KARTA BADANIA
NAZWA BADANIA: A Phase 3, Randomized, Double-blind, Active-Comparator-Controlled Clinical Study to Evaluate the Efficacy and Safety of Bomedemstat (MK-3543) versus Hydroxyurea in Cytoreductive Therapy Naïve Essential Thrombocythemia Participants
NUMER PROTOKOŁU: **MK-3543-007**
WSKAZANIE- Essential Thrombocythemia

5.1 Inclusion Criteria
An individual is eligible for inclusion in the study if the individual meets all of the following criteria:
Type of Participant and Disease Characteristics
1. Based on the WHO diagnostic criteria for myeloproliferative neoplasms (Appendix 8), has a diagnosis of ET and an indication for cytoreductive therapy. Indications for cytoreductive therapy include:
• High-risk patients (history of thrombosis at any age; or age >60 years with JAK2 V617F mutation),
• Acquired VWD and/or disease-related major bleeding,
• Splenomegaly,
• Progressive thrombocytosis and/or leukocytosis,
• Disease-related symptoms (eg, pruritis, fatigue, night sweats), and
• Vasomotor/microvascular disturbances not responsive to ASA (eg, erythromelalgia, headaches/chest pain).
2. Has a bone marrow fibrosis score of Grade 0 or Grade 1, as per a modified version of the European Consensus Criteria for Grading Myelofibrosis (Appendix 10).
3. Has received no prior cytoreductive treatment for their ET.
4. Has a platelet count of >450 × 109/L (450k/µL) assessed up to 72 hours before first dose of study intervention.
5. Has an ANC ≥0.75 × 109/L assessed up to 72 hours before first dose of study intervention.
6. Has a life expectancy of >52 weeks in the opinion of the investigator. 5.1 Inclusion Criteria
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Demographics
7. Is an individual of any sex/gender, at least 18 years of age, at the time of providing the informed consent. Participants Assigned Male Sex at Birth
8. If capable of producing sperm, the participant agrees to the following during the intervention period and for at least the time needed to eliminate the study intervention after the last dose of study intervention. The length of time required to continue contraception for the study intervention is: 6 months.
• Refrains from donating sperm
PLUS either:
• Abstains from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis) and agrees to remain abstinent
OR
• Uses contraception as detailed below unless confirmed to be azoospermic (vasectomized or secondary to medical cause, documented from the site personnel's review of the participant's medical records, medical examination, or medical history interview) as detailed below:
- Uses a penile/external condom when having penile-vaginal intercourse with a nonparticipant of childbearing potential who is not currently pregnant PLUS partner use of an additional contraceptive method, as a condom may break or leak.
Note: Participants capable of producing ejaculate whose partner is pregnant or breastfeeding must agree to use a penile/external condom during each episode of sexual activity in which the partner is at risk of drug exposure via ejaculate.
- Contraceptive use by participants capable of producing sperm should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above the local label requirements are to be followed.
Participants Assigned Female Sex at Birth
9. A participant assigned female sex at birth is eligible to participate if not pregnant or breastfeeding, and at least one of the following conditions applies:
• Is not a POCBP
OR
• Is a POCBP and:
- Uses a contraceptive method that is highly effective (with a failure rate of <1% per year), with low user dependency, or is abstinent from penile-vaginal intercourse as their preferred and usual lifestyle (abstinent on a long-term and persistent basis), as described in Appendix 5 during the intervention period and for at least the time needed to eliminate the study intervention after the last dose of study intervention. The participant agrees not to donate eggs (ova, oocytes) to others or freeze/store eggs during this period for the purpose of reproduction. The length of time required to continue contraception for the study intervention is: 6 months.
- The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.
- Has a negative highly sensitive pregnancy test (urine or serum) as required by local regulations within 24 hours (for a urine test) or 72 hours (for a serum test) before the first dose of study intervention. If a urine test cannot be confirmed as negative (eg, an ambiguous result), a serum pregnancy test is required. In such cases, the participant must be excluded from participation if the serum pregnancy result is positive. Additional requirements for pregnancy testing during and after study intervention are in Section 8.3.5.
- Abstains from breastfeeding during the study intervention period and for at least 180 days after study intervention.
- Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early

undetected pregnancy. length of time required to continue contraception for the study intervention is: 6 months.
- The investigator should evaluate the potential for contraceptive method failure (ie, noncompliance, recently initiated) in relationship to the first dose of study intervention. Contraceptive use by POCBPs should be consistent with local regulations regarding the methods of contraception for those participating in clinical studies. If the contraception requirements in the local label for any of the study interventions are more stringent than the requirements above, the local label requirements are to be followed.
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- Medical history, menstrual history, and recent sexual activity has been reviewed by the investigator to decrease the risk for inclusion of a POCBP with an early undetected pregnancy.

Informed Consent

10. The participant (or legally acceptable representative) has provided documented informed consent and the participant has provided documented assent, when applicable, for the study. The participant (or legally acceptable representative) may also provide consent and the participant may provide documented assent, when applicable, for FBR. However, the participant may participate in the study without participating in FBR.

