SL-401 in Patients with Acute Myeloid Leukemia or Blastic Plasmacytoid Dendritic Cell Neoplasm

Sponsor: Stemline Therapeutics, Inc.
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New York, NY 10022

Study Product: SL-401

Protocol Number: STML-401-0114

IND Number: [redacted]

Study Contacts:

[redacted]

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CONFIDENTIAL – PROPRIETARY INFORMATION

PROTOCOL APPROVAL SIGNATURE

Protocol Title: SL-401 in Patients with Acute Myeloid Leukemia or Blastic Plasmacytoid Dendritic Cell Neoplasm

Protocol Number: STML-401-0114

This study will be conducted in compliance with the clinical study protocol (and amendments), International Council for Harmonisation (ICH) guidelines for current Good Clinical Practice (GCP) and applicable regulatory requirements. Compliance with GCP standards provides public assurance that the rights, safety, and well-being of trial subjects are protected, consistent with the principles that have their origin in the Declaration of Helsinki.

INVESTIGATOR PROTOCOL AGREEMENT

SL-401 in Patients with Acute Myeloid Leukemia or Blastic Plasmacytoid Dendritic Cell Neoplasm

I hereby agree to:

- Conduct the study as outlined in this protocol with reference to national/local regulations and current International Council for Harmonisation / Good Clinical Practice 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: Amendment 12: 17 January, 2019

To be signed by Principal Investigator:

Print Name			
Signature		**Date**	
Institution			

[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)

SL-401 Injection frozen solution (1mg/mL) was approved by the Food and Drug Administration (FDA) on 21 December 2018 for the treatment of BPDCN in adults and in pediatric patients 2 years and older under the name ELZONRIS (tagraxofusp-erzs).

Name of Active Ingredient:

SL-401 (tagraxofusp-erzs)

Study Title:

SL-401 in Patients with Acute Myeloid Leukemia or Blastic Plasmacytoid Dendritic Cell Neoplasm

Protocol Number:

STML-401-0114

Study Phase:

1 / 2

Primary Objectives:

Stage 1 (completed):

- Determine the maximum tolerated dose (MTD), or the maximum tested dose where multiple dose-limiting toxicities (DLTs) are not observed, of SL-401.

Stage 2 (completed):

- Determine the efficacy of SL-401 in patients with blastic plasmacytoid dendritic cell neoplasm (BPDCN), as assessed by objective response rate (ORR).
- Characterize the safety profile of SL-401 at the MTD or maximum tested dose in both patients with acute myeloid leukemia (AML) and BPDCN.

Stage 3 (completed):

- Determine the complete response (CR) rate (i.e., CR + CR [clinical] with minimal residual skin abnormality [CRc]) in patients with first-line BPDCN.
- Characterize the safety profile of SL-401 in patients with first-line BPDCN.

Stage 4:

- Further characterize the efficacy of SL-401 in first-line and relapsed/refractory (R/R) patients with BPDCN following the completion of Stage 2 and Stage 3, respectively, as assessed by the rate of CR (CR + CR with incomplete blood count recovery [CRi] + CRc).
- Further characterize the safety profile of SL-401 among first-line and R/R patients with BPDCN.
- Characterize the efficacy and safety of a lyophilized formulation of SL-401 among R/R and first-line patients with BPDCN.

Secondary Objectives:

- Determine the CR rate (i.e., CR + CRi + CRc) for Stage 1 and Stage 2, and ORR for Stage 3 patients.
- Estimate duration of response (DOR), progression-free survival (PFS), and overall survival (OS) in patients with BPDCN.
- Enable preliminary characterization of the estimated ORR in patients with R/R AML, including in subsets of patients with R/R AML based on pre-treatment blast count, cytogenetics, or CD123 measurement.
- Estimate duration of response, PFS, and OS in patients with AML.
- Characterize the pharmacokinetics (PK) and 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 peripheral blood and 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 response rates).

Study Design:

This is a 4-stage, non-randomized, open-label, dose escalation and expansion, multicenter study. A cycle of therapy is 21 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.

Stage 1: Dose Escalation (completed)

During Stage 1, approximately 9-24 patients will be treated with SL-401 Injection at doses of 7, 9, 12, or 16 µg/kg/day for 5 consecutive days every 21 days. The 16 µg/kg/day dose will be evaluated only in patients with AML. Evaluation of higher doses (in increments of 25% or less) in AML patients may be attempted pending evaluation of the safety/tolerability of the 16 µg/kg/day dose level (these evaluations would be attempted to identify an MTD and will be guided by the criteria [stipulated below] defining safety/tolerability of all dose levels).

Cohorts of 3-6 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 Injection at the next higher dose. No intra-patient dose escalation is allowed. The first cohort of patients will receive SL-401 at a dose of 7 µg/kg/day. After all patients in this cohort complete the first cycle of therapy, the dose for the second cohort of patients will increase by 29% to 9 µg/kg/day, conditional on the DLT rules described below. Similarly, after all patients in the second cohort complete the first cycle of therapy, the dose for the third cohort of patients will increase by 33% to 12 µg/kg/day, conditional on the DLT rules described below. Finally, after all patients in the third cohort complete the first cycle of therapy, the dose for the fourth cohort of patients, consisting only of patients with AML, will increase by 33% to 16 µg/kg/day, conditional on the DLT rules described below.

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

- Any treatment-emergent Grade 4 transaminase or creatine phosphokinase (CPK) elevation, regardless of duration or relationship to SL-401.
- Any treatment-emergent Grade 4 hematologic toxicity (unrelated to persistent leukemia) lasting >21 days after the last infusion of SL-401.
- Any treatment-emergent Grade ≥3 non-hematologic toxicity (unrelated to persistent leukemia), with the exception of Grade 3 laboratory toxicities that resolve to Grade ≤1 or baseline ≤21 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, TPN or hospitalization) or diarrhea associated with suboptimal prophylaxis or treatment.

Beginning with the dose level 7 µg/kg/day of SL-401 Injection, 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 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 of 9 µg/kg/day. If one of the initial 3 patients treated (1/3) experiences a DLT, the cohort will be expanded to include up to an additional 3 patients treated at the same dose 7 µg/kg/day. If only one patient (1/6) from this expanded cohort experiences a DLT, then 3 new patients will be treated at the next higher dose 9 µg/kg/day. Expansion of the 9 µg/kg/day cohort to 6 patients, if necessary, will follow the same rules as the 7 µg/kg/day cohort. The same DLT rules will also apply to the 12 µg/kg/day and 16 µg/kg/day (AML specific) cohorts.

In the event that 2 (or more) patients within a cohort have a DLT, then the MTD will be exceeded and further dose escalation will not occur. The MTD is defined as the dose preceding the dose level at which two patients experience a DLT during treatment Cycle 1. The MTD will be used in Stages 2-4 of the study. 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 two patients treated at the 7 µg/kg/day dose level, 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 two or more patients experience a DLT at the 5 µg/kg/day dose level, the study will be halted.

Stage 1 is complete, with the MTD of SL-401 determined to be 12 µg/kg/day in R/R AML and a maximum tested dose of SL-401 of 12 µg/kg/day in BPDCN. (An MTD was not determined in BPDCN.)

Stages 2-4: Safety Expansion and Efficacy Assessment:

During Stages 2-4, patients will be treated at the MTD or maximum tested dose at which multiple DLTs are not observed during Stage 1, or a lower dose with potentially the most favorable risk/benefit profile.

SL-401 will be supplied as SL-401 Injection frozen solution (1 mg/mL) as described in Section 7.5. A lyophilized formulation (SL-401 for Injection, lyophilized powder, for solution; 1 mg/mL) also will be supplied. All patients enrolled in Stage 4 (both R/R and first-line) subsequent to completion of enrollment in Stage 3 will receive the lyophilized formulation of SL-401. Note that when the lyophilized formulation is introduced, patients who start treatment with SL-401 Injection frozen solution will continue to receive this dosage form throughout the study.

At the time of Protocol Amendment 11, only Stage 4 is open for enrollment.

Tumor Assessments During Stages 2-4

Patients with AML (Stage 2 only)

Assessment of the anti-tumor activity of SL-401 in patients with AML will be assessed by the Investigator as a secondary endpoint using the criteria in Section 16.1, Appendix A. The following

assessments will be performed at baseline within 14 days prior to the first administration of SL-401 and thereafter for determination of tumor response for patients with AML in Stage 2, as follows:

- **Bone marrow aspirates (± biopsy)** 21 (±7) days after the start of Cycles 1 and 2. Patients with evidence of bone marrow involvement prior to study treatment will also have bone marrow evaluations following Cycles 4 and 6 and then every 3 months from Months 6-12; every 6 months from 12 to 24 months; and every 12 months thereafter until there is evidence of relapsed or progressive disease. If the Cycle 1 (Day 21 [±7]) bone marrow examination is empty (i.e., hypocellular) or inadequate, a bone marrow examination should be repeated in 7 (±7) days to document response. If additional time is required to complete the repeat examination, consultation with the Medical Monitor is required. If CD123 flow cytometry or IHC stain assessment was performed on the bone marrow aspiration (± biopsy), the results should be recorded in the electronic case report form (eCRF).
- Collection of **peripheral blood samples** for determination of blasts 21 (±7) days after the start of Cycles 1 and 2. Patients with evidence of peripheral blasts at baseline will also have peripheral blood samples collected 21 (±7) days after the start of Cycles 1 and 2 and 21 (±7) days after the start of every 2nd cycle thereafter (Cycles 4, 6, etc.) until there is evidence of relapsed or progressive disease.

