A Randomized Double Blind, Placebo Controlled Study Evaluating the Efficacy and Safety of Romiplostim Treatment of Thrombocytopenia in Subjects with Low or Intermediate-1 Risk Myelodysplastic Syndrome (MDS)

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To evaluate the efficacy of romiplostim for the treatment of thrombocytopenia in subjects with international prognostic scoring system (IPSS) low or intermediate-1 risk MDS as measured by the number of clinically significant bleeding events.

Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Haematopoietic neoplasms (excl leukaemias and lymphomas)
Study type	Interventional

Summary

ID

NL-OMON39254

Source
ToetsingOnline

Brief title
2006198

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
Myelodysplastic Syndrome

Research involving

Human

Sponsors and support

Primary sponsor: Amgen
Source(s) of monetary or material Support: Farmaceutische Industrie

Intervention

Keyword: MDS, Romiplostim, Thrombocytopenia

Outcome measures

Primary outcome

The primary endpoint is the incidence of clinically significant bleeding events. A clinically significant bleeding event is defined as any bleeding event of grade >= 2 per the modified WHO bleeding scale.

Secondary outcome

The key secondary endpoint is the incidence of platelet transfusion events. A discrete platelet transfusion event is any number of platelet transfusions administered within a 3-day period. Transfusions administered for more than 3 consecutive days will be counted as separate transfusion events every 4th day. Transfusions given in the absence of any bleeding when the platelet count is >10 x 109/L will be captured but will not be counted as a platelet transfusion event for the purpose of this endpoint.

The remaining secondary efficacy endpoints are:

• The overall number of bleeding events

• The total number of units of platelets transfused

• The incidence of platelet hematologic improvement (HI-P) per MDS IWG 2006

guidelines

• The duration of platelet hematologic improvement (HI-P) in the absence of

platelet transfusions per MDS IWG 2006 guidelines

• Overall survival

• Incidence of patient-reported bleeding events (Th-Symptoms)

The safety endpoints are:

• The incidence and severity of all adverse events including clinically

significant changes in laboratory values

• The incidence of disease progression to acute myelogenous leukemia (AML)

• The incidence of neutralizing romiplostim antibody formation and antibodies

that cross-react with eTPO

Study description

Background summary

Myelodysplastic syndromes (MDS) are a heterogeneous group of hematologic malignancies of the pluripotent hematopoietic stem cells. Patients often present with complications related to anemia (fatigue), neutropenia (infections) and/or thrombocytopenia (bleeding). The prognosis of MDS patients is poor. Patients die either from complications associated with cytopenias (infections and bleeding) or transformation to acute myeloid leukaemia (AML). The therapeutic options for MDS remain limited. Even as disease modulating agents are approved for the treatment of MDS, supportive care remains an important treatment option for patients with MDS. Currently there are no thrombopoietic agents indicated for use in MDS. Therefore, platelet transfusions are the only available treatment option (despite the associated risks).
Romiplostim increases platelet production via the thrombopoietin (TPO) receptor and has been shown to be well tolerated and effective in increasing platelet counts in animals, healthy volunteers, patients with Immune Thrombocytopenic

Purpura (ITP), and in patients with MDS.

Study objective

To evaluate the efficacy of romiplostim for the treatment of thrombocytopenia in subjects with international prognostic scoring system (IPSS) low or intermediate-1 risk MDS as measured by the number of clinically significant bleeding events.

Study design

This is a Phase 2, multicenter, randomized, double blind, placebo controlled study designed to assess the efficacy and safety of romiplostim (formerly, AMG 531) treatment in thrombocytopenic MDS subjects.
The study is composed of a 26-week placebo controlled test treatment period (romiplostim versus Placebo), a 2 to 4 week interim wash-out period, a 24-week placebo controlled extended treatment period, and a 4-week follow-up period. During the interim wash-out period, a bone marrow biopsy will be performed in the absence of growth factor to assess changes in the marrow. In the extended treatment period, safety assessments will continue and subjects will be allowed to receive any standard of care treatments for MDS. Subjects will be followed for survival for an additional 60 months following the End of Study (EOS) visit. The End of Trial is defined as the time when the last subject has finished the 60 months of survival follow-up.

Intervention

Approximately 240 thrombocytopenic subjects with IPSS low or intermediate-1 risk MDS will be randomized in a 2:1 allocation to receive romiplostim or placebo weekly via subcutaneous injection during a 26-week test treatment period and subsequent 24-week extended treatment period.

Study burden and risks

Patients will have extra visits when participating in this study, they will be treated weekly with romiplostim or placebo as subcuteneous injection, they will have bone marrow biopsies taken and they will complete patient diaries and questionnaires.

Because romiplostim is an investigational drug that has only been given to a limited number of humans (more than 300), not all potential side effects are currently known. The symptoms most frequently reported are headaches and flu-like symptoms.

Based on data from previous studies with romplostim received to date, other side effects can be:

an increase in the number of platelets to above the normal level (thrombocytosis); after stopping the treatment with romiplostim, the shortage of platelets can worsen temporarily for a short period of time; antibodies against romiplostim can be formed; an allergic reaction to romiplostim can occur; increased fibers (reticulin) in the bone marrow and there is the risk of a temporary increase in the number of blast cells in the bone marrow.

