A Phase 3, Multicenter, Randomized, Double-blind Study to Compare the Efficacy and Safety of Oral Azacitidine Plus Best Supportive Care versus Placebo Plus Best Supportive Care in Subjects with Red Blood Cell Transfusion-dependent Anemia and Thrombocytopenia due to IPSS Lower-risk Myelodysplastic Syndromes.

Published: 28-01-2013
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Primary Objective:To evaluate RBC transfusion independence in the 2 treatment arms (oral azacitidine plus best supportive care versus placebo plus best supportive care) in subjects with RBC transfusion-dependent anemia and thrombocytopenia (platelet...

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

Summary

ID

NL-OMON47302

Source
ToetsingOnline

Brief title
Celgene AZA-MDS-003

Condition

- Haematopoietic neoplasms (excl leukaemias and lymphomas)

Synonym
Myelodysplastic Syndromes, preleukemia

Research involving
Human

Sponsors and support

Primary sponsor: Celgene Corporation
Source(s) of monetary or material Support: Farmaceutische industrie

Intervention

Keyword: Azacitidine, Myelodysplastic Syndromes, Red Blood Cell Transfusion-dependent Anemia, Thrombocytopenia

Outcome measures

Primary outcome

Proportion of subjects in the overall population achieving RBC transfusion

independence with duration >= 84 days (12 weeks)

Secondary outcome

• OS;

• HI-P (IWG 2006 criteria; Cheson et al., Blood, 2006);

• Duration of RBC transfusion independence;

• Time to RBC transfusion independence;

• Proportion of subjects progressing to AML and time to AML progression;

• HI-E (IWG 2006 criteria; Cheson et al., Blood, 2006);

• Proportion of platelet transfusion-dependent subjects at baseline achieving

platelet transfusion independence with duration >= 56 days (8 weeks);

• Duration of platelet transfusion-independence;

• Time to platelet transfusion independence;

• Hematologic response (IWG 2006 criteria; Cheson et al., Blood, 2006);

• Proportion of subjects experiencing clinically significant bleeding events;

• Safety (type, frequency, severity of AEs and relationship of AEs to oral azacitidine/placebo; monitoring for progression to AML and second primary malignancy);

• HRQoL utilizing the Functional Assessment of Cancer Therapy-Anemia (FACT An) and EuroQoL Group EQ-5D-3L (EQ-5D) instruments;

• Measures of healthcare resource utilization.

Study description

Background summary

While, amongst others, subcutaneous azacatidine is approved for the treatment of low-risk MDS in some countries, this treatment is not used often. The primary treatment still remains treatment with ESAs and erythrocytes and/or platelets transfusions. Bone marrow transplantation is only possible for a small group of patients. An oral formulation of azacitidine provides an opportunity to deliver the drug at lower doses over a more prolonged schedule than can be practically achieved with parenteral therapy. In addition, an oral formulation can be taken at home. At least, oral administration may offer better quality of life and possibly a survival advantage. Please refer to protocol dated 01May2012, page 7 (Study Rationale).

Study objective

Primary Objective:
To evaluate RBC transfusion independence in the 2 treatment arms (oral azacitidine plus best supportive care versus placebo plus best supportive care) in subjects with RBC transfusion-dependent anemia and thrombocytopenia (platelet count <= 75 x 109/L) due to IPSS lower-risk MDS.
Secondary Objectives:
To evaluate in both treatment arms overall survival (OS); hematologic

improvement-platelet response (HI-P); duration of RBC transfusion independence and time to RBC transfusion independence; progression to acute myeloid leukemia (AML), and time to AML progression;
hematologic improvement-erythroid response (HI-E); platelet-transfusion independence, duration of platelet transfusion independence,
and time to platelet transfusion independence; hematologic response* clinically significant bleeding events; safety; health-related quality-of-life (HRQoL);
and healthcare resource utilization.

