Title: Single arm, Companion Study to Myelodysplastic Syndrome (MDS) 20090160 Using Darbepoetin alfa for the Treatment of Anaemic Subjects With Myelodysplastic Syndrome

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I have read the attached protocol entitled a "Single Arm, Companion Study to Myelodysplastic Syndrome (MDS) 20090160 Using Darbepoetin alfa for the Treatment of Anaemic Subjects With Myelodysplastic Syndrome", dated 15 April 2013 and agree to abide by all provisions set forth therein.

I agree to comply with the International Conference on Harmonisation (ICH) Tripartite Guideline on Good Clinical Practice (GCP) and applicable national or regional regulations/guidelines.

I agree to ensure that Financial Disclosure Statements will be completed by:

- me (including, if applicable, my spouse [or legal partner] and dependent children)
- my subinvestigators (including, if applicable, their spouses [or legal partners] and dependent children)

at the start of the study and for up to one year after the study is completed, if there are changes that affect my financial disclosure status.

I agree to ensure that the confidential information contained in this document will not be used for any purpose other than the evaluation or conduct of the clinical investigation without the prior written consent of Amgen Inc.

_____
Signature

_____ _____
Name of Investigator Date (DD Month YYYY)

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Protocol Synopsis

Title: Single Arm, Companion Study to Myelodysplastic Syndrome (MDS) 20090160 Using Darbepoetin alfa for the Treatment of Anaemic Subjects With Myelodysplastic Syndrome

Study Phase: 3b

Indication: Myelodysplastic Syndrome

Primary Objective: 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.

Hypothesis: A formal statistical hypothesis will not be tested. Treatment emergent adverse events, progression to AML, and death will be summarised.

Primary Endpoint: Subject incidence of treatment-emergent adverse events

Study Design: This is a phase 3b, multi-centre, open-label, single-arm companion study to the MDS 20090160 study for the treatment of anaemic subjects with MDS. Subjects that complete the active-treatment period of the darbepoetin alfa MDS 20090160 study and meet the eligibility criteria may be enrolled into this study to continue treatment of darbepoetin alfa for up to 73 weeks or until progression to AML, whichever occurs first. AML progression 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) (Vardiman et al, 2009).

Sample Size: The number of subjects will be determined by the number of subjects who are randomised to the darbepoetin alfa 20090160, meet the entry criteria for the protocol, and sign informed consent.

Summary of Subject Eligibility Criteria: This study will enroll MDS subjects that have completed dosing in the active treatment period (up to week 70 or week 71) and the end of the active treatment period (EAOTP) visit of the Darbepoetin alfa MDS 20090160 study. Subjects must have an ongoing clinically relevant erythroid response at week 70 / 71 in the parent study (20090160) per the investigator clinical judgment. Subjects with MDS that have known progression to intermediate-2 or high risk per the MDS International Prognostic Scoring System (IPSS) are not eligible. Subjects who have progressed to acute myelogenous leukemia (AML) are not eligible. For a full list of eligibility criteria, please refer to Section 4.1 and Section 4.2.

Investigational Product

Amgen Investigational Product Dosage and Administration:
Eligible subjects will receive the first dose of subcutaneous (SC) darbepoetin alfa at the same dose that was last administered at the last dosing visit of the active treatment period in the darbepoetin alfa MDS 20090160 study (week 70 or week 71, depending on the dosing frequency in the active treatment period of the 20090160 study).

Investigators may elect to maintain subjects on the same dosing frequency or change the dosing frequency depending on erythroid response and Hb value (see Section 6.2.1.2).

Adjustment to the darbepoetin alfa dose will be made based on the most recent local laboratory Hb value obtained within 1 day before the dosing visit and taking into account transfusion information. Investigators should closely monitor Hb values and hold the dose of IP when the Hb exceeds the 12 g/dL threshold (refer to Section 6.2.1.2 for full dosing guidelines).

Procedures: Vital signs including blood pressure, local laboratory Hb, RBC transfusion data, and safety reporting will be performed at each visit. An end of study (EOS) visit will be performed at week 76, or 3 weeks after last dose of darbepoetin alfa for subjects who withdraw from the study earlier. For a full list of study procedures, including the timing of each procedure, please refer to Section 7 and the Schedule of Assessments (Table 5).

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Statistical Considerations: All study results will be descriptive, with no inferential tests. Treatment-emergent adverse events, progression to AML, and deaths will be summarized with descriptive statistics. Treatment-emergent adverse events will be summarised by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from IP and significant treatment-emergent adverse events will also be provided. For a full description of statistical analysis methods, please refer to Section 10.

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DES version/date	Version 3.0 31 January 2013

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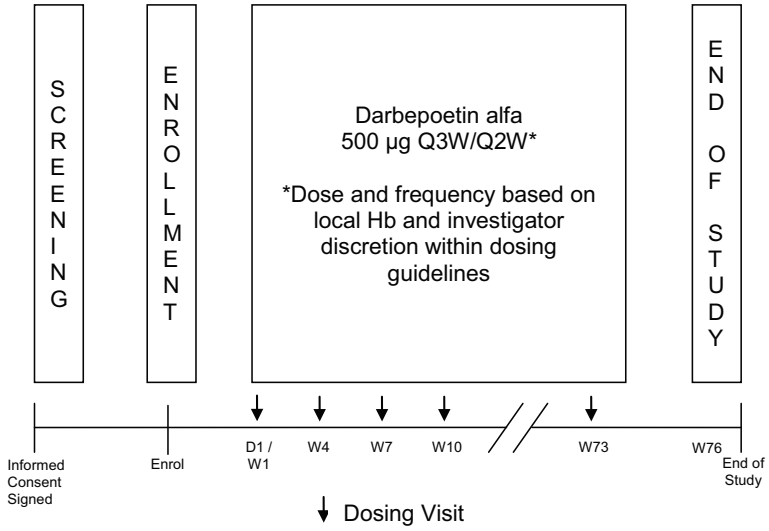
Study Design and Treatment Schema



- Informed Consent, Eligibility Assessments, and Enrollment can occur on the same day
- 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 investigational product (IP). Serious adverse events observed by investigator or reported by the subject that occur through 30 days after last dose of IP must be reported to Amgen.

D = Day; Hb = hemoglobin; Q3W = three-times per week; Q2W = two-times per week; W = week

Study Glossary

Abbreviation or Term	Definition/Explanation
5q-	MDS with isolated del(5q)
ACS	Acute coronary syndrome
AIDS	Acquired Immunodeficiency Syndrome
ALT	Alanine transaminase
AML	Acute myelogenous leukemia
ANC	Absolute neutrophil count
ASCO	American Society of Clinical Oncology
ASH	American Society of Hematology
AST	Aspartate aminotransferase
ATE	Arterial thromboembolic event
Baseline haemoglobin	Haemoglobin value measured on study day 1 (the day of first administration of IP) before administration of IP and assessed by the local laboratory
CI	Confidence interval
CMML	Chronic Myelomonocytic Leukemia
eCRF	Electronic case report form
CTCAE	Common Terminology Criteria for Adverse Events
DGHO	Deutsche Gesellschaft für Hämatologie und Onkologie (German Association for Haematology and Oncology)
DILI	Drug-induced liver injury
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.
Enrol, Enrolled, or Enrolment	Enrolment 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
FAB	French-American-British
GCP	Good Clinical Practice
G-CSF	Granulocyte colony stimulating factor

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Abbreviation or Term	Definition/Explanation
g/dL	Grams per deciliter
Hb	Haemoglobin
ICF	Informed consent form
ICH	International Conference on Harmonisation
ID	Identification
IEC	Independent ethics committee
INR	International normalized ratio
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
IP	Investigational product
IPIM	Investigational Product Instruction Manual
IPSS	International Prognostic Scoring System
IWG	International Working Group
IU	International unit
MDS	Myelodysplastic syndrome
PE	Pulmonary embolism
QW	Once weekly
Q2W	Once every 2 weeks
Q3W	Once every 3 weeks
RA	Refractory anaemia
RAEB	Refractory anaemia with excess blasts
RARS	Refractory anaemia with ring sideroblast
RBC	Red blood cell
rHuEpo	Recombinant human erythropoietin
SC	Subcutaneous
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
TIA	Transient ischemic attack
TVE	Thrombovascular event
µg	Microgram
ULN	Upper limit of normal
VTE	Venous thromboembolic event

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Abbreviation or Term	Definition/Explanation
WHO	World Health Organization
WPSS	WHO classification–based Prognostic Scoring System

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1. OBJECTIVES

Primary Objective

To allow continued 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.

2. BACKGROUND AND RATIONALE

2.1 Disease

Myelodysplastic syndrome (MDS) is a collection of clonal stem-cell disorders with common elements that include variable degrees of ineffective or hypoproliferative granulopoiesis, erythropoiesis, and megakaryopoiesis that can be manifested as quantitative and/or qualitative defects of the affected haematologic cell lines as well as a variable predilection for evolution into acute myelogenous leukemia (AML) (Lichtman, 2000). Some of the myriad disorders that fall under the MDS rubric have an identified cause or association such as drug exposure (eg, alkylating agents such as busulfan or cyclophosphamide [Bernard-Marty et al, 2003] or topoisomerase inhibitors), broad field irradiation, or inherited metabolic defects (eg, Pearson's syndrome [Pearson et al, 1979]). However, the cause of most cases of MDS remains unknown.

These acquired cases of MDS of unknown etiology primarily afflict elderly people, whose median age at diagnosis is between 60 and 75 years (Aul et al, 1998). The occurrence of MDS in individuals under 50 years of age is distinctly uncommon, while cases involving children are rare (Polychronopoulou et al, 2004). Experts generally agree that the incidence of new cases of MDS is rising due to a growing elderly population, improved diagnosis of the condition as well as the increasing use of marrow damaging chemotherapy or radiation therapy in the treatment of various neoplasms (Hamblin, 2002).

Clinical Presentation

Patients with MDS present with variable degrees of cytopenias, with anaemia secondary to ineffective erythropoiesis being the most common presentation, affecting greater than 80% of patients with MDS (Hellström-Lindberg et al, 1997). While some patients come to medical attention due to anaemia discovered by an incidental laboratory test (Heaney and Golde, 1999), many present with fatigue, dyspnea and other symptoms related to low haemoglobin levels (Balducci et al, 2006). As anaemia progresses,

symptoms related to the low haemoglobin levels correspondingly increase. The impact of anaemia on elderly patients, who commonly have co-existing cardiopulmonary disease, is particularly important. When compared to a control population, anaemic patients with MDS show significant impairment of most functional assessment scores and a higher degree of fatigue and dyspnea (Hellström-Lindberg et al, 2003). Further highlighting the negative impact of anaemia is the fact that patients with low risk MDS treated with erythropoiesis-stimulating agents (ESAs) to increase haemoglobin levels show improvement not only in quality of life measures (Jädersten and Hellström-Lindberg, 2009), but also in neurophysiological testing and transcranial Doppler sonography (Clavio et al, 2004).

In addition, clinical data point to the additional prognostic information provided by anaemia at the time of diagnosis. Anaemia at diagnosis added prognostic value to the International Prognostic Scoring System (IPSS) in terms of overall survival, independently stratifying patients within the intermediate IPSS risk categories (intermediate-1 and intermediate-2 risk groups). Specifically, patients with haemoglobin levels less than 10 g/dL had a lower life expectancy than those with haemoglobin levels greater than 10 g/dL, pointing to the pathophysiological importance of anaemia per se (Cazzola and Malcovati, 2008; Kao et al, 2008). The clinical importance of these findings is further underscored by the observations that correction of anaemia by either recombinant human erythropoietin or darbepoetin alfa improved survival in low / intermediate-1 risk MDS patients (Greenberg et al, 2009; Jädersten et al, 2008; Park et al, 2008).

The deleterious effect of anaemia on quality of life has been examined most extensively in oncology patients. Cancer patients with haemoglobin levels greater than 12 g/dL experience significantly fewer anaemia-related symptoms while manifesting better physical / functional well-being and an improved quality of life when compared to cancer patients with haemoglobin levels less than 12 g/dL (Cella, 1997). Other studies show that quality of life increases linearly when elevating the haemoglobin level to the normal range in patients with anaemia (Crawford et al, 2002; Harper and Littlewood, 2005). Another investigation involving 4,162 subjects age 65 years or older that explored the impact of anaemia on mortality, cognition and function revealed baseline impairment in activities of daily living and instrumental activities of daily living that were more severe in anaemic subjects than in their non-anaemic counterparts (Denny et al, 2006).

