SAMENVATTING AZA-MDS-003

TITEL
a phase 3, multicenter, randomized, doubleblind 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

INDICATIE
Treatment of lower-risk (Low or Intermediate-1 [INT-1] risk) Myelodysplastic Syndromes (MDS) according to the International Prognostic Scoring System (IPSS) with red blood cell (RBC) transfusion-dependent anemia and thrombocytopenia

EVALUATIE/ EINDPUNTEN
The primary endpoint is the proportion of subjects in the overall population achieving RBC transfusion independence with duration ≥ 84 days (12 weeks)

GENEESMIDDEL Orale Azazitidine
Bijwerkingen : Misselijkheid, overgeven, koorts, ontsteking van de neusslijmvliezen of neus- en keelpijn; pijn in de borstkas; duizeligheid; hoofdpijn; huiduitslag; blauwe plekken; verminderde eetlust; andere vormen van kanker,anemie, trobopenie, leucopenie , infecties ; spijsverteringsklachten; buikpijn; diarree; koorts; vochtverlies; hartfalenbloedingen ; hypokalemie; verlaagd bewustzijnsniveau, ; angst; slapeloosheid; haaruitval; roodheid van de huid; ernstige allergische reactie op een bloedtransfusie; gewrichts-, bot- of spierpijn; kortademigheid ,hypotensie en epilepsie, trombose,

INCLUSIECRITERIA
Subjects must satisfy the following criteria to be enrolled in the study:
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 RBCs confirmed for a minimum of 84 days immediately preceding randomization
    - Hemoglobin levels at the time of or within 7 days prior to administration of an RBC transfusion must have been ≤ 9.0 g/dL in order for the transfusion to be counted towards RBC transfusion-dependent status. Red blood cell transfusions administered when Hgb levels were > 9.0 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 42 days that are RBC-transfusion-free during the 84 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
5. Have an ECOG performance status of 0, 1, or 2

EXCLUSIECRITERIA

1. IPSS higher-risk (INT-2 or High risk) MDS
2,3 where removed after ammendement, as use of lenalidomide in history
4. CMML, atypical chronic myeloid leukemia (CML) and unclassifiable myeloproliferative disease (MPD)
5. Prior treatment with Azacitidine (any formulation), decitabine or other hypomethylating agent,
6. Prior allogeneic or autologous stem cell transplant
7. History of inflammatory bowel disease , celiac disease , 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 study drug and/or predispose the subject to an increased risk of gastrointestinal toxicity
8. Thrombocytopenia secondary to other possible causes
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 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 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 cervi, Carcinoma in situ of the breast, Incidental histologic finding of prostate cancer
13. Significant active cardiac disease within the previous 6 months, including:
14. Uncontrolled systemic fungal, bacterial, or viral infection
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)
17. Any of the following laboratory abnormalities:
    - -Serum AST/SGOT or ALT/SGPT > 2.5 x upper limit of normal (ULN)
    - -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). 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/dL
19. Known or suspected hypersensitivity to azacitidine or mannitol

STUDIEOPZET/ BEHANDELPLAN

1: Overall Study Design