KARTA BADANIA
NAZWA BADANIA: PHASE I MULTICENTER, OPEN LABEL, DOSEESCALATION STUDY TO DETERMINE THE MAXIMUM TOLERATED DOSE FOR TRICHOSTATIN A IN SUBJECTS WITH RELAPSED OR REFRACTORY HEMATOLOGIC MALIGNANCIES
NUMER PROTOKOŁU: VP-VTR-297-1101
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Each subject must meet the following criteria for inclusion in the study:
1. Subject's age is ≥ 18 years at the time of signing informed consent.
2. Confirmed malignant hematologic disease or lymphoid malignancy that has relapsed or is refractory to standard therapy and has exhausted all available therapies, including Acute Myeloid Leukemia (AML), Acute Lymphoblastic Leukemia (ALL), Myelodysplastic Syndrome (MDS), Chronic Myeloid Leukemia (CML), Chronic Lymphocytic Leukemia (CLL), Multiple Myeloma (MM), Non-Hodgkin's Lymphoma (NHL), and Hodgkin's Disease (HL).
3. Presence of measurable or evaluable disease:
a. ALL: > 5% blasts in the bone marrow.
b. AML: > 20 % blasts in the blood or bone marrow.
c. MDS: classified as intermediate or greater according to the revised International Prognostic Scoring System (IPSS-R) risk category and have ≥ 5% bone marrow blasts.
d. CML: defined by presence of Philadelphia chromosome (Ph) with a myeloproliferative neoplasm (MPN); presence of quantifiable BCR-ABL1 mRNA transcripts.
e. CLL: symptomatic disease that mandates treatment in the opinion of the investigator and is radiologically or clinically evaluable.
f. MM: has measurable disease defined by at least 1 of the following 4 measurements: serum monoclonal protein > or = to 1 g/dL; urine monoclonal protein > or = to 200 mg/24 h; serum free light chain (FLC) assay with involved FLC level > or = to 10 mg/dL provided serum FLC ratio is abnormal; or presence of significant measurable active plasmacytoma mass by PET/CT.
g. B-cell NHL: has measurable disease (at least 1 lesion ≥ 1.5 cm) by CT/PET scan.
a. Subjects with Waldenström's macroglobulinemia are exempt from this requirement if they have symptomatic hyperviscosity or clinically relevant cytopenias and measurable serum monoclonal IgM.
h. HL: All Ann-Arbor stages are eligible
4. Subject has an Eastern Cooperative Oncology Group (ECOG) performance status of ≤ 2.
5. Subject has the following laboratory values within 3 weeks before starting study drug (lab tests may be repeated, as clinically indicated, to obtain acceptable values before failure at screening is concluded but supportive therapies [such as erythropoietin and GCSF] are not to be administered within the week prior to screening tests for ANC or platelet count)

Required Screening Laboratory Values

Organ System	Parameter	Required Value
Hepatic	Serum total bilirubin	≤ 1.5 x ULN (or ≤ 4.0 x ULN if subject has Gilbert syndrome)
	Serum ALT	≤ 3.0 x ULN
	Serum AST	
Renal	eCCr[a]	> 60 ml/min
Pregnancy	β-HCG[b]	Negative
Electrolytes	Serum potassium, magnesium, phosphorus	within normal limits (WNL) for institution
Hematology	ANC	≥ 1.0 x 10^9 /L[e]
	Platelet Count	≥ 75 x 10^9 /L[e]
Endocrinology[f]	PTH	within normal limits (WNL) for institution
	FT4	within normal limits (WNL) for institution
	TSH	within normal limits (WNL) for institution
Coagulation	APTT	not prolonged over normal limits (WNL) for institution
	PT	not prolonged over normal limits (WNL) for institution
	Fibrinogen	≥ 1 g/l
	D-dimer	within normal limits (WNL) for institution [d]
Infection	HIV	Negative HIV antibody[c]
	HBV	Negative HBsAg and negative HBc antibody or positive HBc and negative for HBV DNA by quantitative PCR
	HCV	Negative viral RNA (if HCV antibody is positive)

