STATISTICAL ANALYSIS PLAN

Primary Analysis for the Companion Study for Darbepoeitin Alfa Study 20090160

Protocol Number :	**20130113**
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Does this Statistical Analysis Plan document any analysis with the objective to claim pre-specification?

☐ Yes

☑ No

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Table of Abbreviations

Abbreviation or Term	Definition/Explanation
ACS	Acute coronary syndrome
AE	Adverse Event
AML	Acute myelogenous leukemia
ATE	Arterial thromboembolic event
Baseline hemoglobin	Hemoglobin value measured on study day 1 (the day of first administration of IP) before administration of IP and assessed by the local laboratory
CRF	Case report form
CTCAE	Common Terminology Criteria for Adverse Events
DVT	Deep vein thrombosis
End of study (EOS)	Subjects will not receive IP beyond week 73. The overall end of study will occur once all subjects enrolled and dosed with IP either withdraw from the study early, die, or complete the treatment period of the study. The end of study for an individual subject will occur either when the subject is withdrawn from the study, dies, or completes the final EOS visit.
End of the active treatment period visit (EOATP)	The final required visit in the MDS 20090160 study for subjects that complete IP treatment per protocol through week 72 / 73. Only subjects that complete all IP treatment in the MDS 20090160 study are potentially eligible to participate in the 20130113 study.
Enroll, Enrolled, or Enrollment	Enrollment is defined as the point in time when the subject has completed required screening procedures, all eligibility criteria are met, and the subject receives the first dose of IP on day 1 / week 1.
ESA	Erythropoiesis-stimulating agent
g/dL	Grams per deciliter
Hb	Hemoglobin
ICF	Informed consent form
IP	Investigational product
MDS	Myelodysplastic syndrome
PE	Pulmonary embolism
RBC transfusion	Red blood cell transfusion
SAE	Serious adverse event
SAP	Statistical Analysis Plan
SMQ	Standardized MedDRA query

Abbreviation or Term	Definition/Explanation
Source Data	Information from an original record or 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)].
Study day 1	The first day that protocol specified IP is administered to the subject; Day 1 t is expected to align with the end of the active treatment period visit of the MDS 20090160 study (window +10 days)
TIA	Transient ischemic attack
TVE	Thrombovascular event
μg	Microgram
VTE	Venous thromboembolic event
WHO	World Health Organization

1. INTRODUCTION

This statistical analysis plan (SAP) outlines the statistical analyses to be performed for Amgen protocol 20130113 entitled A Single Arm, Companion Study to Myelodysplastic Syndrome (MDS) 20090160 Using Darbepoetin alfa for the Treatment of Anaemic Subjects With Myelodysplastic Syndrome. The analyses summarized here are beyond the analyses described within the SAP version 3.0, dated on 30 September 2013 for data collected within the scope of Amgen protocol 20090160 entitled A Multicenter, Randomised, Double-blind, Placebo-controlled Study of Darbepoetin Alfa for the Treatment of Anaemic Subjects with Low or Intermediate-1 Risk Myelodysplastic Syndromes (MDS). The objective of this SAP is to pre-specify non Clinical Study Report (CSR) -related analyses.

2. OBJECTIVES

The primary objective of this study is to provide required access of investigational product (darbepoetin alfa) beyond the end of active treatment period of the darbepoetin alfa MDS 20090160 study for subjects that have continued demonstration of benefit from darbepoetin alfa treatment and to describe the safety of longer-term use in this patient population. Treatment with darbepoetin alfa may continue for up to 73 weeks or until progression to AML, whichever occurs first.

2.1 Definitions

Progression to Acute Myelogenous Leukemia (AML)

Progression to AML in this study will be assessed according to World Health Organization (WHO) guidelines (peripheral or blast cells ≥ 20%, presence of pathognomonic AML cytogenetic change, or evidence of marrow blast criteria for erythroleukemia).

Red Blood Cell (RBC) Transfusions

This is defined as any RBC transfusion (includes packed RBCs or whole blood and excludes platelets) given during an assessment period, regardless of hemoglobin concentration level at the time of transfusion or reason for transfusion. Subjects with at least 1 RBC transfusion during the assessment period will be considered “transfused”. Subjects with no RBC transfusions during the assessment period will be considered “not transfused”.

Treatment-emergent Adverse Event

A treatment-emergent adverse event (AE) is any event reported via the AE summary case report form (CRF) with an onset date between study day 1 and EOS.