Patients with BPDCN (Stages 2-4)

Standardized assessment of potential sites of disease involvement (including skin, lymph nodes, blood, bone marrow, and visceral organs) and consistently-defined response criteria will be utilized.

The BPDCN diagnosis will be made or confirmed during screening by the pathology laboratories at the investigative sites. Subsequent to enrollment, pathology material will be submitted for review by the central pathologist for confirmation of the BPDCN diagnosis.

Tumor response will be assessed by the Investigators for all patients with BPDCN, with the Investigator's assessment to be used in the primary analysis. As a supportive assessment, tumor response will be assessed by an Independent Review Committee (IRC). Tumor response will be assessed using the Tumor Response Criteria for Patients with BPDCN presented in Section 16.2, Appendix B. All patients will also be followed for duration of response and survival. The following assessments will be performed at baseline within 14 days prior to the first administration of SL-401 and thereafter for determination of tumor response for patients with BPDCN:

- **Bone marrow aspirates (± biopsy)** samples 21 (±7) days after the start of Cycles 1 and 2. Patients with evidence of bone marrow involvement prior to study treatment will also have bone marrow evaluations following Cycles 4 and 6 and then every 3 months from Months 6-12; every 6 months from 12 to 24 months; and every 12 months thereafter until there is evidence of relapsed or progressive disease.
    - If the Cycle 1 (Day 21 [±7]) bone marrow examination is empty (i.e., hypocellular) or inadequate, a bone marrow examination should be repeated in 7 (±7) days to document response. If additional time is required to complete the repeat examination, consultation with the Medical Monitor is required. If CD123 flow cytometry or IHC stain assessment was performed on the bone marrow aspiration (± biopsy), the results should be recorded in the eCRF.

- **Skin assessments,** including photographs, for patients with skin involvement, and determination of skin disease burden using the Modified Severity Weighted Assessment Tool (mSWAT) (see Section 16.3, Appendix C) 21 (±7) days after the start of Cycles 1 and 2 and 21 (±7) days after the start of every 2nd cycle thereafter (Cycles 4, 6, etc.) until there is evidence of relapsed or progressive disease. Refer to the separate mSWAT Manual for instructions regarding the quantitation of malignant lesions via the mSWAT and response assessment in skin.
  - In situations in which there is substantial reduction of skin lesions (especially when accompanied by disappearance of BPDCN from bone marrow or other sites), a skin biopsy is required. The mSWAT guidance states: "A biopsy of normal appearing skin is unnecessary to assign a complete response. However a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist" (Olsen et al. 2011).
- **Computed tomography (CT) scans** of index lesions 21 (±7) days after the start of Cycles 2, 4 and 6 and 21 (±7) days after the start of every 4th cycle thereafter (for patients with baseline evidence of lymph node or visceral disease) until there is evidence of relapsed or progressive disease. For patients with no baseline evidence of lymph node or visceral BPDCN involvement, subsequent scans should be performed at the end of Cycle 2 (±7 days; or at time of disease progression (PD) if PD occurs prior to end of Cycle 2), 21 (±7) days after the start of Cycle 6, and at Investigator's discretion thereafter. Baseline CT scans should be full-body (chest/ abdomen/pelvis), whereas follow-up scans should document response of index lesions (Cheson et al. 2007).
- Collection of **peripheral blood samples** for determination of blasts 21 (±7) days after the start of Cycles 1 and 2. Patients with evidence of peripheral blasts at baseline will also have peripheral blood samples collected 21 (±7) days after the start of Cycles 1 and 2 and 21 (±7) days after the start of every 2nd cycle thereafter (Cycles 4, 6, etc.) until there is evidence of relapsed or progressive disease.

Study Centers:

This study will be conducted at up to 10 study centers.

Inclusion Criteria:

1. The patient has a diagnosis of AML (Protocol Stage 1 or 2) or BPDCN (Protocol Stages 1-4) according to World Health Organization (WHO) classification (AML; excluding acute promyelocytic leukemia [APL, FAB M3]) or confirmed by hematopathology (BPDCN) (Facchetti et al. 2008).
2. The patient must meet one of the following (a) or (b) or (c):
   (a) Has evidence of persistent or recurrent AML (Protocol Stages 1 or 2) in the peripheral blood and/or bone marrow that is refractory to, or has relapsed from, their most recent prior line of treatment.
   - A prior line of treatment is considered an induction regimen if it involves an approved or investigational cytotoxic chemotherapy agent, biological agent, and/or hypomethylating agent administered alone or in a combination regimen, with the intent to induce robust cytoreduction (i.e., CR).
   - The previous induction regimen may have been a stem cell transplant (SCT) with intent to induce a CR.

- Consolidation and/or maintenance (including SCT) may have been given in CR/CRi, but are not counted as a line of treatment.
- Hydroxyurea will not be considered a prior line of treatment.

(b) Has previously untreated AML (Protocol Stages 1 and 2) and is considered to be at high risk for disease progression and/or is unlikely to derive more than transient benefit from standard therapy by having at least one of the following:

- Treatment-related AML, except if it is associated with favorable cytogenetics (e.g., inversion 16, t[16;16], t[8;21], t[15;17]).
- AML with antecedent hematological disease (e.g., myelodysplastic syndrome [MDS], myelofibrosis, polycythemia vera) and not a candidate for SCT in their current disease state.

(c) Has histological and/or cytological evidence of BPDCN by pathologic assessment at the investigative site according to WHO classification (Facchetti et al. 2008) by a pathologist with expertise in hematologic malignancies, that can be measured for treatment response and is either:

- Previously untreated (i.e., first-line) (Protocol Stages 2-4).
- Persistent or recurrent in the peripheral blood, bone marrow, spleen, lymph nodes, skin, or other sites after previous treatment with at least 1 line of systemic therapy for BPDCN, e.g., stem cell transplant or chemotherapy (Protocol Stages 1, 2, and 4). A pathology specimen must be available for central pathology review for all BPDCN patients enrolled in Stages 2-4.

3. The patient is ≥18 years old.
4. The patient has an ECOG performance score (PS) of 0-2.
5. 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 (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 (133 µmol/L)
   - Serum albumin ≥3.2 g/dL (32 g/L) (please note that albumin infusions are not permitted in order to enable eligibility)
   - Bilirubin ≤1.5 mg/dL (26 µmol/L)
   - Aspartate transaminase (AST) and alanine transaminase (ALT) ≤2.5 times the upper limit of normal (ULN)
6. If the patient is a woman of child bearing potential (WOCBP), she has had a negative serum or urine pregnancy test within 1 week prior to treatment.
7. The patient has signed informed consent prior to initiation of any study-specific procedures or treatment.
8. The patient is able to adhere to the study visit schedule and other protocol requirements, including follow-up for survival assessment.
9. 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 APL (FAB M3).
2. The patient has persistent clinically significant toxicities Grade ≥2 from previous chemotherapy (excluding alopecia, nausea, fatigue, and liver function tests [as mandated in the inclusion criteria]).
3. The patient has received treatment with chemotherapy, wide-field radiation, or biologic therapy within 14 days of study entry.
4. The patient has received treatment with another investigational agent within 14 days of study entry.
5. The patient has previously received treatment with SL-401.
6. The patient has an active malignancy and/or cancer history (excluding AML, BPDCN, or antecedent 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, cervical intraepithelial neoplasia, organ-confined prostate cancer with no evidence of progressive disease.
7. The patient has clinically significant cardiovascular disease (e.g., uncontrolled or any New York Heart Association 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).
8. 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.
9. 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.
10. The patient is receiving immunosuppressive therapy – with the exception of low-dose prednisone (≤10 mg/day) – for treatment or prophylaxis of graft-versus-host disease (GVHD). If the patient has been on immunosuppressive treatment or prophylaxis for GVHD, the treatment(s) must have been discontinued at least 14 days prior to study treatment and there must be no evidence of Grade ≥2 GVHD.
11. 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.
12. The patient is pregnant or breast feeding.
13. The patient has known positive status for human immunodeficiency virus or active or chronic Hepatitis B or Hepatitis C.
14. The patient is oxygen-dependent.
15. The patient has any medical condition which in the opinion of the Investigator places the patient at an unacceptably high risk for toxicities.
16. The patient has AML and requires more than 1g per day of hydroxyurea. (Hydroxyurea is permitted at doses of 1g per day or less).

Investigational Product, Dose, and Mode of Administration:

SL-401 is a novel protein comprised of recombinant human interleukin-3 (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/or tumor bulk of a variety of leukemias and hematopoietic malignancies, including BPDCN and AML, relative to normal hematopoietic stem cells and other hematopoietic cells.

A cycle of therapy is 21 days. SL-401 Injection is provided as an intravenous (IV) injectable and administered as a 15-minute IV infusion for the first 5 consecutive days of a 21-day cycle; refer to the Pharmacy Manual for details regarding SL-401 preparation and administration. 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 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.

Patients who benefit from treatment and do not have evidence of clinically significant progressive disease may receive repeated cycles of SL-401 even if a response, in the judgment of the Investigator, is not attained. Patients should continue to receive SL-401 as long as they may be benefiting from treatment, according to the Investigator; no maximum duration of therapy has been set.

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

- Acetaminophen 650 mg (or equivalent dose of paracetamol) orally (PO)
- Diphenhydramine 50 mg IV (or equivalent dose of another H1-histamine antagonist)
- 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.

