Study of Oral Administration of LP-118 in Patients With Relapsed or Refractory CLL, SLL, MDS, MDS/MPN, AML, CMML-2, MPN-BP, ALL, MF, NHL, RT, MM or T-PLL.

Status: RECRUITING

Eligibility Criteria

Sex: ALL
Age: 13 years and over
Healthy Volunteers: This study is NOT accepting healthy volunteers
Inclusion Criteria:

1. Male or female subjects, ≥ 18 years of age at the time of Screening with the following exception as outlined below:

-For T cell and B cell ALL subjects with age between 13 - 18 years, their body weight shall be ≥ 40 kg.
2. Eligible subject must have an advanced hematologic malignancy including:

Group 1:

Group 1a
* Relapsed or refractory low risk tumor lysis CLL/SLL subjects (ALC < 25 x 109 cells/L and all lymph nodes < 5 cm) who have received at least two prior therapies. Subjects may also have slowly progressed on irreversible BTK inhibitors while on treatment with these agents.
* For CLL/SLL subjects who come off BCR antagonist treatment (BTK inhibitors, P13K inhibitors, etc.) allows washout for 2 days as these subjects, progress quickly after treatment discontinuation and then remain eligible (steroids may be given during these two days to allow disease control).

Group 1b
* Morphologically confirmed diagnosis of MF in accordance with the WHO 2016 revised criteria, that is relapsed, intolerant, and/or refractory and that, in the opinion of the Investigator, subjects who have no available therapies known to provide clinical benefits;
* Morphologically confirmed diagnosis of MDS/MPN, excluding juvenile myelomonocytic leukemia (JMML), in accordance with WHO 2016 revised criteria, that is relapsed and/or refractory and that, in the opinion of the Investigator, subjects who have no available therapies known to provide clinical benefits;
* Chronic myelomonocytic leukemia (CMML) with <9% blasts;
* Or atypical chronic myeloid leukemia (aCML) with Hgb > 10g/dL, WBC count < 50 x 109 cells/L, <10% immature circulating cells;
* Or MDS/MPN with ring sideroblasts and thrombocytosis (MDS/MPN-RS-T) with Hgb > 10g/dL;
* Or myelodysplastic/myeloproliferative neoplasm, unclassifiable (MDS/MPN-UC)
* CMML-2 with 10-19% blasts as defined by WHO 2016 revised criteria that is relapsed and/or refractory to prior HMA therapy;
* Relapsed and/or refractory MPN-BP as defined by WHO 2016 revised criteria that is transformed MPN with >20% myeloid blasts in the peripheral blood or bone marrow, in the opinion of the Investigator, subjects who have no available therapies known to provide clinical benefits;
* MDS subjects with refractory anemia with excess blasts (MDS-EB; subtype MDS-EB-1 or MDS-EB-2) as defined by WHO 2016 revised criteria and/or MDS with high- or very high-risk (risk score > 4.5) per the Revised International Prognostic Scoring System (IPSS-R, refer to Appendix 11; Section 15.13) who have no available therapies known to provide clinical benefit;
* Relapsed or refractory AML subjects (including de novo AML, secondary AML evolving from MDS or MPN or other antecedent hematologic disorder, and therapy-related AML) as defined by WHO 2016 revised criteria, subjects who have no available therapies known to provide clinical benefits; subjects with prior BCL-2 inhibitor therapy are permitted. WBC needs to be ≤ 25 × 109 cells/L at the time of initiating investigational therapy (hydroxyurea is allowed to control WBC prior to and during therapy).

Group 1c
* Relapsed or refractory low risk tumor lysis NHL (NHL histologies [MZL, FL, WM, DLBCL, ATLL, PTCL, AITL, ALCL, MCL] are to be included per the 2016 World Health Organization [WHO] criteria) subjects, must have histologically documented diagnosis of a non-Hodgkin lymphoma as defined in the WHO classification scheme. Subjects have received at least 2 prior therapies and have no available therapies known to provide clinical benefit; For subjects with indolent NHL (Grade 1~3a FL, MZL) who have received two prior systemic therapies and have relapsed or progressed according to 2014 Lugano;
* Low risk tumor lysis transformed follicular, MZL, WM (to large cell or aggressive lymphoma) subjects who must have received at least one prior systemic therapy for the transformed lymphoma (unless combination chemotherapy is not appropriate);
* Low risk tumor lysis Richter transformation (RT): previously treated CLL and biopsy-proven Richter transformation with DLBCL histology after receiving at least one regimen for RT;
* Relapsed or refractory multiple myeloma (MM) subjects who have received a proteasome inhibitor (PI), an immunomodulatory drug (IMiD), and an anti-CD38 and have no treatment options available known to provide clinical benefit;
* Low risk tumor lysis T-cell prolymphocytic leukemia (T-PLL) subjects who have received one therapy for this and are relapsed or refractory;