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Furthermore, cognition in the anaemic subjects as measured by the Short Portable Mental Status Questionnaire was significantly impaired.

Progression to AML

A paradox exists in the clinical presentation of MDS wherein peripheral cytopenias usually co-exist with a normal to hypercellular bone marrow (Bowen, 2005), which is explained in part by augmented intramedullary progenitor cell apoptosis (Bouscary et al, 2000; Parker et al, 1998). As peripheral cytopenias progress during the natural evolution of MDS, important associated clinical problems develop including increased susceptibility to infection due both to neutropenia and neutrophil dysfunction (Hamblin, 1992), and bleeding complications due to thrombocytopenia and platelet dysfunction (Mittelman and Zeidman, 2000). Progressive anaemia secondary to ineffective erythropoiesis exacerbates transfusion dependency, aggravates pre-existing cardiopulmonary conditions, and impairs quality of life (Casadevall et al, 2004). In addition, variable risk of progression to acute leukemia is inherent within the different subtypes of MDS, with the time for 25% of surviving MDS patients to transform to acute leukemia ranging from 9.4 years for those with low risk disease, to 2.4 months for those with high risk disease (Steensma and Bennett, 2006). The development of the IPSS was driven by the differential times to progression to AML in relation to the underlying morphological disease at diagnosis (see Table 1). Especially in low / intermediate-1 risk MDS patients, progression to AML was seen rarely and 25% of low and intermediate-1 patients progressed to AML after 9.4 years and 3.3 years, respectively (Kasner and Luger, 2009). From MDS patient registries, information on early rates of progression to AML reported a rate of approximately 3% within the first 6 months after diagnosis (de Witte et al, 2009).

MDS Classifications: FAB, WHO, IPSS/IPSS-R)and WPSS

Because of the heterogeneity of MDS and multiple classification systems, there has been an array of MDS subclassifications such as “refractory anaemia”, “preleukemia”, “smoldering leukemia” and “myelomonocytic leukemia.” The result has been confusion in how consistently to assess a diagnosis of MDS. In an effort to harmonise MDS classifications, a series of conferences on the subject convened by specialists from France, the United States and the United Kingdom reached a consensus opinion on myelodysplasia designated as the French-American-British (FAB) classification (Bennett et al, 1982). The widespread adoption of the FAB classification of myelodysplastic syndromes produced more consistent interpretations of data in studies

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that addressed a range of key issues including the etiology, prevalence and treatment of these conditions.

With the establishment of a uniform classification, MDS could be better assessed with respect to its prognosis. A group of international experts assessed the clinical outcome of MDS patients from a large database and compiled a prognostic assessment based on clinical characteristics. This IPSS (Appendix F) assigned a score to patients based on factors such as the number of blood cell lineages showing cytopenias, the percentage of blast cells in the bone marrow and karyotype (Greenberg et al, 1997). The IPSS categorised patients by risk of conversion to AML and death (Vardiman et al, 2002; Table 1).

Table 1. IPSS Score and Clinical Outcome

Risk Group	Total Score	Median Survival (years)	Time for 25% to Progress to AML (years)
Low	0	5.7	9.4
Intermediate-1	0.5 – 1.0	3.5	3.3
Intermediate-2	1.5 – 2.0	1.2	1.1
High	≥ 2.5	0.4	0.2

AML = Acute Myelogenous Leukemia; IPSS = International Prognostic Scoring System

Over a period of 5 years, a series of morphologic, immunologic, and cytogenetic workshops on acute lymphocytic leukemia, AML, MDS, and chronic lymphocytic leukemia examined the large body of knowledge with diagnostic and prognostic importance, including immunophenotyping and bone marrow cytogenetics. These criteria added a new and necessary dimension to the classification of MDS, providing important information for staging, prognosis, and therapy. Under the auspices of the European Association of Haematopathologists and the Society for Haematopathology, the World Health Organization (WHO) sponsored a 3-year project to revise and upgrade previous classifications for MDS and other neoplastic diseases of haematopoietic and lymphoid tissues. The WHO classification of MDS largely preserves the FAB structure, with a few notable alterations, of which the most important are (a) recognition of the del(5q) syndrome (ie, 5q-) (when existing as a solitary karyotypic abnormality with medullary blast percentage < 5%, and normal or elevated platelet count) as an independent subtype due to the relatively good prognosis and low risk of evolution to AML, (b) placing patients with bone marrow blast counts of between 20% and 30% within the AML category, and (c) removal of chronic myelomonocytic leukemia (CMML)

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as an MDS subtype and its reclassification as a myeloproliferative disorder (Harris et al, 1999; Vardiman et al, 2009; Vardiman et al, 2002).

Malcovati and colleagues subsequently proposed a new prognostic categorisation for MDS based on the WHO classification which they designated as the WHO classification–based Prognostic Scoring System (WPSS) (Malcovati et al, 2007). In addition to cytology and WHO subtype, the WPSS includes stable transfusion need as a prognostic variable. While the IPSS effectively predicts treatment outcome (Takahashi et al, 1998), the IPSS score is calculated at the time of treatment with the expected survival of the corresponding risk group calculated at diagnosis. In contrast, the WPSS is designed to provide treatment predictions at any time during the course of the disease.

Multiple other factors have been shown to add significant prognostic information to the IPSS: age, ferritin, marrow fibrosis, and further cytogenetic abnormalities (Christiansen et al, 2001; Della Porta et al, 2009; Garcia-Manero et al, 2008; Kantarjian et al, 2008; Padua et al, 1998; Shih et al, 2004; Sole et al, 2005). Underscoring the difficulty incorporating these prognostic factors into 1 system, several other prognostic scoring systems have been proposed; 2 developed by MD Anderson Cancer center, another WHO classification with cytogenetic markers, and a modified WHO that accounts for fibrosis (Bernasconi et al, 2007; Della Porta et al, 2009; Garcia-Manero et al, 2008; Kantarjian et al, 2008). A revised version of the IPSS currently is in development; however, in the interim the IPSS remains the most clinically useful and widely used system in clinical trials.

International Working Group (IWG) Criteria for Treatment Response

As new MDS targeted therapies were introduced, challenges arose in defining treatment efficacy. With the goal of standardising the assessment of treatment response for patients with MDS in clinical trials, a group of independent international experts created the IWG criteria for MDS treatment response in 2000 (Cheson et al, 2000).

These criteria were subsequently modified in 2006 to impart additional levels of clinical relevance to this set of standardised response criteria (Cheson et al, 2006; Table 2). The IWG criteria shown in Table 2 provide a generally accepted measure of treatment response for this variable group of conditions and the ability to standardise outcomes across MDS patients. The clinical use of the criteria and their 2006 update has been recommended by currently available guidelines (eg, Nordic MDS Group Care Program, 2010; Bowen et al, 2003).

Table 2. Haematologic IWG 2006 Response Criteria

Haematologic Improvement	Response Criteria (responses must persist ≥ 8 weeks)
Erythroid Response: (pretreatment haemoglobin < 11.0 g/dL)	Relevant reduction of units of RBC transfusions by an absolute number of at least 4 RBC transfusions/8 weeks compared to the pretreatment transfusion number in the previous 8 weeks. Only RBC transfusions given for a haemoglobin of 9.0 g/dL or less pretreatment will count in the RBC transfusion response evaluation.
	Haemoglobin increase by ≥ 1.5 g/dL
Platelet Response: (pretreatment platelet count < 100 x 10^9/L)	Absolute increase in platelet count of ≥ 30 x 10^9/L for patients starting with a platelet count of > 20 x 10^9/L
	Increase in platelet count from < 20 x 10^9/L to > 20 x 10^9/L and by at least 100%
Neutrophil Response: (pretreatment ANC < 1.0 x 10^9/L)	≥ 100% increase and an absolute ANC increase > 0.5 x 10^9/L

ANC = absolute neutrophil count; IWG = International Working Group; RBC = red blood cell

Within the erythroid response criteria of the IWG 2006 benchmarks is the de facto recognition that patients with IPSS low and intermediate-1 risk MDS include 2 distinct subgroups for which transfusion requirement is the clinical demarcation. Patients who have a high transfusion demand, typically 4 or more units over an 8-week period, may have more rapid clinical progression (Cazzola and Malcovati, 2005). These patients also respond to ESA treatment significantly less robustly than do others in the low and intermediate-1 risk IPSS categories (Hellström-Lindberg, 1995).

For patients with low and intermediate-1 risk MDS without a high transfusion demand, improvement in haemoglobin value is the efficacy parameter of paramount clinical importance (Cheson et al, 2006). The experts who developed the response criteria chose a value of 1.5 g/dL sustained over 8 weeks not as an arbitrary laboratory readout, but rather because “a haemoglobin increase of at least 15 g/L (1.5 g/dL) would be a clinically relevant effect on the erythroid series.”

MDS Treatment Options

Table 3 outlines the classes of approved or reported treatments in patients with MDS. Allogeneic stem cell transplantation remains the sole potentially curative intervention, but stringent qualifications, including an HLA-matched sibling, relative youth and absence of substantial co-morbidities severely limits its use (Scott and Deeg, 2005; Thompson and Luger, 2005). All other interventions are supportive, although the immunomodulatory agent lenalidomide (an analogue of thalidomide) can temporarily

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modify the course of the disease by reversing MDS-related cytopenias in some low-risk MDS patients with deletions of the long arm of chromosome 5 (5q-) (List et al, 2005). Transfusions (RBCs and platelets) and antibiotics are ancillary measures in the care of these patients that transiently address deleterious side effects of the cytopenias.

Table 3. MDS Treatments Used in Clinical Practice

Class of Intervention	Examples
Haematopoietic growth factors	ESAs, G-CSF, thrombopoietic growth factors
Transcriptional modifying therapy	Hypomethylating agents: 5-azacytidine, decitabine histone deacetylase inhibitors (investigational)
Immunomodulating agents	Lenalidomide, thalidomide, anti-thymocyte globulin, cyclosporin A
Intensive chemotherapy	Anthracyclines, cytosine arabinoside
Cure	Allogeneic stem cell transplantation

ESAs = erythropoiesis-stimulating agents; G-CSF = granulocyte colony stimulating factor
Note: These treatments might not have local regulatory approval for use in patients with MDS

Transfusion

Although new therapeutic treatments have shown promise in the treatment of MDS, supportive care remains the primary treatment option for patients with early stage disease (Hofmann and Koeffler, 2005). Transfusions augment the end-product cells in the circulation and are the basic foundation for supportive therapies that buttress the failing erythron, which is the fundamental disease process. Unfortunately, blood product transfusions carry potential undesirable complications including risk of infection with viral agents such as hepatitis and human immunodeficiency virus (Barbara, 2004), acute haemolytic transfusion reactions with potential serious sequelae (Sloop and Friedberg,1995), transfusion-related acute lung injury (Looney et al, 2004), allergic reactions (Gilstad, 2003), iron overload (Franchini and Veneri, 2004) as well as hypervolemia-related exacerbation of congestive heart failure symptoms (Freudenberger and Carson, 2003). Over time, alloimmunisation impairs the efficacy of blood component transfusions, eventually rendering some patients completely refractory to the intervention. In the MDS setting, increasing rates of RBC transfusions further indicate disease progression according to IWG 2006 response criteria definitions (Cheson et al, 2006).

Iron overload is a particularly insidious complication in MDS. Each unit of blood deposits approximately 220 mg of iron in the tissues of these patients, which progressively accumulates because no physiological iron excretion mechanism exists. Less widely

recognised is the fact that iron hyper-absorption occurs in patients with MDS due in large part to the ineffective erythropoiesis intrinsic to the condition (Uchida et al, 1988). The result is that patients with MDS can develop clinically significant iron overload with few or no transfusions. The relatively long life expectancy of patients with low and intermediate-risk MDS makes them susceptible to the complications of iron overload, including congestive heart failure, hepatic injury and cirrhosis that can negatively impact survival (Malcovati et al, 2006). The advent of oral iron chelators to replace the effective, but logistically demanding, deferoxamine mesylate has eased but not eliminated the great challenge that iron loading poses to these patients (Leitch and Vickars, 2009; Yeh et al, 2009).