During the first cycle, patients will receive a starting dose according to their dosing cohort in Stage 1, or the dose carried into Stages 2-4. Potential dose modifications for subsequent cycles relative to the prior cycle dose will be based on the severity and resolution of toxicities. Dose reductions should be discussed with the medical monitor on a case by case basis.

Procedures During Dosing Period:

During each cycle, testing 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 in Table 5, Table 6, Table 7, and Table 8 in Section 9.8.

Withhold SL-401 infusion if any of the following occur:

- Body temperature ≥38°C
- Heart rate ≥130 or ≤40 bpm
- Systolic blood pressure (BP) ≥160 or ≤80 mmHg
- Serum creatinine >1.8 mg/dL (159 µmol/L)
- Serum albumin
    - 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.
- AST >5 times the ULN or ALT >5 times the ULN (SL-401 will be withheld for remainder of study cycle)
- Increase in body weight by ≥1.5 kg over pre-treatment weight on the prior treatment day.

Refer to Section 7.5.5 for dose modifications/delays. Management procedures for capillary leak syndrome (CLS) and associated symptoms are provided in Section 16.5, Appendix E.

Concomitant Medications:

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

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.

Prohibited Medications/Therapies:

An enrolled patient may not receive investigational or approved anticancer or anti-leukemia agents, including cytotoxic chemotherapy agents, hypomethylating agents (5-azacytadine, decitabine or others), or anticancer tyrosine kinase inhibitors (including imatinib, ruxolitinib, sorafenib and others) or therapeutic monoclonal antibodies. Hydroxyurea may be administered (however its use should be discussed with the Medical Monitor).

Assessments:

Assessments for safety, efficacy, and biological effects will be performed according to the schedules outlined in Table 5, Table 6, Table 7, and Table 8 in Section 9.8.

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:

For BPDCN patients, a global assessment paradigm is to be followed for determination of baseline disease and subsequent response evaluations, with all potential disease sites assessed during Screening, including the bone marrow (via aspirate and/or biopsy when an aspirate is not available), blood (via clinical laboratory testing for blasts and hematologic parameters), skin (via visual examination with determination of skin disease burden using mSWAT), lymph nodes, liver, spleen, and other viscera (via CT), and lymph nodes, liver, spleen, and other viscera (via physical examination). Positive sites of disease identified during screening MUST be followed during the study in every response evaluation. (Disease in organs that were disease-positive at screening are to be assessed, documented and recorded in the clinical database, even if the disease disappeared in subsequent response evaluations.) Sites with no evidence of disease during Screening must be documented as such and an assessment that baseline disease is not present are to be adequately documented in source and recorded in the clinical database; thereafter, these sites need not be followed, unless there is evidence of PD.

Efficacy endpoints include ORR, CR rate, duration of response, PFS, and OS. Stem cell transplantation rate following SL-401 therapy and subsequent disease assessments will also be evaluated. Among patients with BPDCN in Stages 2-4, patients with a central pathologist-confirmed diagnosis of BPDCN who received at least one SL-401 infusion will be considered evaluable for the primary analysis of efficacy.

See **Study Design** for a description of efficacy assessments for patients with AML.

Pharmacokinetic (PK) 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. 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. The nominal blood sampling time schedule is summarized in Table 9.

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 9 in Section 9.8. All ECGs will be analyzed by a central facility.

Statistical Methods:

Analysis Populations:

Safety analysis will be performed on the population of patients who have received any amount of study treatment. The primary population for the analysis of efficacy will be the modified intent-to-treat (mITT) population, consisting of those patients who have received at least one dose of study drug. For BPDCN patients, an additional criterion for mITT patients will be a confirmed diagnosis based on central pathology review. BPDCN patients in the mITT population will be said to be evaluable. Additional efficacy analyses will be performed on a per-protocol (PP) population, consisting of those patients who are in the mITT population, are compliant with all major aspects of the protocol, and have received a minimum of 2 cycles of study treatment.

Sample Size:

The sample size was originally planned to be approximately 40-50 patients with BPDCN, including approximately 40 first-line patients planned to be treated with the optimal SL-401 dose as determined in the completed Stage 1 of this study (12 µg/kg/day). In addition, up to approximately 36 patients with relapsed/refractory AML were planned to be enrolled in Stage 2 of the study.

After the maximum number of patients with first-line BPDCN in Stage 3 were enrolled, subsequent first-line BPDCN patients that meet eligibility criteria will be enrolled in Stage 4. Furthermore, any patient with R/R BPDCN enrolled in this study on or after 26 October, 2016, will be allocated to Stage 4. Enrollment will continue in Stage 4 to ensure continued access to SL-401 for BPDCN patients in a clinical trial setting; up to approximately 145 patients (including ~95 BPDCN patients) may be enrolled.

Analysis Conventions:

Analyses will be performed on all patients who received any quantity of SL-401 (i.e., all treated patients).

Summaries will be grouped by disease (BPDCN and AML). For data from BPDCN patients, further categories for summarization will consist of line of therapy (first-line, R/R, and total) and dose (12 µg/kg/day and all doses). Efficacy endpoints will be summarized separately for Stage 3 patients, with an additional summary for all first-line and R/R BPDCN patients across all stages.

Continuous (non-survival related) data will be summarized using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Time to event data will be summarized using frequency and percentage of events and censored observations. Kaplan-Meier analysis will be performed to estimate the 25th percentile, median, and 75th percentile for time to events with corresponding two-sided 95% confidence intervals.

Unless otherwise stated, confidence intervals, when presented, will be constructed at the 2-sided 95% level. For binomial variables, 95% confidence intervals will be constructed using the Clopper Exact method instead of normal approximation.

Data listings will present all data collected on eCRFs by study drug dose, center, Stage of study enrollment, and patient number.

Safety:

Safety data analysis will be performed primarily on the pool of first-line BPDCN patients treated with the 12 µg/kg/day dose level, with additional summaries for patients with R/R BPDCN and across the pool of all BPDCN patients. Separate safety tabulations will be produced for patients with AML, patients who are treated with the lyophilized formulation of SL-401, and an overall pool of all enrolled patients.

Treatment-emergent AEs through 30 days after last SL-401 infusion will be summarized by 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 treatment). Dose-limiting toxicities, Grade ≥3 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:

Efficacy assessments include CR rate (i.e., CR + CRi + CRc), DOR, ORR, PFS, and OS. Efficacy analyses will focus on patients with first-line BPDCN, treated at the 12 µg/kg/day dose level. The analysis of efficacy of SL-401 in these patients will be performed to address several objectives, based on data from the different stages of the study. Descriptive statistical analysis will be performed for patients with R/R disease and for AML patients, with the extent of efficacy data used for these analyses dependent on data maturity and need for regulatory submission.

Analyses by stage are intended as follows. Stage 3 will provide the pivotal results for a potential registrational submission in first-line BPDCN patients as assessed by rate of CR+CRc. Stage 1 and 2 results will be presented, similar to the interim analysis as noted in Section 12.10. Stage 4 results will be presented separately and may be used to further assess consistency across drug formulations, dependent on the extent of available data.

The primary evidence of efficacy will be derived from an analysis of the rate of CR+CRc, as assessed by the Investigator, in patients in Stage 3, accompanied by an evaluation of the durability of these CRs as a key secondary endpoint. A formal statistical analysis will first be performed for the primary efficacy endpoint to test the hypothesis that the rate of CR+CRc in first-line patients in Stage 3 exceeds the lower benchmark value of 10%. The primary analysis will be performed when all patients in Stage 3 have been followed for a minimum of 6 months or discontinued treatment, whichever occurs first. In addition, the durability of CR will be evaluated; refer to Section 12.6.3 for analysis methods for duration.

A number of additional secondary analyses will then be performed, to further evaluate the rate of CR in other stages of the study and to assess additional efficacy parameters in support of the primary analysis results. The analyses of all secondary endpoints will be descriptive, with summaries of secondary endpoints to be evaluated and presented in the following order of importance (as noted above, these

analyses will be performed on data from first-line BPDCN patients treated at the 12 µg/kg/day dose level):

1. Bone-marrow CR (BMCR) and DOR for Stage 3
2. CR rate and DOR for Stages 1 and 2
3. CR rate and DOR for pooled data from Stages 1, 2, 3, and 4
4. ORR and DOR for Stages 1 and 2
5. ORR and DOR for pooled data from Stages 1, 2, 3, and 4
6. Proportion of patients who receive SCT based on pooled data from Stages 1, 2, 3 and 4
7. PFS for Stages 1, 2, 3, and 4
8. OS for Stages 1, 2, 3, and 4

Study Oversight: Monitoring and Review Committees:

The conduct and evaluation of the study will include a DSRC, IRC, and a central pathologist. A charter detailing the operations of each group will be written.

Stage 1 (completed):

During Stage 1 and the initial portions of Stage 2, decisions regarding DLT determination, dose escalation and cohort progression will be made by a DSRC whose membership includes Sponsor representatives and study Investigators.

Stages 2-4 (enrollment completed in Stages 2 and 3):

In Stages 2-4 of the study, the DSRC will conduct a safety data review on an every 1-2-month basis. Periodic safety reviews will be conducted by the Sponsor.

A central pathologist will confirm histopathological BPDCN diagnosis. Tumor response will be assessed by the Investigators for all patients with BPDCN, with the Investigator's assessment to be used in the primary analysis. As a supportive assessment, tumor response was also evaluated by an IRC on a pre-specified subset of patients.

