# Essai Clinique

Généré le 17 mai 2024 à partir de

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| Titre | An Open-Label Phase 1a/1b Dose Escalation and Expansion Cohort Study of SL-172154 (SIRP?-Fc-CD40L) in Combination With Azacitidine or With Azacitidine and Venetoclax for the Treatment of Subjects With Higher-Risk Myelodysplastic Syndrome (MDS) or Acute Myeloid Leukemia (AML) |
| Protocole ID | SL03-OHD-104 |
| ClinicalTrials.gov ID | NCT05275439 |
| Type(s) de cancer | Leucémie myéloïde aiguë (LMA)<br>Syndrome myélodysplasique |
| Phase | Phase I |
| Type étude | Clinique |
| Médicament | SL-172154 (SIRP?-Fc-CD40L) in Combination With Azacitidine or With Azacitidine and Venetoclax |
| Institution | CIUSSS DU CENTRE-OUEST-DE-L'ILE-DE-MONTREAL<br>HOPITAL GENERAL JUIF SIR MORTIMER B.DAVIS<br>3755 rue de la Côte Ste. Catherine, Montréal, QC, H3T 1E2 |
| Ville | |
| Investigateur principal | Dre Sarit Assouline |
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| Statut | Actif en recrutement |
| Date d'activation | 11-10-2023 |
| But étude | SL03-Old Hundred(OHD)-104 is designed as a Phase 1a/1b open label, trial to evaluate the safety, pharmacokinetics (PK), pharmacodynamic (PD), and preliminary efficacy of SL-172154 monotherapy as well as in combination with azacitidine or in combination with Azacitidine and Venetoclax. |
| Critères d'éligibilité | • Subject has voluntarily agreed to participate by giving written informed consent in accordance with ICH/GCP guidelines and applicable local regulations.<br>• Age ≥ 18 years.<br>• For subjects with AML, confirmation of AML diagnosis by 2016 WHO criteria [Arber, 2016] (World Health Organization [WHO] classification, excluding acute promyelocytic leukemia [APL]).<br>• Subjects with MDS must have: Subjects with a diagnosis of any of the following are excluded: Atypical CML, juvenile myelomonocytic leukemia (JMML), chronic myelomonocytic leukemia (CMML), and unclassifiable MDS/ myeloproliferative neoplasm (MPN).<br>  • morphologically confirmed diagnosis of MDS by 2016 WHO criteria [Arber, 2016] with <20% blasts in bone marrow per bone marrow biopsy/aspirate or peripheral blood.<br>  • confirmation of intermediate, high or very high risk category by Revised International Prognostic Scoring System (IPSS-R).<br>• [Dose Escalation Cohort - SL-172154 Monotherapy] Subjects with AML must have relapsed/refractory disease (≥5% blasts by manual aspirate differential, flow cytometry, or immunohistochemistry) following at least 1 prior line of therapy but no more than 4 prior lines of therapy. Subjects with higher-risk MDS must have relapsed/refractory disease following at least 1 prior line but no more than 4 prior lines of therapy.<br>  • Prior hydroxyurea or other supportive care in the form of transfusions or growth factors will not be considered prior therapy.<br>  • Subjects who have undergone allogeneic-hematopoietic cell transplantation (HCT) are eligible if they are at least 6 months post-HCT, have relapsed AML or MDS as defined above, are not on treatment or prophylaxis for graft versus host disease (GVHD) for at |