Therapeutic Interventions

The efficacy of therapeutic interventions in MDS varies tremendously. Factors that contribute to this response heterogeneity include, but are not limited to, patient age, chromosomal abnormalities [eg, del(5q)/5q-] and metabolic anomalies (eg, sideroblastic anaemia). With the plethora of treatment options and the spectrum of conditions that compose the group of myelodysplastic disorders, several professional groups have formulated treatment guidelines, including the Nordic MDS Group Care Program (2010), the Deutsche Gesellschaft für Hämatologie und Onkologie (DGHO; German Association for Haematology and Oncology) (Hofmann et al, 2009), National Comprehensive Cancer Network (NCCN), 2013; Greenberg et al, 2006), the Italian Society of Haematology (Alessandrino et al, 2002), and United Kingdom MDS Guidelines Group (Bowen et al, 2003). The most recent guidelines applicable for Europe, the DGHO and the Nordic MDS Group Care Program guidelines, were based on recent trial data (Greenberg et al, 2009; Jädersten et al, 2008) and recommend ESA treatment for low / intermediate-1 patients with a predictive score of 0 or 1, which includes the requirement that these patients are non-transfusion dependent.

Erythropoiesis-stimulating Agents

Hypoxia is a potent physiological stimulus of endogenous erythropoietin production, and exponential increases in plasma erythropoietin levels have been correlated with progressive degrees of anaemia. In acute hypoxic stress, endogenous erythropoietin production can be elevated by 100- to 1000-fold, although the bone marrow's erythropoietic response to this augmented erythropoietin level is only within the range of 4- to 6-fold (Erslev, 1991; Kendall, 2001). In adults, the primary site of erythropoietin production is the peritubular cells of the kidney, with hepatocytes and fibroblastoid

interstitial cells of the liver being secondary production sites (Fisher, 2003). Abundant evidence suggests that erythropoietin exerts its haematopoietic effects at least in part by preventing apoptosis of erythroid precursor cells. Removal of erythropoietin exerts the same effect as activation of death receptors on erythroid precursor cells with resultant activation of various caspases leading to eventual apoptosis of erythroblasts (Testa, 2004).

Since increased apoptosis of marrow cells is believed to exacerbate peripheral cytopenias in the early stages of MDS, administration of pharmacological doses of exogenous ESA theoretically should exert anti-apoptotic effects upon erythroid precursor cells with consequent amelioration or reversal of MDS-related anaemia. This in turn should lead to higher erythrocyte levels in the blood, greater amounts of oxygen delivered to the tissues, symptomatic improvement, and enhanced quality of life in these MDS patients (Clavio et al, 2004; Spiriti et al, 2005). Furthermore, elevation in haemoglobin levels has been demonstrated to reverse cardiac remodeling and reduce cardiovascular risk. A logistic regression model predicted a 49% reduction in the risk of occurrence of cardiac remodeling with each unit increase in haemoglobin level among anaemic elderly MDS patients (Oliva et al, 2005), further supporting the potential clinical significance of higher haemoglobin levels in anaemic MDS patients.

Recombinant ESAs, including epoetin alfa and darbepoetin alfa, have been employed off-label as pharmacological measures to palliate and/or reverse MDS-associated anaemia (Jädersten et al, 2005; Stasi et al, 2005) especially in low-risk patients, as shown for 37% of low / intermediate-1 risk MDS patients in France (Kelaidi et al, 2010). Emerging data suggest that ESAs may improve MDS patient survival (Greenberg et al, 2009; Jädersten et al, 2008; Park et al, 2008), although this has not been shown in a randomised clinical trial.

The reported rate of response to ESA therapy in MDS patients varies, with values ranging from 0 to 50% (Cazzola, 1999; Rose et al, 1995; Stein et al, 1991; Stone et al, 1994; Zeigler et al, 1993). Many of these trials included patients who had more advanced disease (ie, intermediate-2 risk or high risk) as defined by the subsequently-developed IPSS criteria. A meta-analysis of 205 MDS patients tallied from 17 published studies showed a significant response rate of 16% to ESA treatment (Hellström-Lindberg, 1995). The majority of patients in these studies had refractory anaemia (RA, n=83), refractory anaemia with ring sideroblasts (RARS, n=70) and RA with excess blasts (RAEB, n=45), according to the FAB classification. A significant

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response was defined as a haemoglobin increase of 1.5 g/dL in patients with no transfusion need or a stable haemoglobin without need for transfusion in patients with transfusion need before entry into the study (Hellström-Lindberg, 1995). No uniform assessment of response was possible since these studies preceded development of the IWG erythroid response criteria. Additional predictive factors of ESA responsiveness included the absence of RBC transfusion need with 10.1% of transfusion-requiring MDS patients demonstrating a response to ESA compared to a response rate of 44.4% for those who did not require RBC transfusion. Endogenous erythropoietin level of ≤ 200 U/L was also shown to be associated with an improved erythropoietic response to recombinant human erythropoietin (rHuEpo) (Park et al, 2008). No dose-response relationship was detected for ESA in MDS patients and the maximal dose of ESA did not correlate with time to response.

A randomised study investigated the effects of subcutaneous (SC) rHuEpo administration at a dose of 20,000 IU 3 times a week in conjunction with granulocyte colony-stimulating factor (G-CSF) administered at 105 μg TIW for 12 weeks in MDS patients versus best supportive care (as defined in this study by blood transfusion and iron chelation therapy as needed). An erythroid response rate of 42% was demonstrated in those patients who received the combination cytokine therapy with rHuEpo and G-CSF, whereas a response rate of 0% was demonstrated in those patients who were observed, with administration of transfusions at the treating physicians discretion (DGHO Guideline: Hofmann et al, 2009). The difference in response rates between these 2 groups achieved statistical significance ($P = 0.01$) (Casadevall et al, 2004).

In another randomised, double-blind, placebo-controlled study investigating the efficacy of rHuEpo to reverse the anaemia in low risk MDS patients, an erythroid response rate of 36.8% was demonstrated in the cohort of patients who underwent rHuEpo therapy at a dose of 150 units/kg by SC injection daily for 8 weeks, whereas an erythroid response rate of 10.8% was detected in the cohort of patients who received placebo injections. The difference in response rates between these 2 cohorts achieved statistical significance ($P = 0.007$) (Italian Cooperative Study Group for rHuEpo in Myelodysplastic Syndromes, 1998). The data from this study led to the formulation of the evidence based clinical practice guidelines of the American Society of Clinical Oncology (ASCO) and the American Society of Hematology (ASH) recommending the administration of

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rHuEpo to anaemic patients with low risk MDS. Therefore, best clinical care for patients with MDS currently includes treatment with ESAs.

2.2 Amgen Investigational Product Background

Darbepoetin alfa, an ESA with 2 more consensus N-linked carbohydrate addition sites than rHuEpo, has a longer mean residence time and a 3-fold longer serum half-life than rHuEpo in both dialysis and cancer patients as well as demonstrating augmented in vivo activity (Egrie et al, 2003; Elliott et al, 2004; Jung and Schwartz, 2002; Macdougall et al, 1999) and hence may afford patients convenience in dosing schedules. Darbepoetin alfa is manufactured by recombinant DNA technology using a Chinese hamster ovary mammalian cell line. Darbepoetin alfa was initially approved for the treatment of symptomatic anemia associated with chronic renal failure in patients receiving dialysis as well as patients not on dialysis. Darbepoetin alfa was subsequently approved for the treatment of symptomatic anemia in patients with nonmyeloid malignancy receiving chemotherapy in the European Union and is approved for use in the oncology setting in multiple countries, including the United States, Australia, and Canada.

Several studies have evaluated the use of darbepoetin alfa in anaemic patients with MDS (Gabrilove et al, 2008; Gotlib et al, 2009; Mannone et al, 2006; Moyo et al, 2008; Musto et al, 2005; Park et al, 2008; Patton et al, 2005; Stasi et al, 2005; Villani et al, 2007; Villegas et al, 2011). Some studies evaluated darbepoetin alfa in combination with G-CSF (ie, filgrastim, pegfilgrastim) to address the potential of a synergistic response (Mannone et al, 2006; Park et al, 2008). In all of these studies, efficacy was primarily determined by erythroid response. Unless otherwise noted, an erythroid response was determined using the IWG definitions of major and minor response published in 2000. Several of the studies categorised patients by risk of progression to AML (Gabrilove et al, 2008; Mannone et al, 2006; Park et al, 2008; Villani et al, 2007; Villegas et al, 2011). These prognostic categorisations were derived from the IPSS.

The overall response rate in these trials ranged from 20% to 74%. Response rates were higher in patients with no prior ESA exposure as well as those with baseline endogenous erythropoietin levels below 500 U/L. While the number of subjects in most of the studies was small, the largest included more than 200 subjects.

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Meta-analysis of Darbepoetin alfa Versus Epoetin alfa

Moyo et al (2008) conducted a meta-analysis of 30 clinical studies published from 1990 to 2006 that evaluated the effectiveness of darbepoetin alfa (8 studies [n = 389 evaluable]) or epoetin alfa (22 studies [n = 925 evaluable]) monotherapy for the treatment of patients with MDS related anaemia. This meta-analysis included data from randomised controlled studies as well as single-arm clinical studies and retrospective studies. The objectives of the meta-analysis were to assess erythroid response rates in studies that either did or did not use the IWG definition of response, identify predictors of response, and compare erythroid response rates for the 2 ESAs when adjusted for IWG criteria.

Baseline characteristics of the patients were similar in both the darbepoetin alfa and epoetin alfa studies that used IWG criteria to evaluate response. No significant differences were observed with respect to age, gender, proportion of patients with RA or RARS, transfusion dependency rates, or mean baseline haemoglobin; however, mean baseline serum erythropoietin was significantly lower among darbepoetin alfa-treated patients than among epoetin alfa-treated patients ($P = 0.003$).

The average initial weekly dose of darbepoetin alfa was 176 μg (range: 100 to 315 μg). Among patients who were treated in studies that used the IWG criteria to evaluate response, the pooled estimate of erythroid response among the darbepoetin alfa-treated patients was 59.4% (95% confidence interval [CI]: 49.0 to 69.9), which was not significantly different from the 57.6% (95% CI: 45.1 to 70.0) response rate among patients treated with epoetin alfa ($P = 0.8282$). The dose of darbepoetin alfa was positively correlated with increased erythroid response rates. A response rate of 71.1% was achieved across 235 patients receiving darbepoetin alfa between 166 and 300 μg once weekly (QW). This was significantly greater than the response rate of 52.6% across the 154 patients who received darbepoetin alfa between 100 and 150 μg QW ($P < 0.001$).

Refer to the specific section of the Darbepoetin alfa Investigator's Brochure for additional information related to the physical, chemical, and pharmaceutical properties and formulation.

2.3 Rationale

The rationale of this study is to provide required access to investigational product (IP; darbepoetin alfa) beyond the end of active treatment period of the darbepoetin alfa

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MDS 20090160 study for subjects that continue to benefit from darbepoetin alfa treatment and to describe the safety of longer-term use in this patient population.

The MDS 20090160 study is a phase 3, multicenter, randomised, double-blind, placebo-controlled trial of darbepoetin alfa 500 µg administered Q3W to approximately 180 low or intermediate-1 risk anaemic MDS subjects. The 20090160 study consists of a 3-week screening period, 24-week double-blind treatment period, 48-week active treatment period, and long-term follow-up (LTFU) period.

2.4 Clinical Hypotheses

A formal statistical hypothesis will not be tested. Treatment emergent adverse events, progression to AML, and death will be summarized.

3. EXPERIMENTAL PLAN

3.1 Study Design

This is a phase 3b, multi-center, open-label, single-arm companion study to the phase 3 MDS 20090160 study for the treatment of anaemic subjects with MDS. Subjects that complete the active-treatment period of the darbepoetin alfa MDS 20090160 study and meet the eligibility criteria may be enrolled into this study to continue treatment of darbepoetin alfa for up to 73 weeks or until lack of response to IP, diagnosis of new malignancy, or progression to AML, whichever occurs first. The overall study design is described by a study schema at the end of the protocol synopsis section.

