A Phase 1/2 Study of SL-401 as Consolidation Therapy for Adult Patients with Adverse Risk Acute Myeloid Leukemia in First CR, and/or Evidence of Minimal Residual Disease (MRD) in First CR

Sponsor:	Stemline Therapeutics, Inc. 750 Lexington Avenue, 11th Floor New York, NY 10022
Study Product:	SL-401
Protocol Number:	STML-401-0214
IND Number:	114513
Issue Date:	27 March 2018

Sponsor:

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INVESTIGATOR PROTOCOL AGREEMENT

A Phase 1/2 Study of SL-401 as Consolidation Therapy for Adult Patients with Adverse Risk Acute Myeloid Leukemia in First CR, and/or Evidence of Minimal Residual Disease (MRD) in First CR

I hereby agree to:

- Conduct the study as outlined in this protocol with reference to national/local regulations and current International Council for Harmonisation (ICH) / Good Clinical Practice (GCP) guidelines.
- Discuss and agree upon any modification to the protocol with Stemline Therapeutics, Inc., or representatives hereof.
- Fully co-operate with monitoring and auditing and allow access to all documentation by authorized individuals representing Stemline Therapeutics, Inc., or Health authorities.

Protocol Version / Date: 27 March 2018

To be signed by Principal Investigator:

Print Name	[redacted]		
Signature	[redacted]	**Date**	[redacted]
Institution	[redacted]		

To be signed by Stemline Therapeutics, Inc.:

Print Name	[redacted]		
Signature	[redacted]	**Date**	[redacted]
Title	[redacted]		

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1 Protocol Synopsis

Name of Finished Product:

SL-401 Injection frozen solution (1 mg/mL) / SL-401 for Injection lyophilized powder, for solution (1 mg/mL)

Name of Active Ingredient:

SL-401

Study Title:

A Phase 1/2 Study of SL-401 as Consolidation Therapy for Adult Patients with Adverse Risk Acute Myeloid Leukemia in First CR and/or Evidence of Minimal Residual Disease (MRD) in First CR.

Protocol Number:

STML-401-0214

Study Phase:

1 / 2

Primary Objectives:

The primary objectives are to determine the maximum tolerated dose (MTD), or the maximum tested dose where multiple dose-limiting toxicities (DLTs) are not observed, of SL-401, and to characterize the safety profile of SL-401 at the MTD or maximum tested dose.

Secondary Objectives:

The secondary objectives are to:

- Evaluate the presence of minimal residual disease (MRD) and changes in MRD status during and following SL-401 therapy
- Estimate relapse-free survival (RFS)
- Estimate overall survival (OS)
- Characterize the pharmacokinetics (PK) of SL-401
- Characterize the immunogenicity of SL-401

Exploratory Objectives:

Exploratory objectives are to characterize expression of the interleukin-3 receptor (IL-3R)/CD123 (and other potentially relevant stem cell and disease markers) on leukemia cells in bone marrow (when feasible), to evaluate potential changes in IL-3R/CD123 (and other potentially relevant marker) expressing populations over time, and preliminary correlation of baseline IL-3R/CD123 (and other potentially relevant marker) expression and clinical efficacy (including changes in MRD status).

Study Population:

Approximately 21-33 adult patients diagnosed with acute myeloid leukemia (AML) that is considered adverse risk disease who have achieved a first or second complete remission (CR) or complete remission with incomplete bone marrow recovery (CRi) within 6 months prior to enrollment and are not considered immediate candidates for allogenic stem cell transplant.

Study Design:

This is a non-randomized, open-label, dose escalation study, consisting of 2 stages. A cycle of therapy is 28 days. A Data Safety Review Committee (DSRC), which will include Sponsor representatives, will be established to review the accruing safety data and make safety decisions during the study, including dose escalations in Stage 1 and ongoing monitoring in Stage 2.

Stage 1: Dose Escalation:

During Stage 1, approximately 9-18 patients will be treated with SL-401. The starting dose of SL-401 is 7 µg/kg/day for 5 consecutive days every 28 days, with escalation to 9 and 12 µg/kg/day and potentially higher doses, as warranted by the data.

Three to 6 patients will be treated at each dose level. All patients within a cohort must complete the first cycle of therapy before patients from a new cohort receive SL-401 at the next higher dose. No intra-patient dose escalation is allowed.

A decision to allow treatment at the next higher dose level will depend on the number of patients who experience a DLT during the first cycle. If after 3 patients complete Cycle 1:

- None of the initial 3 patients treated (0/3) experiences a DLT, then dose escalation will proceed and 3 new patients will be treated at the next higher dose.
- One of the initial 3 patients treated (1/3) experiences a DLT, the cohort will be expanded to include an additional 3 patients treated at the same dose.
  - If only 1 patient (1/6) from this expanded cohort experiences a DLT, then 3 new patients will be treated at the next higher dose.
- If 2 or more patients within a cohort have a DLT, then the MTD will be exceeded and further dose escalation will not occur.

If the highest planned treatment dose is completed and determined to be safe and the MTD is not exceeded, the available PK and safety data will be reviewed to assess whether further dose escalation is justified.

A patient who does not complete the first cycle of treatment for reasons other than the occurrence of DLT will be replaced by another patient who will receive the same dose regimen.

In the event that a DLT occurs in 2 or more patients treated at the initial dose level, 7 µg/kg/day, 5 µg/kg/day will be considered by the DSRC as an alternative starting dose. In this event, a new cohort of 3 patients will receive 5 µg/kg/day for the first cycle. The same DLT rules will apply to this dose level. If 2 or more patients experience a DLT at the 5 µg/kg/day dose level, the study will be halted.

Events meeting the criteria for DLT that occur in Cycle 2 or beyond will be considered DLT-level events; dosing of SL-401 in subsequent patients/cohorts will be evaluated and potentially modified based on the chronology, severity, and frequency of these events.

Definition of Dose-limiting Toxicity

During Stage 1, DLT is defined as any of the following occurring during the first cycle of therapy:

- Any treatment-emergent Grade 4 transaminase or CPK elevation (confirmed within 24 hours of initial identification), regardless of duration or relationship to SL-401.
- Any treatment-emergent Grade 4 hematologic toxicity (unrelated to recurrent leukemia or prior AML therapy) lasting > 28 days after the last infusion of SL-401.
- Any treatment-emergent Grade ≥3 non-hematologic toxicity (unrelated to recurrent leukemia), with the exception of Grade 3 laboratory toxicities that resolve to Grade ≤1 or baseline ≤28 days after the last infusion of SL-401, or the following Grade 3 toxicities if they resolve to Grade ≤1 or baseline ≤21 days after the last infusion of SL-401: arthralgia, myalgia, fever responding to treatment, nausea and/or vomiting (excluding cases that require tube feeding, total parenteral nutrition, or hospitalization) or diarrhea associated with suboptimal prophylaxis or treatment.

SL-401-related toxicities are AEs that are considered by the Investigator to be either possibly, probably or

definitely related to investigational SL-401 (Please refer to Section 10.6 for more thorough guidance as to the assessment of "relatedness" in the context of investigational anticancer therapy). It should be noted that although the cycle length is 28 days, cycle duration may extend beyond 28 days in the setting of AEs, which are detailed in Section 7.5.5.

Definition of Maximum Tolerated Dose

The MTD is defined as the dose preceding the dose level at which 2 or more patients experience a DLT during treatment Cycle 1.

The MTD (or a lower dose with a potentially more favorable risk/benefit profile [if identifiable during Stage 1]) will be used in Stage 2 of the study.

Stage 2: Expansion:

During Stage 2, up to 20 additional patients with evidence of MRD as determined locally will be treated at the MTD or maximum tested dose at which multiple DLTs are not observed (identified in Stage 1) so that up to 15 patients with evidence of MRD as determined centrally are evaluable for safety and response at this dose. For inclusion in the study, all patients treated in the expansion phase should have MRD in bone marrow, as determined locally, via at least one of the following modalities: multi-parametric flow cytometry, cytogenetic evaluation, fluorescence *in situ* hybridization (FISH), real-time polymerase chain reaction (PCR), or next-generation gene sequencing. It is anticipated that at approximately 50% of patients evaluated with AML in 1st remission (CR or CRi) will have evidence of MRD.

Tumor Assessments During Stages 1 and 2:

All patients must have a baseline (pre-treatment) bone marrow aspirate (+ biopsy) and peripheral blood sample within 14 days prior to the first administration of SL-401. Subsequent bone marrow aspirate (+ biopsy) and peripheral blood assessments will be made at the end of Cycles 2, 4, and 6, then every 3 months (± 1 month) until Month 12. Bone marrow assessments of MRD for patients at baseline and during treatment will be conducted at a central laboratory, as described in Section 8.11.1 and the Laboratory Manual. No repeat bone marrow is necessary if progressive disease can be unequivocally diagnosed from peripheral blood tests. If the end of Cycle 2 bone marrow examination is empty (i.e., hypocellular) or inadequate, a bone marrow examination should be repeated in 14 (± 7) days to document response status. If additional time is required to complete the repeat examination, consult with the Medical Monitor. CD123 is to be assessed in all bone marrow samples (and, if applicable, tissue samples) by flow cytometry (i.e., CD123 should be added to the panel of markers assessed by flow cytometry of bone marrow aspirates) and immunohistochemistry and the results recorded and captured in the electronic case report form (eCRF). Peripheral blood assessment (differential) will also be performed as indicated for assessment of circulating leukemic blasts.

Patients will also be followed for RFS and OS.

Study Centers:

Patients will be recruited from up to 20 centers in the North America.

Inclusion Criteria:

1. The patient has a diagnosis of AML according to World Health Organization (WHO) criteria.
2. The patient received any induction chemotherapy regimen and may have received post-remission consolidation therapy prior to screening.
3. The patient has achieved a first or second CR or CRi. For patients without evidence of MRD in CR/CRi, CR (or CRi) must have been initially identified within 12 months prior to screening.

   OR

   The patient has achieved first or second CR or CRi with evidence of MRD as determined locally at

least 6 months post stem cell transplant without evidence of acute or chronic graft-versus-host disease post-transplant and has not received immunosuppressant therapy for at least 14 days prior to SL-401 therapy.

4. The patient has adverse risk disease or AML for which there is otherwise a substantial risk of relapse, which includes but is not limited to: adverse karyotype, FLT3 internal tandem duplication (ITD) mutation, history of antecedent hematologic disorder (AHD), therapy-related AML, history of requiring more than 1 cycle of intensive induction chemotherapy to achieve first remission, and/or presence of persistent MRD (detected by cytogenetics, molecular markers, or flow cytometry) at any point after the initial induction cycle. (A more comprehensive listing of karyotypes and mutations indicative of high-risk AML is provided as an appendix to the protocol [Section 15.3 Appendix C]).
5. For patients enrolling in Stage 2, the bone marrow evaluation determined locally within the previous 6 months indicates the presence of MRD. (A more comprehensive listing of methodologies for evaluation of MRD is provided as an appendix to the protocol [Section 15.4 Appendix D]).
6. The patient is not considered to be an immediate candidate for allogeneic stem cell transplant as determined by the investigator.
7. The patient is ≥18 years old.
8. The patient has an Eastern Cooperative Oncology Group (ECOG) performance score (PS) of 0-2.
9. The patient has adequate organ function, including cardiac, renal, and hepatic function:
    - Left ventricular ejection fraction (LVEF) ≥ institutional lower limit of normal as measured by multigated acquisition scan (MUGA) scan or 2-dimensional (2-D) echocardiography (ECHO) within 28 days prior to start of therapy and no clinically significant abnormalities on a 12-lead electrocardiogram (ECG)
    - Serum creatinine ≤1.5 mg/dL
    - Serum albumin ≥3.2 g/dL in the absence of receipt of (IV) albumin within the previous 72 hours.
    - Bilirubin ≤1.5 mg/dL
    - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤2.5 × the upper limit of normal (ULN)
    - Creatine phosphokinase (CPK) ≤2.5 × the ULN.
10. The patient has adequate bone marrow reserve:
    - Absolute neutrophil count (ANC) > 0.5×10^9/L
11. The patient is a woman of child bearing potential (WOCBP) who has had a negative serum or urine pregnancy test within 1 week prior to SL-401 treatment (intervals shorter than 1 week are acceptable if required by institutional guidelines).
12. A written and voluntarily signed informed consent must be obtained from the patient or legally authorized representative, in accordance with local regulations, before the initiation of any study-related procedures. The patient or legally authorized representative must be able to read and understand the informed consent form (ICF).
13. The patient is able to adhere to the study visit schedule and other protocol requirements, including follow-up for survival assessment.
14. The patient (male and female) agrees to use acceptable contraceptive methods for the duration of time on the study, and continue to use acceptable contraceptive methods for 2 months after the last infusion of SL-401.

Exclusion Criteria:

1. The patient has a diagnosis of AML associated with karyotype t(15;17).
2. The patient has persistent and clinically significant Grade ≥2 toxicities from induction or consolidation therapy (excluding alopecia, nausea, fatigue, and liver function tests [as mandated in the inclusion criteria]) not readily managed with supportive measures.
3. The patient received treatment with another investigational agent within 14 days of screening.
4. The patient previously received treatment with SL-401.
5. The patient has an active malignancy and/or cancer history (excluding AML or antecedent myelodysplastic syndrome [MDS]) that may confound the assessment of the study endpoints. Patients with a past cancer history (within 2 years of entry) with substantial potential for recurrence and/or ongoing active malignancy must be discussed with the Sponsor before study entry. Patients with the following neoplastic diagnoses are eligible: non-melanoma skin cancer, carcinoma in situ (including superficial transitional cell carcinoma of the bladder), cervical intraepithelial neoplasia, organ-confined prostate cancer with no evidence of progressive disease.
6. The patient has clinically significant cardiovascular disease (e.g., uncontrolled or any New York Heart Association [NYHA] Class 3 or 4 congestive heart failure, uncontrolled angina, history of myocardial infarction, unstable angina or stroke within 6 months prior to study entry, uncontrolled hypertension or clinically significant arrhythmias not controlled by medication).
7. The patient has uncontrolled, clinically significant pulmonary disease (e.g., chronic obstructive pulmonary disease, pulmonary hypertension) that in the opinion of the Investigator would put the patient at significant risk for pulmonary complications during the study.
8. The patient has known active or suspected central nervous system (CNS) leukemia. If suspected, CNS leukemia should be ruled out with relevant imaging and/or examination of cerebrospinal fluid.
9. The patient has uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, disseminated intravascular coagulation, or psychiatric illness/social situations that would limit compliance with study requirements.
10. The patient is pregnant or breast feeding.
11. The patient has known positive status for human immunodeficiency virus (HIV), active or chronic Hepatitis B or Hepatitis C.
12. The patient is oxygen-dependent.
13. The patient has any medical condition which in the opinion of the Investigator places the patient at an unacceptably high risk for toxicities.

Investigational Product, Dose, and Mode of Administration:

SL-401 is a novel protein comprised of recombinant human IL-3 genetically fused to truncated diphtheria toxin protein. SL-401 targets the IL-3R, which is over-expressed on the cancer stem cells (CSCs) and bulk of various leukemias and hematopoietic malignancies relative to normal hematopoietic stem cells and other hematopoietic cells.

A cycle of therapy is 28 days. SL-401 is provided as an IV injectable and administered as a 15-minute IV infusion for the first 5 consecutive days of a 28-day cycle. In Stage 1, the first cycle of SL-401 must be administered in the inpatient setting, with hospitalization beginning the day of the first infusion of SL-401 (or a prior day) and ending approximately 24 hours after the last infusion of SL-401. Subsequent cycles of SL-401 can be administered in the inpatient setting or in a suitable outpatient ambulatory care setting that is equipped for intensive monitoring of patients with hematopoietic malignancies undergoing treatment, per the discretion of the Investigator and institutional guidelines and capabilities. Patients will be monitored for at least 4 hours following the administration of each infusion of SL-401.

Patients with evidence of ongoing disease control during treatment (without evidence of clinically

significant progressive disease or intolerable toxicity) may receive repeated cycles of SL-401 even if eradication of MRD, in the judgment of the Investigator, is not attained. Patients can receive up to 6 total cycles of SL-401 as long as there is evidence of ongoing AML remission, according to their physician Investigator. The administration of additional cycles of SL-401 (> 6 cycles) must be discussed with the Medical Monitor at which time the individual patient's potential risk/benefit of further treatment will be assessed.

Patients will receive the following premedications approximately 60 minutes before each SL-401 infusion:

- Acetaminophen 650 mg by mouth (PO)
- Diphenhydramine 50 mg IV
- Methylprednisolone 50 mg IV (or an equivalent dose of another corticosteroid)
- Ranitidine 50 mg IV (or an equivalent dosage of another H_2-histamine antagonist)

During the dosing period for each cycle, individual SL-401 infusions may be delayed to allow for toxicity resolution, as detailed in Section 7.5.5.

Concomitant Medications:

Recommended Medications Per Institutional Guidelines/Practices:

Patients may receive the following types of prophylactic therapies/regimens, if indicated by institutional guidelines/practices:

- Antibacterial: ciprofloxacin, levofloxacin, or an equivalent antibiotic
- Antifungal: fluconazole, voriconazole, or an equivalent antifungal
- Antiviral: acyclovir, valacyclovir or an equivalent antiviral

Allowed Medications/Therapies:

All patients may receive supportive care measures as clinically indicated, including prophylactic antibiotics, antihistamines, antiemetics, albumin, fluids (hydration), and supportive measures. Patients may receive growth factor support and/or blood product transfusions as per the discretion of their physician.

Albumin 25 g IV daily should be administered if serum albumin is <3.0 g/dL on days when treatment has been withheld or in the immediate post-treatment period. The Investigator has discretion with regard to frequency of administration.

Prohibited Medications/Therapies:

Prior to discontinuation of SL-401, patients may not receive investigational or non-investigational anticancer or anti-leukemia agents, including cytotoxic chemotherapy agents, hypomethylating agents (5-azacytadine, decitabine, and others), or anticancer tyrosine kinase inhibitors (including imatinib, ruxolitinib, sorafenib, and others) or therapeutic monoclonal antibodies.

Assessments:

Assessments for safety, efficacy, and biological/correlative effects will be performed according to the schedules outlined in Table 5 and Table 6.

Safety Assessments:

Safety assessments include DLTs, adverse events (AEs), serious adverse events (SAEs), physical examinations, vital sign measurements, clinical laboratory evaluations, and reasons for treatment discontinuation due to toxicity. In addition, patients will be monitored for changes in visual acuity and color vision and post-transplantation veno-occlusive disease (VOD).

The AE reporting period for a patient treated in the study begins with the initiation of SL-401 and is continuous through 30 days after the last SL-401 infusion. All AEs that occur in treated patients during

the AE reporting period specified in the protocol must be reported to the Sponsor, whether or not the event is considered related to SL-401. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to SL-401 should also be reported as an AE.

Efficacy Assessments:

Efficacy assessments include RFS, OS, and presence of MRD positive cells during follow-up.

Correlative Studies:

Bone marrow samples will be collected to determine the frequencies of leukemia stem cells and MRD positive cells and changes in intracellular signaling upon SL-401 treatment, and for in vivo engraftment studies. All patient samples will be collected at the treatment sites and immediately shipped to the designated central laboratories for analysis.

Pharmacokinetic (PK) Studies:

An intensive schedule for collection of blood samples after specific infusions during Cycles 1 & 3 of SL-401 will be used to determine plasma concentrations of SL-401. Plasma concentration data over time will be used to characterize the PK disposition of SL-401, to assess any change in the PK properties of SL-401 during the 5-day course of treatment, and relate the PK characteristics of SL-401 to toxicity and disease activity. The nominal blood sampling time schedule is summarized in Table 7.

Immunogenicity Studies:

Blood samples will be collected for the detection of SL-401 reactive antibodies.

Cardiac Assessments:

All patients will have 12-lead ECGs performed according to the schedule in Table 7. All ECGs will be analyzed locally.

Statistical Methods:

Demographic (e.g., gender, age, and race) and baseline characteristics (e.g., ECOG performance status, height, weight, and prior therapy) will be summarized by SL-401 dose group with descriptive statistics.

Treatment-emergent AEs through 30 days after last SL-401 infusion will be summarized by the Medical Dictionary for Regulatory Activities (MedDRA™), Version 13.1 (or higher), System Organ Class and preferred term. The incidences and percentages of patients experiencing each AE preferred term will be summarized with descriptive statistics. AEs will also be summarized by National Cancer Institute Common Terminology Criteria for Adverse Events (NCI-CTCAE), Version 4.03 (or higher), grade and by causality (relationship to study drug). DLTs, Grade 3-4 AEs, SAEs, and AEs resulting in dose modification or treatment discontinuation will also be summarized by preferred term.

Laboratory results will be classified according to NCI-CTCAE, Version 4.03 (or higher). Laboratory results not corresponding to an NCI-CTCAE term will not be graded. Incidences of laboratory abnormalities will be summarized with descriptive statistics.

Vital signs and physical examination results will be summarized with descriptive statistics.

Efficacy analyses will include all patients treated at the MTD or maximum tested dose. The distributions of RFS and OS will be estimated by Kaplan-Meier methodology. The presence of MRD will be summarized at each assessment time point by descriptive statistics. Relapse-free survival will also be summarized for subgroups defined by MRD status (e.g., no MRD at baseline, MRD at baseline converting to no MRD at any time point during follow-up, MRD at baseline and at every time point during follow-up).