2 Abbreviations and Definitions

AE	Adverse Event
ALL	Acute Lymphoid Leukemia
ALP	Alkaline Phosphatase
ALT	Alanine Transaminase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
APL	Acute Promyelocytic Leukemia
Ara-C	Cytosine Arabinoside
AST	Aspartate Transaminase
BM	Bone Marrow
BMA	Bone Marrow Aspiration
BMCR	Bone Marrow Complete Response
BP	Blood Pressure
BPDCN	Blastic Plasmacytoid Dendritic Cell Neoplasm
BSA	Body Surface Area
BTD	Breakthrough Therapy Designation
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CLS	Capillary Leak Syndrome
CML	Chronic Myeloid Leukemia
CNS	Central Nervous System
CPK	Creatine Phosphokinase
CR	Complete Response
CRc	CR [Clinical] with Minimal Residual Skin Abnormality
CRi	Complete Response with Incomplete Bone Marrow Recovery
CSC	Cancer Stem Cell
CT	Computed Tomography
CTCAE	Common Terminology Criteria for Adverse Events

DLT	Dose-Limiting Toxicity
DSRC	Data Safety Review Committee
DT	Diphtheria Toxin
ECG	Electrocardiogram
ECHO	Echocardiogram
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDTA	Ethylenediamine Tetraacetic Acid
FDA	Food and Drug Administration
GLP	Good Laboratory Practice
GVHD	Graft Versus Host Disease
HIPAA	Human Insurance Portability Accountability Act
IB	Investigator Brochure
ICF	Informed Consent Form
ICH	International Council for Harmonisation
ICU	Intensive Care Unit
IHC	Immunohistochemistry
IND	Investigational New Drug Application
IRC	Independent Review Committee
IL-3	Interleukin-3
IL-3R	Interleukin-3 Receptor
INR	International Normalized Ratio
IV	Intravenous Administration
LDH	Lactate Dehydrogenase
LFT	Liver function test
LVEF	Left Ventricular Ejection Fraction
MDS	Myelodysplastic Syndrome
mITT	Modified intent-to-treat
mSWAT	Modified Severity Weighted Assessment Tool

MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition Scan
NCI	National Cancer Institute
ORR	Objective Response Rate
OS	Overall Survival
PD	Progressive Disease
pDCs	Plasmacytoid Dendritic Cells
PK	Pharmacokinetics
PFS	Progression-free Survival
PO	Orally
PP	Per-protocol
PR	Partial Response
PS	Performance Status
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RBC	Red Blood Cell
R/R	Relapsed/Refractory
rIL2	Recombinant Interleukin-2
SAE	Serious Adverse Event
SCT	Stem Cell Transplant
SD	Stable Disease
SGOT	Serum Glutamic Oxaloacetic Transaminase
SGPT	Serum Glutamic Pyruvic Transaminase
TEAE	Treatment-emergent adverse event
TLS	Tumor Lysis Syndrome
ULN	Upper Limit of Normal
VOD	Veno-occlusive disease
WHO	World Health Organization
WOCBP	Women of Childbearing Potential

3 Introduction and Study Rationale

3.1 Blastic Plasmacytoid Dendritic Cell Neoplasm

Blastic plasmacytoid dendritic cell neoplasm (BPDCN) is an uncommon hematological malignancy characterized by the clonal proliferation of malignant plasmacytoid dendritic cells (pDCs) (Facchetti et al. 2003). This neoplasm was originally recognized as a distinct entity in 1994 (Adachi et al. 1994) and the uncertainty regarding its histogenesis was reflected by the multiplicity of terms that were previously used for its designation, including agranular CD4+ natural killer cell leukemia (Brody et al. 1995), blastic natural killer leukemia/lymphoma (DiGiuseppe et al. 1997), and agranular CD4+/CD56+ hematodermic neoplasm (Petrella et al 2002; Herling et al. 2007). In 2001, the World Health Organization (WHO) classification of tumors of hematopoietic and lymphoid tissue proposed the term blastic natural killer (NK) cell lymphoma on the basis of the blastic cytology, and the expression of CD56 in the absence of other lineage specific markers. The relationship of BPDCN to pDCs was hypothesized first by Lucio et al. (1999) and subsequently confirmed by several studies (Petrella et al. 2002; Jacob et al. 2003; Reichard et al. 2005; Urosevic et al. 2005; Chaperot et al. 2004; Bene et al. 2003). The term BPDCN was introduced in 2008 by the updated WHO classification (4th edition) (Facchetti et al. 2008).

BPDCN most commonly affects middle-aged and older patients and is approximately 3.5-fold more common in men than women. The median age at diagnosis is 66 years and is lower for women than men. The true incidence and prevalence of BPDCN, like many other rare diseases without definitive and/or effective therapy, is not precisely known. However, based on a published report (Wang et al. 2012), BPDCN may constitute approximately 0.44% of the incident cases of hematologic cancers annually, or approximately 700 and 1,000 incident cases annually in the United States (US) and Europe, respectively, based on published data of hematologic cancer cases.

BPDCN cells show an immature “blastic” appearance; the diagnosis rests upon the demonstration of CD4 and CD56 expression, together with markers more restricted to PDC (such as CD123 [or the interleukin-3 receptor; IL-3R]) and negativity for lymphoid, NK and myeloid lineage-associated antigens. Immunophenotypic markers frequently, variably and infrequently expressed in BPDCN are detailed in Table 1 (Chaperot et al. 2001, Facchetti et al. 2008, Garnache-Ottou et al. 2009, Herling et al. 2007, Marafioti et al. 2008, Shi et al 2014, Zheng et al. 2012). The diagnosis of BPDCN is enabled by comprehensive evaluation of overall clinical manifestations, the morphologic appearance of blasts on skin, marrow or other biopsy, and a characteristic immunophenotypic profile, as indicated in Table 1.

Table 1: Immunophenotypic Marker Expression in BPDCN

Immunophenotypic Marker	Description
Frequently expressed in BPDCN	
CD4, CD56, CD123 (IL-R3α)	Widely recognized BPDCN markers with significant expression in substantial majority of BPDCN cases.
TCL1(TCL1A) (T cell leukemia/lymphoma)	Lymphoid marker, expressed in majority of BPDCN (and also normal pDCs); also expressed in B- and T-cell ALL.
BDCA-2/CD303	Dendritic cell marker frequently expressed in BPDCN and infrequently expressed in other acute leukemias.
BDCA-4/Neuropilin-1	Dendritic cell marker frequently expressed in BPDCN; may also be expressed in other acute leukemias.
CD2AP (CD2-associated protein)	Adaptor protein frequently expressed in pDCs and BPDCN and infrequently expressed in other acute leukemias.
CD45-RA	T-lymphoid marker, frequently expressed in BPDCN; may also be expressed in acute lymphoid malignancies.
Variably expressed in BPDCN	
HLA-DR	Myeloid precursor with variable expression in BPDCN; may also be expressed in acute myeloid leukemias.
Infrequently expressed in BPDCN	
CD11c, MPO (myeloperoxidase)	Myeloid markers, negative in majority of BPDCN cases.
CD79a	B-lymphoid marker, negative in majority of BPDCN cases.
CD3	T-lymphoid marker, negative in majority of BPDCN cases.

The clinical features and evolution of BPDCN are homogeneous, primarily consisting of 2 patterns (Brody et al. 1995; Herling et al. 2007; Reichard et al. 2005; Petrella et al. 2005; Petrella et al. 1999; Suzuki et al. 2005; Assaf et al. 2007). The first pattern (90% of cases) is characterized by an indolent onset dominated by cutaneous lesions followed by tumor dissemination. The second pattern shows features of an acute leukemia with systemic involvement from the outset, and multiple skin nodules are frequently present (Suzuki et al. 2005). BPDCN most typically presents with skin lesions, as well as extracutaneous malignant disease in the bone marrow, blood, lymph nodes, spleen, and other organs. Despite the frequent appearance of a somewhat indolent clinical presentation at the outset, the course of BPDCN is highly aggressive and the median survival is approximately 12-14 months (Herling et al. 2007; Jacob et al. 2003; Petrella et al. 2005; Bekkenk et al. 2004; Feuillard et al. 2002). The disease also almost always results in a terminal leukemic phase with proliferation of BPDCN blasts in the bone marrow and peripheral blood, leading to decreased blood cell counts with resultant infections, bleeding, and invariably death.

There is currently no standard of care, nor an effective treatment regimen, for BPDCN (Riaz et al. 2014). Previously untreated (first-line) BPDCN patients are typically treated with combination chemotherapy regimens generally used for lymphoma or acute leukemia, often requiring dose reductions or elimination of anthracyclines due to the predominance of elderly patients with this disease. There are only a few large studies (over 40 patients) reported in the literature; the most recent and largest, with over 80 patients, reported a 56% response rate in first-line BPDCN with combination chemotherapy, but response criteria were not elucidated. Median overall survival (OS) from diagnosis is only 8 to 14 months, with elderly patients being at the lower end of this range. Allogeneic stem cell transplant, mostly reserved for younger patients in first complete response (CR) with good performance status, has also been employed but only when patients' disease state and overall physical condition permit. Furthermore, the literature for the treatment of relapsed/refractory (R/R) BPDCN is scattered, limited and inconsistent in the way that clinical benefit is measured and presented, and management beyond first-line is usually not described in the larger retrospective case studies; of 7 published studies involving ≥10 patients, there is only one documented response to ≥2 lines of therapy.

3.2 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 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 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).