The usual risks that are associated with drawing blood are discomfort, pain, redness, swelling, and/or bruising where the blood is taken. Sometimes bleeding can occur at the place where blood is drawn. Fainting and infections are rare occurrences.
The subcutaneous injections of romiplostim/placebo may cause momentary discomfort and possible bruising. One subject reported a mild tingling sensation on the injection place.

Contacts

Public
Quintiles

Minervum 7061
Breda 4817ZK
NL
Scientific
Quintiles

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)

Elderly (65 years and older)

Inclusion criteria

Inclusion Criteria:
•Diagnosis of MDS using the WHO classification
•Per MDS IPSS, low or intermediate-1 risk MDS
•The mean of the two platelet counts taken within 4 weeks prior to randomization must be:
o<= 20 x 109/L, with no individual count >30 x 109/L, with or without a history of bleeding, OR
o<= 50 x 109/L, with no individual count >60 x 109/L with a history of bleeding.
A standard of care platelet count taken prior to Informed Consent may be used as 1 of the 2 counts taken within 4 weeks prior to randomization
•Subjects must be *18 and <= 90 years of age at the time of informed consent. Subjects between 85 and 90 years of age must have been diagnosed with MDS <= 5 years from study start.
•Eastern Cooperative Oncology Group (ECOG) performance status of 0-2
•Adequate liver function, as evidenced by ALT <= 3 times the laboratory normal range, AST <= 3 times the laboratory normal range and total bilirubin <= 2.0 times the laboratory normal range (Adequate liver function for patients with a confirmed diagnosis of Gilbert*s Disease evidenced by ALT <= 3 times the laboratory normal range, and AST <= 3 times the laboratory normal range).
•A serum creatinine concentration <= 2 mg/dl (<= 176.8 *mol/L)
•Bone marrow biopsy and aspirate with cytogenetics within 3 months of starting first dose of investigational product
•Subject or his/her legally acceptable representative provided written informedconsent before any study-specific procedures were initiated (see section 12.1)

Exclusion criteria

Exclusion Criteria:
• Have ever received any disease-modifying treatment for MDS
• Previously diagnosed with intermediate-2 or high risk MDS using the IPSS
• Prior history of leukemia, aplastic anemia, or other non-MDS related bone marrow stem cell disorder
• Prior history of hematopoietic stem cell transplantation
• Persistent peripheral blood monocytosis (>= 3 months with an absolute monocyte count >1,000/*L)
• Prior malignancy (other than in situ cervical cancer, non-melanoma skin cancer, or in situ carcinoma) unless treated with curative intent and without evidence of disease for ³ 3 years before randomization
• Active or uncontrolled infections
• Unstable angina, congestive heart failure (NYHA > class II), uncontrolled hypertension (diastolic >100 mmHg), uncontrolled cardiac arrhythmia, or recent (within 1 year) myocardial infarction

• History of arterial thrombosis (eg, stroke or transient ischemic attack) within the past year
• History of venous thrombosis that currently requires anti-coagulation therapy
• Received IL-11 within 4 weeks of the first dose of investigational product
• Have previously received any thrombopoietic growth factor
• Receipt of G-CSF, peg-G-CSF, or GM-CSF within 4 weeks of the first dose of investigational product
• Planned receipt of peg-G-CSF or GM-CSF after the first dose of investigational product
• Pregnant or breast feeding
• Subjects of reproductive potential who are not using adequate contraceptive precautions, in the judgment of the investigator. Amgen recommends double barrier contraception is used for all applicable patients enrolled on this study. A double barrier method is defined as two methods of contraception, for example 2 actual barrier methods, or one actual barrier method and one hormonal method.
• Known hypersensitivity to any recombinant E coli-derived product (eg, Infergen*, Neupogen*, Somatropin, and Actimmune)
• Previously enrolled in this study
• Inability to comply with study procedures
• Subject currently is enrolled in or has not yet completed at least 30 days since ending other investigational device or drug study(s)

Study design

Design

Study phase:	2
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)
Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Recruitment stopped
Start date (anticipated):	11-05-2009
Enrollment:	8
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	-
Generic name:	Romiplostim

Ethics review

Approved WMO Date:	18-07-2008
Application type:	First submission
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	20-01-2009
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	25-03-2009
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	12-05-2009
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-07-2009
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	07-10-2009
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	22-02-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Approved WMO Date:	14-04-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	24-08-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-10-2010
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	14-03-2011
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	11-07-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	15-08-2013
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)
Approved WMO Date:	13-05-2015
Application type:	Amendment
Review commission:	CMO regio Arnhem-Nijmegen (Nijmegen)

Study registrations

Followed up by the following (possibly more current) registration

No registrations found.

Other (possibly less up-to-date) registrations in this register

No registrations found.

In other registers

Register	ID
EudraCT	EUCTR2007-007258-75-NL
ClinicalTrials.gov	NCT00472290
CCMO	NL23719.091.08