Sample Size:

In Stage 2, up to 20 additional patients with MRD as determined locally will enroll and receive SL-401 at either the MTD or maximum tested dose, so that a total of 15 patients with evidence of MRD as determined centrally are treated at this dose. The assumptions governing sample size are as follows:

- Null hypothesis: eradication of MRD ≤5%
- Alternate hypothesis: eradication of MRD ≥20%
- Type 1 error: 17% one-sided
- Power: >80%

Because no available anti-leukemia therapies (other than allogeneic transplant) are believed to be associated with the eradication of evidence of MRD in this high-risk AML setting, the study would be considered positive if ≥2 of 15 patients in 1st remission (CR) are converted from MRD-positive to MRD-negative status. In a situation where 1 of 15 patients have eradication of MRD, the results may be considered of interest, given the dearth of efficacious therapy in this setting; however, additional data scrutiny will likely be warranted before additional investigations can be considered.

2 Abbreviations and Definitions

Abbreviation	Definition
2-D	2-Dimensional
AE	Adverse Event
AHD	Antecedent Hematologic Disorder
ALL	Acute Lymphoid Leukemia
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
aPTT	Activated Partial Thromboplastin Time
AST	Aspartate Transaminase
BMA	Bone Marrow Aspiration
BP	Blood Pressure
BPDCN	Blastic Plasmacytoid Dendritic Cell Neoplasm
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CLS	Capillary Leak Syndrome
CML	Chronic Myeloid Leukemia
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CR	Complete Remission
CRi	Complete Remission with Incomplete Bone Marrow Recovery
CSC	Cancer Stem Cell
CTCAE	Common Terminology Criteria for Adverse Events
DIC	Disseminated Intravascular Coagulation
DLT	Dose-Limiting Toxicity

Abbreviation	Definition
DNA	Deoxyribonucleic acid
DP	Drug Product
DSRC	Data Safety Review Committee
DT	Diphtheria Toxin
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic Acid
ELISA	Enzyme-linked Immunosorbent Assay
EOI	End-of-Infusion
FDA	Food and Drug Administration
FISH	Fluorescence *In Situ* Hybridization
FLT3-ITD	FLT-3 Internal Tandem Duplications
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
GM-CSF	Granulocyte Macrophage-Colony Stimulating Factor
HIPAA	Human Insurance Portability Accountability Act
HIV	Human Immunodeficiency Virus
Hsp90	Heat Shock Protein 90
IB	Investigator Brochure
IC_{50}	Concentration that Inhibits the Growth of 50% of Leukemia Cells
ICF	Informed Consent Form
ICH	International Council for Harmonisation
IEC	Independent Ethics Committee
IL	Interleukin
IL-3R	Interleukin-3 Receptor

Abbreviation	Definition
IL-3Rα	Alpha Subunit of the Human Interleukin-3 Receptor
IND	Investigational New Drug Application
INR	International Normalized Ratio
IRB	Institutional Review Board
IRT	Interactive Response Technology
ITD	Internal Tandem Duplication
IV	Intravenous
IWG	International Working Group
LAIPs	Leukemia-associated Phenotypes
LDH	Lactate Dehydrogenase
LFT	Liver Function Test
LVEF	Left Ventricular Ejection Fraction
MDS	Myelodysplastic Syndrome
MedDRA	Medical Dictionary for Regulatory Activities
MRC	Medical Research Council
MRD	Minimal Residual Disease
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition Scan
NCI	National Cancer Institute
NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall Survival
PCR	Polymerase Chain Reaction
PD	Progressive Disease
pDCs	Plasmacytoid Dendritic Cells
PFS	Progression-free Survival
PK	Pharmacokinetics
PO	By Mouth

Abbreviation	Definition
PR	Partial Remission
PS	Performance Status
PT	Prothrombin Time
RBC	Red Blood Cell
RFS	Relapse-Free Survival
RPG	Research Point Global
SAE	Serious Adverse Event
SCT	Stem Cell Transplant(ation)
SD	Stable Disease
SOI	Start of Infusion
TEAE	Treatment-emergent adverse event
TLS	Tumor lysis syndrome
TRIS	Tris(hydroxymethyl)aminomethane
ULN	Upper Limit of Normal
US	United States
VOD	Veno-occlusive disease
WBC	White Blood Cell
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

3 Introduction and Study Rationale

3.1 Acute Myeloid Leukemia

Acute Myeloid Leukemia (AML) is characterized by the uncontrolled proliferation of immature myeloid cells in the bone marrow and peripheral blood, resulting in the development of anemia, neutropenia, and thrombocytopenia, and associated complications such as serious infections, bleeding, and fatigue. The American Cancer Society (2013) estimates there will be approximately 14,590 new cases of AML in the United States (US) during 2013, with an estimated 10,370 deaths due to the disease. The median age at diagnosis is 67 years, and 5-year survival across all ages, treatments, and other prognostic subgroups is 24% (National Cancer Institute 2013). The World Health Organization (WHO) classification of AML incorporates morphology, cytogenetics, molecular genetics, and immunologic markers to define clinically relevant disease entities that are universally applicable and prognostically valid with therapeutic implications (Bennett et al. 1976; Brunning et al. 2001; Cheson et al. 1990; Cheson et al. 2007).

3.1.1 First-line Therapy Including Induction and Consolidation

Initial treatment of AML is divided into induction chemotherapy and post-remission, consolidation therapy. To optimize potential for durable remission, patients frequently receive some form of consolidation therapy, which is routinely given to patients aged <60 years and generally involves multiple courses of intensive chemotherapy or stem cell transplantation (SCT) (Dohner et al. 2010). Consolidation therapy is often given only once, or not given at all, to patients who are > 60 years of age. Tolerance of the induction and consolidation phases is directly related to patient characteristics such as age, the presence or absence of comorbidities, and performance status. Strategies for consolidation are generally based on the risk of relapse, with more adverse risk patients receiving more aggressive therapy. Current first-line induction treatments for AML among eligible patients include chemotherapy drugs such as cytarabine, daunorubicin, and mitoxantrone. Post-remission consolidation therapies include dose-intensified cytarabine, and autologous or allogeneic SCT.

Although complete remission (CR) rates after standard first-line induction therapy in AML are relatively high, certain subgroups of patients with AML often cannot tolerate treatment strategies which optimize the probability of durable remissions, or have a high risk of relapse even when available standard therapies are administered. Consequently, National Comprehensive Cancer Network Guidelines (2013) recommend that AML patients with an antecedent hematologic disease (e.g., myelodysplasia, myelofibrosis, polycythemia vera), age > 60 years, or unfavorable cytogenetics (e.g., deletion of 5 or 7 and ≥3 abnormalities) are appropriate candidates for clinical studies with novel agents early in their disease (i.e., as first-line therapy or during an initial remission).

3.1.2 Adverse-Risk AML

In recent decades, there has been substantial progress in the characterization of the genetic and molecular basis of AML and in the identification of both clinical and laboratory-based

prognostic factors. The 2008 WHO classification included many of these factors into the categorization of AML into favorable, intermediate, and adverse risk groups (Swerdlow et al. 2008). The very substantial risk of relapse and mortality for patients with adverse, and even intermediate risk AML, has increasingly been appreciated in recent years, including patients who are able to receive SCT and especially for patients who are not candidates for SCT. Cytogenetic abnormalities that are associated with adverse risk status include chromosomal deletions (-5, -5q, -7, -7q), additions (add[5q], add[7q]), translocations (t[11q23], t[6;9] and many others), inversions (inv[3][q21q26]) and complex abnormalities (≥3 unrelated abnormalities) (Morrissette and Bagg 2011; Hasserjian 2013). In a consolidated analysis of younger adults treated on multiple AML studies sponsored by the United Kingdom's Medical Research Council (MRC), 5-year overall survival for patients with inv(3)/t(3;3) or complex karyotype was less than 10%. It is worth noting that in this analysis, 5-year overall survival for patients with selected intermediate risk AML was less than 35% (Grimwade 2001). Additional AML-related mutations associated with adverse risk include FLT-3 internal tandem duplications (FLT3-ITD). In the aforementioned MRC pooled analysis, 5-year overall survival (OS) for patients with FLT3-ITD mutations was less than 15%. Even in the absence of karyotypic abnormalities, FLT3-ITD mutations are associated with adverse prognosis; in an analysis of patients without cytogenetic abnormalities enrolled on several studies sponsored by the German-Austrian AML Study Group, 5-year overall survival (OS) was less than 30% for patients with FLT3-ITD mutations (and was lower for the subset for whom HLA-matched SCT donors were not available) (Schlenk et al. 2008).

3.1.3 Minimal Residual Disease (MRD) in AML

For AML patients who achieve hematologic remission following induction therapy, the evaluation of MRD confers additional information concerning the risk of relapse and mortality, and increasingly is considered a factor as additional therapeutic options are considered. Multi-parametric flow cytometry for detection of leukemia-associated phenotypes (LAIPs) has become a valuable mechanism for investigation of potential MRD in the bone marrow aspirates of AML patients in remission. LAIPs include asynchronous expression of antigens (i.e., aberrant expression of antigens across maturation stages, such as coexpression of early and late antigens), cross-lineage expression of lymphoid markers, and overexpression or absence of lineage-appropriate markers. Additional methods by which MRD may be evaluated include cytogenetic or fluorescence *in situ* hybridization (FISH) assessment for chromosomal translocations (including those defining adverse risk AML), real-time polymerase chain reaction (PCR)-based assessment of gene mutations, and next generation sequencing for the persistence of somatic mutations in the coding sequence of AML-associated mutations (for example: the MD Anderson Cancer Center 28-gene AML panel, which includes gene mutations associated with adverse risk AML and others including IDH1, IDH2, DNMT3A, ASXL1, TET2, N-RAS, and K-RAS) (Ravandi and Jorgensen 2012; Jorgensen et al. 2011).

The identification of MRD upon achievement of AML remission has been associated with higher rates of relapse and diminished survival in several prospectively treated AML cohorts. In several hundred older AML patients participating in the United Kingdom National Cancer Research Institute AML16 study, patients in CR after a single course of induction therapy had 4-year OS rates of 40% and 18% respectively, depending on the absence or presence of MRD. (A similar difference was identified for patients who were in complete remission after 2 courses of induction therapy.) Survival differences based on MRD status were apparent in patients with both intermediate and adverse risk AML (the paucity of patients with favorable risk AML in this older cohort renders comparison within this group difficult) (Freeman et al. 2013). In the Dutch-Belgian/Swiss Hemato-Oncology Cooperative Group and the Swiss Group for Clinical Cancer Research AML 42A study involving more than 500 younger AML patients (aged 18-60 years), the presence of MRD upon remission was associated with higher relapse rates, which were evident at both early and intermediate (3-4 year) evaluation; the differences were apparent whether MRD was assessed after 1 or 2 induction cycles or after consolidation therapy, and in favorable, intermediate and adverse risk AML patients. As an example, for patients with intermediate risk AML in remission after 2 cycles of induction therapy, 1-year relapse rates were >60% for those with evidence or MRD versus <30% for those without MRD (Terwijn et al. 2013).

3.1.4 Second-line and Subsequent Therapy

Approximately 70% of patients who receive first-line therapy and achieve a first CR would be expected to experience recurrent disease, and a subset of patients who do not derive benefit from first-line therapy would also be candidates for subsequent treatment. In second-line AML, while there are currently no approved treatments, typical therapies include additional chemotherapy, often cytarabine at various dosages and regimens. Unless allogeneic SCT can be performed, patients with relapsed or refractory AML have a poor prognosis; relatively few patients are eligible for SCT due to donor unavailability, advanced age, and significant morbidity with reinduction efforts (Forman and Rowe, 2013).

Following failure of second-line therapy, patients often have depressed bone marrow function and may not be candidates for additional chemotherapy. There are currently no approved treatments for third-line AML, although therapeutic options including supportive care, cytarabine based combinations, and investigational therapies (e.g., hypomethylating agents) are at times implemented. Many of these therapies impart serious toxicities, including cytopenias, that may compound the complications of AML itself, and, in particular, heavily-pretreated AML. Importantly, no currently available treatments have been shown to extend survival in this setting. The median OS for AML patients after failure of second-line treatment, based on 2 large series, is 1.5 months (Giles et al. 2005; Keating et al. 1989). The prognosis of relapsed AML is limited for the majority of afflicted patients.

3.2 Targeting Cancer Stem Cells

The field of cancer stem cells (CSCs) is a new area of cancer biology that may fundamentally alter the approach to oncology drug development. CSCs have been identified in virtually all major tumor types, including leukemia and cancers of the brain, breast, colon, prostate and pancreas (Jordan et al. 2006). CSCs are the highly malignant "seeds" of a tumor that self-renew and generate more mature cells that comprise the bulk of the tumor, or "the tumor bulk." As such, CSCs appear to be responsible for tumor initiation, propagation, and metastasis. Many of the characteristics of CSCs, such as their slow growth, anti-cell death mechanisms, and presence of multi-drug resistance proteins, may enable CSCs to resist therapeutic agents traditionally used to treat cancer. This may be due to the many challenging characteristics of CSCs, including slow growth, presence of multi-drug resistance proteins, anti-cell death mechanisms, and increased activity of cellular mechanisms that repair damaged deoxyribonucleic acid (DNA). CSCs are particularly resistant to chemotherapy, radiation, or targeted therapy relative to tumor bulk.

CSCs have also been shown to increase, as a percentage of total tumor cells, as a result of exposure to a traditional therapy (Bao et al. 2006; Hermann et al. 2008). Consistent with their pivotal role in the development of tumors and relapse, higher amounts of CSCs in patient tumors as a percentage of their entire cancer appear to correlate with poor prognosis. CSC fractions greater than 3.5% and 1% of the entire cancer correlate with poor survival outcomes in patients with AML and brain cancer, respectively (van Rhenen et al. 2005; Zeppernick et al. 2008).

3.3 IL-3 Receptor (IL-3Rα) Over-Expression in AML

The alpha subunit of the human interleukin (IL)-3 receptor (IL-3 α receptor = IL-3Rα, also called multi-colony stimulating factor) is a type I transmembrane glycoprotein belonging to the cytokine receptor superfamily; all the members of this superfamily are characterized by a conserved region homologous to the fibronectin type III domain. The IL-3R is a heterodimer of α (CD123) and β chains, which is shared by IL-3, IL-5, and granulocyte macrophage-colony stimulating factor (GM-CSF) receptors. The receptor, found on pluripotent progenitor cells, induces tyrosine phosphorylation within the cell and promotes proliferation and differentiation within the hematopoietic cell lines**.**

IL-3R is over-expressed on AML blasts and CSCs relative to normal hematopoietic stem cells (Jordan et al. 2000; Jordan et al. 2006; Tehranchi et al. 2010). CD34+/38- CSCs strongly express IL-3R, whereas IL-3R is virtually undetectable on normal CD34+/38- hematopoietic stem cells (Jordan et al. 2000; Jordan et al. 2006). The differential expression of IL-3R between malignant and normal stem cells provides a potential opportunity for a therapeutic window in which to target CSCs with an IL-3R-targeted therapy (e.g., SL-401), while minimizing toxicity to normal bone marrow including normal hematopoietic stem cells.

In addition to AML, IL-3R has also been shown to be differentially expressed on other hematological cancers, including blastic plasmacytoid dendritic cell neoplasm (BPDCN), myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML), acute lymphoid leukemia

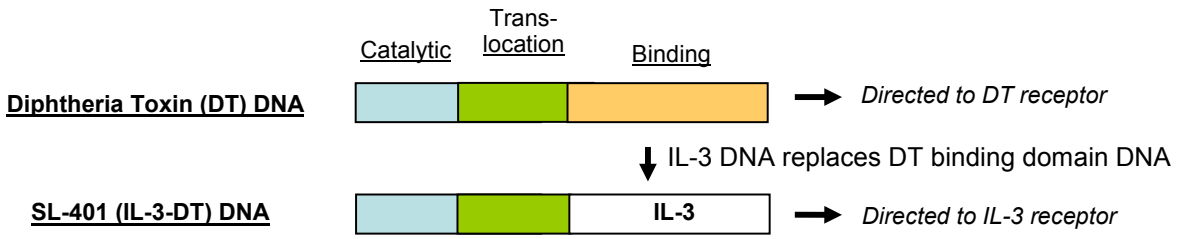
(ALL), hairy cell leukemia, Hodgkin's disease, and certain aggressive non-Hodgkin's lymphomas (e.g., follicular cell, mantle cell, and Burkitt's lymphomas) (Tehranchi et al 2010; Aldinucci et al. 2005; Munoz et al. 2001; Aldinucci et al. 2002; Black et al. 2003; Frolova et al. 2010). Moreover, IL-3R is also over-expressed on CSCs of multiple hematologic malignancies, including CML, MDS, and T-cell ALL (Jordan et al. 2006; Tehranchi et al. 2010; Florian et al. 2006; Lhermitte et al. 2006).

A higher percentage of IL-3R-expressing CSCs within a patient's tumor is associated with poor outcome (Vergez et al. 2011). In particular, AML patients with IL-3R-expressing CSCs that comprise ≥3.5% of their entire leukemia have a worse prognosis than patients with IL-3R-expressing CSCs that comprise <3.5% of their entire leukemia (van Rhenen et al. 2005). Interestingly, IL-3R-rich plasmacytoid dendritic cells (pDCs) have been found to be increased in the bone marrow of patients with multiple myeloma and appear to contribute to disease aggressiveness and resistance to treatment (Chauhan et al. 2009). These findings further validate that IL-3R is an important oncology target in multiple hematologic cancer indications.

3.4 Mechanism of Action of SL-401

Diphtheria toxin (DT) IL-3 fusion protein (designated SL-401 by Stemline Therapeutics, Inc. ["Stemline"]) is a novel biologic targeted therapy directed to the IL-3R. SL-401 is comprised of recombinant human IL-3 genetically fused to a truncated DT in which the binding domain of DT has been replaced with IL-3. As depicted in Figure 1, the IL-3 domain of SL-401 is able to target the agent to leukemia blasts and CSCs that over-express IL-3R, leading to receptor-mediated endocytosis and localization of SL-401 to early endosomes. The translocation domain of DT changes conformation in the acidic environment of the endosome, and the RXRR motif (residues 191-194) located between the catalytic and translocation domains of DT is cleaved by endosomal furin. The translocation domain of DT then inserts into the endosomal membrane. As the TAT-like domain of DT (residues 201-230) interacts with cytosolic heat shock protein 90 (Hsp90) and thioredoxin reductase, the catalytic domain (A fragment) unfolds, is reduced, and translocates to the cytosol. Upon release into the cytosol, the A fragment refolds and catalytically inactivates cellular protein synthesis by adenosine diphosphate-ribosylating the diphthamide residue in domain IV of EF2, leading to apoptosis (Yamaizumi et al. 1978; Deng et al. 2008; FitzGerald et al. 1989; Perentesis et al. 1992; Louie et al. 1997; Ratts et al. 2005; Thorburn et al. 2004).

Figure 1: Schematic of SL-401 Construction



The manner by which SL-401 kills cells is distinct from that of available cancer therapeutics. First, SL-401 is a targeted therapy directed to the IL-3R that is present on CSCs and tumor bulk, but not on normal hematopoietic stem cells. Second, SL-401 utilizes a payload that is not cell cycle-dependent. Therefore, it is designed to kill not just highly proliferative tumor bulk, but also relatively quiescent CSCs. Lastly, SL-401 utilizes a payload that is not subject to multi-drug resistance mechanisms typically used by CSCs to evade traditional therapies. The payload also kills cells in a manner that is distinct from that of other available therapies, which is another reason why SL-401 may be an effective addition to the therapeutic armamentarium against hematologic malignancies.

3.5 Preclinical Studies

In vitro and *in vivo* activity against both leukemia blasts (i.e., tumor bulk) and CSCs of a variety of human leukemia cell lines and primary leukemia cells from patients has been demonstrated using SL-401 (designated as DT388IL3 [Diphtheria Toxin Interleukin-3 Fusion Protein] in these earlier studies) (Angelot-Delettre et al. 2011; Alexander et al. 2000; Frankel et al. 2000).

Potent cytotoxicity against leukemic cells *in vitro* in a dose-dependent fashion was demonstrated for SL-401, with IC_{50} (concentration that inhibits the growth of 50% of leukemia cells) values in the low picomolar range. Notably, and in contrast, normal bone marrow progenitor cells were relatively insensitive. Anti-CSC activity was also exhibited. In particular, the SL-401 inhibited long-term AML colony formation, an assay for stem cell activity, compared with normal human bone marrow. Additionally, engraftment and growth (i.e., tumorigenicity) of AML cells was reduced, relative to normal human bone marrow, when these cells were treated *ex vivo* and reimplanted into immunodeficient mice, which also indicates anti-tumor activity at the level of the CSC (Frankel et al. 2000). Treatment of severe combined immunodeficient mice also significantly reduced engraftment of AML (Feuring-Buske et al. 2002). AML engraftment was reduced by an average of 83% (range, 14–100) and 57% (range, 0–98) after 4 and 12 weeks, respectively (n = 6). Leukemia was not detected in 2 of 6 mice 12 weeks after SL-401 treatment. Repeating treatment every 4 weeks enhanced its effectiveness (Black et al. 2003; Frankel et al. 2000).

The cytotoxicity of SL-401 relates to the level of IL-3R expression on leukemia cells *in vitro* (Frankel et al. 2000). In studies performed to date, leukemia cells with high surface expression of IL-3R have been exquisitely sensitive to SL-401, with IC_{50} values ranging from 1-28 pM, whereas low cellular expression of IL-3R has been associated with higher IC_{50} values, i.e., ~1400 pM (Frankel et al. 2000). Even so, SL-401 plasma concentrations exceeding the entire range of IC_{50} values have been readily achievable in patients receiving SL-401 at doses below the maximum tolerated dose (MTD) in a Phase 1-2 study described in Section 3.6.