3.2.1 First-line Therapy

Initial treatment of AML is divided into induction chemotherapy and post-response, consolidation therapy. To optimize potential for durable response, patients frequently receive some form of consolidation therapy, which is routinely given to patients age <60 and generally involves multiple courses of intensive chemotherapy or stem cell transplant (SCT) (Dohner et al. 2010). Consolidation therapy is often given only once, or not given at all, to patients who are >60 years old. 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 higher 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-response therapies include dose-intensified cytarabine, and autologous or allogeneic SCT.

Although 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 responses, 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).

3.2.2 Second-line 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 R/R 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).

3.2.3 Third-line Therapy

Following failure of second-line therapy, patients often have depressed bone marrow function and are no longer optimal candidates for additional chemotherapy. There are currently no approved treatments for third-line AML, although therapeutic options include supportive care, cytarabine based combinations, and investigational therapies (e.g., hypomethylating agents). 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 two large series, is 1.5 months (Giles et al. 2005; Keating et al. 1989).

3.3 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. 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).

3.4 IL-3 Receptor (IL-3R) Over-Expression in AML

The alpha subunit of the IL-3R (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; (the β chain is shared by IL-3, IL-5, and granulocyte macrophage-colony stimulating factor 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 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; Tehranci et al. 2010; Florian et al. 2006; Lhermitte et al. 2006).

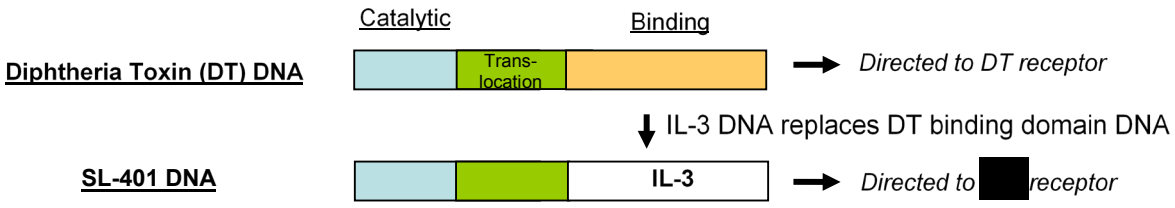
A higher percentage of IL-3R-expressing CSCs within a patient's tumor relates to poor outcome (Vergez et al. 2011). In particular, AML patients with IL-3R-expressing CSCs that comprise ≥3.5% of their entire leukemia have a worse prognosis than patients with IL-3R-expressing CSCs that comprise <3.5% of their entire leukemia (van Rhenen et al. 2005). Interestingly, IL-

3R-rich 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.

3.5 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 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 ADP-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/or 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 may not be 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.

3.6 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, 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 immunodeficiency 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 in a Phase 1-2 study described in Section 3.7.

In addition to being active against AML cells, very potent activity against BPDCN cells was demonstrated. In preclinical studies, the IC_{50} values against BPDCN cell lines derived from patients and primary tumor cells from BPDCN patients were in the femtomolar (i.e., 10^{-15} M) range, which is perhaps the most sensitive tumor cell type to any specific cancer therapeutic known (Chauhan et al. 2009).

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 recently 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 myeloma (Chauhan et al. 2014).

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 2.

Table 2: 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 two 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 with SL-401. The study designs are summarized in Table 3. Note that the doses described in the table and subsequent summary are doses of SL-401.

Table 3: Completed SL-401 Repeat-Dose Toxicity Studies with SL-401, Stemline 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 maximum tolerated dose (MTD) of SL-401 was determined to be 60 µg/kg/day when given as an intravenous slow bolus injection daily for 5 consecutive days.

Study Number	Study Title	Number of Animals	Study Type and Duration	Dose Level(s)	Dose Regimen	Noteworthy Findings
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 intravenous slow bolus injection 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.

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 (dose 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 doses of 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 a dose of 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 doses of 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 maximum tolerated dose (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 three 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 DT388IL3. 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 DT388IL3 clinical study, described in Section 3.7. Therefore, given the non-human primate toxicity results from DT388IL3 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 was selected to be 7 µg/kg/day. Furthermore, based on the previous clinical study, the maximum clinical dose was anticipated to be 12 µg/kg/day for a 5-day consecutive regimen.

3.7 SL-401 Clinical Studies

3.7.1 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 R/R 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 R/R 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 R/R 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).

3.7.2 Current 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 R/R 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 profile associated with SL-401.

An interim analysis of efficacy data was performed on 32 patients with BPDCN enrolled in the study through 29 August, 2016. Findings from this analysis, based on the Investigators' assessment of response, showed that of the 32 BPDCN patients evaluable for response, regardless of line or dose, the objective response rate (ORR) was 84%, and the CR rate (i.e., CR +CR with incomplete blood count recovery [CRi] + CR [clinical] with minimal residual skin abnormality [CRc]) was 56%. Of the 19 first-line patients (all doses) evaluable for response, the ORR was 95%, and the CR rate was 74%. Of the 16 first-line patients treated at 12 µg/kg/day

evaluable for response, the ORR was 100%, and the CR rate was 81%. Analysis of progression-free survival (PFS) showed that of the 16 evaluable first-line patients treated at 12 µg/kg/day, 11 were progression-free. This included 5 patients receiving ongoing SL-401 therapy for ~1-14+ months, all in CR (n=3) or PR (n=2), and 6 patients who sustained a remission while on SL-401 (CR [n=5]; PR [n=1]) and were then successfully bridged to SCT following ~2-6 months of SL-401 therapy; these patients have remained relapse-free up to 16.0+ months post-first SL-401 dose and up to 10.2+ months post-SCT. Median PFS had not been reached.

Of the 13 R/R patients evaluable for response, the ORR was 69%, and the CR rate was 31%.

3.8 Discussion and Rationale for Current Study

The rationale for clinical development of SL-401 for patients with AML or BPDCN is based on the high expression of the IL-3R on AML and BPDCN blasts, the potent preclinical activity of SL-401 against AML and BPDCN cells, the clinical responsiveness observed to date with SL-401, in BPDCN in particular, and the unmet medical need for these indications.

Clinical results with SL-401 indicate that the agent can be safely administered to patients with *de novo* AML, R/R AML, or BPDCN, 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 in Study 50047 and a safe starting dose for subsequent studies, the starting dose selected for this Phase 1/2 study, 7 µg/kg/day (similar to the lowest tested dose for this regimen (7.07 µg/kg/day) in Study 50047), allowed for an initial abbreviated (3 dose level) dose escalation/confirmation stage to an expected maximum tested dose (12 µg/kg/day) that appears to have the most favorable risk/benefit profile.

The SL-401 drug product used in the current study is 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 was to bridge the existing Phase 1/2 experience utilizing the earlier SL-401 drug product 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. 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 weeks with the allowance to delay the start of a subsequent cycle to allow toxicity resolution. This has been confirmed during Stage 1 of the current study, where the majority of patients have been able to receive multiple cycles of SL-401 despite transaminase elevations and hypoalbuminemia during Cycle 1. CLS was the principal DLT in Study 50047 and in the current study. 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 7.5.4. 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.

SL-401 was granted Breakthrough Therapy Designation (BTD) by the US FDA for the treatment of BPDCN in August 2016. In October 2016, the Sponsor conducted an interim analysis of efficacy data from 32 patients with BPDCN enrolled in this study between 06 October, 2014, and 29 August, 2016. A meeting was held with FDA on 20 December, 2016, to review the results of this interim analysis and discuss the continued development of SL-401 for treatment of BPDCN. As an outcome of that meeting, the following changes were made by Amendment 9:

- Enrollment of patients with AML is closed.
- Enrollment of patients with BPDCN is ongoing.
  - Any patient with first-line BPDCN enrolled in this study on or after 26 October, 2016, is included in Stage 3; a sufficient number of patients will be enrolled to ensure 10 evaluable patients are included, with evaluable patients being those with a diagnosis of BPDCN, as confirmed via central pathology review who received at least 1 dose of SL-401. These patients will constitute a standalone pivotal cohort for confirmation of efficacy of SL-401 in first-line BPDCN; for reference in this

protocol, this cohort will be designated Stage 3. The primary endpoint for this pivotal cohort is the CR rate.

  - Any patients with R/R BPDCN enrolled in this study on or after 26 October, 2016, are allocated to Stage 4. After the maximum number of planned first-line BPDCN patients are enrolled in Stage 3, any additional first-line BPDCN patients are to be enrolled in Stage 4. BPDCN patients enrolled in Stage 4 subsequent to completion of enrollment in Stage 3 will receive the lyophilized formulation of SL-401 for Injection.

  - Enrollment will continue in Stage 4 until the study enrollment cap is reached.

- The total study sample size is increased to up to 120 patients (including ~70 patients with BPDCN) in order to adequately assess efficacy and safety of SL-401 in patients with BPDCN in a clinical study setting.

- The inclusion/exclusion criteria for patients with BPDCN and SL-401 dose and treatment schedule are the same across Stages 2-4, with the exception that only first-line BPDCN patients are eligible for Stage 3.

- Safety monitoring to assess visual acuity and color vision, which are potential class toxicities of immunotoxins, and follow-up to determine whether treatment with SL-401 alters the risk of veno-occlusive disease (VOD) after subsequent SCT have been added. Other study procedures and evaluations are the same across Stages 2-4.

Key elements included in Protocol Amendment 10 are as follows:

- The total study sample size is increased to up to 130 patients (including ~80 patients with BPDCN) in order to ensure continued access to SL-401 for BPDCN patients in a clinical study setting.

- Updated enrollment status.

- Updated guidance for toxicity management, including CLS management, to continue reducing the risk of severe CLS and other SL-401-associated toxicities.

