A Phase 2 Proof-of-Concept Study to Separately Evaluate the Activity of Talacotuzumab;(JNJ-56022473) or Daratumumab in Transfusion-Dependent Subjects with Low or;Intermediate-1 Risk Myelodysplastic Syndromes (MDS) who are Relapsed or Refractory to Erythropoiesis-Stimulating Agent (ESA) Treatment

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Ethical review	Approved WMO
Status	Completed
Health condition type	Haematological disorders NEC
Study type	Interventional

Summary

ID

NL-OMON49651

Source
ToetsingOnline

Brief title
56022473MDS2002

Condition

- Haematological disorders NEC

Synonym
MDS, Myelodysplastic Syndrome

Research involving
Human

Sponsors and support

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

Intervention

Keyword: Daratumumab, Myelodysplastic Syndromes (MDS), Talacotuzumab

Outcome measures

Primary outcome

The primary endpoint of this study is 8-week red blood cell (RBC) TI, defined as absence of RBC transfusion during any consecutive 56 days (8 weeks) post randomization. The primary hypothesis of this study is that the treatment with talacotuzumab or daratumumab separately will produce a TI rate 30% or greater against a minimal acceptable value of 15%. The statistical evaluation of the hypothesis will use a Bayesian approach to assess the likelihood of whether a true TI rate \u226415% can be ruled out.

Secondary outcome

nap

Study description

Background summary

Talacotuzumab (JNJ-56022473) is a humanized monoclonal antibody (mAb) that specifically targets the human interleukin-3 receptor alpha chain (IL-3Ra or CD123), and inhibits the signaling through this receptor. Daratumumab is a human immunoglobulin G1 kappa (IgG1\u0138) mAb that binds with high affinity to a unique epitope on CD38, a transmembrane glycoprotein. Preclinical and clinical data indicate that talacotuzumab and daratumumab may eliminate immunosuppressive cell types in the bone marrow microenvironment of patients with MDS. Elimination of MDSCs (by both compounds) and Tregs (daratumumab only) may alter the immunosuppressive microenvironment and allow normal hematopoietic progenitor cells to differentiate, and ultimately improve clinical outcomes. Elimination of CD123+ MDS blasts by talacotuzumab may further alter disease progression.

Study objective

The purpose of this study is to separately evaluate 2 agents with different mechanisms of action that may be effective in subjects with low-risker MDS. The design of this study will allow an unbiased assessment of which agent, if either, will provide benefit to this patient population and further evaluate in clinical development. The generally accepted primary endpoint of transfusion independence has a subjective component based on transfusion practices that can be different across institutions, and randomizing subjects for talacotuzumab or daratumumab treatment with standardized inclusion and exclusion criteria and evaluation procedures will allow a more objective assessment of these 2 different agents.

Study design

Approximately 60 subjects (30 to receive talacotuzumab and 30 to receive daratumumab) will be enrolled in this study. then assigned randomly on a 1:1 basis to receive either talacotuzumab or daratumumab. Transfusion burden is defined as the maximum number of RBC units transfused over any 8 consecutive weeks during the 16 weeks prior to randomization. The study consists of: a Screening Phase of up to 28 days during which subject eligibility will be reviewed and approved by the sponsor prior to randomization, a Treatment Phase that will extend from the first dose on Cycle 1 Day 1 until study drug discontinuation, and a Posttreatment Follow-up Phase beginning once the subject discontinues talacotuzumab or daratumumab. Talacotuzumab will be administered at 9 mg/kg intravenously (IV) every 2 weeks. Daratumumab will be administered at 16 mg/kg IV weekly on Weeks 1 to 8, every 2 weeks for Weeks 9 to 24, and every 4 weeks thereafter. Cycle length is a 28 days for both agents. Study drugs will continue to be administered until disease progression, lack of response, unacceptable toxicity, withdrawal of consent, or study end. The clinical cutoff for the purpose of the primary endpoint analysis will be 6 months after randomization of the last subject. The end of the study is defined as 1 year after the last subject has been randomized or anytime the sponsor

terminates the study.