Interestingly, the bone marrows of patients with multiple myeloma have been demonstrated to contain high quantities of IL-3R-expressing pDCs. These pDCs have since been shown to augment the growth of multiple myeloma and contribute to drug resistance, suggesting that killing pDCs may confer clinical benefit in patients with multiple myeloma (Chauhan et al. 2009). Indeed, SL-401 has been demonstrated to possess potent activity against multiple myeloma cell lines and primary tumor samples, which appears to be related to both direct antitumor and anti-pDC effects of the drug in multiple myeloma (Chauhan et al. 2013).

To support the Phase 1/2 clinical study conducted under the Investigator-sponsored Investigational New Drug Application (IND), repeat-dose toxicity studies with SL-401 were conducted in mice and cynomolgus monkeys. The study designs are summarized in Table 1.

Table 1: Completed SL-401 Repeat-dose Toxicity Studies, Investigator-sponsored IND

Study Type and Duration	Dose Level(s)	Dose Regimen
Mice		
5-day efficacy study, survival data	2 µg (≈ 100 µg/kg)	IP injection daily for 5 days
14-day toxicity study	0.5, 1, 2, 2.5, 3, 3.5, 5, 7, 10 µg (≈ 25, 50, 100, 125, 150, 175, 250, 350, 500 µg/kg)	IP injection 3 times a week for 2 weeks (6 doses)
Monkeys		
14-day toxicity study	40, 60, 100 µg/kg	IV injection every other day (6 doses)
14-day toxicity study	100, 150 µg/kg	IV injection every other day (6 doses)

Stemline has conducted 2 non-Good Laboratory Practice (GLP) toxicity studies in cynomolgus monkeys and one GLP 5-Day toxicity study in cynomolgus monkeys with a 3-week recovery period to confirm target organs of toxicity. The study designs are summarized in Table 2. Note that the doses described in the table and subsequent summary are doses of SL-401.

Table 2: Completed SL-401 Repeat-Dose Toxicity Studies, Company-Sponsored IND

Study Number	Study Title	Number of Animals	Study Type and Duration	Dose Level(s)	Dose Regimen	Noteworthy Findings
2231-001	SL-401: An Intravenous Dose Range Finding Study in Cynomolgus Monkeys	6; 2/sex/group	Non-GLP; 5 days	40, 60, 80 µg/kg	IV injection daily	During the study, on Day 5, the male at 80 µg/kg/day was *euthanized in extremis*, due to SL-401-related clinical signs. Based on clinical observations as well as clinical laboratory values the MTD of SL-401 was determined to be 60 µg/kg/day when given as an IV slow bolus injections daily for 5 consecutive days.
2231-004	SL-401: An Intravenous Pilot Dose Confirmation Study in Cynomolgus Monkeys	4; 1/sex/group	Non-GLP; 5 days	30, 60 µg/kg	IV injection daily	Evidence of sporadic inflammation and hepatic effects in both sexes at both dose levels. Based on clinical observations as well as clinical laboratory values and chemistries the 60 µg/kg/day dose was well-tolerated when given as an IV slow bolus injections daily for 5 consecutive days.
2231-002	SL-401: A 5-Day Intravenous Toxicity Study in Cynomolgus Monkeys with a 3-Week Recovery Period	26; Terminal: 3/sex/group; Recovery: 2/sex/dose group	GLP; 5 days with a 3-week recovery period	Control, 30, 60 µg/kg	IV injection daily	One female administered 60 µg/kg/day was euthanized *in extremis* on Day 6, prior to the scheduled necropsy. The cause of moribundity was severe necrosis of renal cortical tubules (kidneys). Additional dose-related and test article-related microscopic changes were present in brain choroid plexus, kidneys, liver, and thymus.

GLP=Good Laboratory Practice; IV=intravenous; MTD=maximum tolerated dose

Three toxicity studies were conducted with SL-401 at doses ranging from 30 µg/kg/day to 80 µg/kg/day daily for 5 days. Assessment of toxicity was based on mortality, clinical observations, body weights, clinical pathology, and in one study histopathology. The main SL-401 related findings noted were as follows:

- Dose-dependent clinical signs of decreased activity, hunched posture, and sparse hair were observed in males and females at all dose levels. Additionally, signs of decreased appetite were exhibited by all 3 females and one male (60 µg/kg/day), as were reductions

in body weight in males (5-9%) at all dose levels and respective decreases of 6 and 7% in females receiving 80 and 40 µg/kg/day.

- Dose-related test article related findings were observed in clinical pathology parameters; increased liver enzymes (aspartate transaminase [AST] and alanine transaminase [ALT]) in both sexes of all dose groups after the first dose; sporadic evidence of renal injury (increased urea nitrogen and/or creatinine) in both sexes at all dose levels by after the fifth dose interval; sporadic/inconsistent effects on neutrophils, platelet, and/or reticulocyte counts, mostly at 80 µg/kg/day; and mild serum protein alterations in both sexes at all dose levels (increased globulin with decreased albumin).
- Dose-related microscopic changes were present in brain choroid plexus, kidneys, liver, and thymus of animals treated with SL-401 at dose levels of 30 µg/kg/day and 60 µg/kg/day. Inflammation/necrosis degeneration of the choroid plexus was present in terminal males and females at 30 and 60 µg/kg/ day and in recovery males and females at 60 µg/kg/day. Degeneration/necrosis of renal cortical tubules in the kidneys was present in females at 30 and 60 µg/kg/day as well as terminal males at 60 µg/kg/day. Kidneys were within normal limits in all recovery animals. Minimal centrilobular hepatocellular necrosis and mild vacuolation (centrilobular or diffuse) were present in the livers of terminal males at 60 µg/kg/day. Livers were within normal limits in all recovery animals. The thymus of one recovery male at 60 µg/kg/day was reduced in size compared to controls. This finding correlated microscopically to generalized lymphoid depletion.
- Toxicokinetic data in male and female cynomolgus monkeys demonstrated a half-life of approximately 0.5 hour after an intravenous bolus dose. The systemic plasma concentrations of SL-401 following doses of 40, 60, or 80 µg/kg/day showed a corresponding (reasonably proportional) increase in systemic exposure across the doses. There was no effect of pre-existing low level anti-DT specific antibodies. There was no accumulation. Comparison of the first to fifth dose sequence showed there were no appreciable changes in the toxicokinetic exposure profile and there were no notable gender differences in exposure.
- From data collected and evaluated during these 3 studies, it appears that the MTD of SL-401 is between 30 and 60 µg/kg/day, when given as an intravenous slow bolus injection daily for 5 consecutive days.

Based on the collective data from 3 toxicology studies conducted with SL-401, the kidney, liver, and blood vessel manifestations observed were highly consistent with previous toxicity studies. Inflammation and necrosis of epithelial cells lining the choroid plexus was consistent with previous toxicity studies using SL-401. However, severe brain hemorrhage was not observed with SL-401. The highest non-severely toxic dose from the combined toxicity studies in monkeys evaluating SL-401 ranged from 30 µg/kg/day to 60 µg/kg/day, which is equivalent to

9 µg/kg/day to 20 µg/kg/day in humans based on the body surface area (BSA) normalization method. A dose of 7.07 µg/kg/day for 5 days was well-tolerated in the previous SL-401 clinical study, described in Section 3.6. Therefore, given the non-human primate toxicity results from SL-401 together with the full clinical safety database and the confirmatory target organ toxicity findings in 3 additional non-human primate studies with SL-401, the starting clinical dose will be 7 µg/kg/day. Furthermore, based on the previous clinical study, the maximum anticipated clinical dose is 12 µg/kg/day for a 5-day consecutive regimen.

3.6 SL-401 Clinical Studies

3.6.1 Study 50047

The safety and efficacy of SL-401 was evaluated in Study 50047, a multicenter, open-label, dose escalation Phase 1/2 study, in which enrolled patients had relapsed or refractory adult AML, *de novo* AML unfit for chemotherapy, high-risk MDS, CML, or BPDCN (Frankel et al. 2014). [redacted] Recruitment occurred at 5 study centers, 4 in the US and one in Canada. The primary study objective was to determine the MTD, recommend a dose for subsequent disease-directed studies, and document dose-limiting toxicities (DLTs) of escalating doses of a single cycle of SL-401 as a 15-minute IV infusion under two different regimens: every other day for up to 6 doses (Regimen A) or daily for up to 5 doses (Regimen B). The study also characterized the pharmacokinetic (PK) properties (using a non-specific biological assay to measure the plasma concentrations of SL-401) and immune responses associated with these regimens and determined the relationship between disease response and patient disease burden. Follow-up information on adverse events (AEs), laboratory parameters, and OS was also collected during the study.

Ninety-two patients were enrolled and treated with SL-401 in the study; 70 patients had AML (including 59 with relapsed/refractory disease), 12 patients had BPDCN, and the remainder had MDS or CML. The MTD for Regimen A was not identified. The MTD for Regimen B was 16.6 µg/kg/day with hypoalbuminemia and edema, manifestations of capillary leak syndrome (CLS), as the DLT at the 22.1 µg/kg/day dose level. Regimen B at a dose of 12.5 µg/kg/day appeared to have the most favorable risk/benefit profile, with a low incidence of DLTs and multiple major tumor responses.

Hypoalbuminemia (any Grade = 58.7%; Grade ≥3 = 0%) and transaminase elevation (any Grade = 50%; Grade ≥3 = 25%) were the most common Grade ≥3 AE attributed to SL-401, however almost all episodes were transient. Time courses of liver function tests (LFTs) and albumin among the patients treated with Regimen B indicate that LFT elevations tended to peak approximately two weeks after the first infusion of SL-401, while albumin levels, supported by the administration of albumin to patients with serum albumin falling below 3 g/dL, reached a minimum approximately one week after the first infusion. In most cases, levels of the laboratory parameters resolved to near baseline levels by 14-28 days after the first infusion. Other AEs commonly (i.e., any Grade in ≥15% of patients) attributed to SL-401 included fever (any Grade

= 29.3%; Grade ≥3 = 1.1%), hypocalcemia (any Grade = 25.0%; Grade ≥3 = 0%), edema (any Grade = 18.5%; Grade ≥3 = 3.3%), and nausea (any Grade = 16.3%; Grade ≥3 = 0%).

A single cycle of SL-401 was associated with single agent activity in patients with relapsed or refractory AML, including 2 durable CRs of 8 and >25 months duration and 5 partial responses (PRs). OS also appeared to be improved among the most heavily pretreated AML patients compared with historical survival results. Specifically, in AML patients who had progression through at least two previous therapies (i.e., third-line or greater; n = 35), the median OS was 3.6 months, more than double the historical median OS of 1.5 months (Giles et al. 2005). Multiple durable objective responses were also observed among the patients with BPDCN. Among 9 BPDCN patients treated with 12.5 µg/kg/day who were evaluable for response, there were 5 CRs (durations of 3, >3, 5, >7, and >20 months) and 2 PRs yielding a response rate of 78% (two patients treated with 12.5 µg/kg/day and one patient treated with 9.4 µg/kg/day were not evaluable for response).

3.6.2 Ongoing Study STML-401-0114

SL-401 is being investigated in ongoing Stemline-sponsored Study STML-401-0114. Stage 1 of STML-401-0114 employed a traditional 3+3 design and has been completed. A total of 23 patients were enrolled in Stage 1, of whom 9 had BPDCN and 14 had relapsed/refractory AML. SL-401 was investigated at doses of 7, 9, 12, and 16 µg/kg/day IV for up to 5 consecutive days every 21 days (i.e., a multi-cycle regimen). (Only patients with AML received SL-401 at doses of 9 and 16 µg/kg/day.) The maximum tested dose of SL-401 in patients with BPDCN was 12 µg/kg/day; an MTD was not identified in BPDCN.

A complete summary of all AEs attributed to SL-401, including DLTs seen in Stage 1 of the study, is available in the most recent version of the SL-401 Investigator Brochure.

An analysis of safety data available through 28 July, 2016, for 26 patients with BPDCN showed that, overall, 24 (92%) patients have experienced at least 1 treatment-emergent adverse event (TEAE), with 22 (85%) patients experiencing at least 1 ≥Grade 3 TEAE. The most common TEAE was transaminase elevation (either ALT increased [62%] or AST increased [58%]). Overall, 17 (65%) patients have experienced ALT increased and/or AST increased, with these events also being the most common ≥Grade 3 TEAE (each 54%), treatment-related TEAE (54%), and treatment-related ≥Grade 3 TEAE (50%). Transaminase elevations were largely transient and not dose-limiting.

Other most commonly reported TEAEs, regardless of relationship to study drug, were nausea and peripheral edema (each 46%); fatigue, hypoalbuminemia, and pyrexia (each 42%); chills (35%); and anemia and hyperglycemia (each 31%).

The frequency and type of TEAEs were similar between the 12 µg/kg/day and 7 µg/kg/day dose groups, with no indication of dose-relationship.

Twelve (46%) of 26 patients experienced at least 1 serious adverse event (SAE). The only SAEs reported for >1 patient were CLS, pyrexia, and respiratory failure (each 2 patients).

Please consult the most recent SL-401 Investigator Brochure for comprehensive and up-to-date information concerning the safety and efficacy profile associated with the investigational agent.

3.6.3 Discussion and Rationale for Current Study

In June, 2006, Stemline in-licensed development and commercialization rights for SL-401. The SL-401 drug product (DP) to be utilized in the current study (conducted under a new IND) will be manufactured using a commercial-scale process.

The rationale for clinical development of SL-401 for patients with AML is based on the ubiquitous and high expression of the IL-3R on AML blasts, the highly potent preclinical activity of SL-401 against AML cells, the robust clinical responsiveness observed to date with SL-401, and the unmet medical need for this indication.

A specific and compelling rationale exists for the investigation of SL-401 in patients with adverse-risk AML in first remission and/or patients with AML in first remission for whom evidence of MRD has been identified. As described in prior protocol sections, these are patient groups with an especially high probability of disease relapse and limited prognosis, even relative to the overall population of patients with adult AML. Although not conclusively proven, it is highly likely that AML patients in remission harbor leukemia cells that are not detectable by means of traditional morphologic analyses. These cells repopulate and result in relapse and subsequent mortality. It is probable that leukemic stem cells constitute a relevant component of the AML which is not eradicated by standard induction (and consolidation) therapy and contribute substantially to post-remission relapse. As described previously, the high expression of IL-3R on AML blasts, and specifically on leukemic stem cells, may enable SL-401 to inhibit or eradicate AML populations that have not been eliminated by induction/consolidation cytotoxic therapies. The identification of AML populations at particularly high risk for disease relapse represents a scientific advance in recent years, albeit one that has not yet been accompanied by a consistent therapeutic improvement. This remains an area of high unmet need, and agents that specifically eradicate leukemic populations that persist despite cytotoxic induction therapy would represent a therapeutic advance. The current study will enable a preliminary evaluation as to the potential of SL-401 to eradicate MRD in AML when the risk of relapse is substantial.

The prior clinical results with SL-401 indicate that the agent can be safely be administered to patients with *de novo* AML or relapsed/refractory AML with clinical benefit in terms of disease response and extended survival. While 16.6 µg/kg/day for 5 consecutive days was determined to be the MTD and a safe starting dose for subsequent studies, the starting dose selected for Stage 1 of this Phase 1 study, 7 µg/kg/day (the lowest tested dose for this regimen in Study 50047), will allow for an initial abbreviated (2 dose levels) dose escalation/confirmation stage to an expected maximum tested dose (12 µg/kg/day) that appears to have the most favorable risk/benefit profile. During Stage 2 of the study, additional patients will be treated at the maximum tested dose at which multiple DLTs are not observed. Patients may receive up to 6 total cycles of SL-401.

The SL-401 DP used in the current study will be manufactured using a commercial-scale process that will provide study material for all pivotal studies. Consequently, the purpose of the initial stage of the current study is to augment the existing Phase 1/2 experience utilizing SL-401 DP to SL-401 made using a commercial-scale manufacturing process. These initial clinical data will confirm the safety and activity of SL-401 from the commercial scale prior to initiating the pivotal studies. Furthermore, the current study will generate clinical experience in which administration of multiple cycles of SL-401 can be evaluated in patient populations that may derive additional clinical benefit beyond administration of a single cycle.

The LFT and albumin findings from SL-401 in Study 50047 indicate that most patients with clinically meaningful changes in these parameters following administration of SL-401 would be expected to recover to near baseline levels by 3-4 weeks following the initiation of therapy. These results therefore support administration of cycles every 3 or 4 weeks with the allowance to delay the start of a subsequent cycle to allow toxicity resolution. CLS was the principal DLT in Study 50047, but was a relatively uncommon event at doses at or below the MTD. Similarly, CLS is an event associated with treatment with approved doses of denileukin diftitox (Ontak®), a Food and Drug Administration (FDA)-approved treatment for patients with persistent or recurrent cutaneous T-cell lymphoma whose malignant cells express the IL-2 receptor. Treatment of patients with SL-401 at doses below those in which multiple cases of severe CLS were observed in study 50047 is one element by which the risk of this SL-401 associated toxicity will be minimized in the current study.

During Study 50047, risk mitigation measures for CLS were implemented. These included premedication (e.g., an H_1-histamine antagonist, acetaminophen, and a corticosteroid); administration of IV albumin if serum albumin decreased to <3 g/dL; and a diuretic regimen (e.g., furosemide) if patients experienced > 10% weight gain (with no hypotension) concurrent with the administration of a basal parenteral hydration to maintain intravascular volume. In the peri-treatment period, vital signs, weight, serum electrolytes, and albumin were monitored. Similar measures have been incorporated into the current study, as described in Section 7.5.5. Additional precautions, including a requirement that patients have a normal cardiac ejection fraction at study entry, and requiring withholding of treatment in the setting of albumin reductions or weight increases during the dosing period, similar to recommendations concerning the optimal administration of denileukin diftitox, have also been implemented (McCann et al. 2012; Olsen et al. 2001; Prince et al 2009).

Denileukin diftitox also is associated with loss of visual acuity, usually with loss of color vision, with or without retinal pigment mottling. Recovery was reported in some of the affected patients; however, most patients reported persistent visual impairment. This finding is considered related to the IL-2 component of denileukin diftitox. Although SL-401 targets IL-3R rather than IL-2R, patients will be monitored for potential vision loss in this study.

For the most up-to-date summary of safety/efficacy on Stemline-sponsored clinical studies evaluating SL-401, please consult the most recent version of the SL-401 IB.

4 Study Objectives

4.1 Primary Objectives

The primary objectives are to determine the MTD, or the maximum tested dose where multiple DLTs are not observed, of SL-401, and to characterize the safety profile of SL-401 at the MTD or maximum tested dose.

4.2 Secondary Objectives

The secondary objectives are to:

- Evaluate the presence of MRD and changes in MRD status during and following SL-401 therapy
- Estimate relapse-free survival (RFS)
- Estimate OS
- Characterize the PK of SL-401
- Characterize the immunogenicity of SL-401

4.3 Exploratory Objectives

Exploratory objectives are to characterize expression of IL-3R/CD123 (and other potentially relevant stem cell and disease markers) on leukemia cells in bone marrow (when feasible), to evaluate potential changes in IL-3R/CD123 (and other potentially relevant marker) expressing populations over time, and preliminary correlation of baseline IL-3R/CD123 (and other potentially relevant marker) expression and clinical efficacy (including changes in MRD status).

5 Patient Selection

5.1 Study Population

Approximately 21-33 adult patients diagnosed with AML that is considered high-risk disease who have achieved a first or second CR or complete remission with incomplete bone marrow recovery (CRi) within 6 months prior to enrollment and are not considered immediate candidates for allogenic SCT.

5.2 Patient Inclusion Criteria

To be included in the study, a patient must meet the following criteria:

1. The patient has a diagnosis of AML according to WHO criteria.
2. The patient received any induction chemotherapy regimen and may have received post-remission consolidation therapy prior to screening.
3. The patient achieved a first or second CR or CRi. For patients without evidence of MRD in CR/CRi, CR (or CRi) must have been initially identified within 12 months prior to screening.

OR

The patient has achieved first or second CR or CRi with evidence of MRD at least 6 months post stem cell transplant without evidence of acute or chronic graft-versus-host disease post-transplant and has not received immunosuppressant therapy for at least 14 days prior to SL-401 therapy.

4. The patient has adverse risk disease or AML for which there is otherwise a substantial risk of relapse, which includes but is not limited to: adverse karyotype, FLT3 internal tandem duplication (ITD) mutation, history of antecedent hematologic disorder (AHD), therapy-related AML, history of requiring more than 1 cycle of intensive induction chemotherapy to achieve first remission, and/or presence of persistent MRD (detected by cytogenetics, molecular markers, or flow cytometry) at any point after the initial induction cycle. (A more comprehensive listing of karyotypes and mutations indicative of high-risk AML is provided as an appendix to the protocol [Section 15.3 Appendix C]).
5. For patients enrolling in Stage 2, the bone marrow evaluation determined locally within the previous 6 months indicates the presence of MRD. (A more comprehensive listing of methodologies for evaluation of MRD is provided as an appendix to the protocol [Section 15.4 Appendix D]).
6. The patient is not considered to be an immediate candidate for allogeneic stem cell transplant as determined by the investigator.
7. The patient is ≥18 years old.
8. The patient has an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2.
9. The patient has adequate baseline organ function, including cardiac, renal, and hepatic function:
    - Left ventricular ejection fraction (LVEF) ≥ institutional lower limit of normal as measured by multigated acquisition scan (MUGA) scan or 2-dimensional (2-D) echocardiogram (ECHO) within 28 days prior to start of therapy and no clinically significant abnormalities on a 12-lead electrocardiogram (ECG)
    - Serum creatinine ≤1.5 mg/dL
    - Serum albumin ≥3.2 g/dL in the absence of receipt of (IV) albumin within the previous 72 hours
    - Bilirubin ≤1.5 mg/dL
    - AST and ALT ≤2.5 × the upper limit of normal (ULN)
    - Creatine phosphokinase (CPK) ≤2.5 × the ULN.