[a] As calculated by the Cockcroft-Gault formula
[b] For women of childbearing potential only; serum β-HCG must be negative during screening and serum β-HCG or urine dipstick pregnancy test must be negative at Visit 2.
[c] Subjects with a positive HIV antibody may be included provided they have been compliant with antiviral medications for the last 6 months, have a CD4 count within normal limits, are not on any concomitant medications that may interfere with the safety assessment in the study, and do not meet any other exclusion criteria.
[d] If measured concentration exceeds the upper limit of normal clinical assessment of thromboembolism should be considered as per investigator discretion. Subjects with elevated values may be included/continue treatment if no clinical signs of thromboembolism are present.
[e] Not applicable for ALL, AML, and MDS subjects with evidence of bone marrow disease. f If results exceed the normal limit, subjects may be eligible if no clinical signs of thyroid or parathyroid dysfunction
are present.
Abbreviations: ANC=Absolute Neutrophil Count, β-HCG= beta human chorionic gonadotropin, ALT=alanine aminotransferase, AST=aspartate aminotransferase, APTT=activated partial thromboplastin time, DNA=deoxyribonucleic acid, eCCr=estimated creatinine clearance, FT4=free thyroxin, HBc antibody=anti-hepatitis B core antibody, HBsAg=hepatitis B surface antigen, HBV=hepatitis B virus, HCV=hepatitis C virus, HIV=human immunodeficiency virus, Ig=immunoglobulin, PCR=polymerase chain reaction, PT= prothrombin time, PTH= parathyroid hormone, RNA=ribonucleic acid, TSH= thyroid-stimulating hormone, ULN=upper limit of normal

6. Life expectancy ≥ 3 months as determined by the investigator.
7. Male or female subjects of childbearing potential must agree to use double barrier contraception, condoms, sponge, foams, jellies, diaphragm or intrauterine device (IUD), contraceptives (oral or parenteral), Implanon®, injectables, or other avoidance of pregnancy

measures during the study and for 90 days after the last day of treatment. Post-menopausal females (> 45 years old and without menses for > 1 year) and surgically sterilized females are exempt from this criterion.

8. Subject must be able to adhere to the study visit schedule and other protocol requirements

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Subjects will be excluded from the study if any of the following criteria apply:
1. Subject has shown intolerance to trichostatin A, or components of trichostatin A
2. Allogeneic stem cell transplant recipient presenting with graft versus host disease (GVHD) either active or requiring immunosuppression
3. Subject taking any anti-cancer therapy concomitantly (bisphosphonates and denosumab are permitted).
4. Subject previously received any of the following treatments:
a. For CLL or NHL subjects, had treatment with a short course of corticosteroids for symptom relief within 1-week prior to screening
b. Previously received other HDAC inhibitor
5. Subject has second primary malignancy < 2 years of first dose of study treatment (except for adequately treated basal or squamous cell carcinoma, or in situ cancer of the cervix)
6. Subject who received:
a. Experimental therapy or biologic immunotherapy including monoclonal antibodies ≤ 4 weeks prior to the start of study drug administration
b. Prior radiation therapy ≤ 4 weeks or limited field radiotherapy ≤ 2 weeks prior to the start of study
7. Subject with a hypersensitivity to alcohol
8. Subject has undergone major surgery ≤ 2 weeks prior to starting study drug or who have not recovered from side effects to such therapy to < grade 2 CTCAE
9. Subject has impaired cardiac function or conduction defect, including any one of the following:
a. History or presence of ventricular tachyarrhythmia
b. Resting bradycardia defined as < 50 beats per minute
c. QTcF > 450 msec on screening ECG
d. Complete left bundle branch block (LBBB), bifascicular block e. Any clinically significant ST segment and/or T-wave abnormalities
f. Presence of unstable atrial fibrillation (ventricular response rate > 100 bpm). Subjects with stable atrial fibrillation can be enrolled provided they do not meet other cardiac exclusion criteria
g. Myocardial infarction or unstable angina pectoris ≤ 6 months prior to starting study drug
h. Symptomatic congestive heart failure (New York Heart Association class III-IV)
i. Other clinically significant heart disease and vascular disease (e.g. uncontrolled hypertension)
10. Subject taking medications with relative risk or prolonging the QT interval or inducing Torsades de pointes, if such treatment cannot be discontinued or switched to a different medication prior to starting study drug
11. Subject has any other concurrent severe and/or uncontrolled medical conditions (e.g., uncontrolled diabetes, active or uncontrolled infection, chronic obstructive or chronic restrictive pulmonary disease including dyspnea at rest from any cause, uncontrolled thyroid dysfunction) that, in the opinion of the investigator, could cause unacceptable safety risks or compromise compliance with the protocol