A Phase 2, Randomized, Double-blind, Placebo-controlled, Multicenter Study Comparing Siltuximab Plus Best Supportive Care to Placebo Plus Best Supportive Care in Anemic Subjects with International Prognostic Scoring System Low- or Intermediate-1-Risk Myelodysplastic Syndrome

Published: 30-08-2011
Last updated: 28-04-2024

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Ethical review	Approved WMO
Status	Recruitment stopped
Health condition type	Other condition
Study type	Interventional

Summary

ID

NL-OMON35441

Source
ToetsingOnline

Brief title
CNTO328MDS2001

Condition

- Other condition
- Red blood cell disorders

Synonym
myelodysplasia, myelodysplastic syndrome (MDS)

Health condition

myelodysplastic syndrome (MDS)

Research involving
Human

Sponsors and support

Primary sponsor: Janssen-Cilag
Source(s) of monetary or material Support: Janssen BV

Intervention

Keyword: anemia, clinical efficacy, reduction in RBC transfusions

Outcome measures

Primary outcome

The primary objective of the trial (page 10 of protocol) is *to assess the

clinical efficacy of siltuximab, demonstrated by a reduction in RBC

transfusions to treat the anemia of MDS*

Secondary outcome

-To demonstrate symptomatic improvement of subjects treated with siltuximab

compared with the

placebo group

-To compare the number of RBC units transfused to treat the anemia of MDS, and

the proportion of

subjects treated with siltuximab who do not require a RBC transfusion to treat

the anemia of MDS,

from Week 5 to Week 12, compared with the placebo group

-To assess the change in hemoglobin among MDS subjects treated with siltuximab compared with the placebo group

-To compare disease progression (proportion of bone marrow blasts and cytogenetic change) for subjects treated with siltuximab compared with the placebo group

-To assess the safety profile of siltuximab and RBC transfusions among subjects with Low- or Intermediate-1 (INT-1)-risk MDS

-To assess the pharmacodynamics, pharmacokinetics, and antibodies to siltuximab (immunogenicity) in MDS subjects

-To investigate a biomarker profile that predicts response to siltuximab in this MDS population

-To perform an initial validation of a new patient-reported outcome (PRO) instrument (Non-Chemotherapy Anemia Symptom Scale [NCA-SS])

-To assess medical resource utilization (MRU), workforce behavior, and global productivity associated with health status in MDS subjects

Study description

Background summary

- Serum levels of IL-6 are known to be elevated in MDS, raising the possibility that inflammation may play an important role in the anemia associated with this disease. Dysregulated hepcidin is the principal mechanism underlying the anemia of inflammation, and increases in IL-6 have been shown toinduce the synthesis of hepcidin.
- The role of the bone marrow microenvironment in MDS has been investigated. Fibroblasts derived from MDS marrow produced significantly higher levels of IL-6 and tumor necrosis factor-*, (TNF-*), and MDS macrophages produce significantly higher levels of TNF-* than do their normal counterparts.8 In addition, a common morphological change within MDS marrow cells is the presence of abnormal mitochondrial iron accumulation, which is not confined to the refractory anemia with ringed sideroblast subtype of MDS and may contribute to numerous MDS pathophysiologic processes.11 Hepcidin, through its effect on ferroportin, is profoundly involved in control of intracellular iron, raising the possibility that IL-6 may be a mediator of disease progression in MDS

Study objective

The primary objective is to assess the clinical efficacy of siltuximab (a chimeric (murine-human) IgG1* mAb that specifically binds human IL-6 with high affinity and prevents its interaction with the IL-6 receptor, glycoprotein (GP) 80), demonstrated by a reduction in RBC transfusions to treat the anemia of MDS.

Study design

The hypothesis for this study is that a higher proportion of siltuximab-treated subjects will achieve a reduction in RBC transfusions to treat the anemia of Low- and INT-1-risk MDS patients, compared with the placebo group.

Approximately 75 subjects will be randomized in a 2:1 ratio to receive siltuximab (15 mg/kg) administered as a 1 hour infusion every 4 weeks + Best Standard Care (BSA) (Group A) (n=50) or placebo administered as a 1-hour infusion every 4 weeks + BSC (Group B) (n=25). BSC includes RBC transfusion, antimicrobials, white blood cell (WBC) growth factors, platelet transfusions, and thrombopoietic agents, as indicated by institutional guidelines and the clinical status of the subject. The treatment for each subject will be unblinded after 12 weeks of treatment, or at the time of treatment discontinuation, if prior to Week 13. Subjects who complete 12 weeks of treatment may qualify to receive open-label siltuximab as follows:
* Subjects receiving siltuximab who experience treatment failure will discontinue treatment and enter the Posttreatment Period.
* Subjects receiving siltuximab who have not experienced treatment failure may continue to receive open-label siltuximab.
* Subjects receiving placebo who experience treatment failure will have the

option to cross-over to open-label siltuximab. Subjects who do not cross-over to treatment with siltuximab will discontinue treatment and enter the Posttreatment Period.
* Subjects receiving placebo who have not experienced treatment failure are to discontinue treatment and enter the Posttreatment Period. However, at the investigator*s discretion, and after sponsor approval, subjects may cross-over to receive open-label siltuximab.

In addition, treatment may continue until death, unacceptable toxicity, withdrawal of consent, or the clinical cutoff (defined as 24 weeks after the last subject is randomized), whichever occurs first. All subjects who discontinue treatment and who have not withdrawn consent for study participation will have an End of Treatment Visit (4 weeks after the last study agent administration) as well as posttreatment visits at 8 and 12 weeks after the last study agent administration. The study will end approximately 36 weeks after the last subject is randomized. Periodical unblinded data will be reviewed by a Data Monitoring Committee (DMC). An interim analysis for futility only will be conducted after approximately 40 subjects complete 12 weeks of treatment.