Study design

This is a phase 3, multicenter, randomized, double-blind, placebo-controlled, parallel-group study in subjects with RBC transfusion-dependent anemia and thrombocytopenia (ie, platelet count <= 50 x 109/L) due to IPSS lower-risk myeloplastic syndromes. The study consists of 3 phases: screening, double-blind treatment, and follow-up.
Because a hematologic response to treatment with azacitidine may frequently be delayed, it is recommended that subjects receive at least 6 cycles of treatment with IP; however, subjects may be discontinued from treatment at the investigator*s discretion prior to reaching the
recommended minimum number of cycles. Reasons for treatment discontinuation may include disease progression (Appendix A), AE, withdrawal of consent, death, lost to follow-up, or protocol violation. Subjects will be assessed for disease status at the end of Cycle 6, prior to starting Cycle 7. If subjects have met the following criteria, subjects can continue on to Cycle 7 and beyond. If subjects have failed to meet the criteria at the end of Cycle 6, subjects will be discontinued from protocol-prescribed therapy.

Intervention

Patients will receive 300 mg oral azacitidine or placebo after screening during 21 days of each 28 days cycle. Dosage can be amended if needed.

Study burden and risks

Oral azacitidine can have the following side-effects:
Very common (a 10% or more chance that this will happen): anemia (low number of red blood cells which may make you feel weak or tired); low number of white blood cells with or without fever; a decrease in the number platelets (the cells that help your blood to clot); infections (including pneumonia or of the lung, mouth, skin, or urinary tract which may be bacterial, fungal or viral); nausea; vomiting; diarrhea; stomach pain; constipation; feeling tired, unwell, or weak; fever; sore throat with swelling or pain of the nasal membranes or nose; decreased appetite; weight loss; low levels of blood potassium (which may cause fatigue, muscle weakness or cramps, or an irregular heart beat); pain (including muscle, joints, back and chest pain); dizziness; headache;

difficulty sleeping; shortness of breath with or without exercise; rash; itchiness; bruising (including tiny red or purple spots under the skin or other tissue); nosebleeds.
Common (between a 1%-10% chance that this will happen): Bone marrow failure which is a severe reduction of red and white blood cells and platelets (at nearly the same time) which can cause weakness, bruising, or make infections more likely; a very severe infection of the blood which may include a decrease in blood pressure; shivering (chills); indigestion or upset stomach; a disease affecting the gut which can result in fever, vomiting and stomach pain (diverticulitis); pain, swelling, or sores on the inside of the mouth; runny nose or sinus infection; bleeding including from the gums, eye, brain, stomach or rectum (hemorrhoids) or due to a catheter line; muscle spasms; anxiety; sleepiness; blood in the urine; hair loss; redness of the skin; hives; high blood pressure; low blood pressure or dizziness upon standing; fainting; dehydration; fluid around the lungs (pleural effusion).
Uncommon (between a 0.1%-1% chance that this will happen): Allergic reaction (may include difficulty breathing, swelling of the lips, itching, rash or dizziness).
Rare (less than 0.1% that this will happen):
Abnormal kidney function test; kidneys not functioning properly that has rarely led to too much acid in the blood or kidney failure (sometimes fatal); in patient with certain types of cancer, abnormal liver function may occur that has rarely led to decreased level of consciousness related to liver toxicity (sometimes fatal).

For a complete overview please refer to the schedule of events in the protocol. Patients must take two tablets of study medication one time a day with the prescribed amount water during 21 of the 28 days + anti-nausea medication. Patients are asked to complete a diary, herein they note the time of intake of the tablets, amount of tablets taken, if anti-nausea medication is used and the prescribed amount of water has been taken during the intake of the tablets. There is an extended and partly mandatory genetic research together with this research (cytogenetics, pharmacokinetics, biomarkers). Two questionnaires will be taken during the research.

Contacts

Public
Celgene Corporation

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Scientific

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Trial sites

Listed location countries

Netherlands

Eligibility criteria

Age
Adults (18-64 years)
Elderly (65 years and older)