least 6 weeks before administration of study treatment, and have no active GVHD.
    - Subjects must not be eligible for rescue chemotherapy and allogeneic-HCT per local or institutional guidelines at the time of screening.
- [Dose Escalation Cohort - SL-172154 Administered with Azacitidine] Subjects with relapsed/refractory AML and MDS (as defined in Inclusion criterion 5) following at least 1 prior line of therapy but no more than 4 prior lines of therapy. In addition, previously untreated subjects meeting either of the following criteria are eligible for this cohort:
    - Treatment for MDS preceding secondary AML will not be considered as a prior line of therapy for secondary AML.
    - Prior hydroxyurea or other supportive care in the form of transfusions or growth factors will not be considered prior therapy.
    - Subjects who have undergone allogeneic-HCT are eligible if they are at least 6 months post-HCT, have relapsed AML or MDS as defined above, are not on treatment or prophylaxis for GVHD for at least 6 weeks before the first dose of study treatment, and have no active GVHD.
    - Subjects must not be eligible for rescue chemotherapy and allogeneic-HCT per local or institutional guidelines at the time of screening.
    - Previously untreated subjects with AML with known adverse cytogenetics who fall into the adverse ELN risk group and who are unlikely to benefit from standard intensive induction therapy or refuse intensive induction therapy at time of enrollment.
    - Previously untreated subjects with MDS with documentation of at least one TP53 gene mutation or deletion based on a local test. Prior MDS therapy with lenalidomide or other supportive care in the form of transfusions or growth factors is allowed.
- [Dose Expansion Cohort Part A: SL-172154 Administered with Azacitidine] Subjects diagnosed with MDS must be previously untreated. Prior MDS therapy with lenalidomide or supportive care in the form of transfusions or growth factors is allowed. Up to 1 cycle of prior therapy with a hypomethylating agent is permitted. Subjects with newly diagnosed treatment-related MDS are also eligible for enrollment.
- [Dose Escalation - Safety Run-in Cohort AND Dose Expansion Cohort Part B: SL 172154 Administered with Azacitidine and Venetoclax] Subjects with AML must be previously untreated as defined by:
    - Subject must be ineligible for induction therapy with a standard cytarabine and anthracycline induction regimen due to age or co-morbidities as defined by the following:
        - ≥ 75 years of age
        - ≥ 60 to 74 years of age with at least one of the following co-morbidities:
        - Eastern Cooperative Oncology Group (ECOG) Performance Status of 2
        - History of congestive heart failure (CHF) requiring treatment
        - Ejection fraction ≤ 50%
        - Chronic stable angina
        - DLCO ≤ 65% or FEV1 ≤ 65%
        - Creatinine clearance ≥ 30 mL/min to < 45 mL/min
        - Documented contraindication to anthracycline or cytarabine based therapy
    - Subjects with AML with known adverse cytogenetics who fall into the adverse ELN risk group and who are unlikely to benefit from standard intensive induction therapy or refuse intensive induction therapy at time of enrollment are also eligible.
    - Subjects with newly diagnosed secondary AML and who are unlikely to benefit from standard intensive induction therapy or refuse intensive induction therapy at time of enrollment are eligible for enrollment. Subjects with secondary AML after MDS must not have received prior chemotherapy or no more than 2 cycles of prior hypomethylating agent for MDS.
- [Dose Expansion Cohort Part C: SL-172154 Administered Azacitidine]: Subjects with previously untreated de novo AML or secondary AML with TP53 gene mutation or deletion who are unlikely to benefit from standard intensive induction therapy or refuse intensive induction therapy at time of enrollment are eligible. All subjects must have documentation of at least one TP53 gene mutation/deletion based on local test. Subjects with secondary AML after MDS must not have received prior chemotherapy or no more than 2 cycles of prior hypomethylating agent for MDS.
- ECOG Performance Status of 0, 1, or 2.
- Laboratory values must meet the following criteria: Laboratory parameter Threshold value White blood cell count (WBC) ≤ 20 x 109/L (Hydroxyurea is permitted to meet this criterion) Creatinine clearance (CrCl) ≥ 30 mL/min (using modified Cockcroft-Gault formula) ALT/AST ≤ 3 x ULN Total bilirubin ≤ 1.5 x ULN; subjects with isolated indirect hyperbilirubinemia are permitted if direct bilirubin ratio is <35% and total bilirubin is ≤ 3.0 x ULN
- Willing to provide consent for bone marrow aspirate samples at baseline and on-treatment for exploratory research as described in the Schedule of Assessments.
- For subjects with relapsed/refractory disease, recovery from prior anti-cancer treatments including surgery, radiotherapy, chemotherapy or any other anti-cancer therapy to baseline or ≤ Grade 1. (NOTE: Low-grade or controlled toxicities (e.g., alopecia) may be allowed upon agreement by the Medical Monitor)
- Females of childbearing potential (FCBP) must have a negative serum or urine pregnancy test within 72 hours of the first dose of study treatment. NOTE: females are defined as being of childbearing potential unless they are surgically sterile (i.e., have undergone a complete hysterectomy, bilateral tubal ligation/occlusion, bilateral oophorectomy, or bilateral salpingectomy), have a congenital or acquired condition that prevents childbearing or are naturally post-menopausal for at least 12 consecutive months. Documentation of post-menopausal status must be provided. To avoid pregnancy, FCBP must start using a highly

effective method of contraception (i.e., <1% failure rate) at least 14 days prior to initiation of study treatment and continue use during treatment and for 30 days (which exceeds 5 half-lives) after the last dose of SL-172154, or for the duration required by local prescribing information after the last dose of azacitidine (i.e., for sites in UK and Spain, at least 6 months after the last dose of azacitidine in either combination regimen).
- Male subjects with female partners must have azoospermia from a prior vasectomy, an underlying medical condition, or agree to use a highly effective method of contraception (i.e., <1% failure rate) during treatment and for 30 days (which exceeds 5 half-lives) after the last dose of SL-172154, or for the duration required by local prescribing information after the last dose of azacitidine (i.e., for sites in UK and Spain, at least 3 months; for sites in Canada, at least 6 months).

