 1	Defined as the week that the first dose of romiplostim is administered to the subject
Study day	Defined as (calendar date – first dose date) +1
Study treatment period	Defined as the period from the date of first dose of romiplostim till the date of last dose of romiplostim plus one week
Treatment duration for individual subject	Defined as the (last dose date – first dose date)+7 days
Baseline Platelet Count	The average of available platelet counts obtained at screening and pre-treatment prior to dosing.
Study baseline	Other than for platelet count, the baseline is defined as data immediately prior to first dose administration
Platelet response	Defined as platelet count of ≥ 50 $x10^9$/L without rescue medication use for ITP in the past 4 weeks

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7. Analysis Subsets

7.1 Full Analysis Set

The full analysis set will consist of all enrolled subjects. Analyses for demographics and baseline characteristics will use this analysis set.

7.2 Safety Analysis Set

The safety analysis set will consist of all subjects who receive at least 1 dose of romiplostim. The analyses of all safety endpoints will be based on the safety analysis sets.

7.3 Efficacy Analysis Set

The efficacy analysis set will consist of all subjects who receive at least 1 dose of romiplostim. The analyses of all efficacy endpoints will be based on the efficacy analysis sets.

7.4 Per Protocol Analysis Set

The per protocol analysis set will consist of all subjects who receive at least 1 dose of romiplostim and met all eligibility criteria. Sensitivity analysis using the per protocol analysis set may be explored for the primary efficacy endpoint.

8. Interim Analysis and Early Stopping Guidelines

Interim analyses will be conducted to support regulatory filings and accumulating data for this study will be summarized to provide ongoing assessments of the safety of

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romiplostim. These interim analyses will occur at least annually until the end of the study.

9. Data Screening and Acceptance

9.1 General Principles

The objective of the data screening is to assess the quantity, quality, and statistical characteristics of the data relative to the requirements of the planned analyses.

9.2 Data Handling and Electronic Transfer of Data

All data for this study will be received from Amgen's data management department.

9.3 Handling of Missing and Incomplete Data

Missing and incomplete data will be identified through a review of the tables and listings. Attempts will be made to characterize the missing data. In general, data will be analyzed as retrieved from the clinical database except for analyses requiring imputations of missing (or incomplete) dates of adverse events and concomitant ITP medications, and missing platelet counts. The imputed dates will be written to the Case Report Tabulation (CRT) data but not to the raw data retrieved from the clinical database. The imputation algorithm will be described in the Data Definition Table (DDT).

9.4 Outliers

No statistical test for outliers will be performed. Any outliers identified will be investigated by the study team and will be included in the database unless determined to be an error or there is supporting evidence or explanation to justify exclusion. Any outliers excluded from the analysis will be discussed in the Clinical Study Report (CSR), including the reasons for exclusion and the impact of their exclusion on the study.

9.5 Validation of Statistical Analyses

Programs will be developed and maintained, and output will be verified according to processes described in procedures or technical manuals about the "Configuration Management of Statistical Analysis and Reporting Systems", "Statistical Analysis and Reporting System Development and Validation", and "Development of Statistical Analysis and Reporting Systems".

Tables, figures and listings will be produced with validated standard macro programs where standard macros can produce the specified outputs.

The production environment consists of Amgen-supported versions of the SAS System running on the Sun Solaris operating system. Because it is common for multiple versions of SAS to be available during the study period, the SAS version used to

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produce analyses will be documented in the validation documentation and the clinical study report. Allow for use of S-plus as option for exploratory analysis.

10. Statistical Methods of Analysis

10.1 General Principles

Summary statistics will be provided for the primary and secondary endpoints.

10.2 Subject Accountability

The number of subjects who enrolled into the study, received at least 1 dose of investigational product, completed the Investigational Product, completed the study and prematurely withdrew, and the reason for premature withdrawal, will be summarized for all subjects and by age groups (<6, 6-<12, 12-<18 years). The number of subjects who enrolled into the study will be tabulated by center.

10.3 Important Protocol Deviations

Important Protocol Deviations (IPDs) categories are defined by the study team before the first patient visit and updated during the IPD reviews throughout the study prior to database lock. If a snapshot is being taken during the study rather than a database lock at the end of the study, categories should be updated during the IPD reviews throughout the study prior to database lock. These definitions of IPD categories, sub-category codes and descriptions will be used during the course of the study. The final IPD list is used to produce the Summary of IPDs table and the List of Subjects with IPDs. The IPDs will be summarized by categories.