- Updates to reflect agreements and requests made by the FDA, including agreements on the primary efficacy endpoint for Stage 3.

Protocol Amendment 11 provides for additional BPDCN patients to be enrolled in Stage 4.

Protocol Amendment 12 provides details on the timing of analyses of duration of response and overall survival for all cohorts, as well as modifications to certain procedures based on the approved package insert and follow up requirement for patients who received stem cell

transplant following treatment with SL-401, to identify engraftment delays or failures. SL-401 Injection frozen solution (1mg/mL) was approved by the Food and Drug Administration (FDA) on 21 December 2018 for the treatment of BPDCN in adults and in pediatric patients 2 years and older under the name ELZONRIS (tagraxofusp-erzs).

4 Study Objectives

4.1 Primary Objectives

Stage 1 (completed):

- Determine the maximum tolerated dose (MTD), or the maximum tested dose where multiple dose-limiting toxicities (DLTs) are not observed, of SL-401.

Stage 2 (completed enrollment):

- Determine the efficacy of SL-401 in patients with BPDCN, as assessed by ORR.
- Characterize the safety profile of SL-401 at the MTD or maximum tested dose in both patients with AML and BPDCN.

Stage 3 (completed enrollment):

- Determine the CR rate (i.e., CR + CRc) in patients with first-line BPDCN.
- Characterize the safety profile of SL-401 in patients with first-line BPDCN.

Stage 4:

- Further characterize the efficacy of SL-401 in R/R and first-line patients with BPDCN following the completion of Stage 2 and Stage 3, respectively, as assessed by the rate of CR (i.e., CR + CRi + CRc).
- Further characterize the safety profile of SL-401 among first-line and R/R patients with BPDCN.
- Characterize the efficacy and safety of a lyophilized formulation of SL-401 among first-line and R/R patients with BPDCN.

4.2 Secondary Objectives

The secondary objectives are to:

- Determine the CR rate (i.e., CR + CRi + CRc) for Stage 1 and Stage 2, and ORR for Stage 3 patients.
- Estimate duration of response (DOR), PFS, and OS in patients with BPDCN.

- Enable preliminary characterization of the estimated ORR in patients with R/R AML, including in subsets of patients with R/R AML based on pre-treatment blast count, cytogenetics, or CD123 measurement.
- Estimate DOR, PFS, and OS in patients with AML.
- Characterize the pharmacokinetics (PK) and 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 peripheral blood and 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 response rates).

5 Patient Selection

5.1 Study Population

Patients with BPDCN or AML are to be enrolled in this study; refer to Section 5.2 and Section 5.3 for details.

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 (Protocol Stages 1 and 2) or BPDCN (Protocol Stages 1-4) according to WHO classification (AML; excluding acute promyelocytic leukemia [APL, FAB M3]) or confirmed by hematopathology (BPDCN) (Facchetti et al. 2008).
2. The patient must meet one of the following (a) or (b) or (c):
   (a) Has evidence of persistent or recurrent AML (Protocol Stages 1 and 2) in the peripheral blood and/or bone marrow that is refractory to, or has relapsed from, their most recent prior line of treatment.
   - A prior line of treatment is considered an induction regimen if it involves an approved or investigational cytotoxic chemotherapy agent, biological agent, and/or hypomethylating agent administered alone or in a combination regimen, with the intent to induce robust cytoreduction (i.e., CR).
   - The previous induction regimen may have been a SCT with intent to induce a CR.
   - Consolidation and/or maintenance (including SCT) may have been given in CR/CRi, but are not counted as a line of treatment.

- Hydroxyurea will not be considered a prior line of treatment.

(b) Has previously untreated AML (Protocol Stages 1 and 2) and is considered to be at high risk for disease progression and/or is unlikely to derive more than transient benefit from standard therapy by having at least one of the following:

- Treatment-related AML, except if it is associated with favorable cytogenetics (e.g., inversion 16, t[16;16], t[8;21], t[15;17]), and not a candidate for SCT in their current disease state.
- AML with antecedent hematological disease (e.g., MDS, myelofibrosis, polycythemia vera) and not a candidate for SCT.

(c) Has histological and/or cytological evidence of BPDCN by pathologic assessment at the investigative site according to WHO classification (Facchetti et al. 2008) by a pathologist with expertise in hematologic malignancies, that can be measured for treatment response and is either:

- Previously untreated (i.e., first-line) (Protocol Stages 2-4).
- Persistent or recurrent in the peripheral blood, bone marrow, spleen, lymph nodes, skin, or other sites after previous treatment with at least 1 line of systemic therapy for BPDCN, e.g., stem cell transplant or chemotherapy (Protocol Stages 1, 2, and 4). A pathology specimen must be available for central pathology review for all BPDCN patients enrolled in Protocol Stages 2-4.

3. The patient ≥18 years old.
4. The patient has an Eastern Cooperative Oncology Group (ECOG) performance status (PS) of 0-2.
5. The patient has adequate baseline organ function, including cardiac, renal, and hepatic function:

- LVEF ≥institutional lower limit of normal as measured by multigated acquisition (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 (133 µmol/L)
- Serum albumin ≥3.2 g/dL (32 g/L) (please note that albumin infusions are not permitted in order to enable eligibility)
- Bilirubin ≤1.5 mg/dL (26 µmol/L)
- AST and ALT ≤2.5 times the upper limit of normal (ULN)

6. If the patient is a woman of child bearing potential (WOCBP), she has had a negative serum or urine pregnancy test within 1 week prior to treatment.
7. The patient has signed informed consent prior to initiation of any study-specific procedures or treatment.
8. The patient is able to adhere to the study visit schedule and other protocol requirements, including follow-up for survival assessment.
9. 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.

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 APL (FAB M3).
2. The patient has persistent clinically significant toxicities Grade ≥2 from previous chemotherapy (excluding alopecia, nausea, fatigue, and liver function tests [as mandated in the inclusion criteria]).
3. The patient has received treatment with chemotherapy, wide-field radiation, or biologic therapy within 14 days of study entry.
4. The patient has received treatment with another investigational agent within 14 days of study entry.
5. The patient has previously received treatment with SL-401.
6. The patient has an active malignancy and/or cancer history (excluding AML, BPDCN, or antecedent MDS) that may confound the assessment of the study endpoints. Patients with a past cancer history (within 2 years of entry) with substantial potential or 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, cervical intraepithelial neoplasia, organ-confined prostate cancer with no evidence of progressive disease.
7. The patient has clinically significant cardiovascular disease (e.g., uncontrolled or any New York Heart Association 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).
8. 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.

9. 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.
10. The patient is receiving immunosuppressive therapy – with the exception of low-dose prednisone (≤10 mg/day) – for treatment or prophylaxis of graft-versus-host disease (GVHD). If the patient has been on immunosuppressive treatment or prophylaxis for GVHD, the treatment(s) must have been discontinued at least 14 days prior to study treatment and there must be no evidence of Grade ≥2 GVHD.
11. 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.
12. The patient is pregnant or breast feeding.
13. The patient has known positive status for human immunodeficiency virus or active or chronic Hepatitis B or Hepatitis C.
14. The patient is oxygen-dependent.
15. The patient has any medical condition which in the opinion of the Investigator places the patient at an unacceptably high risk for toxicities.
16. The patient has AML and requires more than 1g per day of hydroxyurea. (Hydroxyurea is permitted at doses of 1g per day or less).

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 R/R 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. Given the results from the SL-401 Phase 1/2 study (Study 50047), it was anticipated that the starting dose for Stage 2 of the present study would be 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 began 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 4-stage, non-randomized, open-label, dose escalation and expansion, multicenter study. A cycle of therapy is 21 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.

6.2.1 Stage 1: Dose Escalation

During Stage 1, approximately 9-18 patients will be treated with SL-401 at doses of 7, 9, 12, or 16 µg/kg/day for 5 consecutive days every 21 days. The 16 µg/kg/day dose will be evaluated only in patients with AML. Evaluation of higher doses (in increments of 25% or less [i.e., at 20 µg /kg/day and 25 µg /kg/day levels]) in AML patients may be attempted pending evaluation of the safety/tolerability of the 16 µg/kg/day dose level; these evaluations would be attempted to identify an MTD and will be guided by the criteria (stipulated below) defining safety/tolerability of all dose levels.

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. The first cohort of patients will receive SL-401 at a dose of 7 µg/kg/day. After all patients in this cohort complete the first cycle of therapy, the dose for the second cohort of patients will increase by 29% to 9 µg/kg/day, conditional on the DLT rules described below. The dose for the third cohort of patients will increase by 33% to 12 µg/kg/day, conditional on the DLT rules described below. Finally, after all patients in the third cohort complete the first cycle of therapy, the dose for the fourth cohort of patients, consisting only of patients with AML, will increase by 33% to 16 µg/kg/day, conditional on the DLT rules described below.

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

(a) Any treatment-emergent Grade 4 transaminase or creatine phosphokinase (CPK) elevation, regardless of duration or relationship to SL-401.

(b) Any treatment-emergent Grade 4 hematologic toxicity (unrelated to persistent leukemia) lasting >21 days after the last infusion of SL-401.

(c) Any treatment-emergent Grade ≥3 non-hematologic toxicity (unrelated to persistent leukemia), with the exception of Grade 3 laboratory toxicities that resolve to Grade ≤1 or baseline ≤21 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, TPN 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 protocol 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 21 days, cycle duration may extend beyond 21 days in the setting of AEs, which are detailed in Section 7.5.5. Specific, reversible AEs resulting in a prolongation of Cycle 1 to 28 days will not necessitate a dose-reduction for subsequent cycles and will not be considered DLTs if they occur during Cycle 1.