Inclusion criteria

1. Age >= 18 years at the time of signing the informed consent document
2. Have a documented diagnosis of MDS according to WHO 2008 classification
3. Be RBC transfusion-dependent as defined by:
• Average transfusion requirement of >= 2 units** per 28 days of RBCsconfirmed for a minimum of 56 days immediately preceding randomization (please note that the period covering the transfusion history overlaps with the screening phase)
• Hemoglobin levels at the time of or within 7 days prior to administration of an RBC transfusion must have been <= 10.0 g/dL in order for the transfusion to be counted towards RBC transfusiondependent status. Red blood cell transfusions administered when Hgb levels were > 10.0 g/dL and/or RBC transfusions administered for elective surgery will not qualify as a required transfusion for the purpose of providing evidence of RBC transfusion-dependent status
- No consecutive 28 days that are RBC-transfusion-free during the 56 days immediately preceding randomization
4. Have thrombocytopenia as defined by two platelet counts that are <= 75 x 109/L and >= 21 days apart. The second confirmatory platelet count must be obtained <= 14 days prior to randomization
• At least one platelet count must be centrally analyzed within the 56 day screening period with results of <= 75 x 109/L; the second platelet

count may be centrally or locally analyzed, with results that are also <= 75 x 109/L.
• Prior documented medical history of thrombocytopenia may be used to demonstrate
eligibility for the study if at least one historical platelet count of <= 75 x 109/L was obtained within 56 days of randomization and >= 21 days apart from the centrally
analyzed platelet count.
• If additional platelet counts were obtained during the interim period, these must also have been <= 75 x 109/L. If platelet counts within the interim period are >75 x 109/L, this would be acceptable only if directly associated with a platelet transfusion administered within 7 days prior to the date of the platelet count.
5. Have an ECOG performance status of 0, 1, or 2
6. Females of childbearing potential (FCBP)** may participate, providing they meet the following conditions:
• Agree to use at least two effective contraceptive methods (oral, injectable, or implantable hormonal contraceptive; tubal ligation; intrauterine device; barrier contraceptive with spermicide; or vasectomized partner) throughout the study, and for 3 months following the last dose of IP; and
• Have a negative serum pregnancy test at screening ; and
• Have a negative serum or urine pregnancy test (investigator's discretion; sensitivity of at least 25 mIU/mL) within 72 hours prior to starting IP in the treatment phase (note that the screening serum pregnancy test can be used as the test prior to starting study therapy in the treatment phase if it is performed within the 72-hour timeframe)
7. Male subjects with a female partner of childbearing potential must agree to the use of at least two physician-approved contraceptive methods throughout the course of the study and should avoid fathering a child during the course of the study and for 3 months following the last dose of IP

Exclusion criteria

1. IPSS higher-risk (INT-2 or High risk) MDS
2. Secondary MDS
3. Hypoplastic MDS or other subtype with eligibility for treatment with immunotherapy based on investigator's judgment, unless subject received last dose from prior Chemo~ or Immunotherapy >= 24 weeks prior to randomization
4. CMML, atypical chronic myeloid leukemia (CML) and unclassifiable myeloproliferative disease (MPD)
5. Prior treatment with any of the following:
• Azacitidine (any formulation), decitabine or other hypomethylating

agent
• Lenalidomide, unless the subject received the last dose >= 8 weeks prior to randomization
6. Prior allogeneic or autologous stem cell transplant
7. History of inflammatory bowel disease (eg, Crohn's disease, ulcerative colitis), celiac disease (ie, sprue), prior gastrectomy or upper bowel removal, or any other gastrointestinal disorder or defect that would interfere with the absorption, distribution, metabolism or excretion of the IP and/or predispose the subject to an increased risk of gastrointestinal toxicity
8. Thrombocytopenia secondary to other possible causes, including medication(s), congenital disorder(s), immune disorder(s) (eg, idiopathic thrombocytopenic purpura [ITP]), or microvascular disorder(s) (eg, disseminated intravascular coagulation, hemolytic uremic syndrome, thrombotic thrombocytopenic purpura)
9. Use of any of the following within 28 days prior to randomization:
• cytotoxic, chemotherapeutic, targeted or investigational agents/therapies
• thrombopoiesis-stimulating agents (TSAs; eg, Romiplostim, Eltrombopag, Interleukin-11)
• ESAs and other RBC hematopoietic growth factors (eg, Interleukin-3)
• hydroxyurea
10. Ongoing medically significant adverse events from previous treatment, regardless of the
time period
11. Concurrent use of any of the following:
• iron-chelating agents, except for subjects on a stable or decreasing dose for at least 8 weeks (56 days) prior to randomization
• corticosteroid, except for subjects on a stable or decreasing dose for >= 1 week prior to randomization for medical conditions other than MDS
12. Prior history of malignancies, other than MDS, unless the subject has been free of the disease for >= 3 years. However, subjects with the following history/concurrent conditions are allowed:
• Basal or squamous cell carcinoma of the skin
• Carcinoma in situ of the cervix
• Carcinoma in situ of the breast
• Incidental histologic finding of prostate cancer (T1a or T1b using the tumor, nodes, metastasis [TNM] clinical staging system)
13. Significant active cardiac disease within the previous 6 months, including:
• New York Heart Association (NYHA) class IV congestive heart failure;
• Unstable angina or angina requiring surgical or medical intervention; and/or
• Myocardial infarction
14. Uncontrolled systemic fungal, bacterial, or viral infection (defined as ongoing signs/symptoms related to the infection without improvement despite appropriate antibiotics, antiviral therapy, and/or other