10. The patient has adequate bone marrow reserve:
    - Absolut neutrophil count (ANC) > 0.5×10^9/L
11. If the patient is a woman of child bearing potential (WOCBP), the patient has had a negative serum or urine pregnancy test within 1 week prior to SL-401 treatment (intervals shorter than 1 week are acceptable if required by institutional guidelines).
12. A written and voluntarily signed informed consent obtained from the patient or legally authorized representative, in accordance with local regulations, before the initiation of any study-related procedures. The patient or legally authorized representative must be able to read and understand the informed consent form (ICF).
13. The patient is able to adhere to the study visit schedule and other protocol requirements, including follow-up for survival assessment.
14. The patient (either male or female) agrees to use acceptable contraceptive methods for the duration of time on the study, and continue to use acceptable contraceptive methods for 2 months after the last infusion of SL-401.

5.3 Patient Exclusion Criteria

A patient will not be included in the study if any of the following criteria are met:

1. The patient has a diagnosis of AML associated with karyotypes: t(15;17).
2. The patient has persistent and clinically significant Grade ≥2 toxicities from induction or consolidation therapy (excluding alopecia, nausea, fatigue, and liver function tests [as mandated in the inclusion criteria]) not readily managed with supportive measures.
3. The patient received treatment with another investigational agent within 14 days of screening.
4. The patient has previously received treatment with SL-401.
5. The patient has an active malignancy and/or cancer history (excluding AML or antecedent MDS) that may confound the assessment of the study endpoints. Patients with a past cancer history (within 2 years of entry) and/or ongoing active malignancy or substantial potential for recurrence must be discussed with the Sponsor before study entry. Patients with the following diagnoses are eligible: non-melanoma skin cancer, carcinoma *in situ*, cervical intraepithelial neoplasia, organ-confined prostate cancer with no evidence of progressive disease.
6. The patient has clinically significant cardiovascular disease (e.g., uncontrolled or any New York Heart Association [NYHA] Class 3 or 4 congestive heart failure, uncontrolled angina, history of myocardial infarction, unstable angina or stroke within 6 months prior to study entry, uncontrolled hypertension or clinically significant arrhythmias not controlled by medication).
7. The patient has uncontrolled, clinically significant pulmonary disease (e.g., chronic obstructive pulmonary disease, pulmonary hypertension) that in the opinion of the

Investigator would put the patient at significant risk for pulmonary complications during the study.

8. The patient has known active or suspected central nervous system (CNS) leukemia. If suspected, CNS leukemia should be ruled out with relevant imaging and/or examination of cerebrospinal fluid.
9. The patient has uncontrolled intercurrent illness including, but not limited to, uncontrolled infection, disseminated intravascular coagulation (DIC), or psychiatric illness/social situations that would limit compliance with study requirements.
10. The patient is pregnant or breast feeding.
11. The patient has known positive status for human immunodeficiency virus (HIV), active or chronic Hepatitis B or Hepatitis C.
12. The patient is oxygen-dependent.
13. The patient has any medical condition which in the opinion of the Investigator places the patient at an unacceptably high risk for toxicities.

5.4 Replacement of Patients

At the discretion of the Sponsor, additional patients may be enrolled to supplement patient data compromised due to premature study dropout or other reasons.

6 Investigational Plan

6.1 Dose and Schedule Rationale

Under an [redacted] the MTD of SL-401 as a daily × 5 regimen in a Phase 1 / 2 dose escalation study was determined to be 16.6 µg/kg/day. The principal DLTs consisted of hypoalbuminemia and edema (i.e., CLS), and the incidences of DLTs were 2 of 2 patients at the 22.12 µg/kg/day dose level, 1 of 8 patients at the 16.6 µg/kg/day dose level, and 1 of 18 patients at the 12.5 µg/kg/day dose level. The LFT and albumin results from the Investigator-sponsored study investigating SL-401 indicate that most patients with clinically meaningful changes in these parameters following administration of SL-401 would be expected to recover to near baseline levels by 3-4 weeks following the initiation of therapy. These results therefore support administration of cycles every 3 weeks with the allowance to delay the start of a subsequent cycle to allow toxicity resolution. Furthermore, a single cycle of SL-401 demonstrated single agent activity in patients with relapsed or refractory AML or BPDCN, with the majority of major responses occurring at the 12.5 µg/kg/day dose level. Therefore, the risk/benefit profile of SL-401 appeared to be most favorable at the 12.5 µg/kg/day dose level, and this is the expected dose that will be used in future studies of SL-401 as a single-agent given on multiple cycles (every 3 weeks).

The present study serves to bridge the early Phase 1/2 clinical experience with SL-401 produced using an earlier process to SL-401 made using a commercial-scale manufacturing process, prior to initiating pivotal studies in BPDCN and third-line AML (and possibly other malignant

conditions). Given the results from the SL-401 Phase 1/2 study (Study 50047), it is anticipated the starting dose for Stage 2 of the present study will be the maximum tested dose, or 12 µg/kg/day. However, in the interest of optimizing patient safety and thoroughly evaluating the commercial-scale SL-401, the dose escalation in Stage 1 of the study will begin 2 dose levels below, or 7 µg/kg/day, which was the lowest tested dose for this regimen (7.07 µg/kg/day) in the Phase 1/2 study evaluating SL-401 (Study 50047).

6.2 Overall Study Design

This is a non-randomized, open-label, dose escalation, multicenter study, divided into 2 stages. A cycle of therapy is 28 days. A Data Safety Review Committee (DSRC), which will include Sponsor representatives, will be established to review the accruing safety data and make safety decisions during the study, including dose escalation during Stage 1. The DSRC will also periodically review data during Stage 2 (at least 2 times per year, and more frequently in the event of DLTs, other severe or serious AEs or treatment –related deaths).

6.2.1 Stage 1: Dose Escalation

During Stage 1, approximately 9-18 patients will be treated with SL-401. The starting dose of SL-401 is 7 µg/kg/day for 5 consecutive days every 28 days, with escalation to 9 and 12 µg/kg/day and potentially higher doses planned, as warranted by the data.

Three to 6 patients will be treated at each dose level. All patients within a cohort must complete the first cycle of therapy before patients from a new cohort receive SL-401 at the next higher dose. No intra-patient dose escalation is allowed.

A decision to allow treatment at the next higher dose level will depend on the number of patients who experience a DLT during the first cycle. If after 3 patients complete Cycle 1:

- None of the initial 3 patients treated (0/3) experiences a DLT, then dose escalation will proceed and 3 new patients will be treated at the next higher dose.
- One of the initial 3 patients treated (1/3) experiences a DLT, the cohort will be expanded to include an additional 3 patients treated at the same dose.
  - If only 1 patient (1/6) from this expanded cohort experiences a DLT, then 3 new patients will be treated at the next higher dose.
- If 2 or more patients within a cohort have a DLT, then the MTD will be exceeded and further dose escalation will not occur.

If the highest planned treatment dose is completed and determined to be safe and the MTD is not exceeded, the available PK and safety data will be reviewed to assess whether further dose escalation is justified.

A patient who does not complete the first cycle of treatment for reasons other than the occurrence of DLT will be replaced by another patient who will receive the same dose regimen.

In the event that a DLT occurs in 2 or more patients treated at the initial dose level, 7 µg/kg/day, 5 µg/kg/day will be considered by the DSRC as an alternative starting dose. In this event, a new cohort of 3 patients will receive 5 µg/kg/day for the first cycle. The same DLT rules will apply to this dose level. If 2 or more patients experience a DLT at the 5 µg/kg/day dose level, the study will be halted.

Events meeting the criteria for DLT that occur in Cycle 2 or beyond will be considered DLT-level events; dosing of SL-401 in subsequent patients/cohorts will be evaluated and potentially modified based on the chronology, severity, and frequency of these events.

6.2.1.1 Definition of Dose-limiting Toxicity

During Stage 1, DLT is defined as any of the following occurring during the first cycle of therapy:

- Any treatment-emergent Grade 4 transaminase or CPK elevation (confirmed within 24 hours of initial identification), regardless of duration or relationship to SL-401.
- Any treatment-emergent Grade 4 hematologic toxicity (unrelated to recurrent leukemia or prior AML therapy) lasting > 28 days after the last infusion of SL-401.
- Any treatment-emergent Grade ≥3 non-hematologic toxicity (unrelated to recurrent leukemia), with the exception of Grade 3 laboratory toxicities that resolve to Grade ≤1 or baseline ≤28 days after the last infusion of SL-401, or the following Grade 3 toxicities if they resolve to Grade ≤1 or baseline ≤21 days after the last infusion of SL-401: arthralgia, myalgia, fever responding to treatment, nausea and/or vomiting (excluding cases that require tube feeding, total parenteral nutrition, or hospitalization) or diarrhea associated with suboptimal prophylaxis or treatment.

SL-401-related toxicities are AEs that are considered by the Investigator to be either possibly, probably or definitely related to investigational SL-401 (Please refer to Section 10.6 for more thorough guidance as to the assessment of "relatedness" in the context of investigational anticancer therapy). It should be noted that although the cycle length is 28 days, cycle duration may extend beyond 28 days in the setting of AEs; see Section 7.5.5. Specific, reversible AEs resulting in a prolongation of cycle 1 to 35 days will not necessitate a dose-reduction for subsequent cycles; these are detailed in Section 7.5.5.

6.2.1.2 Definition of Maximum Tolerated Dose

The MTD is defined as the dose preceding the dose level at which 2 or more patients experience a DLT during treatment Cycle 1.

The MTD (or a lower dose with a potentially more favorable risk/benefit profile [if identifiable during Stage 1]) will be used in Stage 2 of the study.

6.2.2 Stage 2: Expansion

During Stage 2, up to 20 additional patients with evidence of MRD as determined locally will be treated at the MTD or maximum tested dose at which multiple DLTs are not observed (identified in Stage 1) so that up to 15 patients with evidence of MRD as determined centrally are evaluable for safety and response at this dose. For inclusion in the study, all patients treated in the expansion phase should have MRD in bone marrow, as determined locally, via at least one of the following modalities: multi-parametric flow cytometry, cytogenetic evaluation, FISH, real-time PCR, or next-generation gene sequencing. It is anticipated that at approximately 50% of patients evaluated with AML in first remission (CR or CRi) will have evidence of MRD.

6.2.3 Tumor Assessments during Stages 1 and 2

All patients must have a baseline (pre-treatment) bone marrow aspirate (+ biopsy) and peripheral blood sample within 14 days prior to the first administration of SL-401. Subsequent assessments will be performed on the following schedules until, in the judgment of the Investigator, there is evidence of relapsed or progressive disease:

- Bone marrow aspirates (+ biopsy) and peripheral blood samples 28 (± 7) days after the start of Cycles 2, 4 and 6, then every 3 months (±1 month) until Month 12. No repeat bone marrow is necessary if non-response or progressive disease can be unequivocally diagnosed from peripheral blood tests.
- If the Cycle 2 (Day 28 [± 7]) bone marrow examination is empty (i.e., hypocellular) or inadequate, a bone marrow examination should be repeated in 14 (± 7) days to document response. If additional time is required to complete the repeat examination, consult with the Medical Monitor.
- Bone marrow will be assessed for morphologic evidence of AML recurrence, and flow cytometric and other cytogenetic/molecular assessments, including evaluation of MRD.
- CD123 is to be assessed in all bone marrow samples (and, if applicable, tissue samples) by flow cytometry (i.e., CD123 should be added to the panel of markers assessed by flow cytometry of bone marrow aspirates) and immunohistochemistry and the results recorded and captured in the electronic case report form (eCRF). (The Cycle 2, 4, and 6, Day 28 [± 7 days] peripheral blood and bone marrow assessment should occur on Day 28 [± 7 days] even in the setting of patients receiving SL-401 over 6-10 days [as opposed to 5 consecutive days]).

Patients will also be followed for RFS and OS.

6.3 Study Duration

Total study duration is expected to be approximately 36 months. Patient enrollment is expected to occur over a 24-month period, with follow-up continuing until assessments of the primary and critical secondary objectives are completed for all treated patients. Please consult Section 7.6.2 regarding recommended procedures and follow-up after treatment discontinuation.

6.4 Study Completion, Survival Extension Period, End-of-Trial

The study is considered complete when sufficient information is available to enable assessment of the primary endpoint and selected secondary endpoints, including MRD eradication in the months following initiation of investigational therapy. In the weeks subsequent to a determination that sufficient information is available for these assessments, a date for database lock will be assigned, and any outstanding inquiries concerning data elements will be resolved. The **Study Completion** date will be the date beyond which study data is no longer entered into the primary database (this study completion date generally precedes the date on which the database lock occurs by several weeks/months).

In the event that patients continue to remain alive and/or alive without evidence of AML recurrence/progression, a **Survival Extension Period** may be implemented, in which patients who are alive (with and without evidence of AML recurrence) will continue to be followed at regular intervals for evidence of disease progression and overall survival status. During this **Survival Extension Period**, Investigators are encouraged to continue evaluation of patients at a schedule appropriate for patients with AML in remission or recurrent AML. Data collection by the Sponsor during this **Survival Extension Period** will be limited to information pertaining to AML disease recurrence (for patients without evidence of disease recurrence at time of database lock) and survival status for all patients alive at time of database lock. Information concerning AEs considered at least possibly related to SL-401 that were unresolved at time of database lock will also be collected. This disease recurrence, survival and unresolved AE data will comprise a **Supplemental Database**. The **End-of-Trial** occurs following the death of the last patient remaining alive during the **Survival Extension Period** follow-up, or at a time when the Investigators/Sponsor conclude that ongoing survival follow-up is no longer advisable/feasible. In situations where all patients have experienced AML recurrence and/or are deceased at time of **Study Completion**/initial database lock, then the **Survival Extension Period/Supplemental Database** will not be considered necessary, and the **End-of-Trial** will occur at the same time as **Study Completion**.

7 Study Treatment Identification, Administration, and Schedule

7.1 Product Manufacturing and Characterization

Refer to the IB for full details of product manufacturing and characterization.

7.2 Recommended Medications per Institutional Guidelines/Practices

It is recommended that patients receive the following types of prophylactic therapies/regimens per institutional guidelines/practices:

- Antibacterial: ciprofloxacin, levofloxacin, or an equivalent antibiotic
- Antifungal: fluconazole, voriconazole, or an equivalent antifungal
- Antiviral: acyclovir, valacyclovir or an equivalent antiviral

7.3 Allowed Medications/Therapies

All patients may receive supportive care measures as clinically indicated, including prophylactic antibiotics, antihistamines, antiemetics, albumin, fluids (hydration), and supportive measures. Patients may receive growth factor support and/or blood product transfusions as per the discretion of their physician.

Albumin 25 g IV daily should be administered if serum albumin is between 3.0-3.5 g/dL (30-35 g/L) on days that dosing occurs or if it is <3.0 g/dL (30 g/L) on days when treatment has been withheld or in the immediate post-treatment period. The Investigator has discretion with regard to frequency of administration per product and institutional guidelines.

7.4 Prohibited Medications/Therapies

Prior to discontinuation of SL-401, patients may not receive investigational or non-investigational anticancer or anti-leukemia agents, including cytotoxic chemotherapy agents, hypomethylating agents (5-azacytadine, decitabine, and others), or anticancer tyrosine kinase inhibitors (including imatinib, ruxolitinib, sorafenib, and others) or therapeutic monoclonal antibodies.

7.5 SL-401

7.5.1 SL-401 Description and Storage

SL-401 is a novel biologic fusion protein comprised of recombinant human IL-3 genetically fused to truncated diphtheria toxin protein. SL-401 targets the IL-3R, which is over-expressed on the CSCs and bulk of various leukemias and hemapoietic malignancies relative to normal hematopoietic stem cells and other hematopoietic cells.

SL-401 drug product is prepared in two formulations and dosage forms.

- SL-401 Injection is a non-preserved, sterile, liquid dosage form supplied in sterile 2 mL glass vials containing 1 mL of sterile SL-401 solution (1 mg/vial) and should be stored frozen at -20°C (±5°C).
- SL-401 for Injection is a non-preserved, sterile, powder for solution supplied in sterile 3 mL glass vials and should be stored at -20°C (±5°C).

Documentation stating the product's expiry date will be provided with each shipment.

7.5.2 Dose, Schedule, and Duration of Treatment

Patients will receive SL-401 by IV infusion over 15 minutes for 5 consecutive days (or 5 doses over a period not to exceed 10 days if postponement is required for toxicity) of a 28-day cycle in the absence of disease progression or other withdrawal criteria.

Refer to the Pharmacy Manual for details regarding SL-401 administration.

Patients with evidence of ongoing disease control during treatment (without evidence of clinically significant progressive disease or intolerable toxicity) may receive repeated cycles of

SL-401 even if eradication of MRD, in the judgment of the Investigator, is not attained. Patients can receive up to 6 total cycles of SL-401 as long as there is ongoing evidence of AML remission, as determined by the Investigator. The administration of additional cycles of SL-401 (> 6 cycles) must be discussed with the Medical Monitor at which time the individual patient's potential risk/benefit of further treatment will be assessed.

7.5.3 SL-401 Premedication and Dose Preparation and Administration

7.5.3.1 Premedication

Patients will receive the following premedication approximately 60 minutes before each SL-401 infusion:

- Acetaminophen 650 mg by mouth (PO)
- Diphenhydramine 50 mg IV
- Methylprednisolone 50 mg IV (or an equivalent dose of another corticosteroid)
- Ranitidine 50 mg IV (or an equivalent dosage of another H_2-histamine antagonist)

7.5.3.2 SL-401 Dosage Preparation

SL-401 is administered as a 15-minute IV infusion. SL-401 is prepared for administration by the pharmacy. The total per-patient dose is calculated based on patient body weight in kilograms (kg) including one decimal place, and the patient's dosing cohort, as described in Section 6.2 (µg/kg dose × patient weight in kg, including one decimal place [example: 7 µg/kg × 70.3kg]). Additional dose preparation supplies and instructions are provided in detail within the Pharmacy Manual.

7.5.3.3 Inpatient and Outpatient Setting for Dose Administration

In Stage 1, the first cycle of SL-401 must be administered in the inpatient setting, with hospitalization beginning the day of the first infusion of SL-401 (or a prior day) and ending approximately 24 hours after the last infusion of SL-401. Subsequent cycles of SL-401 can be administered in the inpatient setting or in a suitable outpatient ambulatory care setting that is equipped for intensive monitoring of patients with hematopoietic malignancies undergoing treatment, per the discretion of the Investigator and institutional guidelines and capabilities. Patients will be monitored for at least 4 hours following the administration of each SL-401 infusion.

7.5.4 Patient Monitoring Procedures During the SL-401 Dosing Period

During each cycle, tests and procedures that may result in withholding of a scheduled SL-401 infusion, largely based on unresolved manifestations of fluid retention and/or other relevant acute toxicities during daily dosing, are described below and summarized in Table 5 and Table 6.

Vital Signs: Blood pressure, heart rate, respiration rate, body temperature, and pulse oximetry during dosing period (usually Days 1, 2, 3, 4 and 5): immediately prior to infusion, immediately

after completion of infusion, and 30, 60, and 240 minutes post-infusion; and Days 8, 15, 21 and 28.

Diagnostic Tests:

- During dosing period prior to SL-401 infusion (usually Days 1, 2, 3, 4, 5) and Days 8, 15, 21 and 28: Complete blood count (CBC) with differential, platelets, sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, total protein, albumin, calcium, phosphorus, uric acid, total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), prothrombin time (PT) or International Normalized Ratio (INR), and activated partial thromboplastin time (aPTT)
- Days 1 (prior to SL-401 infusion), 8, 15, 21, and 28: routine urinalysis
- For temperature ≥38°C, draw blood culture × 2, and collect urine for urinalysis and culture

7.5.5 Dose Delays/Modifications and Management Procedures for Toxicities Associated with SL-401

During the dosing period for each cycle, individual SL-401 infusions may be delayed to allow for toxicity resolution.

If dosing is resumed within a cycle, any subsequent doses in that cycle must be administered within the first 10 days of that cycle; thus, patients may receive fewer than 5 doses during a given study cycle. SL-401 may be resumed at the same dose or a reduced dose for Grade 3/4 toxicities (see Table 3 and Section 7.5.5.11).

7.5.5.1 Capillary Leak Syndrome and Associated Symptoms

CLS is associated with vascular endothelial injury related to fusion protein administration and may occur 3 – 8 days after initiation of treatment.

Patients may exhibit symptoms of **hypotension,** fluid overload, evidenced by **weight gain** or edema, nausea, and anorexia, shortness of breath and, at times, confusion and muscle injury. Findings may include **hypoalbuminemia**, reductions in blood oxygen saturation, and evidence of pulmonary edema on chest x-ray. **These symptoms may present individually or as part of CLS.**

Refer to Section 7.5.5.1.1, Section 7.5.5.1.2, and Section 7.5.5.1.3 for the management of the individual symptoms of hypotension, increase in body weight, and hypoalbuminemia. If the constellation of symptoms is considered to be potentially representative of CLS, the patient is to be managed as described in Section 7.5.5.1.4.

7.5.5.1.1 Symptomatic Hypotension

Withhold SL-401 for patients with a systolic blood pressure (BP) ≤80 mmHg.

Symptomatic hypotension is to be treated with a bolus of normal saline or its equivalent at the discretion of the investigator, with SL-401 held (postponed) until resolution.

During the dosing period, if BP fails to improve with boluses of fluids totaling 1 liter of normal saline or its equivalent, further standard measures to correct the BP will be undertaken; regardless of the rapidity or delay in resolution, SL-401 will be withheld on that day. If hypotension persists such that further treatment is not feasible during the day of the intended dose and the following day, no further SL-401 will be administered to the patient for that cycle.