Group 1d
* Relapsed or refractory ALL with dexamethasone run-in [5 days, dexamethasone 10mg/m2 (divided BID)];
* Or r/r ALL in remission but with detectable MRD (MRD +) by any detection method per institution standard of practice;
* IT chemo (per institutional SOC) is permitted prior to LP-118 C1D1 dosing, and then concomitantly on treatment if in best interest of the subject;
* Relapsed or refractory ALL subjects with B cell phenotype who have received at least two prior therapeutic regimens (such as multi-agent chemotherapy and/or tyrosine kinase inhibitors including bosutinib, dasatinib, imatinib, nilotinib or ponatinib) and failed, or are currently ineligible/intolerant for CD19-based target therapy (e.g. Blinatumomab); Relapsed or refractory ALL subjects with T cell phenotype who have received at least one prior therapy and failed.
* Relapsed or refractory ALL subjects with age between 13 - 18 years and have body weight ≥ 40kg. ALL subjects with B cell phenotype who have

* Relapsed or refractory ALL subjects with age between 13 - 18 years and have body weight ≥ 40kg, ALL subjects with B cell phenotype who have received at least two prior therapeutic regimens (such as multi-agent chemotherapy and/or tyrosine kinase inhibitors including bosutinib, dasatinib, imatinib, nilotinib or ponatinib) and progressed, or are currently ineligible/intolerant for CD19-based target therapy (e.g. Blinatumomab); Relapsed or refractory ALL subjects with T cell phenotype who have received at least one prior therapy and progressed.

Group 2
* Relapsed or refractory intermediate and high risk tumor lysis CLL/SLL subjects who have received at least two prior therapies;
* Relapsed or refractory intermediate and high risk tumor lysis NHL (NHL histologies [MZL, FL, WM, DLBCL, ATLL, PTCL, AITL, ALCL, MCL] are to be included per the 2016 World Health Organization [WHO] criteria) subjects, must have histologically documented diagnosis of a non-Hodgkin lymphoma as defined in the WHO classification scheme. Subjects have received at least 2 prior therapies and have no available therapies known to provide clinical benefit; For subjects with indolent NHL (Grade 1~3a FL, MZL) who have received two prior systemic therapies and have relapsed or progressed according to 2014 Lugano;
* Intermediate and high risk tumor lysis transformed follicular, MZL, WM (to large cell or aggressive lymphoma) subjects who must have received at least one prior systemic therapy for the transformed lymphoma (unless combination chemotherapy is not appropriate);
* Intermediate and high risk tumor lysis Richter transformation (RT): previously treated CLL and biopsy-proven Richter transformation with DLBCL histology after receiving at least one regimen for RT;
* Intermediate and high risk tumor lysis T-cell prolymphocytic leukemia (T-PLL) subjects who have received one therapy for this and are relapsed or refractory;
3. For Group 1d ALL subjects only, white blood cell (WBC) count ≤ 25 × 109 cells/L at the time of enrollment (glucocorticoids or hydroxyurea is permitted to control WBC count prior to and during therapy).
4. Eastern Cooperative Oncology Group (ECOG) performance score ≤ 2.
5. Adequate cardiac function defined as shortening fraction of ≥ 40% by 2D echocardiogram without Doppler.
6. Subject must have adequate bone marrow (independent of growth factor support), coagulation, renal, and hepatic function, per laboratory reference ranges at Screening as follows:

Bone marrow criteria:
* Group 1 (r/r low risk tumor lysis CLL/SLL (ALC < 25 x 109 cells/L and all lymph nodes < 5 cm), NHL, RT, MM, T-PLL):
* Absolute Neutrophil Count (ANC) ≥ 1 x 109/L (An exception is for subjects with an ANC<1 x 109/L and bone marrow heavily infiltrated with underlying disease)
* Platelets ≥ 50 x 109/L on day of screening (entry platelet count must be independent of transfusion with 14 days of screening);
* Hemostasis criteria: Activated partial thromboplastin time (APPT) and prothrombin time (PT) ≤ 1.5 × the upper limit of normal (ULN);
* Renal function criteria: Serum creatinine ≤ ULN (per local institution reference range) or Calculated creatinine clearance (Cr Cl) ≥ 60 mL/min using 24-hour CrCl OR by Cockcroft-Gault formula using actual body weight.
* Hepatic function criteria: Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 3.0 × ULN; bilirubin ≤ 1.5 × ULN (except subjects with Gilbert's Syndrome, who may have a bilirubin > 1.5 × ULN, per discussion between the Investigator and the Medical Monitor).
7. Females of childbearing potential (i.e., non-postmenopausal for at least 2 years or surgically sterile) and non-sterile males must practice at least 1 of the following methods of birth control with their partner(s) throughout the study and for 90 days after discontinuing study drug:

- Total abstinence from sexual intercourse as the preferred lifestyle of the subject; periodic abstinence is not acceptable;
- Surgically sterile partner(s) by vasectomy, bilateral orchiectomy, bilateral tubal ligation, bilateral oophorectomy or hysterectomy;
- Intrauterine device;
- Hormonal contraceptives (oral, parenteral, vaginal ring or transdermal) associated with inhibition of ovulation initiated for at least 1 month prior to study drug administration.

    1. Females of childbearing potential must have a negative pregnancy result as follows:
- At Screening on a serum sample obtained within 7 days prior to the first study drug administration, and
- Prior to dosing on a urine or serum sample obtained on the first day of study drug administration if ithas been > 7 days since obtaining the serum pregnancy test results in Screening.
- If a urine pregnancy test at any timepoint during the study is positive or indeterminate, a serum pregnancy test will be performed for confirmation

    1. Male subjects must refrain from sperm donation, from initial study drug administration until 90 days after the last dose of study drug.
    2. Subject must be able to understand and voluntarily sign and date an informed consent form (ICF), approved by an IRB, prior to any protocol-related procedures.

Exclusion Criteria:

A subject will not be eligible for study participation if he/she meets any of the following criteria.

1. Subjects who have undergone autologous/allogeneic hematopoietic stem cell transplantation (HSCT) therapy within 60 days of the first dose of LP-118, or subjects on immunosuppressive therapy post-HSCT at the time of Screening, or currently with clinically significant graft-versus-host disease (GVHD) as per treating physician (Subjects in relapse after allogeneic transplantation must be off treatment with systemic immunosuppressive agents for at least 4 weeks. The use of topical steroids and/or up to 20 mg/day prednisone or equivalent systemic steroids for ongoing GVHD is permitted.
2. Subject has a history of other malignancies within past 12 months that are active and could result in competing risks. These cases shall be discussed with the Medical Monitor with the exception below.

- Subject with breast cancer or prostate cancer on endocrine therapy with stable disease;
- Continuation of maintenance therapy in patients with adequately treated malignancy
- Adequately treated in situ carcinoma of the cervix uteri;
- Basal cell carcinoma of the skin or localized squamous cell carcinoma of the skin;
- Previous malignancy confined and surgically resected (or treated with other modalities) with curative intent.
- Cancer with expected survival of 2 years or more or that will not confound evaluation of LP-118 treatment

    1. Subject has received any of the following therapies within 14 days or 5 half-lives (whichever is shorter) prior to the first dose of LP-118,

or has not recovered to ≤ Grade 2 clinically significant AEs of the previous therapy (excluding neuropathy):

- Any anti-neoplastic therapy including chemotherapy, hormonal therapy, radiotherapy, biologic or immunotherapy, targeted small molecule agents, etc. (corticosteroid therapy < 20 mg/day prednisone equivalent according to institutional guidelines to treat disease associated symptoms are permitted);
- For MF subjects who come off JAK2 antagonists, allow washout for 2 days as these subject's progress quickly after treatment discontinuation and remain eligible (steroids may be given during these two days to allow disease control).
- Subjects in need of immediate cytoreduction should be excluded.
- Any investigational therapy.
- Live vaccines

1. Subject has received the following medications, therapies, or natural products within 7 days prior to the first dose of LP-118:

- Cytochrome P450, family 3, subfamily A (CYP3A) strong inhibitors (itraconazole, etc.), or substrates (Appendix 19);
- Subject has received strong Cytochrome P450, family 3, subfamily A (CYP3A) inducers within 14 days prior to the first dose of LP-118 (Appendix 19);
- Grapefruit, grapefruit products, Seville oranges (including marmalade containing Seville oranges) or Star fruit;
- There is a 28-day washout period required for subjects who have had prior CAR-T treatment if there is no evidence of cytokine release syndrome (CRS) or other adverse events related to the CAR-T treatment, per discussion with the Medical Monitor.