treatment)
15. Known Human Immunodeficiency Virus (HIV) or Hepatitis C (HCV) infection, or evidence of active Hepatitis B Virus (HBV) infection
16. Abnormal coagulation parameters (PT > 15 seconds, PTT > 40 seconds, and/or INR > 1.5). After consultation with the medical monitor, higher than normal range levels may be acceptable if the subject is being treated with a stable dose of anticoagulants for thrombotic prophylaxis (ie with atrial fibrillation, previous thromboembolic event, mechanical cardiac valve replacement or presence of lupus or antiphospholipid antibodies). The decision to include such patients would be the responsibility of the investigator.
17. Any of the following laboratory abnormalities:
• Serum AST/SGOT or ALT/SGPT > 2.5 x upper limit of normal (ULN) unless these abnormal liver function test(s) can be attributed to iron overload as demonstrated by a serum transferrin saturation of > 65% and a serum ferritin of > 1000 µg/L
• Serum bilirubin > 1.5 x ULN. Higher levels are acceptable if these can be attributed to active red blood cell precursor destruction within the bone marrow (ie, ineffective erythropoiesis) or in the presence of known history of Gilbert Syndrome. Subjects are excluded if there is evidence of autoimmune hemolytic anemia manifested as a corrected reticulocyte count of > 2% with either a positive Coombs' test or over 50% of indirect bilirubin
• Serum creatinine > 2.5 x ULN
18. Known clinically significant anemia due to iron, vitamin B12, or folate deficiencies, or autoimmune or hereditary hemolytic anemia, or gastrointestinal bleeding. Iron deficiency would be determined by a bone marrow aspirate stain for iron, the transferrin saturation (iron/total iron binding capacity [Fe/TIBC] <= 20%), or serum ferritin <= 15 ng/mL
19. Known or suspected hypersensitivity to azacitidine or mannitol
20. Pregnant or lactating females

Study design

Design

Study phase:	3
Study type:	Interventional
Intervention model:	Parallel
Allocation:	Randomized controlled trial
Masking:	Double blinded (masking used)

Control:	Placebo
Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	11-05-2015
Enrollment:	12
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Vidaza
Generic name:	Oral Azacitidine
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO Date:	28-01-2013
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	08-01-2014
Application type:	First submission
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	28-05-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-06-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	09-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	30-10-2014
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	13-05-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-06-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	16-09-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	21-09-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	12-11-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-12-2015
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-01-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	09-02-2017
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	19-02-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	20-03-2018
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	18-05-2018
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Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	24-05-2018
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Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
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Approved WMO Date:	16-01-2019
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Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	23-01-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO	

Date:	05-03-2019
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	10-12-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	11-12-2020
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	22-11-2021
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	03-01-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	01-10-2022
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	14-02-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	02-07-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)
Approved WMO Date:	04-08-2023
Application type:	Amendment
Review commission:	METC Universitair Medisch Centrum Groningen (Groningen)

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	EUCTR2012-002471-34-NL
ClinicalTrials.gov	NCT01566695
CCMO	NL42297.042.13

Study results

Date completed: 26-07-2018

Results posted: 17-12-2024

First publication
01-01-1900