Critères d'exclusion

- [Monotherapy and Combination Regimen Dose Escalation Cohorts] Prior treatment with:
    - CAR-T cell therapy within 3 months from the first dose of the study drug.
    - Prior treatment with anti-CD47 targeting agent or CD40 agonist within 28 days prior to the first dose of study treatment.
    - Prior treatment with signal-regulatory protein alpha (SIRPα)-targeting agent.
    - Other experimental therapies for AML or MDS within 14 days or at least 5 half-lives (whichever is shorter) prior to the first dose of study treatment.
- Evidence of active CNS involvement with leukemia.
- Subjects requiring agents other than hydroxyurea to control blast counts within 14 days prior to the first dose of study treatment.
- Evidence of active bleeding or bleeding diathesis or major coagulopathy (including familial).
- [Only for Cohorts Including Venetoclax in the Regimen] Subject has received strong and/or moderate CYP3A inducers within 7 days prior to the first dose of venetoclax.
- Use of systemic corticosteroids (>10 mg daily of prednisone or equivalent) or other non-steroidal immunosuppressive medication, current or within 14 days of the first dose of study treatment with the following exceptions (i.e., the following are allowed within 14 days of first dose):
    - Topical, intranasal, inhaled, ocular, intraarticular corticosteroids
    - Physiological doses of replacement steroid (e.g., for adrenal insufficiency)
    - Steroid premedication for hypersensitivity reactions (e.g., reaction to IV contrast) or a brief course of treatment of non-autoimmune conditions (e.g., transfusion reactions, delayed-type hypersensitivity reaction caused by contact allergen).
- Receipt of live attenuated vaccine within 30 days of first dose of SL-172154 treatment.
- Subject has active, uncontrolled infection (e.g., viral, bacterial, or fungal). Subjects are eligible if infection is controlled with antibiotics, antivirals and/or antifungals.
- [Only for Cohorts Including Venetoclax in the Regimen] Subject has a malabsorption syndrome or other condition that precludes the enteral route of administration.
- Symptomatic peptic ulcer disease or gastritis, active diverticulitis, other serious gastrointestinal disease associated with diarrhea within 6 months of first dose of study treatment.
- Clinically significant or uncontrolled cardiac disease including any of the following:
    - Myocarditis
    - Unstable angina within 6 months from first dose of study treatment
    - Acute myocardial infarction within 6 months from first dose of study treatment
    - Uncontrolled hypertension
    - NYHA Class III or IV congestive heart failure
    - Clinically significant (symptomatic) cardiac arrhythmias (e.g., sustained ventricular tachycardia, second- or third- degree atrioventricular (AV) block without a pacemaker, circulatory collapse requiring vasopressor or inotropic support, or arrhythmia not stabilized on therapy)
- Subject has chronic respiratory disease that requires continuous oxygen, or significant history of renal, neurologic, psychiatric, endocrinologic, metabolic, immunologic, hepatic, cardiovascular disease, or any other medical condition that in the opinion of the Investigator would adversely affect his/her participation in the study.
- Subjects who have had any major surgical procedure within 14 days of first dose of study treatment.
- Subject is a woman who is pregnant or breast feeding or planning to become pregnant or breast feed while enrolled in this study.
- Psychiatric illness/social circumstances that would limit compliance with study requirements and substantially increase the risk of AEs or compromised ability to provide written informed consent.
- Presence of another malignancy that requires active therapy and that in the opinion of the Investigator and Sponsor would interfere with the monitoring of disease assessments in this study.
- Known hypersensitivity to any of the study medications including excipients of azacitidine.
- Has undergone solid organ transplantation.
- Known or active human immunodeficiency virus (HIV) infection
- Known or active infection with hepatitis B (positive for hepatitis B surface antigen [HbsAg]) or hepatitis C virus ([HCV]; if HCV antibody (Ab) test is positive check for HCV ribonucleic acid [RNA]).

NOTE: Hepatitis B virus (HBV): Subjects who are hepatitis B core antibody [HbcAb]-positive but HbsAg-negative are eligible for enrollment. HCV: Subjects who are HCV Ab-positive but HCV RNA-negative are eligible for enrollment.