Intervention

nap

Study burden and risks

nap

Contacts

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NL
Scientific
Janssen-Cilag

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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. 18 years of age;2. MDS according to World Health Organization criteria confirmed by bone marrow aspirate and biopsy within 12 weeks prior to first dose. A local laboratory report from this diagnostic bone marrow aspirate and biopsy must be approved by the sponsor.;3. IPSS low risk or intermediate-1 risk MDS;4. RBC transfusion dependent;- Received at least 4 units of RBCs over any 8 consecutive weeks during the 16 weeks prior to randomization- Pretransfusion Hb must have been \u22649.0 g/dL;Source documentation for transfusions verified by the sponsor.;5. Relapsed/refractory to ESA treatment; the sponsor must verify this diagnosis as defined by meeting any of the criteria below:;- Received at least 8 weeks of treatment with a minimum weekly dose of epoetin alfa 40,000 U, epoetin beta 30,000 U or darbepoetin alfa 150 mcg (or equivalent;agent/dose) without having achieved a Hb rise \u22651.5 g/dL or decreased RBC;transfusion requirement by at least 4 units over 8 weeks;- Transfusion dependence or reduction in Hb by \u22651.5 g/dL after hematologic;improvement, in the absence of another explanation;;- Endogenous serum EPO level >500 mU/mL;Source documentation for failure of ESA treatment verified by the sponsor;6. Adequate iron stores, defined as transferrin saturation greater than 20% and serum ferritin greater than 400 ng/mL, measured within the screening period, or adequate iron stores as demonstrated by recent (within 12 weeks prior to first dose) bone marrow examination with iron stain.;7. ECOG performance status 0, 1 or 2 ;8. Hematology laboratory test values within the following limits:;- ANC \u22651.0 x 10 to the 9th/L (ie, \u22651,000/mm3) independent of growth factor support. For the screening ANC to be considered growth factor independent, a 7-day period after stopping the growth factor should be observed, or 7 half-lives of growth factor used, whichever is longer.;- Platelets \u226550 x 10 to the 9th/L independent of platelet transfusion support. For the screening platelets to be considered independent of platelet transfusion support, platelet count must be stable for 3-4 days after the transfusion.;9. Biochemical laboratory test values must be within the following limits:;- Aspartate aminotransferase (AST), alanine aminotransferase (ALT) \u22642.5 times;the upper limit of normal (x ULN);- Creatinine clearance >40 mL/min;- Total bilirubin \u22643.0 x ULN, except for subjects with Gilbert syndrome;10. Women of childbearing potential and men who are sexually active must be practicing highly effective method of contraception (failure rate of <1% per year when used consistently and correctly) during and after the study. Contraceptive use by men or women should be consistent with local regulations regarding the use of contraceptive methods for subject participating in clinical studies. Men must agree to not father a child or donate sperm during and after the study. Women must agree not to donate eggs (ova, oocytes) for the purpose of assisted reproduction. For females and males, these restrictions apply for at least 3 months after the last dose of study drug.;11. A woman of childbearing potential must have a negative highly sensitive serum;(B-human chorionic gonadotropin [B-hCG]) or urine pregnancy test at Screening.;12. Each subject (or their legally acceptable representative) must sign an informed consent form (ICF) indicating that he or she understands the purpose of and procedures required for the study and are willing to participate in the study. Subject must be willing and able to adhere to the prohibitions and restrictions specified in this protocol.

Exclusion criteria

1. Known allergies, hypersensitivity, or intolerance to talacotuzumab and daratumumab or

their excipients;2. Received any chemotherapy, immunomodulatory or immunosuppressive therapy, corticosteroids (>30 mg/day prednisone or equivalent) within 28 days prior to randomization;3. Received other treatments for MDS within 28 days prior to first dose (eg, azacitidine, decitabine, lenalidomide, ESA (8 weeks for long-acting ESAs);4. History of hematopoietic stem cell transplant;5. Del (5q) karyotype unless treatment with lenalidomide has failed. Failure is defined as either: ;1) having received at least 3 months of lenalidomide treatment without RBC;transfusion benefit (IWG 2006); ;2) progression or relapse after hematologic improvement with lenalidomide (IWG 2006); ;3) discontinuation of lenalidomide due to toxicity; or ;4) unable to receive lenalidomide due to a contraindication. Source documentation for lenalidomide treatment failure must be verified by the sponsor.;6. Anemia attributed to factors other than MDS (including hemolysis, chronic renal failure, hepatitis, gastrointestinal bleeding);7. Major surgery within 4 weeks prior to first dose (excludes the placement of a vascular access device and other minor surgical procedures);8. Active malignancy other than MDS \u22643 years before first dose, except:;- Adequately treated non-melanoma skin cancer or lentigo maligna without current evidence of disease;- Adequately treated cervical carcinoma in situ without current evidence of disease;9. Clinically significant cardiovascular disease including:;- myocardial infarction within 6 months of screening;- unstable or uncontrolled disease/condition related to or affecting cardiac function (eg, unstable angina, cardiac disease meeting New York Heart Association;Class 3-4 definition);- uncontrolled or symptomatic cardiac arrhythmias;- screening 12-lead ECG showing a baseline corrected QT interval (QTc) >470 msec;10. Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal;11. Known moderate or severe persistent asthma within the past 2 years or uncontrolled asthma of any classification. Note that subjects who currently have;controlled intermittent asthma or controlled mild persistent asthma are allowed to participate in the study.;12. Uncontrolled active systemic infection requiring IV antibiotics;13. Known history of human immunodeficiency virus (HIV) infection;14. Active systemic hepatitis infection requiring treatment or other clinically active liver disease;15. Females who are pregnant or are breastfeeding;16. Any life-threatening illness, medical condition, or organ system dysfunction that, in the investigator\u2019s opinion, could compromise the subject\u2019s safety, or put the study outcomes at undue risk. Any condition for which, in the opinion of the investigator, participation would not be in the best interest of the subject (eg, compromise the well-being) or that could prevent, limit, or confound the protocol-specified assessments

Study design

Design

Study phase:	2
Study type:	Interventional
Masking:	Open (masking not used)
Control:	Uncontrolled

Primary purpose:	Treatment

Recruitment

NL

Recruitment status:	Completed
Start date (anticipated):	24-07-2017
Enrollment:	3
Type:	Actual

Medical products/devices used

Product type:	Medicine
Brand name:	Daratumumab
Generic name:	Darzalex
Product type:	Medicine
Brand name:	Talacotuzumab
Generic name:	Talacotuzumab
Registration:	Yes - NL outside intended use

Ethics review

Approved WMO

Date:	22-12-2016
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	16-02-2017
Application type:	First submission
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	29-03-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

Approved WMO

Date:	12-05-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-06-2017
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	28-02-2018
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	08-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-01-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	14-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-03-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)
Approved WMO Date:	15-07-2019
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek

	(Assen)
Approved WMO Date:	13-05-2020
Application type:	Amendment
Review commission:	BEBO: Stichting Beoordeling Ethiek Bio-Medisch Onderzoek (Assen)

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	EUCTR2016-003328-22-NL
ClinicalTrials.gov	NCT03011034.
CCMO	NL59721.056.16

Study results

Date completed:	16-03-2020
Results posted:	04-10-2022

URL result
URL
Type
int
Naam
M2.2 Samenvatting voor de leek
URL

Internal documents

File