7.5.5.1.2 Increase in Body Weight

Withhold SL-401 infusion if body weight increases by ≥1.5 kg over pre-treatment weight on the previous treatment day.

Patients with an increase in body weight of ≥1.5 kg from the previous day may be treated with fluid restriction and/or diuretics (e.g., furosemide), as clinically indicated, and should also receive albumin 25 g IV daily or every 12 hours as clinically feasible until weight gain has resolved, as indicated in Appendix E. Dosing within a cycle may resume only if ≥1.5 kg weight gain has resolved. If dosing is resumed, any subsequent doses in that cycle must be administered within the first 10 days of that cycle.

7.5.5.1.3 Hypoalbuminemia

Patients are to have serum albumin measurements performed daily until completion of SL-401 administration.

- In settings in which albumin is reduced to 3.0-3.5 g/dL (30-35 g/L) or by ≥ 0.5 g/dL (5 g/L) below the level at the start of the cycle, withhold SL-401 infusion and administer albumin 25 g IV daily or every 12 hours as clinically feasible until serum albumin is both ≥3.5 g/dL and not reduced by ≥0.5 g/dL from the level at the start of the cycle prior to resuming treatment with SL-401 in the same cycle.
- In settings in which albumin is reduced to <3.0 g/dL (30 g/L) or by more than 1.0 g/dL (10 g/L) below the level at the start of the cycle (i.e., from 4.3 g/dL to 3.2 g/dL), withhold SL-401 infusions for the duration of that particular cycle. Albumin should be administered until the albumin level is at least above 3.5g/dL. Consultation with the medical monitor is advised.
- Dosing in the next cycle may resume if albumin remains at 3.5 g/dL without additional albumin infusions.

Albumin infusions are supportive measures, and are not intended to enable treatment in settings in which hypoalbuminemia would otherwise preclude SL-401 administration.

7.5.5.1.4 Capillary Leak Syndrome

Withhold SL-401 infusion for patients with clinical signs and symptoms consistent with CLS.

If CLS is identified, 1 mg/kg/day of methylprednisolone (or an equivalent) should be administered until resolution or as clinically indicated along with administration of albumin as specified in Appendix E.

Ongoing CLS or CLS with clinical/hemodynamic instability

SL-401 administration during the cycle may not resume if there are signs or symptoms of CLS along with evidence of hemodynamic instability, significant clinical deterioration or changes in albumin, defined as a decrease to <3.0 g/dL or reduction by >1.0 g/dL from the start of the cycle or CLS elements have not resolved.

SL-401 administration may only resume in the next cycle if all CLS elements have resolved, and the patient is hemodynamically stable and laboratory values have recovered to a level that permits dosing.

CLS without clinical/ hemodynamic instability

In the setting of signs/symptoms of CLS that DID NOT include hemodynamic instability OR significant clinical deterioration OR reductions in albumin that would prevent further dosing, SL-401 administration in that cycle may be delayed and resume if there is no evidence of ongoing CLS, pending discussion with the study Medical Monitor.

Any subsequent SL-401 is to be administered on days *subsequent* to the identification of the abnormality (not the same day). If dosing is resumed, any subsequent doses in that cycle must be administered within the first 10 days of that cycle. SL-401 administration in subsequent cycles may resume per the normal schedule after Day 28 of the previous cycle.

Also see Appendix E for summary of recommended actions.

7.5.5.2 Chills, Anaphylaxis, and Hypersensitivity Reactions

Withhold SL-401 infusion for chills, anaphylaxis and hypersensitivity reactions.

Chills associated with SL-401 administration may be treated with meperidine 12.5-50 mg IV or morphine sulphate 1-2 mg IV (or equivalent doses of other opiates). Anaphylaxis and hypersensitivity reactions associated with rash, fever, urticaria, bronchospasm, and/or angioedema will be treated with 100 mg IV methylprednisolone (or an equivalent corticosteroid) and 25-50 mg IV diphenhydramine (or equivalent H1-histamine antagonist). More severe symptoms will also be treated with 0.3 mL epinephrine (1:1000) IV once. Patients with anaphylactic (Grade 4) reactions or Grade ≥3 hypersensitivity reactions should not receive additional infusions of SL-401.

In the setting of Grade 1-2 hypersensitivity reactions, administration of subsequent SL-401 may be attempted provided that any systemic symptoms of the prior Grade 1-2 hypersensitivity reaction resolved within 24 hours with appropriate supportive measures. Premedication for patients with prior Grade 1-2 hypersensitivity reactions should include the agents specified in Section 7.5.3; additional premedication may be provided at the Investigator's discretion and should be discussed with the Medical Monitor or designee. Please consult Section 10.7 concerning recommended optimal reporting of SL-401-related hypersensitivity reactions.

Blood (serum) samples (10 mL, for immunogenicity) will be collected anytime during the study when clinical manifestations are observed suggesting either an infusion related reaction or drug hypersensitivity.

7.5.5.3 Transaminase (AST/ALT) Elevations

In settings in which transaminases (AST/ALT) are elevated to >5 × ULN, no subsequent SL-401 will be administered for the duration of the cycle.

7.5.5.4 Body Temperature ≥38°C

For temperature ≥38°C, draw blood culture × 2, and collect urine for urinalysis, as clinically indicated. SL-401 may be administered pending resolution, provided that an appropriate evaluation for infectious etiologies has been undertaken, and provided that the Investigator determines that there is minimal likelihood of uncontrolled systemic infection including sepsis; this may occur on the same day as the temperature elevation, or on subsequent days.

7.5.5.5 Serum Creatinine >1.8 mg/dL (159 µmol/L)

Withhold SL-401 infusion until serum creatinine resolves to ≤1.8 mg/dL (159 µmol/L). Dosing may resume upon recovery of serum creatinine if this occurs within the first 10 days of a cycle.

7.5.5.6 Tachycardia, Bradycardia, or Hypertension

Withhold SL-401 infusion for patients with a heart rate ≥130 or heart rate ≤40 bpm or systolic BP ≥160 mmHg until resolution.

7.5.5.7 Tumor Lysis Syndrome

Treatment with cytotoxic cancer therapies in the setting of high tumor burden may cause rapid tumor lysis syndrome (TLS) and associated electrolyte and renal disturbances. A low incidence of TLS has been reported with SL-401. The Sponsor advises continued awareness of the possibility of acute and potentially life-threatening TLS in patients with high disease burden.

Serum chemistries to monitor TLS are included in the daily laboratory tests during SL-401 infusion (e.g., creatinine, potassium, phosphorus, uric acid, LDH). In the event of evidence of TLS, local standards should be followed to monitor and treat TLS. For example, IV hydration in addition to other measures to maintain urine output, hypouricemic agents, and additional interventions to correct electrolyte abnormalities may be given at the discretion of the Investigator.

7.5.5.8 Cytokine Release Syndrome

Cytokine release syndrome results from an excessive immune response with elevated circulating cytokines that can cause symptoms ranging from flu-like symptoms, confusion, and rigors to a potentially fatal sepsis syndrome with circulatory collapse. The Sponsor recommends vigilance and appropriate clinical management that may include, hydration, steroids, and/or anti-IL-6 agents at the investigator's discretion.

7.5.5.9 Other Toxicities

Hold dose for clinically significant Grade 3/4 toxicities for the current cycle, with the exception of the following Grade 3 toxicities, if deemed appropriate by the Investigator:

- Arthralgia
- Myalgia
- Fever responding to treatment with no active infection
- Nausea and/or vomiting, or diarrhea associated with suboptimal prophylaxis and/or treatment
- Reversible clinical chemistry abnormalities (refer to Sections 7.5.5.1.3, 7.5.5.3, and 7.5.5.5 for details regarding albumin, liver transaminases, and creatinine).

Refer to Section 7.5.5.10.1 for further instruction regarding dose delay and reduction.

7.5.5.10 Dose Modifications/Delays and Management Procedures for Other Toxicities Associated with SL-401

7.5.5.10.1 Nonhematological Toxicity

Table 3 summarizes the dose modification guidelines for SL-401-related nonhematological toxicities (other than those identified in Section 7.5.5.1 through Section 7.5.5.8).

Table 3: Dose Delays/Modifications for Other SL-401-Related Nonhematological Toxicity

CTCAE Grade	SL-401 Dose Adjustment/Delays
Any Grade 1-2 toxicities	• No dose adjustment or delay
Grade 3 with resolution to Grade ≤1 or baseline by Day 28 of cycle	• No dose adjustment or delay
Grade 3 without resolution to Grade ≤1 or baseline by Day 28 of cycle	• Delay the start subsequent cycle by up to 14 days (i.e., up to 42 days since the first dose in the previous cycle). – If after 14 days the toxicity resolves to Grade ≤1 or baseline, no dose adjustment required and the cycle may start. – If after 14 days the toxicity has not resolved, monitor weekly until resolution; discuss additional dosing and schedule with the Medical Monitor.
Grade 4 (excluding transient [≤14 days] asymptomatic transaminase or CPK elevations) with resolution to Grade ≤1 or baseline by Day 28 of cycle	• Reduce dose for subsequent cycle (see Section 7.5.5.11) and the cycle may start.

CTCAE Grade	SL-401 Dose Adjustment/Delays
Grade 4 without resolution to Grade ≤1 or baseline by Day 28 of cycle	• Delay the start subsequent cycle by up to 14 days (i.e., up to 42 days since the first dose in the previous cycle). • If after 14 days the toxicity resolves to Grade ≤1 or baseline, resume dosing at a reduced dose (see Section 7.5.5.11). • If after 14 days the toxicity has not resolved, monitor weekly until resolution; discuss additional dosing and schedule with the Medical Monitor

Note that delays in start of subsequent cycles greater than 3 weeks (6 weeks following the start of the prior treatment cycle) will be acceptable only after discussion with the Medical Monitor regarding the potential risk/benefit of further treatment.

7.5.5.10.2 Hematological Toxicity

Patients with neutropenia or thrombocytopenia as a consequence of their disease do not require treatment interruptions for myelosuppression. Dose-modifications in these patients should be considered on a case-by-case basis and discussed with the Medical Monitor. The following guidelines can be used for these patients:

- Patients with a response and pre-cycle counts of neutrophils >1000/µL and platelets >50,000/µL who have sustained low counts of neutrophils <500/µL and/or platelets <20,000/µL for more than 2 consecutive weeks in the current cycle, may receive a subsequent cycle of SL-401 at a reduced dose, at the Investigator's discretion.
- If there are persistent blasts in the peripheral blood or >5% blasts in the bone marrow, continue treatment regardless of neutrophil and platelet count and give supportive care as needed.
- If no evidence of leukemia in the bone marrow, consider holding (postponing) therapy until recovery of neutrophils to ≥1000/µL and platelets ≥50,000/µL, then resume SL-401 at the same or reduced dose according to guidelines mentioned above.

7.5.5.11 Dose Reduction Schedule

Table 4 summarizes the potential reduced dose for a subsequent cycle relative to the starting dose or dose for a prior cycle. The reason(s) for all dose modifications must be recorded in the eCRF.

Table 4: Reduced Dose Relative to Dose in Prior Cycle

Dose for a Given Cycle	Reduced Dose for Subsequent Cycle
12 µg/kg/day	9 µg/kg/day
9 µg/kg/day	7 µg/kg/day
7 µg/kg/day	5 µg/kg/day

Dose changes should only occur once a cycle has been completed. Intra-cycle dose modifications will not be permitted. Potential dose modifications will be based on the severity and resolution of toxicities. Once the dose has been reduced a subsequent increase is not permitted. Cases requiring >1 dose reduction should be discussed with the Medical Monitor.

If doses >12 µg/kg/day are explored, consult with the Medical Monitor for potential reduced doses for subsequent cycles.

7.6 Treatment Discontinuation

7.6.1 Criteria for Treatment Discontinuation

SL-401 treatment may be discontinued for any of the following reasons:

- Patient withdrawal of consent
- Occurrence of unacceptable toxicity, including DLT
- SL-401 related anaphylaxis or Grade ≥3 hypersensitivity reaction
- Requirement for > 1 dose reduction unless there is evidence of MRD eradication or sustained AML remission (beyond Cycle 2), in which case additional dose reductions are permitted, however, these reductions must be discussed with the Medical Monitor and documented in the context of ongoing AML response.
- Disease recurrence/progression
- Intercurrent illness that prevents further administration of SL-401
- Patient non-compliance
- Occurrence of pregnancy
- Completion of 6 cycles of treatment. (The administration of additional cycles of SL-401 [beyond 6 cycles] may be considered in the setting of MRD eradication, sustained AML remission, or other evidence of sustained anti-leukemia benefit in the opinion of the Investigator. Administration of SL-401 beyond 6 cycles must be discussed with the Medical Monitor at which time the individual patient's potential risk/benefit of further treatment will be assessed).

- Investigator's decision

The reason for SL-401 discontinuation and the date of discontinuation should be recorded in the eCRF.

7.6.2 Procedures and Follow-up after Treatment Discontinuation

The evaluation during which the Investigator determines that SL-401 will be discontinued should be considered the End of Treatment Evaluation; all tests and procedures for the End of Treatment Evaluation are listed in Table 6. In addition, patients should be followed for a minimum of 30 days after the last infusion of SL-401 for assessment of AEs (including potential new AEs and potential change/resolution of existing AEs).

If the patient is in CR/PR at the time of discontinuation, tumor assessments should continue to be performed as described in Section 8.11 until, in the judgment of the Investigator, there is evidence of relapsed or progressive disease. Beyond the End of Treatment Evaluation and 30-day follow up (safety/AE assessment), it is requested that subsequent follow-up occur approximately every 90 days for ascertainment of survival status.

If the patient discontinues SL-401 treatment and also withdraws consent for collection of future information, no further evaluations should be performed and no additional data should be collected as part of the study. The Sponsor will only retain and use any data collected before withdrawal of consent.

Please consult Section 6.4 for recommendations concerning ongoing follow-up of patients alive with or without evidence of disease progression at the time of Study Completion/assessment of primary and critical secondary endpoints.

8 Study Procedures

8.1 Patient Selection

Patients with AML in first remission (CR or CRi) and who otherwise meet the inclusion/exclusion criteria will be recruited for enrollment into the study. Patients will be advised of the clinical protocol by the Investigator. If the patient is interested and is potentially eligible for participation in the study, he/she will be provided with the ICF to review and sign. The ICF includes a detailed explanation of the study design and the potential risks and benefits of treatment. Patients who agree to participate in the study will be provided with a copy of the signed consent form; the original signed consent document will be filed in the patient's medical record. Only eligible and consenting patients will be entered into the study.

Patients will be screened by the site's Investigator or study nurse/coordinator prior to study entry. All patients enrolled on the study will be entered into a patient registration log at each site. Each screened patient will be assigned a sequential patient/study screening number with digits indicating site number and patient study number (e.g., XX-YYY, where XX denotes site number and YYY denotes patient study number as assigned at screening). Original screening records and source documents should be kept for all patients, including those who fail to meet

the patient eligibility requirements and any completed eCRFs should be retained for monitoring and auditing. Each patient's data obtained from subsequent evaluations should be recorded and evaluated in the source documents and eCRF. Prior to treatment, the Investigator will re-confirm patient eligibility criteria and assignment of the correct patient study number.

8.2 Medical History

Medical history includes current and past medical conditions and smoking history, date of AML diagnosis, prior AML treatment, response to prior treatment, and date of relapse, if applicable. Information concerning any prior malignant diagnoses with particular focus on cytotoxic therapies received for prior malignancies (i.e., dates/duration of anthracycline for prior breast cancer) is to be collected whenever feasible.

8.3 Prior and Concomitant Medication

Medications taken within 28 days prior to screening and throughout the study are to be collected and recorded.

8.4 ECOG Performance Status

See Section 15.2 for a scoring guide.

8.5 Physical Examination

Physical examination includes evaluation by body system and height (at screening only).

8.6 Vital Signs

Vital signs include temperature, heart rate, respiration rate, pulse oximetry, and BP. Collection should occur after the patient has been sitting for 3-5 minutes.

8.7 Electrocardiograms

All patients will have a 12-lead ECG performed at the screening visit and pre-treatment visit (Study Day 0 or 1), as well as on Day 28 (± 3 days, and Day 35 [± 3 days] only if delayed end of cycle) of each cycle. During the days when patients are undergoing PK sampling (Cycles 1 and 3, infusions 1 and 5), an ECG will be performed at 3 distinct time points (triplicates) within 5 minutes prior to each PK sample collection pre-infusion and at 30 and 60 minutes post-infusion (see Table 7). An ECG should be performed after patient is supine for 5 minutes. All ECGs will be analyzed locally.

8.8 Clinical Laboratory Tests

The following assessments should be done per the visit schedule and processed by the local laboratory.

- Hematology: Minimally, scheduled hematology collections should include white blood cell (WBC) count, differential white cell count (lymphocytes, monocytes, basophils, eosinophils, and neutrophils), red blood cell (RBC) count, hematocrit, hemoglobin and platelet count.

- Serum albumin: May be a component of the serum chemistry panel. See Section 7.5.5.1.3 for administration of albumin if serum albumin decreases to <3.0 g/dL in the immediate post-treatment period.
- Serum electrolytes and chemistry: Sodium, potassium, bicarbonate, chloride, BUN, creatinine, glucose, ALT, albumin, alkaline phosphatase (ALP), AST, bilirubin (total, direct, and indirect), calcium, creatine phosphokinase (CPK), magnesium, LDH, phosphate, total protein, and uric acid.
- Coagulation parameters: PT and/or INR and aPTT.
- Urinalysis: Appearance, color, pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilinogen, and occult blood.

8.9 Urine or Serum Pregnancy Test

A urine or serum pregnancy test will be performed within 1 week prior to treatment for WOCBP who are not on acceptable birth control measures. The pregnancy test should be performed at the clinical research site and processed by the local laboratory.

8.10 Vision Assessment

All patients will be questioned regarding any changes in visual acuity and/or color vision. Patients who have experienced any ≥Grade 2 study drug-related changes in vision (CTCAE v4.03 Grade) will have an ophthalmologic consultation and/or examination performed. In the event any abnormalities are detected, the patient will be followed up as per the recommendations of the consulting ophthalmologist. Management of treatment-related ocular disorders with inflammatory characteristics should include corticosteroid eye drops and/or other measures, as indicated by an ophthalmologist. In the setting of persistent study drug-related ocular disorders ≥Grade 2, consultation with the study's Medical Monitor is required.

8.11 Tumor Assessments

Following determination of eligibility, locally, the following assessments must be performed centrally at baseline (after local determination of eligibility, but prior to receiving investigational treatment on study) within 14 days prior to the first administration of SL-401, and on the following schedules until, in the judgment of the Investigator, there is evidence of relapsed or progressive disease.

8.11.1 Bone Marrow and Peripheral Blood Examinations including Biological/Target/ Correlative Studies by Central Laboratory

Bone marrow aspirates (+ biopsy) will be collected within 14 days prior to first administration of SL-401 and 28 (± 7) days after the start of Cycles 2, 4 and 6, every 3 months (± 1 month) thereafter through 12 months after start of SL-401, and thereafter at the discretion of the Investigator. If the Cycle 2 (Day 28 (± 7 day) bone marrow examination is empty (i.e., hypocellular) or inadequate, a bone marrow examination should be repeated in 14 (± 7) days to document response. If additional time is required to complete the repeat examination,

consult with the Medical Monitor. The Cycle 2, 4 or 6, Day 28 (± 7 days) bone marrow assessment should occur on Day 28 (± 7 days) even in the setting of patients receiving SL-401 over 6-10 days (as opposed to 5 consecutive days).

For adequate MRD assessment, it is critical that the first aspirate from each bone marrow collection: 1) consists of 2 mL of BM aspirate in its entirety; and 2) be shipped in its entirety via priority overnight to the central processing laboratory ([redacted], Attn: [redacted]), as described in the Laboratory Manual. Additional bone marrow may be used for local assessment at the Investigator's discretion.

Results of bone marrow examinations will be provided to the Investigator by the central laboratory within 1 week of sample receipt.

8.12 Pharmacokinetic Studies

An intensive schedule for collection of blood samples after specific infusions during Cycles 1 and 3 of SL-401 will be used to determine plasma concentrations of SL-401. The concentration of SL-401 in plasma samples will be determined by a sensitive and specific sandwich enzyme-linked immunosorbent assay (ELISA) method at a contract laboratory according to industry GLP bioanalytical practices. Plasma concentration data over time will be used to characterize the PK disposition of SL-401, to assess any change in the PK properties of SL-401 during the 5-day course of treatment or between cycles of treatment, and relate the PK characteristics of SL-401 to immunogenicity, toxicity, and disease activity.

Collectively, the SL-401 plasma concentration-time data will be analysed by conventional non-compartmental PK methods to define the fundamental PK properties of SL-401. Furthermore, if supported by the adequacy of the data, a population PK model will be developed, in which the effects of various potentially relevant co-variants (i.e., gender, age, IL-3R expression, immunogenicity) on relevant PK parameters, will be evaluated. Sample collection requires that the actual date and time (24-hour clock) that the SL-401 treatment begins (start of infusion, SOI) and ends (end of infusion, EOI) will be recorded as will be the date and time (24-hour clock time) of all blood samples.

Detailed instructions for collecting, processing, storing, and shipping the samples are provided in a separate procedure manual. [redacted]

Blood samples will be collected into ethylenediaminetetraacetic acid (EDTA) tubes (lavender top, at least 6 mL each); upon collection, the samples should be inverted gently several times to ensure adequate mixing of the EDTA anticoagulant and whole blood. Within approximately 30 minutes of collection, samples should be centrifuged in a refrigerated centrifuge to separate the plasma. An aliquot of the plasma (> 1 mL) will be transferred to a clean tube, tightly sealed, labelled appropriately and stored frozen at -70°C or below prior to analysis in the validated immunoassay.