The study endpoints are defined in Section 10.1.1.

3.2 Number of Sites

Approximately 50 sites in Europe are expected to participate in the parent darbepoetin alfa MDS study (20090160). The total number of sites that may participate in this companion study is not known at this time; however, a minimum of 1 site will participate.

3.3 Number of Subjects

Participants in this clinical investigation shall be referred to as “subjects.”

It is estimated that approximately 20% of the subjects that complete the double-blind treatment and active treatment periods of the parent study (20090160) may be eligible to enroll; however, not all subjects may consent, nor will the majority of sites participate in the companion study .

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3.4 Replacement of Subjects

This is a companion study for subjects originally randomised to the darbepoetin alfa 20090160 study. Subjects must complete the 20090160 in order to be eligible for participation in this study, thus subjects will not be replaced.

3.5 Estimated Study Duration

3.5.1 Study Duration for Subjects

The maximum individual treatment duration for subjects that enter this companion study is approximately 73 weeks. The overall study duration is dependent upon the length of the enrollment period for the parent study (20090160).

3.5.2 End of Study

The study will end when all subjects complete the treatment period through week 73 and the End of Study (EOS) visit or are withdrawn from investigational product due to loss of response or disease progression or withdraw informed consent or die (see Section 8.3).

4. SUBJECT ELIGIBILITY

Investigators will be expected to maintain a screening log of all potential study candidates that includes limited information about the potential candidate (eg, date of screening). This log may be completed and updated via an Interactive Voice Response (IVR)/Interactive Web Response (IWR) system. Before any study-specific procedure, the appropriate written informed consent must be obtained (see Section 11.1).

4.1 Inclusion Criteria

4.1.1 General

101	Subject or subject's legally acceptable representative has provided informed consent prior to any study-specific activities/procedures being initiated;
102	Subject must continue LTFU within parent study (20090160);
103	Subject understands that darbepoetin alfa treatment will not be provided by Amgen past week 73;
104	Subject completes dosing in the active treatment period (through week 70 or week 71) and completed the end of the active treatment period (EOATP) visit of the parent study (20090160);

4.1.2 Disease-related

105	Subject must have an ongoing clinically relevant erythroid response as assessed by the Investigator using current response criteria (ie, IWG response criteria);

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4.2 Exclusion Criteria

4.2.1 Disease-related

201 Transfusion dependence defined as receiving a total of ≥ 4 units of RBC transfusion in the previous 8-week period prior to enrolment;

202 Known diagnosis of acute myelogenous leukemia (AML) or marrow collagen fibrosis;

203 Known refractory anaemia with excess blast-2 (RAEB-2);

204 Known diagnosis of intermediate-2 or high risk MDS per IPSS;

4.2.2 Medications or Other Treatments

205 Subjects received thrombopoiesis-stimulating factors (eg, eltrombopag, romiplostim) in the MDS 20090160 study or planning to receive such agents during the study;

206 Subjects receiving any investigational agents/devices not currently approved by the country's regulatory authority for the indication of use.

5. SUBJECT ENROLLMENT

Before subjects begin participation in any study-specific activities/procedures, Amgen requires a copy of the site's written independent ethics committee (IEC) approval of the protocol, informed consent form (see Section 11.2). Subjects must personally sign and date the IEC- and Amgen-approved informed consent form before commencement of study-specific procedures.

Each subject who enters into the screening period for the study will receive a unique subject identification (ID) number before any study-related activities/procedures are performed. The start of screening is defined when the subject signs of the informed consent form. The subject identification number will be assigned by the interactive voice response system (IVRS) and must remain constant throughout the entire clinical study. This number will be used to identify the subject throughout the clinical study and must be used on all study documentation related to that subject. Subjects that screen fail are not eligible for rescreening into the study. The site will be required to enter the subjects' ID number from the MDS 20090160 study into the IVRS.

A subject is considered enrolled when the investigator decides that the subject has met all eligibility criteria. The investigator is to document this decision and date, in the subject's medical record and on the enrollment electronic case report form (eCRF).

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6. TREATMENT PROCEDURES

6.1 Classification of Product

The Amgen Investigational Product used in this study includes open-label darbepoetin alfa. The Investigational Product Instruction Manual (IPIM), a document external to this protocol, contains detailed information regarding the storage, preparation, and administration of darbepoetin alfa.

6.2 Investigational Product

6.2.1 Amgen Investigational Product

Darbepoetin alfa will be manufactured and packaged by Amgen Inc. and distributed using Amgen clinical study drug distribution procedures. The investigational product, darbepoetin alfa, is provided in single dose vials of human serum albumin-free polysorbate solution that is a clear, colorless, sterile, preservative-free protein solution. Each vial will contain 500 μg, 300 μg, 200 μg, or 100 μg of darbepoetin alfa per mL. For dose adjustment and stopping guidance, refer to Section 6.2.1.1. The dose, frequency, date of administration, box number of investigational product is to be recorded on each subject's eCRF.

The day of the first dose of IP (darbepoetin alfa) will be considered study day 1. Investigational product should be administered subcutaneously (SC) by the appropriately trained and designated study personnel at the dosing schedule outlined in the Schedule of Assessments (Table 5).

6.2.1.1 Dosage, Administration, and Schedule

Darbepoetin alfa will be open-label. The first dose and dosing frequency of darbepoetin alfa on day 1 / week 1 should carry forward from the last dose and frequency from the parent study (darbepoetin alfa MDS 20090160 study) administered at week 70 / 71. The day 1 / week 1 visit should align within +10 days of the EOATP visit at week 72 / 73 from the darbepoetin alfa MDS 20090160 study.

The dosing schedule is described by a schema in the protocol synopsis.

6.2.1.2 Dosage Adjustments, Delays, Rules for Withholding or Restarting, Permanent Discontinuation

There will be no interactive voice recognition system (IVRS) guidance for IP dosing in this protocol. The IVRS will only be used in this study to track IP supply to sites and will allocate a IP box number based on the IP dose information entered by the site.

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Each subject entering the study will continue the last IP dose and frequency from the parent study (20090160). The investigator may choose to increase the dose of darbepoetin alfa with the maximum dose permitted of 500 µg Q2W. Dose increases should follow a step-wise approach, (eg, 300 µg to 500 µg; 200 µg to 300 µg) with at least 8 weeks at a given dose before the dose may be increased.

The frequency of darbepoetin alfa administration may also be changed, eg, from Q2W to Q3W dosing. No two Q3W or Q2W doses should be administered within any contiguous 14-day or 7-day period, respectively.

The Investigators should use their clinical judgment to assess the best dose and frequency considering risks and benefits, and subject needs. Adjustments to the darbepoetin alfa dose should be made based on the most recent local hemoglobin (Hb) value obtained within 1 day before the dosing visit. Dosing information and local Hb values will be recorded in the eCRF. The reason for a dose change is to be recorded on the eCRF.

Investigators should closely monitor each subjects' Hb values and suspend the dose of IP when the Hb exceeds the 12 g/dL threshold. IP should temporarily be withheld until Hb falls to ≤ 11.0 g/dL at which time IP may be restarted at a dose that is reduced from the previous dose (ie, 500 µg to 300 µg; 300 µg to 200 µg; 200 µg to 100 µg. Table 4 provides an outline of the recommended dose reductions.

Subjects will be permanently discontinued from darbepoetin alfa treatment and will complete the EOS visit at the next scheduled study visit if at any time the:

- subject loses erythroid response defined as Hb decrease of ≥ 1 g/dL compared to day 1 (Hb averaged over 8 weeks)
- subject becomes transfusion dependent defined as ≥ 4 units of RBC transfusion relative to previous 8 weeks prior to enrolment

Table 4. IP Dose Reductions

Dose	No Previous Dose Reduction	1 Previous Dose Reduction	2 Previous Dose Reductions	3 Previous Dose Reductions
500 µg Q3W	IP Reinstated at / Reduced to 300 µg Q3W	IP Reinstated at / Reduced to 200 µg Q3W	IP Reinstated at / Reduced to 100 µg Q3W	IP Discontinued
500 µg Q2W	IP Reinstated at / Reduced to 300 µg Q2W	IP Reinstated at / Reduced to 200 µg Q2W	IP Reinstated at / Reduced to 100 µg Q2W	IP Discontinued

Q3W = every 3 weeks; Q2W = every 2 weeks

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A maximum of 3 dose reductions are permitted during the study. Should a subject meet the criteria for a fourth dose reduction, the subject will be permanently discontinued from IP treatment and will complete the EOS visit at the next scheduled study visit.

At any time during the study, the investigator may withhold or discontinue IP for any subject who experiences a severe or life-threatening adverse event. In the case of uncontrolled blood pressure, hypertensive crisis, or occurrence of thromboembolic event, the recommendation is for the investigator to withdraw the subject from IP. Investigational product must also be discontinued for a subject upon the investigator's determination of progression to AML, or diagnosis of new malignancy.

Subjects that are withdrawn from IP should complete the EOS visit approximately 3 weeks after the last IP dosing visit.

6.3 Concomitant Therapy

Throughout the study, investigators may prescribe any concomitant medications or treatments deemed necessary to provide adequate supportive care except for those listed in Section 6.6. Key concomitant therapies are to be collected from informed consent through the end of study. Collect the therapy name, indication, dose, unit, frequency, and start and stop dates and record in the applicable eCRF (See Section 7.2.6).

6.4 Hepatotoxicity Stopping and Rechallenge Rules

Subjects with abnormal hepatic laboratory values (eg, alkaline phosphatase, aspartate aminotransferase [AST], alanine transaminase [ALT], total bilirubin or international normalized ratio [INR]) or signs/symptoms of hepatitis may meet the criteria for withholding of investigational product or other protocol-required therapies. Withholding is either permanent or conditional depending upon the clinical circumstances discussed below (as specified in the Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation, July 2009).

6.4.1 Criteria for Permanent Withholding of Amgen Investigational Product due to Potential Hepatotoxicity

Amgen investigational product should be discontinued permanently and the subject should be followed according to the recommendations in Appendix A (Additional Safety Assessment Information) for possible drug-induced liver injury (DILI), if all the following criteria are met:

- total bilirubin > 2x upper limit of normal (ULN) or INR > 1.5
- increased AST or ALT from the relevant baseline value as specified below:

Baseline AST or ALT value	AST or ALT elevation
< ULN	> 3x ULN

- and no other cause for the combination of laboratory abnormalities is immediately apparent; important potential causes for abnormal AST/ALT or total bilirubin values include, but are not limited to:
  - Obstructive gall bladder or bile duct disease
  - Viral or alcoholic hepatitis (eg, Hepatitis A/B/C/D/E, Epstein-Barr Virus, cytomegalovirus, Herpes Simplex Virus, Varicella, etc)
  - Hypoxic or ischemic hepatopathy or congestive hepatopathy in association with significant right sided heart failure
  - Concomitant administration of other hepatotoxins, including drugs that inhibit bilirubin glucuronidation (eg, indinavir, atazanavir, irinotecan) or herbal or dietary supplements
  - Heritable disorders causing impaired glucuronidation (eg, Gilbert's Syndrome); alpha-one antitrypsin deficiency
  - Autoimmune hepatitis
  - Nonalcoholic Steatohepatitis (NASH) or other "fatty liver disease"

If an alternative cause for hepatotoxicity is identified or less stringent conditions developed than what is noted above, determine if investigational product should be permanently or temporarily discontinued based on patient population and/or severity of the hepatotoxicity or event, as deemed appropriate for the safety of the subject.

6.4.2 Criteria for Conditional Withholding of Amgen Investigational Product due to Potential Hepatotoxicity

For subjects that do not meet the criteria for permanent withholding of investigational product outlined above, Amgen investigational product should be withheld if any of the following criteria are met and the subject should be evaluated for DILI:

- Elevation of either AST or ALT according to the following schedule:

Baseline AST or ALT value	AST or ALT elevation
Any	> 8x ULN at any time
Any	> 5x ULN but < 8x ULN for ≥ 2 weeks
Any	> 5x ULN but < 8x ULN and unable to adhere to enhanced monitoring schedule

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- clinical signs or symptoms that are, in the opinion of the Investigator, consistent with hepatitis (such as right upper quadrant pain/tenderness, fever, nausea, vomiting, jaundice, rash or eosinophilia > 5%). If such signs or symptoms are coupled with ALT or AST elevations > 3x ULN, investigational product should be withheld, or
- total bilirubin > 3x ULN at any time
- alkaline phosphatase > 8x ULN at any time

Amgen investigational product should be withheld pending investigation into alternative causes of DILI. If investigational product is withheld, the subject should be followed according to recommendations in Appendix A for possible DILI. Rechallenge may be considered if an alternative cause, such as acute Hepatitis B infection, is discovered and the laboratory abnormalities resolve to normal or baseline (Section 6.4.3).