Beginning with the dose level 7 µg/kg/day of SL-401, 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 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 of 9 µg/kg/day. If one of the initial 3 patients treated (1/3) experiences a DLT, the cohort will be expanded to include up to an additional 3 patients treated at the same dose 7 µg/kg/day. If only one patient (1/6) from this expanded cohort experiences a DLT, then 3 new patients will be treated at the next higher dose 9 µg/kg/day. Expansion of the 9 µg/kg/day cohort to 6 patients, if necessary, will follow the same rules as the 7 µg/kg/day cohort. The same DLT rules will also apply to the 12 µg/kg/day and 16 µg/kg/day (AML specific) cohorts.

In the event that 2 patients within a cohort have a DLT, then the MTD will be exceeded and further dose escalation will not occur. The MTD is defined as the dose preceding the dose level at which 2 patients experience a DLT during treatment Cycle 1. The MTD will be used in Stages 2-4 of the study. 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 patients treated at the 7 µg/kg/day dose level, 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.

Stage 1 is complete, with the MTD of SL-401 determined to be 12 µg/kg/day in R/R AML and a maximum tested dose of SL-401 of 12 µg/kg/day in BPDCN. (An MTD was not determined in BPDCN.)

6.2.2 Stages 2-4

During Stages 2-4, patients will be treated at the MTD or maximum tested dose at which multiple DLTs are not observed during Stage 1, or a lower dose with potentially the most favorable risk/benefit profile. At the time of Protocol Amendment 11, only Stage 4 is open for enrollment.

SL-401 will be supplied as SL-401 Injection frozen solution (1 mg/mL) as described. A lyophilized formulation (SL-401 for Injection, lyophilized, powder, for solution; 1 mg/mL) also will be supplied. All patients enrolled in Stage 4 (both first-line and R/R) subsequent to completion of enrollment in Stage 3 will receive the lyophilized formulation of SL-401. Note that when the lyophilized formulation is introduced, patients who start treatment with SL-401 Injection frozen solution will continue to receive this dosage form throughout the study.

6.2.2.1 Patients with AML (Stage 2 only)

The primary objective for patients with AML enrolled in Stage 2 is to characterize the safety profile of SL-401 at the MTD or maximum tested dose in patients with AML. Assessment of the anti-tumor activity of SL-401 in patients with AML will be assessed by the Investigator as a secondary endpoint using the criteria in Section 16.1, Appendix A. The following assessments will be performed at baseline within 14 days prior to the first administration of SL-401 and thereafter for determination of tumor response for these patients, as follows:

- **Bone marrow aspirates (± biopsy)** 21 (±7) days after the start of Cycles 1 and 2. Patients with evidence of bone marrow involvement prior to study treatment will also have bone marrow evaluations following Cycles 4 and 6 and then every 3 months from Months 6-12; every 6 months from 12 to 24 months; and every 12 months thereafter until there is evidence of relapsed or progressive disease. If the Cycle 1 (Day 21 [±7]) bone marrow examination is empty (i.e., hypocellular) or inadequate, a bone marrow examination should be repeated in 7 (±7) days to document response. If additional time is required to complete the repeat examination, consultation with the Medical Monitor is required. If CD123 flow cytometry or IHC stain assessment was performed on the bone marrow aspiration (± biopsy), the results should be recorded in the electronic case report forms (eCRFs).

- Collection of **peripheral blood samples** for determination of blasts 21 (±7) days after the start of Cycles 1 and 2. Patients with evidence of peripheral blasts at baseline will also have peripheral blood samples collected 21 (±7) days after the start of Cycles 1 and 2 and 21 (±7) days after the start of every 2nd cycle thereafter (Cycles 4, 6, etc.) until there is evidence of relapsed or progressive disease.

6.2.2.2 Patients with BPDCN (Stages 2-4)

Standardized assessment of potential sites of disease involvement (including skin, lymph nodes, blood, bone marrow, and visceral organs) and consistently-defined response criteria will be utilized.

The BPDCN diagnosis will be made or confirmed during Screening by the pathology laboratories at the investigative sites. Subsequent to enrollment, pathology material will be submitted for central pathology review for confirmation of the BPDCN diagnosis.

Tumor response will be assessed by the Investigators for all patients with BPDCN, with the Investigator's assessment to be used in the primary analysis. As a supportive assessment, tumor response will be assessed by an Independent Review Committee (IRC) in a pre-specified subset of patients. Tumor response will be assessed using the Tumor Response Criteria for Patients with BPDCN presented in Section 16.2, Appendix B. All patients will also be followed for DOR and survival. The following assessments will be performed at baseline within 14 days prior to the first administration of SL-401 and thereafter for determination of tumor response for patients in Stages 2-4:

- **Bone marrow aspirates (± biopsy)** samples 21 (±7) days after the start of Cycles 1 and 2. Patients with evidence of bone marrow involvement prior to study treatment will also have bone marrow evaluations following Cycles 4 and 6 and then every 3 months from Months 6-12; every 6 months from 12 to 24 months; and every 12 months thereafter until there is evidence of relapsed or progressive disease.

  - If the Cycle 1 (Day 21 [±7]) bone marrow examination is empty (i.e., hypocellular) or inadequate, a bone marrow examination should be repeated in 7 (±7) days to document response. If additional time is required to complete the repeat examination, consultation with the Medical Monitor is required. If CD123 flow cytometry or IHC stain assessment was performed on the bone marrow aspiration (± biopsy), the results should be recorded in the eCRF.

- **Skin assessments,** including photographs, for patients with skin involvement, and determination of skin disease burden using mSWAT (see Section 16.3, Appendix C) 21 (±7) days after the start of Cycles 1 and 2 and 21 (±7) days after the start of every 2nd cycle thereafter (Cycles 4, 6, etc.) until there is evidence of relapsed or progressive disease. Refer to the separate mSWAT Manual for instructions regarding the quantitation of malignant lesions via the mSWAT and response assessment in skin.

  - In situations in which there is substantial reduction of skin lesions (especially when accompanied by disappearance of BPDCN from bone marrow or other sites), a skin biopsy is required. The mSWAT guidance states: "A biopsy of normal appearing skin is unnecessary to assign a complete response. However a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist" (Olsen et al. 2011).

- **CT scans** of index lesions 21 (±7) days after the start of Cycles 2, 4 and 6 and 21 (±7) days after the start of every 4th cycle thereafter (for patients with baseline evidence of lymph node or visceral disease) until there is evidence of relapsed or progressive disease. For patients with no baseline evidence of lymph node or visceral BPDCN involvement, subsequent scans should be performed at the end of Cycle 2 (±7 days; or at time of disease progression (PD) if PD occurs prior to end of Cycle 2), 21 (±7) days after the start of Cycle 6, and at Investigator's discretion thereafter. Baseline CT scans should be full-body (chest/ abdomen/pelvis), whereas follow-up scans should document response of index lesions (Cheson et al. 2007).

- Collection of **peripheral blood samples** for determination of blasts 21 (±7) days after the start of Cycles 1 and 2. Patients with evidence of peripheral blasts at baseline will also have peripheral blood samples collected 21 (±7) days after the start of Cycles 1 and 2 and 21 (±7) days after the start of every 2nd cycle thereafter (Cycles 4, 6, etc.) until there is evidence of relapsed or progressive disease.

6.3 Study Duration

Patient enrollment is expected to occur over a 52-month period, with follow-up continuing for a minimum of 12 months on each patient. Total study duration is expected to be approximately 60 months. Please consult Section 7.6.2 regarding recommended procedures and follow-up after treatment discontinuation.

6.4 Study Completion

The study is considered complete when sufficient information is available to enable assessment of the primary endpoint and selected secondary endpoints. The **Study Completion** date will be the date beyond which study data are 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).

7 Study Treatment Identification, Administration, and Schedule

7.1 Product Manufacturing and Characterization

Refer to the Investigator Brochure (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

Please refer to Section 11 regarding investigational or approved anticancer agents prohibited during study participation.

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/or tumor bulk of a variety of leukemias and hematopoietic malignancies, including BPDCN and AML, 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

SL-401 is administered by IV infusion over 15 minutes for 5 consecutive days of a 21-day cycle.

- In Stage 1, SL-401 is administered at escalating doses of at 7, 9, 12, or 16 µg/kg/day.
- In Stages 2-4, all patients will receive SL-401 at a dose of 12 µg/kg/day.

The dose of SL-401 will be dependent upon the patient's baseline body weight in kg (day of initial infusion for Cycle 1). This dose will be recalculated if there is a 10% (or greater) change in body weight from baseline. The aliquot is calculated from the µg/kg dose × patient weight in kg (including one decimal place; all patient doses are calculated in µg/kg body weight). Dose changes should only occur once a cycle has been completed. Intra-cycle dose modifications will not be permitted.

Patients who benefit from treatment and do not have evidence of clinically significant progressive disease may receive repeated cycles of SL-401 even if a response, in the judgment of the Investigator, is not attained. Patients will continue to receive SL-401 as long as they may be benefiting from treatment, according to the Investigator; until the study is completed. No maximum duration of therapy has been set.