Samples will be collected immediately prior to the start of the infusion of SL-401, immediately after end of infusion (time recorded), then 15, 30, 45, 60, 90, 120, 180, and 240 minutes after the completion of the infusion (see Table 7). It is recognized that it is not always possible to obtain the specimens at the precise time points specified above, although it requested that sites make every effort to do so; it is essential that the precise time of infusion and times of subsequent PK sampling be recorded diligently).

The nominal blood sampling time schedule is summarized in Table 7 for the following SL-401 treatment days:

- Cycles 1 and 3, infusion 1 (i.e., Day 1)
- Cycles 1 and 3, infusion 5 (i.e., usually Day 5)

8.13 Immunogenicity Studies

Peripheral blood samples (5 mL) will be collected (serum red top tube, no additive) for the detection and characterization of SL-401 reactive antibodies according to the schedule provided below.

- Cycle 1: Day 1 (pre-infusion), Day 15, and Day 28 (± 3 days)
- Cycle 2, 3, 4, 5, or 6: Day 1 (pre-infusion) and Day 28 (± 3 days). A separate Day 1 (pre-infusion) sample does not need to be drawn if the Day 28 sample from the prior cycle has been drawn no more than 24 hours prior to the first infusion of the next cycle to be given. In that case, the data for the Day 28 sample may be used both as the Day 28 sample for the prior infusion as well as the Day 1 (pre-infusion) sample, avoiding the necessity to draw 2 blood samples in close proximity.
- At least 16 to up to 20 weeks after the last SL-401 dose.
- If there are clinical manifestations suggesting either an infusion-related reaction or drug hypersensitivity, an immunogenicity sample should be obtained, as indicated in Section 7.5.5.2.

If infusions are held (postponed) for any reason, an immunogenicity sample must be collected within 3 ± 3 days after completion of the last SL-401 infusion for the cycle.

Samples for immunogenicity assessment will be evaluated by a central laboratory facility. Detailed instructions for collecting, processing, storing, and shipping the samples will be provided in a separate procedure manual.

In the setting of detection of SL-401 reactive antibodies, plasma from corresponding specimens may be evaluated for SL-401 levels (PK analysis). Plasma from patients without SL-401 reactive antibodies would then be utilized as a control for this PK analysis.

Following the required immunogenicity and PK evaluations, if additional serum or plasma is available, this serum and/or plasma may be used for evaluation of other relevant markers (for example IL-3 levels) if considered appropriate by the Sponsor or principle Investigator.

9 Schedule of Events

The study schedule of events is summarized in Table 5, Table 6, and Table 7.

9.1 Study Day -14 to -4: Screening

The following evaluations will be performed on Study Day -14 to -4 to determine the patient's eligibility for the study and in anticipation of study drug:

- Informed consent
- Inclusion / Exclusion criteria
- Medical history, including prior therapy and concomitant medications
- ECOG PS
- Physical examination, including vision assessment
- Urine or serum pregnancy test
- Vital signs and weight
- 12-lead ECG
- ECHO or MUGA scan (within 28 days prior to start of first cycle of study drug)
- Clinical laboratory tests: hematology, serum electrolytes and chemistry (including albumin), coagulation parameters, and urinalysis
- Bone marrow aspiration (+ biopsy) within 14 days prior to start of first cycle of study drug.

Investigators will maintain a confidential log of all patients who have been screened for participation in the study whether or not the patient was eligible for study participation.

9.2 Study Day -1 to 0: Procedures Prior to Start of Treatment

- Concomitant medication assessment
- Physical examination
- Vital signs and weight
- 12-lead ECG
- Clinical laboratory tests: hematology, serum electrolytes and chemistry (including albumin)

9.3 Cycle 1

9.3.1 Study Days 1 – 5 (Up to Study Day 10 if Infusion(s) Held): Pre-Infusion

- Inpatient admission (Study Day 1) or treatment at a suitable outpatient facility
- Vital signs and weight
- AE and SAE monitoring
- Clinical laboratory tests: hematology, serum electrolytes and chemistry (including albumin), coagulation parameters, and urinalysis (Day 1 only for urinalysis)
- Collection of peripheral blood for immunogenicity (infusion 1) and PK sampling (infusions 1 and 5) immediately prior to the start of the infusion
- 12-lead ECG
- Diphenhydramine 50 mg IV 60 minutes prior to infusion
- Acetaminophen 650 mg PO 60 minutes prior to infusion
- Methylprednisolone 50 mg IV (or an equivalent dose of another corticosteroid) 60 minutes prior to infusion
- Ranitidine 50 mg IV (or an equivalent doses of another H_2-histamine antagonist) 60 minutes prior to infusion

9.3.2 Study Days 1 – 5 (Up to Study Day 10 if Infusion(s) Held): Infusion

- 12-lead ECG (infusions 1 and 5) performed at 3 distinct time points (triplicates) at pre-infusion and within 5 minutes prior to each PK sample collection at 30 and 60 minutes post-infusion
- Collection of peripheral blood for PK sampling (infusions 1 and 5) collected immediately after end of infusion (time recorded), then 15, 30, 45, 60, 90, 120, 180, and 240 minutes after the completion of the infusion
- 15-minute IV infusion of SL-401 at required dose
- Vital signs: immediately after completion of infusion and 30, 60, and 240 minutes post-infusion
- Monitoring for at least 4 hours
- AE and SAE monitoring

NOTE: For Cycle 1, SL-401 must be administered in the inpatient setting, with hospitalization beginning the day of the first infusion of SL-401 (or a prior day) and ending 24 hours after the last infusion of SL-401. Subsequent cycles of SL-401 can be administered in the inpatient setting or in a suitable outpatient ambulatory care setting that is equipped for intensive

monitoring of patients with hematopoietic malignancies undergoing treatment, per the discretion of the Investigator and institutional guidelines and capabilities. Patients will be monitored for at least 4 hours following the administration of each infusion of SL-401.

9.3.3 Study Day 8 ± 3 Days, or 3 ± 3 Days After Completion of Infusions if Infusion(s) Held

- Concomitant medication assessment
- Clinical laboratory tests: hematology, serum electrolytes and chemistry (including albumin), coagulation parameters, and urinalysis
- AE and SAE monitoring

9.3.4 Study Day 15 ± 3 Days

- Concomitant medication assessment
- Clinical laboratory tests: hematology, serum electrolytes and chemistry (including albumin), coagulation parameters, and urinalysis
- Collection of peripheral blood for immunogenicity (serum)
- AE and SAE monitoring

9.3.5 Study Day 21 ± 3 Days

- Concomitant medication assessment
- Clinical laboratory tests: hematology, serum electrolytes and chemistry (including albumin), coagulation parameters, and urinalysis
- Monitoring for changes in visual acuity and color vision
- AE and SAE monitoring

9.3.6 Study Day 28 ± 3 Days, Then Every 7 ± 3 days: Delayed End of Cycle for Toxicity Resolution Only if Required

- Concomitant medication assessment
- ECOG PS
- Physical examination
- Vital signs and weight
- 12-lead ECG
- Clinical laboratory tests: hematology, serum electrolytes and chemistry (including albumin), coagulation parameters, and urinalysis
- Collection of peripheral blood (serum) for immunogenicity

- AE and SAE monitoring

9.4 Cycles 2 – 6

9.4.1 Days 1 – 5 (Up to Day 10 if Infusion(s) Held): Pre-Infusion

- Inpatient admission (Day 1) or treatment at a suitable outpatient facility
- Concomitant medications
- Vital signs and weight
- 12-lead ECG
- Clinical laboratory tests: hematology, serum electrolytes and chemistry (including albumin), coagulation parameters, and urinalysis (Day 1 only for urinalysis)
- Collection of peripheral blood for immunogenicity (infusion 1) immediately prior to the start of the infusion
- AE and SAE monitoring
- Diphenhydramine 50 mg IV 60 minutes prior to infusion
- Acetaminophen 650 mg PO 60 minutes prior to infusion
- Methylprednisolone 50 mg IV (or an equivalent dose of another corticosteroid) 60 minutes prior to infusion
- Ranitidine 50 mg IV (or an equivalent doses of another H_2-histamine antagonist) 60 minutes prior to infusion

9.4.2 Days 1 – 5 (Up to Day 10 if Infusion(s) Held): Infusion

- 12-lead ECG (Cycle 3 only, infusions 1 and 5) performed at 3 distinct time points (triplicates) within 5 minutes prior to each PK sample collection pre-infusion and 30 and 60 minutes post-infusion (also Cycle 1: see Section 9.3)
- Collection of peripheral blood for PK sampling (Cycle 3 only; infusions 1 and 5) collected pre-infusion, immediately after end of infusion (time recorded), and then 15, 30, 45, 60, 90, 120, 180, and 240 minutes after the completion of the infusion (also cycle 1: see Section 9.3)
- 15-minute IV infusion of SL-401 at required dose
- Vital signs: immediately after completion of infusion and 30, 60, and 240 minutes post-infusion
- Monitoring for at least 4 hours
- AE and SAE monitoring

9.4.3 Day 8 ± 3 Days, or 3 ± 3 Days after Completion of Infusions if Infusion(s) Held

- Concomitant medication assessment
- Clinical laboratory tests: hematology, serum electrolytes and chemistry (including albumin), coagulation parameters, and urinalysis
- AE and SAE monitoring

9.4.4 Day 15 ± 3 Days

- Concomitant medication assessment
- Clinical laboratory tests: hematology, serum electrolytes and chemistry (including albumin), coagulation parameters, and urinalysis
- AE and SAE monitoring

9.4.5 Day 21 ± 3 Days

- Concomitant medication assessment
- Clinical laboratory tests: hematology, serum electrolytes and chemistry (including albumin), coagulation parameters, and urinalysis
- Monitoring for changes in visual acuity and color vision
- AE and SAE monitoring

9.4.6 Day 28 ± 3 Days, Then Every 7 ± 3 days: Delayed End of Cycle for Toxicity Resolution Only if Required

- Concomitant medication assessment
- ECOG PS
- Physical examination
- Vital signs and weight
- 12-lead ECG
- Clinical laboratory tests: hematology, serum electrolytes and chemistry (including albumin), coagulation parameters, and urinalysis
- Collection of peripheral blood for immunogenicity (serum)
- AML remission/response assessment: bone marrow aspiration (+ biopsy) at the end of Cycles 2, 4, and 6, and every 3 months (± 1 month) thereafter through 12 months after start of SL-401 and thereafter at the discretion of the Investigator. Bone marrow (2 mL) will be prioritized for assessment of MRD. Any additional bone marrow (+ biopsy) remaining (~5 mL) will be aliquoted for disease response assessment and in vivo

engraftment studies. CD123 is to be assessed in all bone marrow samples (and, if applicable, tissue samples).

- AE and SAE monitoring

Note: For clinical (i.e., concomitant medications, AE assessment, or physical examination) or laboratory assessments stipulated at both Day 28 of a given cycle and Day 1 of a subsequent cycle, separate Day 1 (pre-infusion) assessments/samples do not need to be obtained if the Day 28 assessment/sample from the prior cycle is obtained no more than 24 hours prior to the first infusion of the next cycle to be given. In that case, the data for the Day 28 assessment/sample may be used both as the Day 28 assessment/sample for the prior cycle as well as the Day 1 (pre-infusion) assessment/sample, avoiding the necessity to conduct redundant assessments or draw 2 blood samples in close proximity.

9.5 End of Treatment

- ECOG PS
- Physical examination
- Vital signs and weight
- Monitoring for changes in visual acuity and color vision
- Bone marrow aspiration (+biopsy)

9.6 Safety Monitoring: Through 30 Days after Last Infusion

- Concomitant medications
- AE and SAE monitoring
- Survival status

9.7 Survival Monitoring: Approximately Every 90 Days after End of Treatment

- Survival status and response/disease progression status (for patients in PR/CR at End of Treatment), continuing until assessments of the primary and secondary objectives are completed for all patients; survival status may be performed by telephone contact.
- Patients who undergo SCT will be followed for the occurrence of VOD as part of survival monitoring.
- A blood sample for immunogenicity studies will be collected at least 16 weeks to up to 20 weeks after the last SL-401 dose.

Table 5: Study Events Schedule for Cycle 1 (Study Day -14 to Study Day 28-35)

		Cycle 1					
	Study Day -14 to -4	**Study Day -1 to 0**	**Study Days 1-5 (Up to Study Day 10 if Infusion(s) Held) SL-401 Treatment**		**Study Day 8±3[n], 15±3, and 21±3**	**Study Day 28±3[o]**	**Study Day 35±3, Then Every 7±3 days**
Tests and Observations	***Screening***	***Pre-treatment***	***Pre-Infusion***	***Infusion***		***End of Cycle[o]***	***Delayed End of Cycle for Toxicity Resolution Only if Required***
Informed consent form	X						
Inclusion/exclusion criteria	X						
Medical history including prior therapy, concomitant medications	X						
Concomitant Medications		X			X	X	X
ECOG performance status	X					X	X
Physical examination	X	X				X	
Pregnancy test [a]	X						
Vital signs and weight[b]	X	X	X	X		X	X
12-lead ECG[c]	X	X	X	X (Infusions 1, 5)		X	X
ECHO or MUGA scan[d]	X						
Hematology[e]	X	X	X		X	X	X
Serum electrolytes[f]	X	X	X		X	X	X
Serum albumin[g]	X	X	X		X	X	X
Serum chemistry[h]	X	X	X		X	X	X
Coagulation parameters: PT/INR, aPTT	X		X		X	X	X
Urinalysis[i]	X		X (Infusion 1)		X	X	X
Tumor response assessment: Bone marrow aspiration + biopsy[j]	X						
Administration of premeds [k]			X				
SL-401 administration[l]				X			
Pharmacokinetic sampling[m]			X (Infusions 1, 5)	X (Infusions 1, 5)			
Immunogenicity sampling			X (Infusion 1)		X (day 15)	X	
Vision assessment	X				X (day 21)		
AE and SAE monitoring			X	X	X	X	X

a Urine or serum pregnancy test must be performed within 1 week prior to treatment in women of childbearing potential.

b Vital signs should be performed after patient is sitting for 3-5 minutes. If during dosing period, vital signs should be taken immediately prior to infusion, immediately after completion of infusion, and 30, 60, and 240 minutes post-infusion.

c All patients will have a 12-lead ECG performed at the screening visit and pre-treatment visit, as well as Day 28. During the days when patients are undergoing PK sampling (Cycles 1 & 3, infusions 1 and 5), an ECG will be performed at 3 distinct time points (triplicates) within 5 minutes prior to each PK sample collection pre-infusion and at 30 and 60 minutes post-infusion (see footnote (m) and Table 6).

d MUGA or 2-D ECHO to quantify LVEF. Must be completed within 28 days prior to start of first cycle of study drug.

e To be collected prior to SL-401 infusion if during dosing period. Hematology includes WBC count with differential, RBC count, hematocrit, hemoglobin and platelet count.

f To be collected prior to SL-401 infusion if during dosing period. Electrolytes include sodium, potassium, bicarbonate, chloride, BUN, creatinine and glucose.

g To be collected prior to SL-401 infusion if during dosing period. Serum albumin may be a component of the chemistry panel (h). See protocol for administration of albumin if serum albumin decreases to <3.0 g/dL during treatment days or in the immediate post-treatment period.

h To be collected prior to SL-401 infusion if during dosing period. Serum chemistry includes electrolytes (see above, footnote f) and the following: ALT, albumin, ALP, AST, bilirubin (total, direct, and indirect), calcium, creatine phosphokinase (CPK), magnesium, LDH, phosphate, total protein, and uric acid.

i To be collected prior to SL-401 infusion if during dosing period. Urinalysis includes appearance, color, pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilinogen, and occult blood.

j Morphology and differential WBC/blast count on aspirate. Baseline must be performed within 14 days prior to the first administration of SL-401. Subsequent bone marrow aspirates (+ biopsy) will be performed at the end of Cycles 2, 4 and 6 and every 3 months (± 1 month) thereafter through 12 months after the start of SL-401 and at the Investigator's discretion thereafter. If the end-of- Cycle 2/4/6 bone marrow aspirate (+ biopsy) is empty, hypocellular, or inadequate, a bone marrow examination should be repeated within 14 (± 7) days to document response. All bone marrow samples collected on study will be assessed centrally. Bone marrow (2 mL aliquot) will be prioritized for assessment of MRD at the [redacted]. Additional bone marrow (~5 mL) is to be aliquoted for tumor assessment and for translational evaluation at MD Anderson Cancer center. CD123 is to be assessed in all bone marrow samples (and, if applicable, tissue samples) by flow cytometry (i.e., CD123 should be added to the panel of markers assessed by flow cytometry of bone marrow aspirates) and immunohistochemistry and the results recorded and captured in the eCRF.

k Refer to Section 7.5.2 – Premedication and Administration.

l Following treatment with premedication, SL-401 will be administered as a 15-minute infusion for the first 5 consecutive days of a 28-day cycle. Individual SL-401 infusions may be delayed to allow for toxicity resolution; all infusions should be completed within 10 days. Patient must be monitored for 4 hours post infusion.

m Plasma samples (6 mL each) will be collected immediately prior to the start of the infusion of SL-401, immediately after end of infusion (time recorded), then 15, 30, 45, 60, 90, 120, 180, and 240 minutes after completion of the infusion during infusions 1 (i.e., Study Day 1) and 5 (i.e., Study Day 5) during Cycles 1 & 3 (see (c)).

n For patients who live a considerable distance from the Study Center, for whom weekly travel to the Study Center is not feasible, the Day 8, 15, and 21 (±3 days) laboratory assessments (blood and urine) may be submitted to a local laboratory, although the results must be evaluated by the Study team. Concomitant medication and AE monitoring on these days will take place via telephone contact. In situations where SL-401 is not administered over 5 consecutive days (i.e., treatment delays because of AEs or other factors) and an infusion is to be administered on Day 8, all pre-infusion/infusion evaluations should be conducted, in addition to concomitant medications recorded. Upon completion of the 5th Cycle 1 infusion (Day 8, 9 or 10), the blood/urine/concomitant medication and AE assessments should be planned for Day 15, as indicated in the table.

o The end-of-the cycle evaluations (Day 28 or thereafter) may also serve as the pre-infusion evaluations for Cycle 2; these do not need to be duplicated on successive days unless there is an abnormality or other clinically relevant reason for repeat evaluation.

Table 6: Study Events Schedule for Cycles 2-6 and Subsequent Follow-up

	Cycle 2-6							
	Days1-5 (Up to Day 10 if Infusion(s) Held) SL-401 Treatment		Day 8±3[m], 15±3 and 21±3	Day 28±3[n]	Day 28±3, Then Every 7±3 days	End of Treatment	Safety: Through 30 Days After Last Infusion	Survival: Every 90 Days After Last Infusion
Tests and Observations	***Pre-Infusion***	***Infusion***		***End of Cycle[n]***	***Delayed End of Cycle for Toxicity Resolution Only if Required***			
Concomitant Medications	X		X	X	X		X	
ECOG performance status				X	X	X		
Physical examination				X		X		
Vital signs and weight[a]	X	X		X	X	X		
12-lead ECG[b]	X	X (Cycle 3; infusions 1 & 5)		X	X			
Hematology[c]	X		X	X	X			
Serum electrolytes[d]	X		X	X	X			
Serum albumin[e]	X		X	X	X			
Serum chemistry[f]	X		X	X	X			
Coagulation parameters: PT/INR, aPTT	X		X	X	X			
Urinalysis[g]	X (Infusion 1)		X	X	X			
Tumor response assessment: Bone marrow aspiration + biopsy [h]				X (Cycle 2, 4, 6)		X[h]		
Administration of premeds [i]	X							
SL-401 administration[j]		X						
Pharmacokinetic sampling[k]	X (Cycle 3; Infusions 1 &5)	X (Cycle 3; Infusions 1 &5)						
Immunogenicity sampling	X (Infusion 1)			X				X[l]
Vision assessment			X (day 21)			X		
AE and SAE monitoring	X	X	X	X	X	X	X	
Long-term Follow-up[l]							X	X

a Vital signs should be performed after patient is sitting for 3-5 minutes. If during dosing period, vital signs should be taken immediately prior to infusion, immediately after completion of infusion, and 30, 60, and 240 minutes post-infusion.

b All patients will have a 12-lead ECG performed at the screening visit and pre-treatment visit, as well as Day 28. Because PK evaluations will only be performed during Cycles 1 & 3, additional ECGs during the minutes/hours following SL-401 infusions are not required for Cycles 2, 4-6.

c To be collected prior to SL-401 infusion if during dosing period. Hematology includes WBC count with differential, RBC count, hematocrit, hemoglobin and platelet count.

d To be collected prior to SL-401 infusion if during dosing period. Electrolytes include sodium, potassium, bicarbonate, chloride, BUN, creatinine and glucose.

e To be collected prior to SL-401 infusion if during dosing period. Serum albumin may be a component of the chemistry panel (f). See protocol for administration of albumin if serum albumin decreases to <3.0 g/dL during treatment days or in the immediate post-treatment period.

f To be collected prior to SL-401 infusion if during dosing period. Serum chemistry includes electrolytes (see above, footnote d) and the following: ALT, albumin, ALP, AST, bilirubin (total, direct, and indirect), calcium, creatine phosphokinase (CPK), magnesium, LDH, phosphate, total protein, and uric acid.

g To be collected prior to SL-401 infusion if during dosing period. Urinalysis includes appearance, color, pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilinogen, and occult blood.

h Morphology and differential WBC/blast count on aspirate. Baseline must be performed within 14 days prior to the first administration of SL-401. Subsequent bone marrow aspirates (+ biopsy) will be performed at the end of Cycles 2, 4 and 6 and every 3 months (± 1 month) thereafter through 12 months after the start of SL-401 and at the Investigator's discretion thereafter. If the end-of- Cycle 2/4/6 bone marrow aspirate (+ biopsy) is empty, hypocellular, or inadequate, a bone marrow examination should be repeated within 14 (± 7) days to document response. All bone marrow samples collected on study will be assessed centrally. Bone marrow (2 mL aliquot) will be prioritized for assessment of MRD at the [redacted]. Additional bone marrow (~5 mL) is to be aliquoted for tumor assessment and for translational evaluation at MD Anderson Cancer center. CD123 is to be assessed in all bone marrow samples (and, if applicable, tissue samples) by flow cytometry (i.e., CD123 should be added to the panel of markers assessed by flow cytometry of bone marrow aspirates) and immunohistochemistry and the results recorded and captured in the eCRF.

i Refer to Section 7.5.2 – Premedication and Administration.

j Following treatment with premedication, SL-401 will be administered as a 15-minute infusion for the first 5 consecutive days of a 28-day cycle. Individual SL-401 infusions may be delayed to allow for toxicity resolution, all infusions should be completed within 10 days. Patient must be monitored for 4 hours post infusion. (The administration of additional cycles of SL-401 (beyond 6 cycles) may be considered in the setting of MRD eradication, sustained AML remission, or other evidence of sustained anti-leukemia benefit in the opinion of the Investigator. Administration of SL-401 beyond 6 cycles must be discussed with the Medical Monitor at which time the individual patient's potential risk/benefit of further treatment will be assessed).

k Plasma samples (6 mL each) will be collected immediately prior to the start of the infusion of SL-401, immediately after end of infusion (time recorded), then 15, 30, 45, 60, 90, 120, 180, and 240 minutes after the start of the infusion during infusions 1 (i.e., Day 1) and 5 (i.e., Day 5) of Cycles 1 & 3. PK evaluation will not be performed for Cycles 2, 4-6.

l After the follow-up visit, patients will then be followed every 90 days for survival status for at least one year following the start of SL-401. The survival follow-up may be by telephone contact. Patients who undergo SCT will be followed for the occurrence of VOD as part of long-term follow-up. A blood sample for immunogenicity studies will be collected at least 16 weeks to up to 20 weeks after the last SL-401 dose.

m For patients who live a considerable distance from the Study Center, for whom weekly travel to the Study Center is not feasible, the Day 8, 15, and 21 (±3 days) laboratory assessments (blood and urine) may be submitted to a local laboratory, although the results must be evaluated by the Study team. Concomitant medication and AE monitoring on these days will take place via telephone contact. In situations where SL-401 is not administered over 5 consecutive days (i.e., treatment delays because of AEs or other factors) and an infusion is to be administered on Day 8, all pre-infusion/infusion evaluations should be conducted, in addition to concomitant medications recorded. Upon completion of the 5th Cycle 1 infusion (Day 8, 9 or 10), the blood/urine/concomitant medication and AE assessments should be planned for Day 15, as indicated in the table.

n The end-of-the cycle evaluations (Day 28 or thereafter) may also serve as the pre-infusion evaluations for the subsequent cycles; these do not need to be duplicated on successive days unless there is an abnormality or other clinically relevant reason for repeat evaluation.