6.4.3 Criteria for Rechallenge of Amgen Investigational Product After Potential Hepatotoxicity

The decision to rechallenge the subject should be discussed and agreed upon unanimously by the subject, Investigator, and Amgen.

If signs or symptoms recur with rechallenge, then Amgen investigational product should be permanently discontinued. Subjects who clearly meet the criteria for permanent discontinuation (as described in Section 6.4.1) should never be rechallenged.

6.5 Product Complaints

A product complaint is any written, electronic or oral communication that alleges deficiencies related to the identity, quality, durability, reliability, safety, effectiveness, or performance of any investigational or non-investigational product(s) or device(s).

Any product complaint(s) associated with an investigational product(s) or non-investigational product(s) or device(s) supplied by Amgen are to be reported according to the instructions provided in the IPIM.

6.6 Excluded Treatments or Procedures During the Treatment Period

During the treatment period, subjects should not receive any investigational agents/devices not currently approved by the country's regulatory authority for any indication. Subjects also should not receive thrombopoiesis-stimulating factors (eg, eltrombopag, romiplostim). No other medications are prohibited during treatment period.

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7. STUDY PROCEDURES

7.1 Schedule of Assessments

Table 5. Schedule of Assessments

	Screen / Enroll	Active Treatment Period	End of Study[g]
Study Week	72 / 73[a] / Day 1	Q3W or Q2W dosing up to week 73 (Q3W)	76
Informed Consent	x		
Medical history	x		
Physical examination	x		
Physical measurements (height and weight)[b]	x	performed at each visit	x
Vital Signs (heart rate, temperature, blood pressure)	x	performed at each visit	x
Assess for signs and symptoms of clinically relevant TVE	x	performed at each visit	x
Adverse Events (AEs), Serious Adverse Events (SAEs)[c]	x	performed at each visit	x
Key concominant medications, and red blood cell (RBC) transfusions	x	Assessed at each visit and throughout the study	
Local laboratory haemoglobin for dosing decision[d]	x	performed at each visit	
IP (darbepoetin alfa) administration[e]	x	performed at each visit	
Darbepoetin alfa antibody sample collection	x[f]		x

a. Last visit of the MDS 20090160 study at week 72 / 73 is the first dosing visit for 20130113.

b. Height only collected as part of screening. Weight collected at each visit.

c. AEs and SAEs will be reported throughout the study through 30 days after last dose of IP (darbepoetin alfa).

d. Dosing will occur Q3W ± 6 day or Q2W ± 6 days. No 2 Q3W or Q2W doses should be administered within any contiguous 14-day or 7-day period, respectively. Dosing decision based on local lab Hb taken within 1 day before IP dosing visit (See Protocol Section 6.2.1.2 for dosing guidelines).

e. Results of local laboratory Hb must be available and reviewed prior to IP adminstration.

f. A Day 1 antibody sample is not required if appropriately collected in the MDS 20090160 study at the End of the Active Treatment Period (EOATP) visit.

g. End of Study (EOS) visit at week 76 or 3 weeks after last dose of IP from Q3W or Q2W dosing for subjects that end IP early.

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7.2 General Study Procedures

Refer to the Schedule of Assessments (Table 5) for an outline of the procedures required at each study visit. The investigator at each site is responsible for ensuring that all study procedures are performed as specified in the protocol.

Each subject or their legally authorised representative must personally sign and date the Amgen- / IEC-approved informed consent form (ICF) before any study-specific procedures are performed. The ICF may be reviewed and signed/dated within 8 weeks of the screening assessments.

Demographic data collection including sex, date of birth, age, race, and ethnicity will be collected in order to study their possible association with subject safety data.

Each study visit may occur over a 2 consecutive day period. Study assessments including local laboratory Hb testing may be performed up to 1 day prior to the day of IP administration. For each study visit, all study procedures should be performed prior to IP administration.

7.2.1 Medical History

The Investigator or designee will collect a targeted medical history on the following: diabetes, hypertension (HTN), cerebrovascular accident (CVA), transient ischemic attack (TIA), peripheral vascular disease (PVD), myocardial infarction (MI), coronary artery, disease (CAD), congestive heart failure (CHF), cardiac arrhythmia, thromboembolic event, autoimmune disease, endocarditis, chronic obstructive pulmonary disease (COPD), pulmonary fibrosis, gastrointestinal bleeding, cholecystolithiasis (gall stones), pancreatitis, hepatitis, haemochromatosis, cirrhosis, urolithiasis (kidney stones), other vascular disease. Record all findings on the medical history eCRF. Adverse events that are ongoing at the end of the 20090160 study will not be reported as medical history, but will be carried forward as ongoing on the 20130113 study adverse event eCRF.

7.2.2 Physical Examination

A complete physical examination will be performed on all subjects during screening (a complete physical examination performed within 21 days prior to the start of screening may be used).

7.2.3 Physical Measurements

Height in centimeters and weight in kilograms should be measured without shoes. Height will be collected as part of screening assessments. Weight will be collected at every study visit.

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7.2.4 Vital Signs

The following measurements must be performed: systolic/diastolic blood pressure, heart rate, and temperature at every study visit. Subject should be in a supine position in a rested and calm state for at least 5 minutes before blood pressure assessments are conducted. The position selected for a subject should be the same that is used throughout the study and documented on the vital signs eCRF.

7.2.5 Thrombovascular Events

All subjects will be monitored closely at each visit for clinical signs and symptoms of thrombovascular events (TVEs):

- Arterial thromboembolic events [ATEs]:
  - stroke;
  - transient ischemic attack [TIA];
  - acute coronary syndromes [ACS]; and
  - other arterial thrombosis/embolism; and
- Venous thromboembolic events [VTEs]:
  - deep vein thrombosis [DVT];
  - pulmonary embolism [PE]); and
  - other venous thrombosis (excluding superficial venous thrombosis).

If any signs or symptoms are present, the subject will undergo specific laboratory and medical imaging studies to confirm TVEs. The medical imaging study or studies selected will depend on the anatomic site of the suspected TVE or organ of involvement (eg, Doppler ultrasound, venography, ventilation perfusion lung scan, angiography, magnetic resonance imaging [MRI]). If a TVE is confirmed, appropriate medical care according to standard local clinical practice should be initiated immediately and the TVE will be recorded in the eCRF.

7.2.6 Concomitant Medication and Red Blood Cell Transfusion

Key concomitant medications and RBC transfusion details will be collected from screening to the EOS visit. Concomitant medications include, but are not limited to, the use of any ESA or non-protocol specified dose of IP, haematopoietic growth factors, iron supplements, anti-hypertensive agents, anticoagulation therapies, and biological response modifiers (eg, thalidomide, lenalidomide, arsenic trioxide, azacitidine, decitabine.

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The date of transfusion and number of units and volume, reason for transfusion, the associated pre-transfusion Hb value, and any associated AEs will be recorded in the eCRF.

7.2.7 Adverse Events Reporting

Adverse events that occur beginning on day 1 through the EOS visit will be reported using the applicable eCRF. All serious adverse events occurring from the date the subject signs the ICF through 30 days after the last dose of IP will be reported to Amgen.

Adverse events ongoing at the end of the parent study (20090160) will be carried forward to the eCRF of this study.

Refer to Section 9.2 for more detail on adverse events reporting.

7.2.8 Screening and Enrollment

The following procedures are to be completed during the screening period as noted in the Schedule of Assessments (Table 5):

- Confirmation that the Informed Consent Form has been signed
- Registration in IVR system
- Physical examination
- Physical measurements (height and weight)
- Demographic data including sex, date of birth, race, and ethnicity
- Complete medical history
- Heart rate, temperature, blood pressure
- Adverse event reporting
- Key concomitant medications and RBC transfusion history
- Local laboratory Hb assessment (if applicable)
- IP box number assignment in IVRS (if applicable)
- IP dose administration (if applicable)

Screening assessment, enrollment, and the day of first dose of IP may occur on the same day provided that the subject meets all eligibility criteria prior to IP dosing. The day of first dose may occur up to 10 days after the screening visit to accommodate scheduling. Local laboratory Hb results must be available and reviewed prior to each IP dose administration.

7.2.9 Treatment

Treatment begins when the first dose of protocol-required therapies is administered to a subject. The following procedures will be completed during the treatment period at the

times designated in the Schedule of Assessments (Table 5). Administration of IP will occur after completion of all study specific assessments as shown below:

- Weight
- Heart rate, temperature, blood pressure
- Adverse event reporting
- Key concomitant medications and RBC transfusion history
- Local laboratory Hb assessment
- IP box number assignment in IVRS
- IP dose administration

Subjects that end darbepoetin alfa treatment early will complete an EOS visit 3 weeks ± 7 days after last dose of darbepoetin alfa (Section 7.2.10).

7.2.10 End of Study Visit

- Weight
- Heart rate, temperature, blood pressure
- Adverse event reporting
- Key concomitant medications and RBC transfusion history
- Anti-darbepoetin alfa antibody specimen collection
- Registration of EOS visit in IVRS

7.3 Antibody Testing Procedures

Blood samples for antibody testing are to be collected on day 1 (prior to darbepoetin alfa dosing) and at the EOS visit for the measurement of anti-darbepoetin alfa binding antibodies. A Day 1 antibody sample is not required if the antibody specimen was appropriately collected in the MDS 20090160 study at the EOATP visit.

Samples testing positive for binding antibodies will also be tested for neutralizing antibodies and may be further characterized for quantity/titer, isotype, affinity and presence of immune complexes. Additional blood samples may be obtained to rule out anti-darbepoetin alfa antibodies during the study.

Sites will be notified of any positive neutralizing antibody results to darbepoetin alfa. If results are not provided, no neutralizing antibodies to darbepoetin alfa have been detected.

Subjects who test positive for neutralizing antibodies to darbepoetin alfa at the final scheduled study visit will be asked to return for additional follow-up testing. This testing

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is to occur approximately every 3 months starting from when the site has been notified of the positive result, until: (1) neutralizing antibodies are no longer detectable or (2) the subject has been followed for a period of at least 1 year (± 4 weeks) post administration of darbepoetin alfa. All follow-up results, both positive and negative will be communicated to the sites. More frequent testing (eg, every month) or testing for a longer period of time may be requested in the event of safety-related concerns.

Subjects who test positive for binding, non-neutralizing antibodies and have clinical sequelae that are considered potentially related to an anti-darbepoetin alfa antibody response may also be asked to return for additional follow-up testing.

8. WITHDRAWAL FROM TREATMENT, PROCEDURES, AND STUDY

8.1 Subject's Decision to Withdraw

Subjects have the right to withdraw from the study at any time and for any reason without prejudice to their future medical care by the physician or at the institution.

Subjects (or a legally acceptable representative) can decline to continue receiving investigational product and/or other protocol-required therapies or procedures at any time during the study but continue participation in the study. If this occurs, the investigator is to discuss with the subject the appropriate processes for discontinuation from investigational product and must discuss with the subject the options for continuation of the Schedule of Assessments (Table 5) and collection of data, including endpoints and adverse events. The investigator must document the change to the Schedule of Assessments (Table 5) and the level of follow-up that is agreed to by the subject (eg, in person, by telephone/mail, through family/friends, in correspondence/communication with other physicians, from review of the medical records).

Withdrawal of consent for a study means that the subject does not wish to receive further protocol-required therapies or procedures, and the subject does not wish to or is unable to continue further study participation. Subject data up to withdrawal of consent will be included in the analysis of the study, and where permitted, publically available data can be included after withdrawal of consent. The investigator is to discuss with the subject appropriate procedures for withdrawal from the study.

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8.2 Investigator or Sponsor Decision to Withdraw or Terminate Subject's Participation Prior to Study Completion

The investigator and/or sponsor can decide to withdraw a subject from IP, protocol procedures, or the study as a whole at any time prior to study completion.

