KARTA BADANIA
NAZWA BADANIA: A Phase 2a/2b, Open-label, Proof of Concept (Phase 2a) and Open-label (Phase 2b), Multicenter, Efficacy, and Safety Study of AG-946 in Participants With Anemia Due to Lower-Risk Myelodysplastic Syndromes
NUMER PROTOKOŁU: **AG946-C-002**
WSKAZANIE- C - Nowotwory

Inclusion Criteria
5.1.1. Phase 2a
Participants are eligible to be included in the Phase 2a part of the study only if all the following criteria apply:
1. At least 18 years of age at the time of providing informed consent
2. Documented diagnosis of MDS according to World Health Organization (WHO) classification, that meets IPSS-R classification (Appendix 3) of lower-risk disease (risk score: ≤3.5) and <5% blasts as determined by the participant's bone marrow biopsy/aspirate during the Screening Period
3. Nontransfused or with LTB, based on transfusion history from the participant's medical record, according to revised IWG 2018 criteria (Appendix 4):
a. NTD: <3 RBC units in the 16-week period before administration of the first dose of study drug and no transfusions in the 8-week period before administration of the first dose of study drug, or
b. LTB: 3 to 7 RBC units in the 16-week period before administration of the first dose of study drug and <4 RBC units in the 8-week period before administration of the first dose of study drug
4. An Hb concentration <11.0 g/dL during the 4-week Screening Period
5. Eastern Cooperative Oncology Group (ECOG) Performance Status score of 0, 1, or 2
6. If taking iron chelation therapy, the iron chelation therapy dose must have been stable and started ≥56 days before administration of the first dose of study drug
7. For women of childbearing potential (WOCBP) and men with partners who are WOCBP, must be abstinent of sexual activities that may result in pregnancy as part of their usual lifestyle or agree to use 2 forms of contraception, 1 of which must be considered highly effective, from the time of providing informed consent, throughout the study, and for 28 days after the last dose of study drug for women and 90 days after the last dose of study drug for men. The second form of contraception can be an acceptable barrier method (see Appendix 1 for the definition of WOCBP and acceptable contraception methods).
8. Written informed consent from the participant before any study-related procedures are conducted and willing to comply with all study procedures for the duration of the study
5.1.2. Phase 2b
Participants are eligible to be included in the Phase 2b part of the study only if all the following criteria apply: 1. At least 18 years of age at the time of providing informed consent
2. Documented diagnosis of MDS according to WHO classification that meets IPSS-R classification (Appendix 3) of lower-risk disease (risk score: ≤3.5) and <5% blasts as determined by the participant's bone marrow biopsy/aspirate during the Screening Period
3. Nontransfused, with LTB, or with HTB, based on transfusion history from the participant's medical record, according to revised IWG 2018 criteria (Appendix 4):
a. NTD: <3 RBC units in the 16-week period before randomization and no transfusions in the 8-week period before randomization, or
b. LTB: 3 to 7 RBC units in the 16-week period before randomization and <4 RBC units in the 8-week period before randomization, or
c. HTB: ≥8 RBC units in the 16-week period before randomization and ≥4 RBC units in

the 8-week period before randomization
4. An Hb concentration <11.0 g/dL during the 4-week Screening Period
5. Up to 2 prior therapies including erythropoiesis-stimulating agents (ESAs) (eg, erythropoietin [EPO], EPO + granulocyte colony-stimulating factor [G-CSF]) and/or luspatercept
6. ECOG Performance Status score of 0, 1, or 2
7. If taking iron chelation therapy, the iron chelation therapy dose must have been stable and started ≥56 days before randomization
8. For WOCBP and men with partners who are WOCBP, must be abstinent of sexual activities that may result in pregnancy as part of their usual lifestyle or agree to use 2 forms of contraception, 1 of which must be considered highly effective, from the time of providing informed consent, throughout the study, and for 28 days after the last dose of study drug for women and 90 days after the last dose of study drug for men. The second form of contraception can be an acceptable barrier method (see Appendix 1 for the definition of WOCBP and acceptable contraception methods).
9. Written informed consent from the participant before any study-related procedures are conducted and willing to comply with all study procedures for the duration of the study

5.2. Exclusion Criteria

5.2.1. Phase 2a

Participants are excluded from the Phase 2a part of the study if any of the following criteria apply:

1. Known history of acute myeloid leukemia (AML)
2. Secondary MDS, defined as MDS that is known to have arisen as a result of chemical injury or treatment with chemotherapy and/or radiation for other diseases
3. Prior exposure to a pyruvate kinase activator, treatment administered for high-risk MDS (hypomethylating agents [HMAs], isocitrate dehydrogenase [IDH] inhibitors, or allogeneic or autologous stem cell transplant), and/or disease-modifying agents (eg, immunomodulatory drugs such as lenalidomide). If a participant received ≤1 week of treatment with a disease-modifying agent ≥8 weeks before administration of the first dose of study drug, then they may not be excluded, at the Investigator's discretion.
4. Currently receiving treatment with luspatercept, EPO, or G-CSF. Treatment with EPO or G-CSF must have been stopped for ≥28 days before administration of the first dose of study drug; treatment with luspatercept must have been stopped for ≥65 days before administration of the first dose of study drug.
5. History of active and/or uncontrolled cardiac or pulmonary disease within 6 months before providing informed consent, including but not limited to:
a. New York Heart Association Class III or IV heart failure or clinically significant dysrhythmia
b. Myocardial infarction, unstable angina pectoris, or unstable hypertension; high risk thrombosis; hemorrhagic, embolic, or thrombotic stroke; deep venous thrombosis; or pulmonary or arterial embolism
c. Heart rate–corrected QT interval using Fridericia's method of ≥470 milliseconds for female participants and ≥450 milliseconds for male participants, except for right or left bundle branch block
d. Severe pulmonary fibrosis as defined by severe hypoxia, evidence of right-sided heart failure, and radiographic pulmonary fibrosis >50%
e. Severe pulmonary hypertension as defined by severe symptoms associated with hypoxia, right-sided heart failure, and oxygen indicated
6. History of hepatobiliary disorders, as defined by:
a. Serum AST >2.5 × upper limit of normal (ULN) (unless due to hemolysis and/or hepatic iron deposition) and ALT >2.5 × ULN (unless due to hepatic iron deposition)
b. Serum bilirubin >ULN, if the elevation is associated with clinically symptomatic choledocholithiasis, cholecystitis, biliary obstruction, or hepatocellular disease
7. Renal dysfunction, as defined by an estimated glomerular filtration rate (eGFR) <45 mL/min
8. Active infection requiring systemic antimicrobial therapy at the time of providing informed consent. If antimicrobial therapy is required during the Screening Period, screening procedures should not be performed while antimicrobial therapy is being administered, and the last dose of antimicrobial therapy must be administered ≥7 days before administration of the first dose of study drug.
9. Major surgery within 12 weeks before administration of the first dose of study drug. Participants must have completely recovered from any previous surgery before

administration of the first dose of study drug.
10. History of any malignancy, except for nonmelanomatous skin cancer in situ, cervical carcinoma in situ, or breast carcinoma in situ. Participants must not have active disease or have received anticancer treatment ≤5 years before providing informed consent.
11. Positive test for hepatitis C virus (HCV) antibody (Ab) with evidence of active HCV infection, or positive test for hepatitis B surface antigen (HBsAg) 12. Positive test for HIV-1 Ab or HIV-2 Ab
13. Absolute neutrophil count (ANC) <500/µL (0.5 × 109 /L)
14. Platelet count ≤75,000/µL (75 × 109 /L) assessed in the absence of platelet transfusions within 28 days before Screening
15. Nonfasting triglyceride concentration >500 mg/dL
16. Receiving inhibitors of P-glycoprotein (P-gp) that have not been stopped for ≥5 days or a time frame equivalent to 5 half-lives (whichever is longer) before administration of the first dose of study drug
17. Current enrollment or past participation (within 4 weeks or a time frame equivalent to 5 half-lives of the investigational study drug before administration of the first dose of study drug or, whichever is longer) in any other clinical study involving an investigational treatment or device
18. Known allergy to AG-946 or its excipients (silicified microcrystalline cellulose, croscarmellose sodium, sodium stearyl fumarate, and the Opadry® II Blue film coat [polyvinyl alcohol, titanium dioxide, macrogol/polyethylene glycol, talc, FD&C blue #2/indigo carmine aluminum lake/E132])
19. Pregnant or breastfeeding
20. Any medical, hematologic, psychological, or behavioral condition(s) or prior or current therapy that, in the opinion of the Investigator, may confer an unacceptable risk to participating in the study and/or could confound the interpretation of the study data. Also excluded are:
• Participants who are institutionalized by regulatory or court order
• Participants with any condition(s) that could create undue influence (including but not limited to incarceration, involuntary psychiatric confinement, and financial or familial affiliation with the Investigator or Sponsor)
5.2.2. Phase 2b
Participants are excluded from the Phase 2b part of the study if any of the following criteria apply:
1. Known history of AML
2. Secondary MDS, defined as MDS that is known to have arisen as a result of chemical injury or treatment with chemotherapy and/or radiation for other diseases
3. Prior exposure to a pyruvate kinase activator, including exposure to AG-946 in the Phase 2a part of this study, treatment administered for high-risk MDS (HMAs, IDH inhibitors, or allogeneic or autologous stem cell transplant), and/or disease-modifying agents (eg, immunomodulatory drugs such as lenalidomide). If a participant received ≤1 week of treatment with a disease-modifying agent ≥8 weeks before randomization, then they may not be excluded, at the Investigator's discretion. 4. Currently receiving treatment with luspatercept, EPO, or G-CSF. Treatment with EPO or G-CSF must have been stopped for ≥28 days before administration of the first dose of study drug; treatment with luspatercept must have been stopped for ≥65 days before randomization.
5. History of active and/or uncontrolled cardiac or pulmonary disease within 6 months before providing informed consent, including but not limited to:
a. New York Heart Association Class III or IV heart failure or clinically significant dysrhythmia
b. Myocardial infarction, unstable angina pectoris, or unstable hypertension; high risk thrombosis; hemorrhagic, embolic, or thrombotic stroke; deep venous thrombosis; or pulmonary or arterial embolism
c. Heart rate–corrected QT interval using Fridericia's method of ≥470 milliseconds for female participants and ≥450 milliseconds for male participants, except for right or left bundle branch block
d. Severe pulmonary fibrosis as defined by severe hypoxia, evidence of right-sided heart failure, and radiographic pulmonary fibrosis >50%
e. Severe pulmonary hypertension as defined by severe symptoms associated with hypoxia, right-sided heart failure, and oxygen indicated
6. History of hepatobiliary disorders, as defined by:

a. Serum AST >2.5 × ULN (unless due to hemolysis and/or hepatic iron deposition) and ALT >2.5 × ULN (unless due to hepatic iron deposition)
b. Serum bilirubin >ULN, if the elevation is associated with clinically symptomatic choledocholithiasis, cholecystitis, biliary obstruction, or hepatocellular disease
7. Renal dysfunction, as defined by an eGFR <45 mL/min
8. Active infection requiring systemic antimicrobial therapy at the time of providing informed consent. If antimicrobial therapy is required during the Screening Period, screening procedures should not be performed while antimicrobial therapy is being administered, and the last dose of antimicrobial therapy must be administered ≥7 days before randomization.
9. Major surgery within 12 weeks before randomization. Participants must have completely recovered from any previous surgery before randomization.
10. History of any malignancy, except for nonmelanomatous skin cancer in situ, cervical carcinoma in situ, or breast carcinoma in situ. Participants must not have active disease or have received anticancer treatment ≤5 years before providing informed consent.
11. Positive test for HCV Ab with evidence of active HCV infection, or positive test for HBsAg
12. Positive test for HIV-1 Ab or HIV-2 Ab
13. ANC <500/µL (0.5 × 109
/L)
14. Platelet count <50,000/µL (50 × 109
/L) assessed in the absence of platelet transfusions within 28 days before Screening. 15. Nonfasting triglyceride concentration >500 mg/dL
16. Receiving inhibitors of P-gp that have not been stopped for ≥5 days or a time frame equivalent to 5 half-lives (whichever is longer) before randomization
17. Current enrollment or past participation (within 4 weeks or a time frame equivalent to 5 half-lives of the investigational study drug before randomization or, whichever is longer) in any other clinical study involving an investigational treatment or device
18. Known allergy to AG-946 or its excipients, including placebo (silicified microcrystalline cellulose, microcrystalline cellulose, croscarmellose sodium, mannitol, sodium stearyl fumarate, magnesium stearate, and the Opadry® II Blue film coat [polyvinyl alcohol, hypromellose, titanium dioxide, lactose monohydrate, macrogol/polyethylene glycol, triacetin, talc, FD&C blue #2/indigo carmine aluminum lake/E132])
19. Pregnant or breastfeeding
20. Any medical, hematologic, psychological, or behavioral condition(s) or prior or current therapy that, in the opinion of the Investigator, may confer an unacceptable risk to participating in the study and/or could confound the interpretation of the study data. Also excluded are:
• Participants who are institutionalized by regulatory or court order
• Participants with any condition(s) that could create undue influence (including but not limited to incarceration, involuntary psychiatric confinement, and financial or familial affiliation with the Investigator or Sponsor)