Table 7: Time Points for Pharmacokinetic Blood Draws and ECGs

	Day			
	Cycles 1 and 3: Day 1/Infusion 1		Cycles 1 and 3: Day 5/Infusion 5	
Collection Timepoint	**ECG**	**PK**	**ECG**	**PK**
Pre-Infusion	X	X	X	X
Immediately After End of Infusion (time recorded)		X		X
15 Minutes Post-Infusion		X		X
30 Minutes Post-Infusion	X	X	X	X
45 Minutes Post-Infusion		X		X
60 Minutes Post-Infusion	X	X	X	X
90 Minutes Post-Infusion		X		X
120 Minutes Post-Infusion		X		X
180 Minutes Post-Infusion		X		X
240 Minutes Post-Infusion		X		X

10 Adverse Events and Safety Evaluation

The AE reporting period for a patient treated in the study begins with the initiation of SL-401 and is continuous through 30 days after the last SL-401 infusion. All AEs that occur in treated patients during the AE reporting period specified in the protocol must be reported to the Sponsor, whether or not the event is considered related to SL-401. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to SL-401 should also be reported as an AE.

All patients should be monitored per institutional guidelines for at least 4 hours following the administration of each infusion of SL-401. The Principal Investigator, who is a physician, or medical staff responsible for study conduct and safety evaluations, should be available during the administration SL-401 and follow-up to assess, treat, or report as necessary any AE or SAE that may occur.

10.1 Definitions

All observed or volunteered AEs regardless of suspected causal relationship to SL-401 will be reported as described below.

10.1.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a study patient who is administered a medicinal product (drug or biologic); the event may or may not have a causal relationship with the medicinal product. Examples of AEs include, but are not limited to, the following:

- Clinically significant symptoms and signs including:
  - Worsening of signs and symptoms of the disease under study; disease progression without worsening of signs and symptoms as assessed by bone marrow aspiration (BMA) or other methods should not be reported as AEs.
  - Signs and symptoms resulting from drug overdose, abuse, misuse, withdrawal, sensitivity, dependency, interaction, or toxicity.
  - All possibly related and unrelated illnesses, including the worsening of a preexisting illness.
  - Injury or accidents. Note that if a medical condition is known to have caused the injury or accident (hip fracture from a fall secondary to dizziness), the medical condition (dizziness) and the outcome of the accident (hip fracture from a fall) should be reported as 2 separate AEs.
- Abnormalities in physiological testing or physical examination findings that require clinical intervention or further investigation (beyond ordering a repeat confirmatory test).
- Laboratory abnormalities that meet any of the following (Note: merely repeating abnormal test, in the absence of any of the below conditions, does not constitute an AE. Any abnormal test result that is determined to be an error does not require reporting as an AE):
  - Test result that is associated with accompanying symptoms
  - Test result that requires additional diagnostic testing or medical/surgical intervention
  - Test result that leads to significant additional concomitant drug treatment or other therapy
  - Test result that is considered to be an AE by the Investigator or Sponsor

Note that VOD occurring post-SCT and any changes in visual acuity and/or color vision will be followed as adverse events of special interest.

10.1.2 Serious Adverse Event (SAE)

An AE that meets one or more of the following criteria/outcomes is classified as serious:

- Results in death;
- Is life-threatening (at immediate risk of death);
- Requires admittance to the hospital or prolongation of existing hospitalization;
- Results in persistent or significant disability/incapacity;
- Results in congenital anomaly/birth disfigurements among the offspring of the patients;
- Events with medical significance or needing medical intervention to prevent the occurrence of any of the above events.

Medical judgment should be exercised in deciding whether expedited reporting is appropriate in other situations, such as important medical events that may not be immediately life-threatening or result in death or hospitalization, but may jeopardize the patient or may require intervention to prevent one of the other outcomes listed in the definition above. Serious also includes any other event that the Investigator or Sponsor judges to be serious, or which is defined as serious.

AEs associated with in-patient hospitalization, or prolongation of an existing hospitalization, are considered serious. Any initial admission, even if the duration is less than 24 hours is considered serious. In addition, any transfer within the hospital to an acute/intensive care unit is considered serious. However, the following hospitalizations should not be considered serious:

- Hospitalization or prolonged hospitalization in the absence of precipitating clinical adverse events as follows:
    - Admission for treatment of preexisting condition not associated with the development of a new AE or with a worsening of the preexisting condition
    - Administrative admission (e.g., for a yearly physical examination)
    - Protocol-specified admission during the study (e.g., admission for SL-401 treatment)
    - Preplanned treatments or surgical procedures
    - Admission exclusively for the administration of blood products

Progress of the disease under study (including signs and symptoms of progression) should not be reported as an SAE unless the outcome is fatal during the study or within the safety reporting period. If the disease under study has a fatal outcome during the study or within the safety reporting period, then the event leading to death must be recorded as an AE and as a SAE with CTCAE Grade 5. Disease progression is NOT an SAE; however, some sequelae of disease progression (i.e., pain, thrombocytopenia) may be reported as AEs or SAEs (generally not related to investigational therapy).

The onset date of an SAE is defined as the date on which the event initially met serious criteria (e.g., the date of admission to a hospital). The end date is the date on which the event no longer met serious criteria (e.g., the date the patient was discharged from a hospital).

10.2 Period of Observation

Clinical signs and symptoms and AEs (regardless of relationship to study drug) will be collected continuously from the first day of SL-401 treatment to 30 days following the last infusion of SL-401. All SAEs and AEs judged to be related to study drug will be collected throughout the follow-up period.

Conditions that the patient experienced prior to SL-401 treatment should be recorded in the patient medical history section of the eCRF. All the AEs should be followed-up at the discretion of the Investigator until the symptoms dissipate or become stable even if AEs continue beyond the period of observation. AEs unresolved at the end of the observation period will be considered "ongoing" with an undetermined outcome; however, if after the period of observation completes but prior to the completion of the study, additional outcome information becomes available, it will be reported. The severity of the signs, symptoms, or AEs should be determined using the National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE), Version 4.03. A complete CTCAE list can be downloaded at http://evs.nci.nih.gov/ftp1/CTCAE/About.html.

All clinically meaningful abnormal test results should be retested. Abnormal test results that are difficult to associate with the study drug should be followed until normalized or until the abnormity could be clearly attributed to another cause. Abnormal test results should not be reported as AEs unless they meet the criteria outlined in Section 10.1.1.

10.3 Pre-existing Conditions

A pre-existing condition will not be reported as an AE unless the condition worsens by at least one CTCAE grade during the study. The pre-existing condition, however, must be recorded in the screening eCRF as a pre-existing condition and all related concomitant medication administered for the condition recorded in the baseline (prior) concomitant medication eCRF.

10.4 Pregnancy

WOCBP and men with partners of childbearing potential must be using an adequate method of contraception to avoid pregnancy throughout the study and for up to 8 weeks after the study in such a manner that the risk of pregnancy is minimized. WOCBP include any female who has experienced menarche and who has not undergone successful surgical sterilization (hysterectomy, bilateral tubal ligation, or bilateral oophorectomy) or is not postmenopausal (defined as amenorrhea ≥12 consecutive months; or women on hormone replacement therapy with documented serum follicle-stimulating hormone level ≥35 mIU/mL). Even women who are using oral, implanted, or injectable contraceptive hormones or mechanical products, such as an intrauterine device or barrier methods (diaphragm, condoms, spermicides) to prevent pregnancy,

are practicing abstinence, or whose partner is sterile (e.g., vasectomy), should be considered to be of childbearing potential.

WOCBP must have a negative serum or urine pregnancy test at screening. If the pregnancy test is positive, the patient must not receive study therapy and must not be enrolled in the study.

Sexually active WOCBP must use an effective method of birth control during the course of the study, in a manner such that the risk of failure is minimized.

Prior to study enrollment, WOCBP must be advised of the importance of avoiding pregnancy during study participation and the potential risk factors for an unintentional pregnancy. This information will be included in the ICF that must be signed by the patient.

In addition, all WOCBP or fertile men with partners of childbearing potential should be instructed to contact the Investigator immediately if they suspect they or their partner might be pregnant (e.g., missed or late menstrual period) at any time during study participation.

If following initiation of study drug, it is subsequently discovered that a patient is pregnant or may have been pregnant at the time of exposure to study therapy, including during at least 2 months after product administration, study therapy will be permanently discontinued in an appropriate manner. Exceptions to discontinuation may be considered for life-threatening conditions only after consultation with the Sponsor and Medical Monitor or as otherwise specified in this protocol. The Investigator must immediately notify the Sponsor and Medical Monitor of this event.

Protocol-required procedures for study discontinuation and follow-up must be performed on the patient unless contraindicated by pregnancy (e.g., x-ray studies). Other appropriate pregnancy follow-up procedures should be considered if indicated. In addition, the Investigator must report to the Sponsor follow-up information regarding the course of the pregnancy, including perinatal and neonatal outcome. Infants should be followed for a minimum of 8 weeks.

10.5 Documentation and Reporting of Adverse Events by Investigator

The Investigator is to report all directly observed AEs spontaneously reported by the patient using concise medical terminology. In addition, each patient will be questioned about AEs at each clinic visit following initiation of treatment. The question asked will be “Since your last clinic visit have you had any health problems?” or a similar question to assess health status.

The AE reporting period for this study begins upon initiation of SL-401 treatment and ends 30 days after the last infusion of SL-401. All AEs are to be reported on the AE eCRF.

All AEs that occur in study patients during the AE reporting period specified in the protocol must be reported to the Sponsor, whether or not the event is considered study drug-related. In addition, any untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to the investigational product should also be reported as an AE.

Each AE is to be classified by the Investigator as serious or non-serious. This classification of the gravity of the event determines the reporting procedures to be followed. If a SAE occurs, reporting will follow local and international regulations, as appropriate.

For any event that meets one of the SAE criteria, the Investigator must notify the Safety Contact **within 24 hours** of the knowledge of the occurrence. To report the SAE, complete the SAE form and email to the Safety Contact (email address listed below) or fax the completed paper SAE form to the Safety Contact (fax number listed below) within 24 hours of awareness.

[redacted]

[redacted]

Each SAE should be followed until resolution, or until such time as the Investigator determines its cause or determines that, it has become stable.

Within 24 hours of receipt of follow-up information, the Investigator must update the SAE form electronically in the EDC system for the study and submit any supporting documentation (e.g., patient discharge summary or autopsy reports) to the Safety Contact via fax or e-mail.

The Sponsor will report AEs, which are unexpected and reported as serious and associated with use of the study drug, to the US FDA and all participating clinical sites. For events that are fatal or life-threatening, unexpected, and associated with use of the investigational product, a 7-Day Alert Report will be submitted to the FDA within 7 calendar days of receipt of the SAE information. For all other events that are serious, unexpected, and associated with the use of the investigational medicinal product, a written report will be made no more than 15 calendar days from the date the Sponsor learns of the event.

10.6 Assessment of Causal Relationship to SL-401

In this study, the investigational medicinal product is SL-401. The relationship of an AE to the investigational product should be classified using the following guidelines:

- Related: A temporal relationship exists between the event onset and administration of SL-401. It cannot be readily explained by the patient's clinical state, intercurrent illness, or concomitant therapies. In case of cessation or reduction of the dose, the event abates or resolves and reappears upon rechallenge. This includes events that are considered possibly, probably, or definitely related to SL-401.
- Not Related: Evidence exists that the AE has an etiology other than the study drug (e.g., pre-existing condition, underlying disease, intercurrent illness, or concomitant medication). This includes events that are considered probably not or not related to SL-401. It should be emphasized that ineffective study drug treatment should not be considered as causally related in the context of AE reporting (in other words, disease progression is not considered an AE; however some sequelae of disease progression may be reported as AEs and should generally be reported as AEs not related to investigational therapy).

An Investigator who is qualified in medicine must make the determination of relationship to the investigational product for each AE. The Investigator should decide whether, in his or her medical judgment, there is a reasonable possibility that the event may have been caused by the investigational product. The following factors for study drug relationship should be referenced when making a determination of "related" or "not related."

- The temporal sequence from study drug administration: The event should occur after the study drug is given. The length of time from study drug exposure to event should be evaluated in the clinical context of the event.
- Underlying, concomitant, intercurrent diseases: Each report should be evaluated in the context of the natural history and course of the disease being treated and any other disease the patient may have.
- Concomitant medication: The other medications the patient is taking or the treatment the patient receives should be examined to determine whether any of them might be recognized to cause the event in question.
- Known response pattern for this class of study drug: Clinical and/or preclinical data may indicate whether a particular response is likely to be a class effect.
- Exposure to physical and/or mental stresses: The exposure to stress might induce adverse changes in the recipient and provide a logical and better explanation for the event.
- The pharmacology and PK of the study drug: The known pharmacologic properties (absorption, distribution, metabolism, and excretion) of the study drug should be considered.

10.7 Grading of Adverse Event Severity

To report AEs on the eCRFs, the Investigator will use the severity grading as described in NCI-CTCAE, Version 4.03.

Every effort should be made by the Investigator to assess the AE according to CTCAE criteria. If the Investigator is unable to assess severity because the term is not described in NCI-CTCAE Version 4.03, severity of MILD, MODERATE, SEVERE, LIFE-THREATENING, or DEATH may be used to describe the maximum intensity of the adverse event. For purposes of consistency, these intensity grades are defined as follows:

- Mild (Grade 1): does not interfere with patient's usual function
- Moderate (Grade 2): interferes to some extent with patient's usual function
- Severe (Grade 3): interferes significantly with patient's usual function
- Life-threatening (Grade 4): results in immediate risk of patient's death
- Death (Grade 5): results in patient's death

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met one of the criteria for serious events.

It is requested that when reporting AEs for which potentially redundant CTCAE terms exist, Investigators utilize the more clinically-oriented terminology (for example, "anemia" is preferable to "hemoglobin decreased").

It is also requested that in the setting of a hypersensitivity reaction or suspected hypersensitivity reaction considered by the Investigator to be related to investigational therapy, that Investigators report both the specific symptoms associated with the reaction (i.e., "urticaria," "chills," "dyspnea," etc.) and also report the appropriate term indicating the hypersensitivity reaction ("allergic reaction," or "infusion related reaction" or "anaphylaxis" if appropriate [General Disorders and Immune System Disorders; CTCAE v4.03, pages 57 and 65]).

11 Statistical Analysis

11.1 General Considerations

Analyses will be performed on all patients that received any quantity of SL-401 (i.e., all treated patients). The baseline value for a given variable is defined as the last measurement for the variable prior to the first infusion of SL-401. Day 1 for each individual patient is defined as the date the patient receives their first infusion of SL-401.

11.2 Determination of Sample Size

The primary objectives of the study are to determine the MTD or the maximum tested dose where multiple DLTs are not observed (Stage 1), and to further characterize the safety profile of SL-401 at this dose (Stages 1 and 2). The anticipated same size is sufficient to evaluate these objectives.

A secondary objective is to characterize the anti-tumor activity of SL-401. In Stage 2, up to 20 additional patients with MRD as determined locally will enroll and receive SL-401 at either the MTD or maximum tested dose, so that a total of 15 patients with evidence of MRD, as determined centrally, are treated at this dose. The assumptions governing sample size are as follows:

- Null hypothesis: eradication of MRD $\leq$5%
- Alternate hypothesis: eradication of MRD $\geq$20%
- Type 1 error: 17% one-sided
- Power: >80%

Because no available anti-leukemia therapies (other than allogeneic transplant) are believed to be associated with the eradication of evidence of MRD in this high-risk AML setting, the study

would be considered positive if ≥2 of 15 patients in 1st remission (CR) are converted from MRD-positive to MRD-negative status. (In a situation where 1 of 15 patients has eradication of MRD, the results may be considered of interest, given the dearth of efficacious therapy in this setting).

11.3 Demographics and Baseline Characteristics

Demographic (e.g., gender, age, and race) and baseline characteristics (e.g., ECOG PS, height, weight, and prior therapy) will be summarized by SL-401 dose group with descriptive statistics.

11.4 Analyses of Safety Data

Safety assessments include DLTs, AEs, SAEs, physical examinations, vital sign measurements, ECGs, clinical laboratory evaluations, and reasons for treatment discontinuation due to toxicity.

Treatment-emergent AEs through 30 days after last SL-401 infusion will be summarized by Medical Dictionary for Regulatory Activities (MedDRA™), Version 13.1 (or higher), system organ class and preferred term. The incidences and percentages of patients experiencing each AE preferred term will be summarized with descriptive statistics. AEs will also be summarized by NCI-CTCAE, Version 4.03 (or higher), grade and by causality (relationship to study drug). Dose-limiting toxicities, Grade 3-4 AEs, SAEs, and AEs resulting in dose modification or treatment discontinuation will also be summarized by preferred term.

Laboratory results will be classified according to NCI-CTCAE, Version 4.03. Laboratory results not corresponding to an NCI-CTCAE term will not be graded. Incidences of laboratory abnormalities will be summarized with descriptive statistics.

Vital signs, physical examination results, and ECGs will be summarized with descriptive statistics.

11.5 Analyses of Efficacy Data

Efficacy assessments include rates of MRD eradication (conversion), relapse (progression)-free survival (PFS), and OS. Response/remission will be assessed using International Working Group (IWG) criteria for AML (Cheson et al. 2003). Response criteria for AML are summarized in Section 15.1. All efficacy outcomes will be presented by subgroups defined by disease and line of therapy in study (1st line, 2nd line, etc.).

11.5.1 Eradication (Conversion) of MRD

The rate of MRD eradication (conversion) is defined as the proportion of patients with evidence of MRD prior to initial therapy with investigational SL-401 for whom MRD cannot be detected upon subsequent (post treatment) assessments. This will be evaluated both as rates of MRD eradication at a single assessment (with subsequent evidence of MRD) and rates of MRD eradication at multiple (2 or more consecutive) time points following initiation of investigational SL-401. Exact 1-sided 95% confidence intervals will be calculated for the rates of MRD eradiation (conversion).

11.5.2 Relapse (progression) – free Survival (RFS/PFS)

Relapse-free survival is defined as the proportion of patients who remain free of AML recurrence (hematologic) and alive. According to current WHO classification, a myeloblast population comprising greater than 5% of nucleated cells in the bone marrow or blood is required for diagnosis of AML relapse following CR/CRi (if no peripheral blasts are present, then a confirmation aspirate is required ≥1 week subsequent to the aspirate at which >5% blasts were identified). RFS will be evaluated via Kaplan-Meier analysis (in which patients who are lost to follow-up or who are not evaluable for recurrence have data censored), and via direct proportional analysis (percentage of patients receiving treatment [or treatment at MTD or otherwise derived Stage 2 dose] who are alive and without evidence of AML recurrence). Median, 6- and 12-month RFS rates will be evaluated.