8.2.1 Reasons for Removal From IP Treatment

Reasons for removal from protocol-required IP include any of the following:

- subject request
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, protocol-specified criteria (see Section 6.2.1.2 and Section 6.4.3), pregnancy)
- decision by sponsor (other than subject request or safety concern)
- death
- lost to follow-up
- decision by Sponsor (other than subject request, safety concern, lost to follow-up)

8.2.2 Reasons for Removal From the Study

Reasons for removal of a subject from the study are:

- decision by Sponsor
- withdraw of consent from study
- death
- lost to follow-up
- safety concern (eg, due to an adverse event, ineligibility determined, protocol deviation, non-compliance, protocol-specified criteria (see Section 6.2.1.2 and Section 6.4.3), pregnancy)

9. SAFETY DATA COLLECTION, RECORDING, AND REPORTING

9.1 Adverse Events

9.1.1 Definition of Adverse Events

An adverse event is defined as any untoward medical occurrence in a clinical trial subject. The event does not necessarily have a causal relationship with study treatment. The investigator is responsible for ensuring that any adverse events observed by the investigator or reported by the subject are recorded in the subject's medical record.

The definition of adverse events includes worsening of a pre-existing medical condition. Worsening indicates that the pre-existing medical condition (eg, diabetes, migraine headaches, gout) has increased in severity, frequency, and/or duration, and/or has an association with a significantly worse outcome. A pre-existing condition that has not

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worsened during the study or involves an intervention such as elective cosmetic surgery or a medical procedure while on study, is not considered an adverse event.

For situations when an adverse event or serious adverse event is due to MDS, report all known signs and symptoms. Death due to disease progression in the absence of signs and symptoms should be reported as the primary tumor type (eg, metastatic pancreatic cancer). Note: the term "disease progression" should not be used to describe the adverse event.

The investigator's clinical judgment is used to determine whether a subject is to be removed from treatment due to an adverse event. In the event a subject, or subject's legally acceptable representative requests to withdraw from protocol-required therapies or the study due to an adverse event, refer to Section 8.1 for additional instructions on the procedures recommended for safe withdrawal from protocol-required therapies or the study.

9.1.2 Definition of Serious Adverse Events

A serious adverse event is defined as an adverse event that meets at least one of the following serious criteria:

- fatal
- life threatening (places the subject at immediate risk of death)
- requires in-patient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- congenital anomaly/birth defect
- other medically important serious event

An adverse event would meet the criterion of "requires hospitalization", if the event necessitated an admission to a health care facility (eg, overnight stay).

If an investigator considers an event to be clinically important, but it does not meet any of the serious criteria, the event could be classified as a serious adverse event under the criterion of "other medically important serious event". Examples of such events could include allergic bronchospasm, convulsions, blood dyscrasias, drug-induced liver injury, or events that necessitate an emergency room visit, outpatient surgery, or urgent intervention.

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9.2 Reporting of Adverse Events

9.2.1 Reporting Procedures for Adverse Events That Do Not Meet Serious Criteria

The investigator is responsible for ensuring that all adverse events observed by the investigator or reported by the subject that occur beginning on day 1 visit through the EOS are reported using the applicable eCRF (eg, Adverse Event Summary). Adverse events that are ongoing at the end of the MDS 20090160 will be transferred to the applicable adverse event eCRF.

The investigator must assign the following adverse event attributes:

- Adverse event diagnosis or syndrome(s), if known (if not known, signs or symptoms),
- Dates of onset and resolution (if resolved),
- Severity [and/or toxicity per protocol],
- Assessment of relatedness to IP, and
- Action taken.

The adverse event grading scale used will be the Common Terminology Criteria for Adverse Events (CTCAE). The grading scale used in this study is described in Appendix A. The investigator must assess whether the adverse event is possibly related to IP. This relationship is indicated by a “yes” or “no” response to the question: Is there a reasonable possibility that the event may have been caused by the IP?

The criteria for grade 4 in the CTCAE grading scale differs from the regulatory criteria for serious adverse events. It is left to the investigator’s judgment to report these grade 4 abnormalities as serious adverse events.

If the severity of an adverse event changes from the date of onset to the date of resolution, record a single event for each level of severity on the Adverse Event Summary eCRF.

The investigator is responsible for reviewing laboratory test results and determining whether an abnormal value in an individual study subject represents a clinically significant change from the subject’s baseline values. In general, abnormal laboratory findings without clinical significance (based on the investigator's judgment) are not to be recorded as adverse events. However, laboratory value changes that require treatment or adjustment in current therapy are considered adverse events. Where applicable, clinical sequelae (not the laboratory abnormality) are to be recorded as the adverse event.

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The Investigator is expected to follow reported adverse events until stabilization or reversibility.

9.2.2 Reporting Procedures for Serious Adverse Events

The investigator is responsible for ensuring that all serious adverse events observed by the investigator or reported by the subject that occur after signing of the informed consent through 30 days after the last dose of IP are to be recorded in the subject's medical record and are submitted to Amgen. The serious adverse event must be submitted to Amgen within 24 hours following the investigator's knowledge of the event via the applicable eCRF.

After the protocol-required reporting period defined above, the investigator does not need to actively monitor subjects for serious adverse events. However, if the investigator becomes aware of a serious adverse event after this protocol-required reporting period, the investigator will report the event to Amgen within 24 hours following the investigator's knowledge of the event. SAEs reported outside of the protocol-required reporting period will be captured within the safety database as clinical trial cases for the purposes of expedited reporting.

If the electronic data capture (EDC) system is unavailable to the site staff to report the Serious Adverse Event, the information is to be reported to Amgen via an electronic Serious Adverse Event (eSAE) Contingency Report Form within 24 hours of the investigator's knowledge of the event. See Appendix B for a sample of the Serious Adverse Event Worksheet/electronic Serious Adverse Event Contingency Report Form. For EDC studies where the first notification of a Serious Adverse Event is reported to Amgen via the eSerious Adverse Event Contingency Report Form, the data must be entered into the EDC system when the system is again available.

In addition to the attributes listed in Section 9.2.1, the investigator must also complete the Serious Adverse Event section of the Adverse Event Summary eCRF.

The investigator must assess whether the serious adverse event is possibly related to any study mandated activity or procedure. This relationship is indicated by a "yes" or "no" response to the question: "Is there a reasonable possibility that the SAE may have been caused by a study activity/procedure"?

The investigator is expected to follow reported serious adverse events until stabilization or reversibility.

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New information relating to a previously reported serious adverse event must be submitted to Amgen. All new information for serious adverse events must be sent to Amgen within 24 hours following knowledge of the new information. The investigator may be asked to provide additional follow-up information, which may include a discharge summary or extracts from the medical record. Information provided about the serious adverse event must be consistent with that recorded on the applicable eCRF (eg, Adverse Event Summary eCRF).

If a subject is permanently withdrawn from protocol-required therapies because of a serious adverse event, this information must be submitted to Amgen.

Amgen will report serious adverse events and/or suspected unexpected serious adverse reactions as required to regulatory authorities, investigators/institutions, and IECs in compliance with all reporting requirements according to local regulations and good clinical practice.

The investigator is to notify the appropriate IEC of serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures and statutes.

9.3 Pregnancy and Lactation Reporting

If a pregnancy occurs in a female subject, or female partner of a male subject, while the subject is taking protocol-required therapies report the pregnancy to Amgen as specified below.

In addition to reporting any pregnancies occurring during the study, investigators should monitor for pregnancies that occur after the last dose of protocol-required therapies through 1 month after the end of IP.

The pregnancy should be reported to Amgen's global Pregnancy Surveillance Program within 24 hours of the investigator's knowledge of the event of a pregnancy. Report a pregnancy on the Pregnancy Notification Worksheet (Appendix C). The Pregnancy Surveillance Program (PSP) will seek to follow the pregnant woman throughout her pregnancy and her baby up to 12 months after birth.

If a lactation case occurs while the female subject is taking protocol-required therapies report the lactation case to Amgen as specified below.

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In addition to reporting a lactation case during the study, investigators should monitor for lactation cases that occur after the last dose of protocol-required therapies through 1 month after last dose of IP.

Any lactation case should be reported to Amgen's global Lactation Surveillance Program (LSP) within 24 hours of the investigator's knowledge of event. Report a lactation case on the Lactation Notification Worksheet (Appendix C).

10. STATISTICAL CONSIDERATIONS

10.1 Study Endpoints, Analysis Sets, and Covariates

10.1.1 Study Endpoint

Primary Endpoint: Subject incidence of treatment-emergent adverse events

10.1.2 Analysis Sets

The analysis set will include all subjects who enrolled in the study and received at least 1 dose of the investigational product (darbepoetin alfa).

10.1.3 Covariates and Subgroups

No planned subgroups or covariates will be used in the analysis of the study.

10.2 Sample Size Considerations

No sample size estimation is required. The number of subjects will be determined by the number of subjects who are randomised to the darbepoetin alfa 20090160 study and meet the entry criteria for the protocol. It is estimated that approximately 20% of the subjects that complete the double-blind treatment and active treatment periods of the darbepoetin alfa 20090160 study might be eligible to enroll; however, not all subjects may consent, nor will the majority of sites participate in the companion study.

10.3 Planned Analyses

No formal hypothesis will be tested. All study results will be descriptive. Treatment emergent adverse events, progression to AML and death will be summarised.

10.4 Planned Methods of Analysis

No statistical inferential tests will be done. Incidence of treatment-emergent adverse events will be analyzed using the analysis set. Descriptive summary statistics will be provided for demographic data, cumulative doses, and patient disposition data. Important protocol deviations will be provided. Missing data will not be imputed. Data collected in the study will not be combined with 20090160 study data.

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Subject incidence of all treatment emergent adverse events will be tabulated by system organ class and preferred term. Tables of fatal adverse events, serious adverse events, adverse events leading to withdrawal from IP and significant treatment emergent adverse events will also be provided.

The incidence and percentage of subjects who develop anti-darbepoetin alfa antibodies (binding and if positive, neutralizing) at any time will be tabulated.

11. REGULATORY OBLIGATIONS

11.1 Informed Consent

An initial sample informed consent form is provided for the investigator to prepare the informed consent document to be used at his or her site. Updates to the template are to be communicated formally in writing from the Amgen Clinical Study Manager to the investigator. The written informed consent document is to be prepared in the language(s) of the potential patient population.

Before a subject's participation in the clinical study, the investigator is responsible for obtaining written informed consent from the subject or legally acceptable representative after adequate explanation of the aims, methods, anticipated benefits, and potential hazards of the study and before any protocol specific screening procedures or any IP is administered. A legally acceptable representative is an individual or other body authorized under applicable law to consent, on behalf of a prospective subject, to the subject's participation in the clinical study.

The acquisition of informed consent and the subject's agreement or refusal of his/her notification of the primary care physician is to be documented in the subject's medical records, and the informed consent form is to be signed and personally dated by the subject or a legally acceptable representative and by the person who conducted the informed consent discussion. The original signed informed consent form is to be retained in accordance with institutional policy, and a copy of the signed consent form is to be provided to the subject or legally acceptable representative.

If a potential subject is illiterate or visually impaired and does not have a legally acceptable representative, the investigator must provide an impartial witness to read the informed consent form to the subject and must allow for questions. Thereafter, both the subject and the witness must sign the informed consent form to attest that informed consent was freely given and understood.

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11.2 Independent Ethics Committee

A copy of the protocol, proposed informed consent form, other written subject information, and any proposed advertising material must be submitted to the IEC for written approval. A copy of the written approval of the protocol and informed consent form must be received by Amgen before recruitment of subjects into the study and shipment of Amgen investigational product.

The investigator must submit and, where necessary, obtain approval from the IEC for all subsequent protocol amendments and changes to the informed consent document. The investigator is to notify the IEC of deviations from the protocol or serious adverse events occurring at the site and other adverse event reports received from Amgen, in accordance with local procedures.

The investigator is responsible for obtaining annual renewal throughout the duration of the study. Copies of the investigator's reports and the IEC continuance of approval must be sent to Amgen.

11.3 Subject Confidentiality

The investigator must ensure that the subject's confidentiality is maintained for documents submitted to Amgen.