1. Subject has a significant history of renal, neurologic, psychiatric, pulmonary, endocrinologic, metabolic, immunologic, cardiovascular, or hepatic disease that, in the opinion of the Investigator, would adversely affect his/her participation in this study. Any other medical or social condition deemed by the investigator to be likely to interfere with a subject's ability to participate in the study, place the subject at unacceptable risk or interfere with the interpretation of the results. For subjects who have required surgical intervention for any above diseases within the past 6 months, a discussion with the Investigator and the Medical Monitor is needed.
2. Subject has baseline prolongation of the heart rate-corrected QT (QTcF) interval ≥ 480 ms (calculated per Fridericia's formula [QTcF = QT/RR (1/3)])), a cardiovascular disability status of New York Heart Association Class ≥ 2 or associated other significant screening ECG or ultrasonic cardiogram abnormalities, per Investigator's judgement. For any subject with underlying RBBB or LBBB, cardiology review is needed to correct QTcF calculation using Sponsor recommended formula.
3. Subject has significant a history of congenital long QT syndrome or Torsades de Pointes (TdP), uncontrolled or symptomatic arrhythmias, congestive heart failure, myocardial infarction, stroke, or intracranial hemorrhage within 6 months prior to the first dose of LP-118.
4. Subject exhibits evidence of other clinically significant uncontrolled condition(s) including, but not limited to:

- Uncontrolled active systemic infection (bacterial, fungal, viral);
- Known poorly controlled human immunodeficiency virus (HIV) or active hepatitis B or C infection (active hepatitis B defined as HbsAg positive, or HbcAb positive with detectable HBV DNA load; active hepatitis C defined as HCV antibody positive with HCV RNA positive);
- Unexplained fever > 38.5°C within 7 days prior to the first dose of study drug administration (at the discretion of the Investigator if the fever is considered attributed to the subject's malignancy or an explained infection may be enrolled).

1. A female subject is pregnant or breast-feeding.
2. Subject incapacity to swallow oral medications, with any malabsorption condition, known dysphagia, short-gut syndrome, gastroparesis, or other conditions that, in the opinion of the Investigator, may limit the ingestion or gastrointestinal absorption, distribution, metabolism and excretion of drugs administered orally.
3. Subjects with known and active central nervous system (CNS) involvement at Screening.
4. Subjects with known hypersensitivity to any of the components of LP-118 (see Investigators Brochure for a list of components).
5. Subjects who are taking QT-prolonging drugs that are known to cause Torsades de Pointes (TdP) (See Appendix 17 for the list of medications that are associated with TdP). In the event a prohibited medication might cause TdP, the PI must first determine if the risk to benefit is in favor of the subject and then discuss with the Medical Monitor about that particular medication on a case-by-case basis.
6. Major surgery within 14 days prior to the first dose of study drug.

Conditions & Interventions

Interventions:
DRUG: LP-118
Conditions:
Non Hodgkin Lymphoma, Richter Transformation, Multiple Myeloma, T-cell-prolymphocytic Leukemia, Acute Myeloid Leukemia, Acute Lymphocytic Leukemia, Myeodysplastic Syndrome, Myelodysplastic/Myeloproliferative Neoplasm, Myelofibrosis, Chronic Lymphocytic Leukemia, Small Lymphocytic Lymphoma, Chronic Myelomonocytic Leukemia-2, Myelodysplastic Neoplasm in Blast Phase
Keywords:
Hematological Malignancies, Relapsed, Refractory

More Information

Description:
This is a Phase 1, multi-center, open-label study with a dose-escalation phase (Phase 1a) and a cohort expansion phase (Phase 1b), to evaluate the safety, tolerability, and PK profile of LP-118 under a once daily oral dosing schedule in up to 100 subjects.

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Phase: PHASE1
IRB Number:

IRB Number:
System ID: NCT04771572