10.4 Demographic and Baseline Characteristics

Summaries of demographics and baseline characteristics will be provided based on the Full Analysis Set. The following demographic and baseline characteristics will be summarized for the full analysis set using descriptive statistics: age, age groups, race, sex, height, weight, platelet counts, baseline hematology, baseline physical examination, baseline vital signs, and medical history.

10.5 Efficacy Analyses

The efficacy analysis will be based on the Efficacy Analysis Set, which includes all subjects who receive at least one dose of romiplostim.

Summary statistics of platelet counts and responses will be provided weekly at Week 1 to 8 and then every 4 weeks for all subjects in the efficacy analysis set and by age groups (<6, 6-<12, 12-<18 years). Platelet response is defined as platelet count

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≥ 50 x 10^9/L. Platelet counts within 4 weeks after rescue medication use will not be deemed as platelet responses.

The percentage of time with platelet response starting from Week 2 in the first 6 months of the treatment period will be estimated for all treated subjects and by age groups (<6, 6-<12, 12-<18).

The percentage of time with platelet response from Week 2 till the end of the treatment period will be estimated for all treated subjects and by age groups (<6, 6-<12, 12-<18).

The percentage of time with an increase in platelet counts ≥ 20 x 109/L above baseline starting without rescue medication use during past 4 weeks from Week 2 until the end of the treatment period will be estimated for all treated subjects and by age groups (<6, 6 <12, 12-<18).

The proportion of subjects who used rescue medication for ITP during the study will be summarized by preferred terms. Rescue medication is defined as any medication or transfusion, other than romiplostim and excluded medications, that is administered after enrollment to the subject during screening or throughout the treatment period with the intent of raising platelet counts or prevent bleeding and includes concomitant medications for ITP where the dose and/or schedule is increased.

The proportion of subjects who achieved sustained platelet response for 24 weeks or longer will be summarized. A sustained platelet response is defined as a platelet count ≥ 50 x 109/L without the use of any ITP medications.

The proportion of subjects who had a splenectomy during the study will be summarized for the subjects who entered this study without splenectomy.

Number and percentage of subjects who started self-administration of romiplostim during the study will be summarized.

10.6 Safety Analyses

The safety analysis will be based on the Safety Analysis Set, which includes all subjects who receive at least one dose of romiplostim administration.

10.6.1 Adverse Events

The safety endpoint for this study is the exposure adjusted rates of adverse events. The exposure adjusted incidence rates as well as subject incidence rates of adverse events will be summarized by system organ class and by preferred term according to the MedDRA dictionary. Exposure adjusted rate is defined as total number of events divided

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by time of duration when subjects were under observation. The summary includes all treatment-emergent adverse events recorded from the start of investigational product on this study, or any worsening of conditions present at baseline before dosing in this study. This summary for adverse events will be performed for the following categories

- All adverse events
- Romiplostim related adverse events/serious adverse events
- Serious adverse events
- Grade 3 or above adverse events
- Adverse events leading to withdrawal from the study
- Adverse events of interest (hemorrhage events, etc.)

In addition, incidence and exposure adjusted rates of adverse events by period may also be explored. The overall summary of exposure adjusted incidence rates as well as subject incidence rates of adverse events by age groups (<6, 6-<12, 12-<18 years), race, sex will also be provided.

Subject listings for all adverse events, serious adverse events, and adverse events leading to withdrawal from the study will be provided.

10.6.2 Laboratory Test Results

Summary statistics are provided for blood chemistry and complete blood counts at each time point. Shift tables between the worst post-baseline and baseline values are provided (based on the National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 3.0).

10.6.3 Vital Signs

Summary statistics are provided for vital signs at protocol-specific scheduled visits.

10.6.4 Antibody Formation

A table summarizing the number and percentage of subjects with anti-romiplostim antibodies and antibodies that cross-react with endogenous thrombopoietin (eTPO) is provided at each time point. A listing of subjects with positive anti-romiplostim antibodies and antibodies that cross-react with eTPO is also provided.

10.6.5 Exposure to Investigational Product

Descriptive statistics will be produced to describe the exposure to investigational product by treatment group.

Summary statistics are calculated for cumulative dose (by µg and µg/kg) and average weekly dose (by µg/week and µg/kg/week). Exposure summary by age group and

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splenectomy status are also provided. Summary for weight based dose are provided weekly for Week 1-8 and then every 4 weeks.

A listing of investigational product administration, including weight based dose and reason for ending investigational product is provided.

10.6.6 Exposure to Concomitant Medication

The number and proportion of subjects receiving concomitant medications for ITP during the treatment period will be summarized by preferred term as coded by the World Health Organization Drug (WHO DRUG) dictionary.

11. Changes From Protocol-specified Analyses

There are no changes to the protocol-specified analyses.

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