- Subjects are to be identified by a unique subject identification number.
- Where permitted, date of birth is to be documented and formatted in accordance with local laws and regulations.
- On the eCRF demographics page, in addition to the unique subject identification number, include the age at time of enrollment.
- For Serious Adverse Events reported to Amgen, subjects are to be identified by their unique subject identification number, initials (for faxed reports, in accordance with local laws and regulations), and date of birth (in accordance with local laws and regulations).
- Documents that are not submitted to Amgen (eg, signed informed consent forms) are to be kept in confidence by the investigator, except as described below.

In compliance with International Conference on Harmonisation (ICH) – Good Clinical Practices (GCP) Guidelines, it is required that the investigator and institution permit authorized representatives of the company, of the regulatory agency(s), and the IEC direct access to review the subject's original medical records for verification of study related procedures and data. Direct access includes examining, analyzing, verifying, and reproducing any records and reports that are important to the evaluation of the study. The investigator is obligated to inform and obtain the consent of the subject to

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permit such individuals to have access to his/her study related records, including personal information.

11.4 Investigator Signatory Obligations

Each clinical study report is to be signed by the investigator or, in the case of multi-center studies, the coordinating investigator.

The coordinating investigator, identified by Amgen, will be any or all of the following:

- a recognized expert in the therapeutic area
- an Investigator who provided significant contributions to either the design or interpretation of the study
- an Investigator contributing a high number of eligible subjects

12. ADMINISTRATIVE AND LEGAL OBLIGATIONS

12.1 Protocol Amendments and Study Termination

If Amgen amends the protocol, agreement from the Investigator must be obtained. The IEC must be informed of all amendments and give approval. The investigator **must** send a copy of the approval letter from the IEC to Amgen.

Amgen reserves the right to terminate the study at any time. Both Amgen and the Investigator reserve the right to terminate the Investigator's participation in the study according to the study contract. The investigator is to notify the IEC in writing of the study's completion or early termination and send a copy of the notification to Amgen.

Subjects may be eligible for continued treatment with Amgen investigational product by an extension protocol or as provided for by the local country's regulatory mechanism. However, Amgen reserves the unilateral right, at its sole discretion, to determine whether to supply Amgen investigational product and by what mechanism, after termination of the study and before the product is/are available commercially.

12.2 Study Documentation and Archive

The investigator is to maintain a list of appropriately qualified persons to whom he/she has delegated study duties. All persons authorized to make entries and/or corrections on eCRFs will be included on the Amgen Delegation of Authority Form.

Source documents are original documents, data, and records from which the subject's eCRF data are obtained. These include but are not limited to hospital records, clinical and office charts, laboratory and pharmacy records, diaries, microfiches, radiographs, and correspondence.

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The Investigator and study staff are responsible for maintaining a comprehensive and centralized filing system of all study related (essential) documentation, suitable for inspection at any time by representatives from Amgen and/or applicable regulatory authorities.

Elements include:

- Subject files containing completed eCRFs, informed consent forms, and subject identification list
- Study files containing the protocol with all amendments, Investigator's Brochure, copies of prestudy documentation, and all correspondence to and from the IEC and Amgen
- Investigational product-related correspondence including Investigational Product Accountability Record(s), Return of Investigational Product for Destruction Form(s), Final Investigational Product Reconciliation Statement, as applicable.

In addition, all original source documents supporting entries in the eCRFs must be maintained and be readily available.

Retention of study documents will be governed by the Clinical Trial Agreement.

12.3 Study Monitoring and Data Collection

The Amgen representative(s) and regulatory authority inspectors are responsible for contacting and visiting the investigator for the purpose of inspecting the facilities and, upon request, inspecting the various records of the clinical study (eg, eCRFs and other pertinent data) provided that subject confidentiality is respected.

The Amgen Clinical Monitor is responsible for verifying the eCRFs at regular intervals throughout the study to verify adherence to the protocol; completeness, accuracy, and consistency of the data; and adherence to local regulations on the conduct of clinical research. The Clinical Monitor is to have access to subject medical records and other study related records needed to verify the entries on the eCRFs.

The investigator agrees to cooperate with the clinical monitor to ensure that any problems detected in the course of these monitoring visits, including delays in completing eCRFs, are resolved.

In accordance with ICH GCP and the sponsor's audit plans, this study may be selected for audit by representatives from Amgen's Global Compliance Auditing function (or designees). Inspection of site facilities (eg, pharmacy, protocol-required therapy storage areas, laboratories) and review of study related records will occur to evaluate the study

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conduct and compliance with the protocol, ICH GCP, and applicable regulatory requirements.

Data capture for this study is planned to be electronic:

- All source documentation supporting entries into the eCRFs must be maintained and readily available.
- Updates to eCRFs will be automatically documented through the software's "audit trail".
- To ensure the quality of clinical data across all subjects and sites, a clinical data management review is performed on subject data received at Amgen. During this review, subject data are checked for consistency, omissions, and any apparent discrepancies. In addition, the data are reviewed for adherence to the protocol and GCP. To resolve any questions arising from the clinical data management review process, data queries and/or site notifications are created in the EDC system database for site resolution and closed by Amgen reviewer.
- The investigator signs only the Investigator Verification Form for this electronic data capture study. This signature indicates that investigator inspected or reviewed the data on the eCRF, the data queries, and the site notifications, and agrees with the content.

Amgen (or designee) will perform self-evident corrections to obvious data errors in the clinical trial database, as documented in the Study Specific Self Evident Corrections Plan. Examples of obvious data errors that may be corrected by Amgen (or designee) include deletion of obvious duplicate data (eg, same results sent twice with the same date with different visit-week 4 and early termination) and clarifying "other, specify" if data are provided (eg, race, physical examination). Each investigative site will be provided a list of the types of corrections applied to study data at the initiation of the trial and at study closeout.

12.4 Investigator Responsibilities for Data Collection

The investigator is responsible for complying with the requirements for all assessments and data collection (including subjects not receiving protocol-required therapies) as stipulated in the protocol for each subject in the study. For subjects who withdraw prior to completion of all protocol-required visits and are unable or unwilling to continue the Schedule of Assessments (Table 5), the investigator can search publically available records [where permitted]) to ascertain survival status. This ensures that the data set(s) produced as an outcome of the study is/are as comprehensive as possible.

12.5 Language

eCRFs must be completed in English. TRADENAMES® (if used) for concomitant medications may be entered in the local language.

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All written information and other material to be used by subjects and investigative staff must use vocabulary and language that are clearly understood.

12.6 Publication Policy

To coordinate dissemination of data from this study, Amgen encourages the formation of a publication committee consisting of several investigators and appropriate Amgen staff, the governance and responsibilities of which are set forth in a Publication Charter. The committee is expected to solicit input and assistance from other investigators and to collaborate with authors and Amgen staff as appropriate as defined in the Publication Charter. Membership on the committee (both for investigators and Amgen staff) does not guarantee authorship. The criteria described below are to be met for every publication.

Authorship of any publications resulting from this study will be determined on the basis of the Uniform Requirement for Manuscripts Submitted to Biomedical Journals (International Committee of Medical Journal Editors), which states:

- Authorship credit should be based on (1) substantial contributions to conception and design, acquisition of data, or analysis and interpretation of data; (2) drafting the article or revising it critically for important intellectual content; (3) final approval of the version to be published. Authors should meet conditions 1, 2, and 3.
- When a large, multicenter group has conducted the work, the group should identify the individuals who accept direct responsibility for the manuscript. These individuals should fully meet the criteria for authorship defined above.
- Acquisition of funding, collection of data, or general supervision of the research group, alone, does not justify authorship.
- All persons designated as authors should qualify for authorship, and all those who qualify should be listed.
- Each author should have participated sufficiently in the work to take public responsibility for appropriate portions of the content.

All publications (eg, manuscripts, abstracts, oral/slide presentations, book chapters) based on this study must be submitted to Amgen for review. The Clinical Trial Agreement among the institution, investigator, and Amgen will detail the procedures for, and timing of, Amgen's review of publications.

12.7 Compensation

Any arrangements for compensation to subjects for injury or illness that arises in the study are described in the Compensation for Injury section of the Informed Consent that is available as a separate document.

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14. APPENDICES

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Appendix A. Additional Safety Assessment Information

Adverse Event Grading Scale

The Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 is available at the following location:
http://ctep.cancer.gov/protocolDevelopment/electronic_applications/ctc.htm

Drug-induced Liver Injury Reporting & Additional Assessments

Reporting

To facilitate appropriate monitoring for signals of DILI, cases of concurrent AST/ALT and total bilirubin elevation according to the criteria specified in Section 6.4.1 require the following:

- The event is to be reported to Amgen as a serious adverse event within 24 hours of discovery or notification of the event (ie, before additional etiologic investigations have been concluded)
- The appropriate eCRF (eg, Adverse Event CRF) that captures information necessary to facilitate the evaluation of treatment-emergent liver abnormalities are to be completed and sent to the Amgen.

Other events of hepatotoxicity and potential DILI are to be reported as serious adverse events if they meet the criteria for a serious adverse event defined in Section.9.2

Additional Clinical Assessments and Observation

All subjects in whom investigational product(s) or protocol-required therapies is/are withheld (either permanently or conditionally) due to potential DILI or who experience AST/ALT elevations >3x ULN are to undergo a period of “close observation” until abnormalities return to normal or to the subject’s baseline levels. Assessments that are to be performed during this period include:

- Repeat liver chemistries within 24-48 hours (ALT, AST, alkaline phosphase, total bilirubin); in cases of total bilirubin > 2x ULN or AST/ALT much greater than 3x ULN, retesting is to be performed within 24 hours
    - Subjects are to be monitored at least twice weekly; testing frequency may decrease to once per week or less if laboratory abnormalities stabilize or the investigational product(s) or protocol-required therapies has/have been discontinued and the subject is asymptomatic
- Obtain prothrombin/INR, fractionated bilirubin and any other potentially relevant laboratory evaluations of liver function or disease
- Obtain complete blood count (CBC) with differential to assess for eosinophilia
- Obtain appropriate blood sampling for pharmacokinetic analysis if this has not already been collected

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- Obtain a more detailed history of:
  - Prior and/or concurrent diseases or illness
  - Exposure to environmental and/or industrial chemical agents
  - Symptoms (if applicable) including right upper quadrant pain, hypersensitivity type reactions, fatigue, nausea, vomiting and fever
  - Prior and/or concurrent use of alcohol, recreational drugs and special diets
  - Concomitant medications (including non-prescription medicines & herbal and dietary supplements)
- Initiate full viral and autoimmune hepatitis evaluation (serologies for hepatitis A, B, C, D, E, Epstein-Barr Virus, Herpes Simplex Virus, etc); evaluate for other potential causes of DILI including but not limited to: NASH, hypoxic/ischemic hepatopathy, and biliary tract disease
- Obtain gastroenterology or hepatology consult
- Perform appropriate liver imaging or biopsy if clinically indicated; strongly consider these tests in cases of concurrent transaminase and total bilirubin elevation as specified in Section 6.4.1
- Follow the subject until all laboratory abnormalities return to baseline or normal. The "close observation period" is to continue for a minimum of 4 weeks after investigational product discontinuation.