- A treatment-emergent serious adverse event (SAE) is any event reported with an onset date between the date the subject signs the Informed Consent Form (ICF) through 30 days after the last dose of IP.
- Day 1 / week 1 dosing visit is expected to align with the end of the active treatment period (EOATP) visit of the MDS 20090160 study (window +10 days)
- End of Study visit performed 3 weeks ± 7 days after last dose of IP.

Thrombovascular event (TVE)

Thrombovascular events are adverse events that include arterial thromboembolic events (ATEs) and venous thromboembolic events (VTEs). These events will be coded using MedDRA version 17 (or higher) and identified using a Standardized MedDRA Query (SMQ 20000081, "embolic and thrombotic events" excluding terms from the sub-SMQ 20000083, "embolic and thrombotic events, vessel type unspecified and mixed arterial and venous") or more appropriate query available at the time of analysis. ATEs and VTEs are described below:

- **Arterial thromboembolic event (ATE)**
  ATEs include stroke, transient ischemic attack (TIA), acute coronary syndromes (ACS), and other arterial thrombosis/embolism. These events will be coded using MedDRA version 17 (or higher) and identified using the sub-SMQ 20000082 ("embolic and thrombotic events, arterial") or more appropriate query available at the time of analysis.
- **Venous thromboembolic event (VTE)**
  VTEs include deep vein thrombosis (DVT), pulmonary embolism (PE), and other venous thrombosis excluding superficial venous thrombosis. These events will be coded using MedDRA version 17 (or higher) and identified using the sub-SMQ 20000084 ("embolic and thrombotic events, venous") or more appropriate query available at the time of analysis. In addition, VTEs will be distinguished by whether or not they were confirmed by imaging. The primary analysis of VTEs will include fatal VTEs and VTEs confirmed by imaging; a sensitivity analysis will summarize all VTEs regardless of severity or confirmation.

3. COVARIATES

No covariates will be used in the analysis of the study.

4. ENDPOINT CATEGORIES AND ANALYSES

4.1 Safety Endpoints

4.1.1 Endpoints

Primary Endpoint: Subject incidence of treatment-emergent adverse events

4.1.2 Analysis Methods

Total enrollment is projected to be less than 10 subjects from 1 country. Given the small population, no summary statistics (descriptive or otherwise) will be provided. Listings will be provided for patient disposition data, baseline demographics, baseline characteristics, IP administration, and important protocol deviations. Listings will also be generated for the primary endpoint of all treatment-emergent adverse events by system organ class and preferred term. In addition, listings will be provided, by system organ class and preferred term, of all fatal adverse events, serious adverse events, adverse events leading to withdrawal from IP and significant treatment emergent adverse events. Progression to AML will also be summarized in a listing.

Listings of subjects who develop anti-darbepoetin alfa antibodies (binding and if positive, neutralizing) at any time will also be provided.

Missing data will not be imputed. Data collected in the study will not be combined with Amgen 20090160 study data.

5. LIST OF PLANNED TABLES, FIGURES, AND LISTINGS

The following listings will be provided:

- Listing of demographics and baseline characteristics including: enrollment date, sex, age at enrollment, height, weight, heart rate, temperature, blood pressure, and hemoglobin at enrollment
- Listing of treatment emergent adverse events and significant treatment emergent adverse events by system organ class and preferred term
- Listing of fatal adverse events by system organ class and preferred term
- Listing of serious adverse events by system organ class and preferred term
- Listing of adverse events leading to withdrawal from IP by system organ class and preferred term
- Listing of subjects that progressed to AML
- Listing of exposure to IP may include: the number of weeks of dosing, the total number of doses, the average weekly dose (μg/week), the average dose

administered (μg/dose), the cumulative dose administered (μg), the weight-adjusted average dose administered (μg/kg/dose), and the weight-adjusted cumulative dose administered (μg/kg)

- Listing of Important Protocol Deviations
- Listing of all RBC transfusions given on-study
- Listing of development of anti-darbepoetin alfa antibodies (binding and if positive, neutralizing) at any timepoint
- Listing of Thrombovascular Events including:
    - Arterial thromboembolic events [ATEs]: stroke; transient ischemic attack [TIA]; acute coronary syndromes [ACS]; other arterial thrombosis/embolism;
    - Venous thromboembolic events [VTEs]: deep vein thrombosis [DVT]; pulmonary embolism [PE]); and other venous thrombosis (excluding superficial venous thrombosis).