11.5.3 Overall Survival

OS is defined as the time from the date of first infusion of SL-401 to the date of death from any cause. The distribution for OS will be estimated by Kaplan-Meier methodology.

11.6 Pharmacokinetic and immunogenicity Analyses

Planned PK and immunogenicity analyses will be described in separate analysis plans.

11.7 Blinding

This is an open-label study.

12 Emergency Procedures

12.1 Emergency Contact

In emergencies, the Investigator should contact the Medical Monitor by telephone at the number listed on the title page of the protocol.

12.2 Emergency Identification of Investigational Products

Since this is an open-label study, the investigational treatment and patient number will be identified on the package labeling.

12.3 Emergency Treatment

During a patient's participation in the study, the Investigator and/or institution should ensure that adequate medical care is provided to a patient for any AEs, including clinically significant laboratory values, related to the study.

13 Ethical and Regulatory Considerations

13.1 Good Clinical Practice

As the Sponsor of this clinical study, Stemline has the overall responsibility for the conduct of the study, including assurance that the study meets the requirements of applicable regulatory authorities. Stemline will maintain compliance with the FDA Code of Federal Regulations

(CFR), ICH Guideline E6, Declaration of Helsinki, and GCP Guidelines. The study must receive approval from an Institutional Review Board (IRB) or Independent Ethics Committee (IEC) prior to commencement. The Investigator will conduct all aspects of this study in accordance with applicable national, state, and local laws of the pertinent regulatory authorities.

The Sponsor is responsible for obtaining IRB approvals, providing Investigators with information required to conduct the study, ensuring proper investigative site monitoring, verifying that appropriate patient informed consent is obtained, submitting an IND application to FDA, and ensuring that the IRB and regulatory agencies are promptly informed of significant new information regarding the study.

13.2 Delegation of Investigator Responsibilities

The Investigator must ensure that all persons assisting with the study are adequately informed about the protocol, any amendments to the protocol, the study drugs, and their study-related duties and functions. The Investigator should maintain a list of sub-investigators and other appropriately qualified persons to whom he or she has delegated significant study-related duties.

13.3 Patient Information and Informed Consent

Before being admitted to the clinical study, the patient must consent to participate after the nature, scope, and possible consequences of the clinical study have been explained in a language understandable to him or her. An ICF that includes both information about the study and the consent form will be prepared and given to the patient. This document will contain all ICH, GCP, and locally required regulatory elements. The ICF must specify who informed the patient and be approved by the Institution's IRB. Copies of the ICF used in the study must contain the IRB-approval stamp (if applicable) and version date. The Investigator must keep the original executed ICF including the patients' signatures and the signing dates properly stored in a secured location at the study site with an additional copy of the ICF attached to the patients' eCRFs and therapy records.

After reading the ICF, the patient must give consent in writing. The written informed consent will be obtained prior to conducting any study-related procedures or tests. The patient's consent must be confirmed at the time of consent by the dated signature of the person conducting the informed consent discussions. If the patient agrees to participate in the study, the patient and the Investigator must sign both copies of the ICF. A copy of the signed ICF must be given to the patient or the patient's legally authorized representative. The signed ICF must be available for verification by the Sponsor's designated monitors or FDA inspectors.

The date of the signed ICF will also be noted in the patient's medical chart. Patients should be informed of new information learned during the study, which may affect their decision to continue participation in the study. The Investigator should inform the patient's primary physician about the patient's participation in the study if the patient has a primary physician and if the patient agrees to the primary physician being informed.

13.4 Confidentiality

The Investigator(s) and the Sponsor or its authorized representative will preserve the confidentiality of all patients and donors participating in the study, in accordance with GCP, local regulations and to the extent applicable the Health Insurance Portability and Accountability Act of 1996 (HIPAA).

Patient names will not be supplied to the Sponsor or its authorized representative. Only the patient study numbers and (if permitted by the institution) patient initials will be recorded in the eCRF, and if the patient name appears on any other document (e.g., pathologist report), it must be obliterated before a copy of the document is supplied to the Sponsor or its authorized representative. Study findings stored on a computer will be stored in accordance with local data protection laws. Patients will be told that representatives of the Sponsor, its authorized representative, IRB or IEC, or regulatory authorities may inspect their medical records to verify the information collected, and that all personal information made available for inspection will be handled in strictest confidence and in accordance with local data protection law. The Investigator will maintain a personal patient identification list (patient numbers with the corresponding patient names) to enable records to be identified.

13.5 Protocol Amendments

Any changes that affect patient safety or welfare will be submitted to the IRB/IEC and Regulatory Authority (where applicable) for approval prior to implementation. The Investigator and the Sponsor must approve all amendments. No amendment will be implemented until approved and signed by all parties. Exceptions to this are when the Investigator considers that the patient's safety is compromised.

Once the study has started, amendments should be made only in exceptional cases. The changes then become part of the study protocol.

13.6 IRB/IEC Approval and Reporting

The Investigator must obtain appropriate IRB approval prior to study initiation. A copy of the written approval from the IRB and a copy of the approved ICF should be sent to the Sponsor or its delegate. It is also necessary to submit a list of the IRB members (including their Institutional affiliations, gender makeup, and occupations) or supply a statement from the IRB specifying that the membership complies with applicable regulations.

The study protocol, patient information and consent form, the IB, available safety information, patient recruitment procedures (e.g., advertisements), information about payments and compensation available to the patients and documentation evidencing the Investigator's qualifications should be submitted to the IRB/IEC for ethical review and approval according to local regulations, prior to the study start. The written approval should identify all documents reviewed by name and version.

Any changes to the protocol must be approved by the Sponsor in writing unless the change is proposed to assure safety of the patient. In the non-emergent setting, following agreement on the proposed changes, an amendment to the protocol will be submitted by the Sponsor to the IRB for approval prior to implementation of the change. Any change made emergently must be documented in the patient's medical record.

If required by legislation or the IRB/IEC, the Investigator must submit to the IRB/IEC:

- Information on serious or unexpected AEs as soon as possible;
- Periodic reports on the progress of the study.

13.7 Closure of the Study

The Sponsor, its authorized representative, or the Investigator has the right to close this study at any time. The IRB/IEC must be informed, if required by legislation. Should the study be closed prematurely, all unused SL-401 will be reconciled with dispensing records, documented, and, if directed by the Sponsor, destroyed at the study site after completion of accountability by the site monitor.

13.8 Record Retention

The Sponsor will maintain copies of correspondences, records of shipment and disposition of study drug, adverse effects, and other records related to the clinical study and the signed Investigator agreements. Retained records will enable the tracing of patients who have participated in the study. Notes of patients who have enrolled in the study must be retained if the patient has died.

Study documents must be retained by the Investigator for a minimum of 2 years after the last approval of a marketing application in an ICH region and until there are no pending or contemplated marketing applications in an ICH region or at least 2 years have elapsed since the formal discontinuation of clinical development of the investigational product. These documents should be retained for a longer period, however, if required by the applicable regulatory requirements or by an agreement with the Sponsor. It is the responsibility of the Sponsor to inform the Investigator when storage of these documents is no longer required. The Investigator should contact the Sponsor if the site’s archiving arrangements change at any time.

13.9 Liability and Insurance

Liability and insurance provisions for this study are provided in the Investigator’s contract.

13.10 Financial Disclosure

Prior to study initiation the Investigator will be asked to sign a clinical trial agreement. All Investigators will be required to sign a Financial Disclosure Form in accordance with 21 CFR Part 54, Financial Disclosure by Clinical Investigators.

13.11 Study Monitoring and Auditing

All aspects of the study will be carefully monitored by the Sponsor or its designee for compliance to applicable government regulations with respect to current good clinical practice and current standard operating procedures. Monitoring functions will be performed in compliance with 21CFR§812.43(d) and 21CFR§812.46. Direct access to the on-site study documentation and medical records must be ensured.

13.11.1 Study Monitoring and Source Data Verification

The Investigator is responsible for the validity of all data collected at the site and must accept the various monitoring procedures employed by the Sponsor. The purpose of monitoring is to verify the rights and well-being of human patients are protected; that study data are accurate, complete, and verifiable with source data; and that the study is conducted in compliance with the protocol, GCP and the applicable regulatory requirements.

Sites will be monitored to identify and reconcile any differences between the completed eCRFs and medical records, and review source documents for accuracy, completeness, and legibility. The monitor will review completed data forms and study documentation for accuracy, completeness, and protocol compliance. In addition, the Sponsor will evaluate any protocol deviations and take corrective action as necessary.

The Sponsor will review significant new information, including unanticipated AEs and ensure that such information is provided to all reviewing IRBs. This information will also be provided to the FDA, other regulatory authorities, and Investigators worldwide in accordance with local regulations. The monitor's responsibilities include site visits, participation in initial study sessions, review of eCRFs, source documents and results, and ensuring clear communication between Investigators and the Sponsor.

The monitor will query any missing or spurious data with the Investigator, which should be resolved in a timely manner. A monitoring log will be maintained recording each visit, the reason for the visit, the monitor's signature, and Investigator's or designee's confirmation signature.

13.11.2 Study Documentation

The Investigator must provide the Sponsor with the following documents prior to enrollment and maintain the currency of these documents throughout the course of the study.

- Completed and signed FDA Form 1572.
- All applicable country-specific regulatory forms.
- Current signed and dated curricula vitae for the Investigator, sub-investigators, and other individuals having significant investigator responsibility who are listed on the FDA Form 1572 or equivalent, or the clinical study information form.

- Copy of the current medical license of the principal Investigator, any sub-investigators and any other individuals having significant responsibility as listed on FDA Form 1572.
- A financial disclosure form for the Principal Investigator and any other persons listed on FDA Form 1572.
- Copy of the IRB/IEC approval letter for the protocol and informed consent. All advertising, recruitment, and other written information provided to the patient must be approved by the IRB/IEC. Written assurance of continuing approval (at least annually) as well as a copy of the annual progress report submitted to the IRB/IEC must also be provided to the Sponsor.
- Copy of the IRB/IEC-approved informed consent document.
- A list of the IRB/IEC members or a Federalwide Assurance number.
- Copy of the protocol sign-off page signed by the Investigator.
- Fully executed Clinical Trial Agreement, including budget.
- A written document containing the name, location, certification number, and date of certification of each laboratory to be used for laboratory assays and those of other facilities conducting tests. This document should be returned along with the laboratory director's curricula vitae and active medical license. List of normal laboratory values and units of measure for all laboratory tests required by the protocol.

The sites will also be asked to maintain a Delegation of Authority Log, pharmacy logs, temperature logs, personal patient identification log, and monitoring visit logs during this study.

13.11.3 Site Audits

For the purpose of compliance with GCP and regulatory agency guidelines, it may be necessary for Sponsor authorized Quality Assurance personnel and/or authorized personnel from an external regulatory agency to conduct an audit/inspection of an Investigational site. These site reviews may be planned or spontaneous and occur at any stage during the study. The purpose of an audit is to assess the quality of data with regard to accuracy, adequacy, and consistency, and to assure that studies are in accordance with GCP, protocol, and Regulatory Agency guidelines.

The Investigator should promptly notify the Sponsor or its authorized representative of any audits by any regulatory authorities and promptly forward copies of any audit reports received to the Sponsor or its authorized representative.

Electronic data systems will be in accordance with applicable aspects of 21 CFR Part 11, ICH Guidelines, GCP, and HIPAA.

13.12 Documentation and Use of Study Findings

13.12.1 Documentation of Study Findings

Source documentation will be maintained to document the treatment and study course of a patient and to substantiate the integrity of the study data submitted for review to regulatory agencies. Source documentation for Stemline-sponsored studies will include, but not be limited to, worksheets, hospital and/or clinic or office records documenting patient visits including study and other treatments or procedures, medical history and physical examination information, laboratory and special assessments results, drug accountability records, and medical consultations (as applicable).

Laboratory and diagnostic reports including but not limited to: local laboratory hematology and chemistry results, bone marrow biopsy reports, bone marrow aspirate reports, ECHO readings, and MUGA readings may be collected by the study monitor during the course of the study. Every effort should be made by the site to de-identify personal patient information from these reports and replaces with the patient's study identification number.

13.12.2 Use of Study Findings

All information concerning the product, as well as any matter concerning the operation of the Sponsor, such as clinical indications for the drug, its formula, methods of manufacture, and other scientific data relating to it, that have been provided by the Sponsor and are unpublished, are confidential and must remain the sole property of the Sponsor. The Investigator will agree to use the information only for the purposes of carrying out this study and for no other purpose unless prior written permission from the Sponsor is obtained. The Sponsor has full ownership of the eCRFs completed as part of the study.

All publications and presentations of the results of the Study are governed by the applicable provisions of the Clinical Trial Agreement between the Sponsor and the institution. By signing the study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the Sponsor. If necessary, the authorities will be notified of the Investigator's name, address, qualifications, and extent of involvement. The Investigator may not publish or present any information on this study without the express written approval of the Sponsor. Additionally, the Sponsor may, for any reason, withhold approval for publication or presentation. If the Investigator is to be an author of a publication manuscript prepared by the Sponsor, the Sponsor will allow the Investigator 30 days for full review of the manuscript before publication. Such manuscript or materials should be provided for Sponsor review only after the final database is available.

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15 Appendices

15.1 Appendix A. Tumor Response Criteria for Patients with AML

Note: Because all patients in the current study will have CR/CRi upon study entry, these response criteria are to be used primarily for identification of relapse and/or progressive disease.

Response	Location	Criteria
Complete Remission (CR)	Marrow	• Normalization of blast percentage (≤5%) • No detectable Auer rods
	Peripheral Blood	• Normalization neutrophil count (≥1,000/μL) and platelet count (≥100,000/μL) • Absence of leukemic blasts
	Extramedullary	• No extramedullary disease (CNS or soft tissue)
CR with incomplete blood count recovery (CRi)	Marrow	• Normalization of blast percentage (≤5%)
	Peripheral Blood	• Incomplete recovery of neutrophil and/or platelet count • Absence of leukemic blasts
	Extramedullary	• No extramedullary disease (CNS or soft tissue)
Partial Remission (PR)	Marrow	• Decrease by ≥50% in blast percentage to 5 - 25% or to ≤5% with Auer rods present
	Peripheral Blood	• Normalization neutrophil count (≥1,000/μL) and platelet count (≥100,000/μL)
Stable Disease (SD)		• Failure to achieve at least a PR, but no evidence of progression for at least 8 weeks
Relapse after CR/CRi	Marrow	• Blast percentage > 5% (if no peripheral blasts, then confirmation aspirate required ≥1 week later)
Relapse after PR	Marrow	• Blast percentage ≥25% (if no peripheral blasts, then confirmation aspirate required ≥1 week later)
Progressive Disease (PD)	Marrow	≥50% increase in blasts from baseline
	Peripheral Blood	One or more of the following: ≥50% decrease from peak remission levels in platelets or granulocytes; Reduction in hemoglobin concentration by at least 2 g/dL; Transfusion dependence

15.2 Appendix B. ECOG Performance Status

Grade	Description
0	ABLE TO CARRY OUT ALL NORMAL ACTIVITIES WITHOUT RESTRICTION.
1	RESTRICTED IN PHYSICALLY STRENUOUS ACTIVITY BUT AMBULATORY AND ABLE TO CARRY OUT WORK OF A LIGHT OR SEDENTARY NATURE.
2	AMBULATORY AND CAPABLE OF ALL SELF-CARE BUT UNABLE TO CARRY OUT ANY WORK ACTIVITIES: UP AND ABOUT MORE THAN 50% OF WAKING HOURS.
3	CAPABLE OF LIMITED SELF-CARE; CONFINED TO BED OR CHAIR MORE THAN 50% OF WAKING HOURS.
4	COMPLETELY DISABLED; CANNOT CARRY ON SELF-CARE; TOTALLY CONFINED TO BED OR CHAIR.

15.3 Appendix C. Additional Definitions of Adverse Risk AML

As detailed in protocol inclusion criteria #4, patients are eligible if they have adverse-risk disease including adverse karyotype. Adverse karyotype, as determined by cytogenetic evaluation, includes the following:

inv(3)(q21q26)/ t(3;3)(q21;q26)
t(3;21)(q26.2;q22.1)*
t(1;3)(p36.3;q21.1)
t(3;5)(q25;q34)*
-5*/ del(5q)*/ add(5q)
-7*/ del(7q)*/ add(7q)
t(11q23)
    including: t(11;16)(q23;p13.3)*/ t(2,11)(p21;q23)*
t(8;16)(p11;13)
t(6;9)(p23;q34)
abnormal 17p (translocation or del*)
    including: i(17q)*
-17
complex karyotype [≥3 unrelated abnormalities]*

** indicates that a karyotype may also be considered an MDS-related abnormality.*

In the event that a karyotype (not listed above) is identified which the Investigator believes is associated with a high risk of AML relapse and no other criteria are present (i.e., antecedent hematologic disorder, presence of MRD), consideration for inclusion may be discussed with the Medical Monitor and documentation of the relapse risk included in the patient's study/medical record.

Other AML-related mutations and fusion genes/re-arrangements that are considered adverse-risk, with or without a concomitant karyotypic abnormality, include the following:

Mutations:

FLT3-ITD [internal tandem duplication]
MLL including MLL-PTD [partial tandem duplication]
TP53

Fusion genes:

MLL re-arrangements including MLL-CBP
RUNX1-RPL22L1, RUNX1-MDS1-EVI1.

15.4 Appendix D. Minimal Residual Disease (MRD) Definitions

MRD in the bone marrow of patients with AML in remission may be detected by one or more of the following laboratory methodologies:

1. Multi-parametric flow cytometry for detection of LAIPs. LAIPs include asynchronous expression of antigens (i.e., aberrant expression of antigens across maturation stages, such as coexpression of early and late antigens), cross-lineage expression of lymphoid markers, and overexpression or absence of lineage-appropriate markers. (Several populations with different LAIPs may be identified within a single patient/case).
2. Cytogenetic or FISH assessment for chromosomal translocations and deletions (partial or entire), including those detailed in the prior section/appendix as defining high-risk AML, and chromosomal abnormalities associated with favorable or intermediate-risk AML that persist following induction therapy and hematologic CR/CRi. These intermediate/favorable-risk abnormalities include:

   t(9,11)(p21;q23)
   -Y
   +8 (trisomy 8)
   t(8,21)(q22;q22)
   inv(16)(p13.1q22)/ t(16;16;)(p13.1;q22).

   (Although the core binding factor leukemias [CBF-AML, involving the t(8,21) and inv(16) abnormalities] have historically been associated with relatively good prognosis, relatively recent data suggest that patients with CBF-AML and concomitant FLT-ITD mutations and/or evidence of MRD following induction therapy may be at significant risk for relapse, with post-CR relapse risk approaching or exceeding 50%).
3. Real-time PCR based assessment of gene mutations including those detailed in the prior section/appendix as defining high-risk AML, and mutations associated with favorable/intermediate-risk AML that persist following induction therapy and hematologic CR/CRi. These favorable/intermediate-risk abnormalities include: RUNX1T1-RUNX1, CBFB-MYH11, MLLT3-MLL, RBM15-MKL1, MLL-ELL, MLL-MLLT1.
4. Next generation sequencing for the persistence of somatic mutations in the coding sequence of AML-associated genes, including the MDACC-based 28-gene AML panel (which includes gene mutations considered definitive of high-risk AML, and other AML associated mutations including: IDH1, IDH2, DNMT3A, ASXL1, TET2, N-RAS, K-RAS and others) and the Dana Farber Cancer Institute 95-gene sequencing panel.

15.5 Appendix E. CLS Management Guidance

CLS Element	Time of Presentation	Recommended Action	SL-401 Dosing Management
Serum albumin <3.2 g/dL (without albumin supplementation)	Prior to 1st SL-401 administration	**Do not dose** (patient not eligible for participation)	
Serum albumin <3.5 g/dL **OR** reduced by ≥0.5 g/dL from pre-dose value (with or without albumin supplementation A **pre-dose body weight** that is increased by ≥1.5 kg over the previous day's pre-dose weight	During SL-401 dosing[1]	• For the CLS element of albumin decrease: ▪ Administer albumin 25 g IV (q12h or more frequently as practical) until serum albumin is both ≥3.5 g/dL and not reduced by ≥0.5 g/dL from pre-dose value • For the CLS element of body weight increase: ▪ Administer albumin 25 g IV (q12h or more frequently as practical), and manage fluids and blood pressure, as clinically indicated, until body weight increase has resolved (i.e. the increase is no longer greater than 1.5 kg from the previous day's pre-dose weight)	• Hold SL-401 dosing until the relevant CLS element has resolved as specified by Recommended action[2]
Edema, fluid overload and/or **hypotension**		• Administer albumin 25 g IV (q12h, or more frequently as practical) until serum albumin is ≥3.5 g/dL • Administer 1 mg/kg of methylprednisolone (or an equivalent) per day, until resolution of CLS element or as clinically indicated • Aggressive management of fluids status, which could include intravenous fluids and/or diuretics, until resolution of CLS element or as clinically indicated	

1. For patients eligible for treatment with SL-401 with serum albumin >3.2 g/dL but <3.5 g/dL on the day of dosing, IV albumin (25 g) is recommended prior to administration of SL-401 to increase the serum albumin to ≥3.5 g/dL before the 1st dose of SL-401.
2. SL-401 administration may resume in the same cycle if all CLS elements have resolved and the patient did not require measures to treat hemodynamic instability. SL-401 administration should be held for the remainder of the cycle if CLS elements have not resolved or the patient required measures to treat hemodynamic instability (even if resolved), and SL-401 administration may only resume in the next cycle if all CLS elements have resolved, and the patient is hemodynamically stable.