Appendix B. Sample Serious Adverse Event Reporting Form

AMGEN Study # 20130113 darbepoetin alfa	**Electronic Serious Adverse Event (eSAE) Contingency Reporting Form** **For Restricted Use**

Complete either Section A *or* Section B and follow the instructions provided:

Section A

☐ **EDC system (eg, Rave) is active for this study but is not accessible to allow reporting within 24 hours of the Investigator's knowledge of the event. I am submitting (check/complete all that apply):**

☐ An event that applies to a specialty CRF page titled _____ (eg, clinical fracture)

☐ Screening event (as defined by the protocol) | OR | ☐ On-study event (as defined by the protocol)

- *Complete ONLY Sections 1, 2 and 3 (page 1)*
- *Sign and date the signature section following Section 3*
- *Fax completed page of the form to the number noted in the header above Section 1*

Section B

☐ **Access to the EDC system (eg, Rave) has either not begun or has ended for this study. I am submitting (check all that apply):**

☐ Screening event (as defined by the protocol)
- ☐ This is a new event report
- ☐ This is follow-up information for a previously reported event

OR

☐ Event after access to the EDC system (eg, Rave) has ended (*provide subject's End of Study date in Section 2*)
- ☐ This is a new event report
- ☐ This is follow-up information for a previously reported event

- *Complete ALL sections of the form (all 3 pages)*
- *Sign and date the signature section at the end of the form*
- *Fax completed form (all 3 pages) to the number noted in the header above Section 1*

<<For completion by Amgen prior to providing to sites: SELECT OR TYPE IN A FAX#>>

1. SITE INFORMATION

Site Number	Investigator	Country

Reporter	Phone Number	Fax Number
	( )	( )

2. SUBJECT INFORMATION

Subject ID Number	Date of Birth	Sex	Race	If applicable, provide End of Study date
	Day Month Year	☐F ☐M		

If this is a follow-up to an event reported in the EDC system (eg, Rave), provide the adverse event term: _____
and start date: Day _____ Month _____ Year _____

3. SERIOUS ADVERSE EVENT

Provide the date the Investigator became aware of this Serious Adverse Event Information: Day____ Month____ Year____

Serious Adverse Event Diagnosis or Syndrome If diagnosis is unknown, enter Signs / Symptoms When Final Diagnosis is known, enter as Adverse Event *List one event per line. If event is fatal, enter the Cause of Death. Entry of "Death" is not acceptable, as this is an outcome.*	Date Started Day Month Year	Date Ended Day Month Year	Check only if event occurred before first dose of IP	Enter Serious Criteria code (see codes below)	Relationship Is there a reasonable possibility that the event may have been caused by IP? No✓	Yes✓	Relationship Is there a reasonable possibility that the event may have been caused by an Amgen device? No✓	Yes✓	If yes, what device?	Outcome of Event Resolved Not resolved Fatal Unknown	Check only if event is related to study procedure eg, biopsy

Serious Criteria: **01** Fatal; **02** Immediately life-threatening; **03** Required/prolonged hospitalization; **04** Persistent or significant disability /incapacity; **05** Congenital anomaly / birth defect; **06** Other medically important serious event

If you temporarily cannot access the EDC system (eg, Rave), sign below and submit ONLY this page to the number noted in the header above Section 1.

Signature of Investigator or Designee -	Title	Date
I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.		

FORM-056006 Page 1 of 3 *Version 3.0 Effective Date 04-FEB-2013*

AMGEN Study # 20130113 darbepoetin alfa	**Electronic Serious Adverse Event (eSAE) Contingency Reporting Form** **For Restricted Use**

If **access to the EDC system (eg, Rave) has either not begun or has ended for this study, *complete the remainder of this form.***

Site Number	Subject ID Number

4. Was subject hospitalized or was a hospitalization prolonged due this event? ☐No ☐Yes, If yes, please complete all of Section 4

Date Admitted Day Month Year	Date Discharged Day Month Year

5. Was IP administered prior to this event? ☐No ☐Yes, If yes, please complete all of Section 5

IMP: _____	Initial Start Date	Prior to, or at time of Event				Action Taken with Product
		Date of Dose	Dose	Route	Frequency	01 Still being Administered 02 Permanently discontinued 03 Withheld
	Day Month Year	Day Month Year				
☐ (✓) Blinded						
☐ (✓) Open Label						

6. RELEVANT CONCOMITANT MEDICATIONS (eg, chemotherapy) Any Relevant Medications? ☐ No ☐ Yes, If yes, please complete:

Medication Name(s)	Start Date Day Month Year	Stop Date Day Month Year	Co-suspect No✓	 Yes✓	Continuing No✓	 Yes✓	Dose	Route	Freq.	Treatment Med No✓	 Yes✓

7. RELEVANT MEDICAL HISTORY ***(include dates, allergies and any relevant prior therapy)***

8. RELEVANT LABORATORY VALUES ***(include baseline values)*** Any Relevant Laboratory values? ☐ No ☐ Yes, If yes, please complete:

Test											
Unit											
Date Day Month Year											

AMGEN Study # 20130113 darbepoetin alfa	**Electronic Serious Adverse Event (eSAE) Contingency Reporting Form** **For Restricted Use**

Site Number	Subject ID Number

9. OTHER RELEVANT TESTS ***(diagnostics and procedures)*** Any Other Relevant tests? ☐ No ☐ Yes, If yes, please complete:

Date (Day Month Year)	Additional Tests	Results	Units

10. CASE DESCRIPTION ***(Provide narrative details of events listed in section 3)*** Provide additional pages if necessary. For each event in section 3, where relationship=Yes, please provide rationale.

Signature of Investigator or Designee -	Title	Date
I confirm by signing this report that the information on this form, including seriousness and causality assessments, is being provided to Amgen by the investigator for this study, or by a Qualified Medical Person authorized by the investigator for this study.		

FORM-056006 Page 3 of 3 *Version 3.0 Effective Date 04-FEB-2013*

Appendix C. Pregnancy and Lactation Notification Worksheets

AMGEN® Pregnancy Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line

US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: 20130113

Study Design: ■ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (____)_____ **Fax** (____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Gender:** ☐ Female ☐ Male **Subject DOB:** mm ___ / dd ___ / yyyy____

4. Amgen Product Exposure

Amgen Product	Dose at time of conception	Frequency	Route	Start Date
				mm___/dd___/yyyy____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm ___/dd___/yyyy____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Pregnancy Information

Pregnant female's LMP mm ___ / dd ___ / yyyy_____ ☐ Unknown

Estimated date of delivery mm___ / dd___ / yyyy_____ ☐ Unknown ☐ N/A

If N/A, date of termination (actual or planned) mm___ / dd___ / yyyy_____

Has the pregnant female already delivered? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If yes, provide date of delivery: mm ___/ dd___/ yyyy_____

Was the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Amgen maintains a Pregnancy Surveillance Program that collects data about pregnancy of women who have been exposed to an Amgen product directly or via male sexual partner. Information from this program and from other sources of information, will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during pregnancy.

Effective Date: March 27, 2011 Page 1 of 1

AMGEN Lactation Notification Worksheet

Fax Completed Form to the Country-respective Safety Fax Line
SELECT OR TYPE IN A FAX# US: +888 814 8653

1. Case Administrative Information

Protocol/Study Number: 20130113

Study Design: ☑ Interventional ☐ Observational (If Observational: ☐ Prospective ☐ Retrospective)

2. Contact Information

Investigator Name _____ **Site #** _____

Phone (_____)_____ **Fax** (_____)_____ **Email** _____

Institution _____

Address _____

3. Subject Information

Subject ID # _____ **Subject Date of Birth:** mm_____ / dd_____/ yyyy_____

4. Amgen Product Exposure

Amgen Product	Dose at time of breast feeding	Frequency	Route	Start Date
				mm_____/dd_____/yyyy_____

Was the Amgen product (or study drug) discontinued? ☐ Yes ☐ No

If yes, provide product (or study drug) stop date: mm _____/dd_____/yyyy_____

Did the subject withdraw from the study? ☐ Yes ☐ No

5. Breast Feeding Information

Did the mother breastfeed or provide the infant with pumped breast milk while actively taking an Amgen product? ☐ Yes ☐ No

If No, provide stop date: mm_____/dd_____/yyyy_____

Infant date of birth: mm_____/dd_____/yyyy_____

Infant gender: ☐ Female ☐ Male

Is the infant healthy? ☐ Yes ☐ No ☐ Unknown ☐ N/A

If any Adverse Event was experienced by the mother or the infant, provide brief details:_____

_____

_____

Form Completed by:

Print Name: _____ **Title:** _____

Signature: _____ **Date:** _____

Amgen maintains a Lactation Surveillance Program that collects data about women who have been exposed to an Amgen product while breastfeeding. Information from this program and from other sources of information will contribute to knowledge that ultimately could help patients and their doctors in the future make more informed decisions about taking an Amgen medication during lactation.

Effective Date: 03 April 2012, version 2. Page **1** of **1**

Appendix D. WHO Classification of Acute Myeloid Leukemia (AML) and Related Neoplasms

Acute myeloid leukemia with recurrent genetic abnormalities
AML with t(8;21)(q22;q22); *RUNX1-RUNX1T1*
AML with inv(16)(p13.1q22) or t(16;16)(p13.1;q22); *CBFB-MYH11*
APL with t(15;17)(q22;q12); *PML-RARA*
AML with t(9;11)(p22;q23); *MLLT3-MLL*
AML with t(6;9)(p23;q34); *DEK-NUP214*
AML with inv(3)(q21q26.2) or t(3;3)(q21;q26.2); *RPN1-EVI1*
AML (megakaryoblastic) with t(1;22)(p13;q13); *RBM15-MKL1*
Provisional entity: AML with mutated NPM1
Provisional entity: AML with mutated CEBPA
Acute myeloid leukemia with myelodysplasia-related changes
Therapy-related myeloid neoplasms
Acute myeloid leukemia, not otherwise specified
AML with minimal differentiation
AML without maturation
AML with maturation
Acute myelomonocytic leukemia
Acute monoblastic/monocytic leukemia
Acute erythroid leukemia
Pure erythroid leukemia
Erythroleukemia, erythroid/myeloid
Acute megakaryoblastic leukemia
Acute basophilic leukemia
Acute panmyelosis with myelofibrosis
Myeloid sarcoma
Myeloid proliferations related to Down syndrome
Transient abnormal myelopoiesis
Myeloid leukemia associated with Down syndrome
Blastic plasmacytoid dendritic cell neoplasm

(Vardiman et al, 2009)

Appendix E. Erythroid Response Rates From 7 Prospective, Single Arm Studies of Darbepoetin alfa Alone or in Combination With G-CSF in Patients With MDS

Reference	Initial Darbepoetin alfa Dose/Schedule	Evaluable Patients	Overall Response	Major Response	Minor Response
Darbepoetin alone					
Gabrilove 2008 **N = 209**	500 μg Q3W 53/55week period Dose escalation: 500 μg Q2W after 6 weeks of treatment	ESA naïve n = 144	74%	59%	15%
		ESA treated n = 62	50%	34%	16%
Stasi 2005 **N = 53**	150 μg QW 24 weeks Dose escalation: 300 μg QW after 12 weeks of treatment	All ESA naïve n = 48	24 (50%)	21 (44%)	3 (6%)
Musto 2005 **N = 37**	150 μg QW 12 weeks Dose escalation: not allowed per protocol	ESA naïve n = 29	13 (45%)	11 (38%)	2 (7%)
		ESA treated n = 8	2 (25%)	2 (25%)	0 (0%)
Darbepoetin plus G-CSF					
Mannone 2006 **N = 66**	300 μg QW 12 weeks Dose escalation: not allowed per protocol GCSF was added to nonresponders after 12weeks	ESA naïve n = 49	38 (78%)	32 (65%)	6 (12%)
		ESA treated n = 13	8 (62%)	3 (24%)	5 (38%)
Villegas 2011 **N = 44**	300 μg QW 24 weeks Dose escalation: not allowed per protocol Filgrastim 300 μg QW was added to nonresponders	Not specified n = 44	32 (73%)	27 (61%)	5 (11%)
Villani 2007 **N = 15**	500 μg Q3W Dose escalation: not allowed per protocol Pegfilgrastim 6 mg Q3W for 9 weeks was added to nonresponders after 9 weeks	All ESA treated n = 15	3 (20%)	N/A	N/A
Gotlib 2009 **N = 24**	4.5 μg/kg QW. Dose escalation:9 μg/kg QW after 6 weeks of treatment GCSF 2.5 μg/kg BIW for 6 weeks was added to nonresponders after 12 weeks	All ESA naïve n = 24	16 (67%)	12 (50%)	4 (17%)

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Appendix F. International Prognostic Scoring System (IPSS) for MDS

	Score Value				
Prognostic Variable	0	0.5	1.0	1.5	2.0
BM blasts (%)	<5	5-10	—	11-20	21-30
Karyotype*	Good	Intermediate	Poor		
Cytopenias	0/1	2/3			

Scores for risk groups are as follows: Low, 0; INT-1, 0.5-1.0; INT-2, 1.5-2.0; and High, ≥2.5.

* Good, normal, −Y, del(5q), del(20q); Poor, complex (≥3 abnormalities) or chromosome 7 anomalies; Intermediate, other abnormalities.

(Greenberg et al, 1997, page 2085)

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