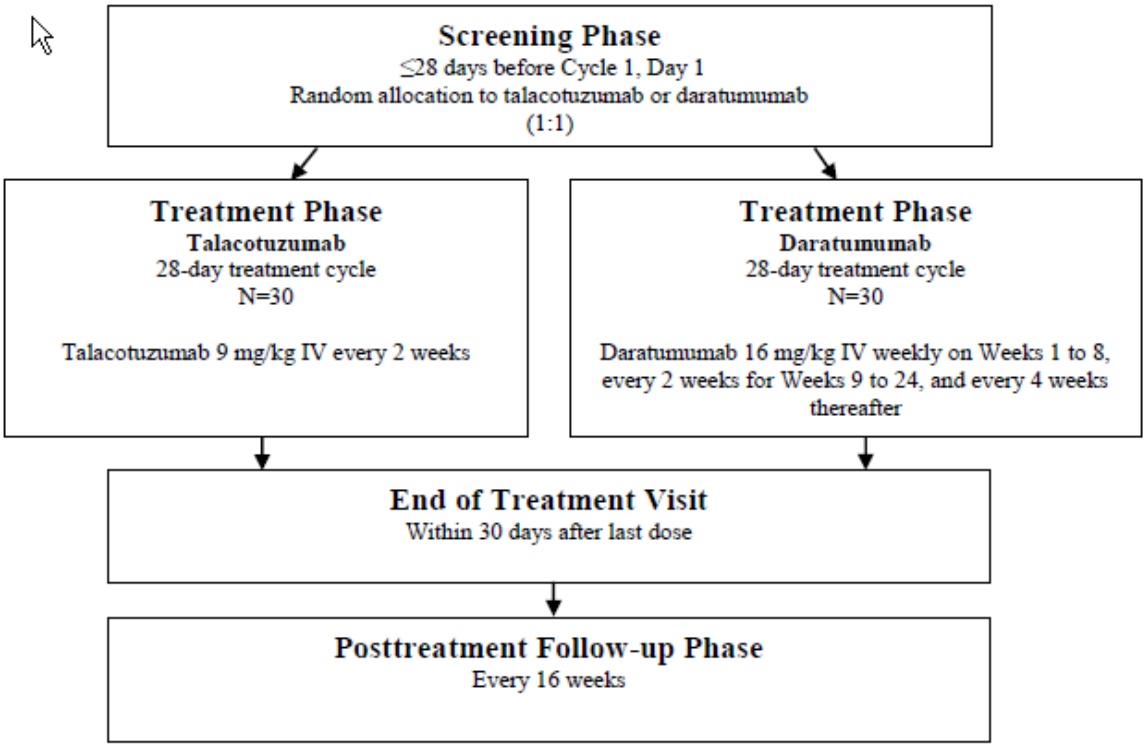
SAMENVATTING MDS2002

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

NB: de Talacotuzumab arm is gesloten. Alleen inclusie in Daratumumab-arm



INCLUSION CRITERIA

Each potential subject must satisfy all of the following criteria to be enrolled in the study:

- ☐ Subject is ≥ 18 years of age the time of signing the informed consent form (ICF).
- ☐ MDS according to World Health Organization (WHO, Attachment 1) 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.
- ☐ IPSS low risk or intermediate-1 risk MDS
- ☐ 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 ≤9.0 g/dL

  Source documentation for transfusions verified by the sponsor.

- 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 ≥1.5 g/dL or decreased RBC transfusion requirement by at least 4 units over 8 weeks
    - Transfusion dependence or reduction in Hb by ≥1.5 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
- 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.
- ECOG performance status 0, 1 or 2
- Hematology laboratory test values within the following limits:
    - ANC ≥1.0 x 109/L (ie, ≥1,000/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 ≥50 x 109/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.
- Criterion numbering modified per Amendment 2

  Biochemical laboratory test values must be within the following limits:
    - Aspartate aminotransferase (AST), alanine aminotransferase (ALT) ≤2.5 times the upper limit of normal (x ULN)
    - Creatinine clearance >40 mL/min
    - Total bilirubin ≤3.0 x ULN, except for subjects with Gilbert syndrome
- 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.
- A woman of childbearing potential must have a negative highly sensitive serum (β-human chorionic gonadotropin [□-hCG]) or urine pregnancy test at Screening.
- 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

Any potential subject who meets any of the following criteria will be excluded from participating in the study:

- Known allergies, hypersensitivity, or intolerance to talacotuzumab and daratumumab or their excipients (refer to Investigator's Brochure)
- Received any chemotherapy, immunomodulatory or immunosuppressive therapy, corticosteroids (>30 mg/day prednisone or equivalent) within 28 days prior to randomization
- Received other treatments for MDS within 28 days prior to first dose (eg, azacitidine, decitabine, lenalidomide, ESA (8 weeks for long-acting ESAs)
- History of hematopoietic stem cell transplant
- 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.
- Anemia attributed to factors other than MDS (including hemolysis, chronic renal failure, hepatitis, gastrointestinal bleeding)
- Major surgery within 4 weeks prior to first dose (excludes the placement of a vascular access device and other minor surgical procedures)
- Active malignancy other than MDS ≤3 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
- 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, Attachment 4)
    - uncontrolled or symptomatic cardiac arrhythmias
    - screening 12-lead ECG showing a baseline corrected QT interval (QTc) >470 msec
- Known chronic obstructive pulmonary disease (COPD) with a forced expiratory volume in 1 second (FEV1) <50% of predicted normal
- Known moderate or severe persistent asthma within the past 2 years (see Attachment 5), 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.
- Uncontrolled active systemic infection requiring IV antibiotics
- Known history of human immunodeficiency virus (HIV) infection
- Active systemic hepatitis infection requiring treatment or other clinically active liver disease