Additional Categories

11. Is able to swallow capsules
12. Is eligible to receive hydroxyurea in the opinion of the investigator in accordance with local and/or institutional guidelines or product labeling.
13. Has an ECOG Performance Status of 0 to 2 assessed within 7 days before the start of study intervention
14. HIV-infected participants must have well controlled HIV on ART, defined as:
a. Participants on ART must have a CD4+ T-cell count ≥350 cells/mm3 at the time of screening
b. Participants on ART must have achieved and maintained virologic suppression defined as confirmed HIV RNA level below 50 or the LLOQ (below the limit of detection) using the locally available assay at the time of screening and for at least 12 weeks before screening c. It is advised that participants must not have had any AIDS-defining opportunistic infections within the past 12 months
d. Participants on ART must have been on a stable regimen, without changes in drugs or dose modification, for at least 4 weeks before study entry (Day 1) and agree to continue ART throughout the study
e. The combination ART regimen must not contain any antiretroviral medications that interact with CYP3A4 inhibitors/inducers/substrates (https://www.fda.gov/drugs/drug-interactions-labeling/drug-development-and-drug-interactions-table-substrates-inhibitors-and-inducers)
15. Adequate organ function as defined in the following table (Table 3). Specimens must be

collected within 3 days before the start of study intervention.

Table 3 Adequate Organ Function Laboratory Values

System	Laboratory Value
Hematological	
Hemoglobin (or hematocrit)	10 to 16 g/dL (and hematocrit <45%)[a]
Renal	
Measured or calculated creatinine clearance [b]	≥30 mL/min
Hepatic	
Total bilirubin	≤1.5 × ULN OR direct bilirubin ≤ULN for participants with total bilirubin levels >1.5 × ULN
AST (SGOT) and ALT (SGPT)	≤2.5 × ULN
Coagulation	
International normalized ratio (INR) OR prothrombin time (PT) Activated partial thromboplastin time (aPTT)	≤1.5 × ULN unless participant is receiving anticoagulant therapy as long as PT or PTT is within therapeutic range of intended use of anticoagulants

ALT (SGPT)=alanine aminotransferase (serum glutamic pyruvic transaminase); AST (SGOT)=aspartate aminotransferase (serum glutamic oxaloacetic transaminase); GFR=glomerular filtration rate; ULN=upper limit of normal.

[a] Transfusion and/or phlebotomy to reach threshold not permitted.

[b] Cockcroft-Gault CrCl formula = [[140 – age (yr)] × weight(kg)] / [72 × serum Cr (mg/dL) × 0.85 for females]

16. Participants who are HBsAg positive are eligible if they have received HBV antiviral therapy for at least 4 weeks and have undetectable HBV viral load before randomization.
Note: Participants should remain on antiviral therapy throughout study intervention and follow local guidelines for HBV antiviral therapy post completion of study intervention.
Hepatitis B screening tests are not required unless:
• Known history of HBV infection
• As mandated by local health authority 17. Participants with history of HCV infection are eligible if HCV viral load is undetectable
at screening.
Note: Participants must have completed curative antiviral therapy at least 4 weeks before randomization.
Hepatitis C screening tests are not required unless:
• Known history of HCV infection
• As mandated by local health authority
Refer to Appendix 7 for country-specific requirements.
5.2 Exclusion Criteria
An individual must be excluded from the study if the individual meets any of the following criteria:
Medical Conditions
1. Known immediate or delayed hypersensitivity reaction or idiosyncrasy to any study intervention and/or their excipients, or to drugs chemically related to bomedemstat or LSDi (ie, MAOIs) that contraindicates participation.
2. History of any illness/impairment of gastrointestinal function that might interfere with drug absorption (eg, chronic diarrhea or history of gastric bypass surgery), confound the study results or pose an additional risk to the patient by participation in the study.
3. Evidence at the time of Screening of increased risk of bleeding due to one of the following:

History of severe thrombocytopenia or platelet dysfunction unrelated to a myeloproliferative disorder or its treatment
• Known hereditary bleeding disorder (eg, dysfibrinogenemia, factor IX deficiency, hemophilia, VWD, fibrinogen deficiency, or other clotting factor deficiency)
• Active or chronic bleeding within 8 weeks prior to randomization
• An autoimmune disorder causing bleeding
4. History of a malignancy, unless potentially curative treatment has been completed with no evidence of malignancy for 2 years.
Note: The time requirement does not apply to participants who underwent successful definitive resection of basal cell carcinoma of the skin, squamous cell carcinoma of the skin, or carcinoma in situ, excluding carcinoma in situ of the bladder
5. HIV-infected participants with a history of Kaposi's sarcoma and/or Multicentric Castleman's Disease. Prior/Concomitant Therapy
6. Use of prohibited medication within 14 days of first dose of study intervention (eg, all hematopoietic growth factors, MAOIs, strong inhibitors and inducers of CYP3A4 or CYP2D6, drugs such as chloroquine whose metabolites are known to inhibit CYP3A4 or CYP2D6, Class 1c antiarrhythmics such as propafenone that are known to cause thrombocytopenias, etc.) or expected to require any of these medications during study treatment (see Section 6.5).
Prior/Concurrent Clinical Study Experience
7. Has received an investigational agent or has used an investigational device within 4 weeks prior to study intervention administration.
Diagnostic Assessments
8. Has an active infection requiring systemic therapy
Other Exclusions
9. Has had major surgery ≤4 weeks prior to first dose of study intervention or has not recovered from side effects of major surgery >4 weeks prior to first dose.
10. Has a history or current evidence of any condition, therapy, laboratory abnormality, or other circumstance that might confound the results of the study or interfere with the individual's ability to cooperate with the requirements of the study, such that it is not in the best interest of the individual to participate, in the opinion of the treating investigator.
Refer to Appendix 7 for country-specific requirements.