Intervention

see study design

Study burden and risks

Regarding the study, the patients will have up to 16 visits, when they participate in the blinded phase and then follow-up phase only. If the patient and doctor choose for the open-label phase, then there is an extra monthly visit for the injection. During these visits the usual physical tests will be performed and a blood sample will be taken by the patient, also the patient will be asked to complete 4 questionnaires. These visits will take the patient maximal 4 hours.

Taking blood may cause bruising at the place where the needle goes into the skin. The patient may experience discomfort or pain from the bone marrow bioptsy / puncture. And the patient may have a reaction to the injection.

It is estimated that the overall safety profile will be similar to the experience to date. All details regarding the product Siltuximab are documentated in the Investigator Brochure.

Contacts

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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. At least 18 years of age (or the legal age of consent in the jurisdiction in which the study is taking place)
2. Confirmed diagnosis of MDS, according to WHO or FAB pathologic classification, with an IPSS score 0, 0.5, or 1.0, indicating Low- or INT-1- risk disease. Subjects with 5q- or PDGFR gene mutations are eligible if they are intolerant to or have failed prior specific therapy (eg, lenalidomide and imatinib mesylate).
3. Documented RBC transfusion of at least 2 units of RBC for the treatment of the anemia of MDS in the 8 weeks preceding the start of the Screening Period.
4. Adequate iron stores, demonstrated by either the presence of stainable iron in the bone marrow or a serum ferritin of > 100 ng/mL
5. ECOG performance status score of 0 to 2
6. Symptomatic anemia (defined by a score > 0 on the NCA-SS).
7. Women of childbearing potential must agree to use adequate birth control measures during the study and for 3 months after receiving the last dose of study agent, and have a negative serum or urine beta human chorionic gonadotropin (beta hCG) pregnancy test at

screening. Men must agree to use a double barrier method of birth control and to not donate sperm during the study and for 3 months after receiving the last dose of study agent
8.Be willing and able to adhere to the prohibitions and restrictions specified in this protocol
9.Sign an informed consent document indicating that they understand the purpose of and procedures required for the study and are willing to participate in the study

Exclusion criteria

1.Had treatment with ESAs, androgens, hypomethylating agents, immunomodulatory drugs (IMiDs), or other agents targeting IL-6 or its receptor within 4 weeks of randomization
2.Any condition that, in the opinion of the investigator, would make participation not be in the best interest (eg, compromise the well-being) of the subject or that could prevent, limit, or confound the protocolspecified assessments (eg, has a history of clinically significant, uncontrolled disease of the pulmonary, cardiovascular, endocrine, neurologic, gastrointestinal, or genitourinary systems that is not attributable to MDS). Subjects with Chronic Myelomonocytic Leukemia (CMML) are to be excluded from the study.
3.Causes other than MDS contributing to anemia, such as Vitamin B12 or folate deficiency, bleeding, hemolysis, hemoglobinopathy, or chronic renal failure
4.Known unmanageable allergies, hypersensitivity, or intolerance to monoclonal antibodies or to murine, chimeric, or human proteins or their excipients
5.A history of seropositivity for human immunodeficiency virus (HIV), hepatitis B virus (HBV), or hepatitis C virus (HCV) (Note: HBV antibodypositivity is not a reason for exclusion from the study) 6.Received an investigational drug (including investigational vaccines) or used an invasive investigational medical device within 30 days or 5 half lives before randomization or is currently enrolled in an investigational study
7.Had a modification of an effective preexisting therapy for the explicit purpose of entering the study.
8.Is a woman who is pregnant, or breast-feeding, or planning to become pregnant or is a man who plans to father a child while enrolled in this study or within 12 weeks after the last dose of study agent
9.Had hospitalization for infection or major surgery, (eg, requiring general anesthesia) within 2 weeks before randomization or will not have fully recovered from surgery. Note: subjects with planned surgical procedures to be conducted under local anesthesia may participate
10.Been vaccinated with live, attenuated vaccines within 4 weeks of randomization
11.Has clinically significant laboratory abnormalities: *Platelets < 20 x 109/L *Estimated glomerular filtration rate (eGFR) <=20 mL/min *Aspartate aminotransferase (AST)/alanine aminotransferase (ALT) * 2.5 x upper limit of normal (ULN) *Bilirubin > 2.5 x ULN *Alkaline phosphatase * 3 x ULN
12.Is an employee of the investigator or study site, with direct involvement in the proposed study or other studies under the direction of that investigator or study site, as well as family members of the employees or the investigator NOTE: Investigators should ensure that all study enrollment criteria have been met at screening. If a subject's status (including laboratory results) changes after screening but before the first dose of study agent is given such that they now meet an exclusion criterion, then they should be excluded from participation in the study

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):	29-03-2012
Enrollment:	4
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Siltuximab
Generic name:	CNTO 328

Ethics review

Approved WMO Date:	30-08-2011
Application type:	First submission
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl
Approved WMO Date:	10-11-2011

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	06-01-2012
Application type:	First submission
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Approved WMO Date:	08-02-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	13-02-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	17-02-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	12-04-2012
Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden)
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Approved WMO Date:	18-04-2012

Application type:	Amendment
Review commission:	METC Leiden-Den Haag-Delft (Leiden) metc-ldd@lumc.nl

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	EUCTR2011-000261-12-NL
CCMO	NL37687.098.11