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 (or equivalent dose of paracetamol) orally (PO)
- Diphenhydramine 50 mg intravenously (IV) (or equivalent dose of another H1-histamine antagonist)
- Methylprednisolone 50 mg IV (or an equivalent dose of another corticosteroid)
- Ranitidine 50 mg IV (or an equivalent dosage of another H2-histamine antagonist)

7.5.3.2 SL-401 Dosage Preparation

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 assigned dose (µg/kg dose × patient weight in kg, including one decimal place [example: 7 µg/kg × 70.3kg]). The dose of SL-401 will be dependent upon the patient's baseline body weight in kg (day of initial infusion for Cycle 1). This dose will be recalculated if there is a 10% (or greater) change in body weight from baseline. Additional dose preparation supplies and instructions for both SL-401 formulations utilized in this study are described in detail within the Pharmacy Manual

7.5.3.3 Inpatient and Outpatient Setting for Dose Administration

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.

7.5.4 Patient Monitoring Procedures During the SL-401 Dosing Period

To assess relevant acute toxicities, testing and procedures summarized below are to be performed and results are to be reviewed prior to each scheduled SL-401 infusion (refer to Section 9.8 Table 5, Table 6, Table 7, and Table 8 for more detail):

- Vital signs including blood pressure, heart rate, respiration rate, body temperature, and pulse oximetry:
    - During daily dosing (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.
    - Days 8, 15, and 21.
- Diagnostic blood tests during daily dosing (usually Days 1, 2, 3, 4 and 5) and Days 8, 15, and 21 as follows:
    - Hematology: complete blood count (CBC) with differential, platelet count;
    - Serum Electrolytes and Chemistry: sodium, potassium, bicarbonate, chloride, blood urea nitrogen (BUN), creatinine, glucose, alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase, (AST), bilirubin (total, direct, and indirect), calcium, creatine phosphokinase (CPK), magnesium, lactate dehydrogenase (LDH), phosphate, total protein, uric acid;
    - Coagulation: prothrombin time (PT) or International Normalized Ratio (INR), and activated partial thrombin time (aPTT).
- Routine urinalysis on Day 1 (prior to SL-401 infusion), and Days 8, 15, and 21.

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. Details are presented in Table 4.

Monitor vital signs and check albumin, transaminases, and creatinine prior to preparing each dose of ELZONRIS.

Table 4: Recommended ELZONRIS Dose Modifications

Parameter	Severity Criteria	Dose Modification
Serum albumin	Serum albumin < 3.5 g/dL or reduced ≥ 0.5 g/dL from value measured prior to initiation of the current cycle	See CLS Management Guidelines (Appendix E)
Body weight	Body weight increase ≥ 1.5 kg over pretreatment weight on prior treatment day	See CLS Management Guidelines (Appendix E)
Aspartate aminotransferase (AST) or alanine aminotransferase (ALT)	ALT or AST increase > 5 times the upper limit of normal	Withhold SL-401 until transaminase elevations are ≤ 2.5 times the upper limit of normal.
Serum creatinine	Serum creatinine > 1.8 mg/dL (159 micromol/L) or creatinine clearance < 60 mL/minute	Withhold SL-401 until serum creatinine resolves to ≤ 1.8 mg/dL (159 micromol/L) or creatinine clearance ≥ 60 mL/minute.
Systolic blood pressure	Systolic blood pressure ≥ 160 mmHg or ≤ 80 mmHg	Withhold SL-401 until systolic blood pressure is < 160 mmHg or > 80 mmHg.
Heart rate	Heart rate ≥ 130 bpm or ≤ 40 bpm	Withhold SL-401 until heart rate is < 130 bpm or > 40 bpm.
Body temperature	Body temperature ≥ 38°C	Withhold SL-401 until body temperature is < 38°C.
Hypersensitivity reactions	Mild or moderate	Withhold SL-401 until resolution of any mild or moderate hypersensitivity reaction. Resume ELZONRIS at the same infusion rate.
	Severe or life-threatening	Discontinue SL-401 permanently.

Dose reductions should be discussed with the medical monitor on a case by case basis.

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 AML/BPDCN response (beyond Cycle 1), 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/BPDCN response

- Disease recurrence/progression
- Intercurrent illness that prevents further administration of SL-401
- Patient non-compliance
- Occurrence of pregnancy
- Investigator's decision

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

In settings in which there is preliminary but not conclusive evidence of disease progression (i.e., new skin lesions of indeterminate etiology, new lymph nodes ≤1.5cm, modest increase in bone marrow blast percentage subsequent to an initial marked reduction, appearance of new blast population on bone marrow evaluation by means of flow cytometry or other molecular methodology without increase in blast percentage consistent with PD), additional SL-401 cycles may be administered, provided that the Investigator documents that the evidence of potential disease progression is inconclusive and that the overall risk/benefit assessment favors additional investigational therapy. Additional SL-401 may also be administered in situations of mixed response BPDCN in which response/progression is not consistent between a given patient's disease sites, provided that the Investigator documents that the overall risk/benefit assessment favors additional investigational therapy. In such situations, it is essential that relevant findings and assessments are documented, and that areas of potential disease progression are followed closely on subsequent assessments.

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 and Table 8 (in Section 9.8). 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, disease assessments should continue to be performed as described in Section 8.12 on an every 6-week basis (±1 week) through 6 months post-C1D1 and then on an every 90-day basis or 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 survival status. (If the patient is in CR/PR at the time of discontinuation, disease assessments should continue to be performed as described in Section 8.12 on an every 6-week basis (±1 week) through 6 months post-C1D1 and then on an every 90-day basis or until, in the judgment of the Investigator, there is evidence of relapsed or

progressive disease. Patients who undergo SCT will be followed for the occurrence of VOD and engraftment delay or failure as part of survival monitoring.

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 BPDCN or R/R AML who have previously received at least one line of therapy for their disease, previously untreated AML that is considered high risk for disease progression, 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 or BPDCN diagnosis, prior AML/BPDCN 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 Disease Confirmation (Patients with BPDCN in Stages 2-4)

For patients with BPDCN enrolled in Stages 2-4, the BPDCN diagnosis will be made or confirmed during Screening by the pathology laboratories at the investigative sites. Subsequent to enrollment, pathology material will be submitted for review by the central pathologist for confirmation of the BPDCN diagnosis.

Pathology material will consist of pathology slides (or tissue blocks) and associated pathology reports for all organ sites evaluated for BPDCN via histopathology/ cytopathology. In situations in which submission of slides or blood smears is considered not feasible, submission of representative electronic images of histopathology will be permitted. Pathology submission will also include reports of all immunohistochemistry evaluations for BPDCN and other hematologic-malignancy-associated markers, and reports of flow cytometry performed on bone marrow aspirate (or blood if applicable) for BPDCN and other hematologic-malignancy-associated markers. Submission of scatter-plots of flow cytometric evaluation is strongly encouraged.

8.4 Prior and Concomitant Medication

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

8.5 ECOG Performance Status

See Section 16.4 for a scoring guide.

8.6 Physical Examination

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

8.7 Vital Signs

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

8.8 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 Day 21 (±3 days), and Day 28 (±3 days) only if delayed end of cycle) of each cycle. During the days when patients are undergoing PK sampling (during Cycle 1, infusions 1 and 5; Cycle 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 9 in Section 9.8). An ECG should be performed after patient is supine for 5 minutes. All ECGs will be analyzed by a central facility.

8.9 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, neutrophils), red blood cell (RBC) count, hematocrit, hemoglobin and platelet count.
- Serum albumin: May be a component of the serum chemistry panel. See Appendix E for management of changes in albumin values.
- Serum electrolytes and chemistry: Sodium, potassium, bicarbonate, chloride, blood urea nitrogen (BUN), creatinine, glucose, ALT, albumin, ALP, AST, bilirubin (total, direct, and indirect), calcium, CPK, magnesium, LDH, phosphate, total protein, and uric acid.
- Coagulation parameters: PT and/or INR, aPTT.
- Urinalysis: Appearance, color, pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilinogen, and occult blood.

8.10 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.

8.11 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 (NCI 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.

8.12 Tumor Assessments and Disease Response Assessment

8.12.1 Stage 1

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. In addition, patients with BPDCN must have a baseline skin assessment (with biopsies and/or for patients with skin involvement) and full-body CT scan within 14 days prior to the first administration of SL-401. Subsequent assessments for response will be performed on the following schedules until, in the judgment of the Investigator, there is evidence of relapsed or progressive disease:

- All patients in Stage 1: bone marrow aspirates (± biopsy) 21 (±7) days after the start of Cycles 1 and 2, and thereafter at a schedule determined by the Investigator in consultation with the Sponsor. If the Cycle 1 (Day 21 [±7]) bone marrow examination is empty (i.e., hypocellular) or inadequate, a bone marrow examination should be repeated

in 7 (±7) days to document response. If additional time is required to complete the repeat examination, consultation with the Medical Monitor is required. If CD123 flow cytometry or IHC stain assessment was performed on the bone marrow aspiration (± biopsy), the results should be recorded in the eCRF.

- BPDCN patients: skin assessments (with biopsies and/or photographs for patients with skin involvement) 21 (±7) days after the start of Cycles 1 and 2 and 21 (±7) days after the start of every 2nd cycle thereafter (Cycles 4, 6, etc.). CT scans of index lesions 21 (±7) days after the start of Cycles 2 and 4 and 21 (±7) days after the start of every 4th cycle thereafter (approximately every 12 weeks).

Tumor response will be assessed by the Investigator using the criteria in Section 16.1, Appendix A (AML), and Section 16.2, Appendix B (BPDCN).

8.12.2 Stage 2, Patients with AML

The following disease assessments will be performed at baseline within 14 days prior to the first administration of SL-401 and thereafter for determination of tumor response for patients with AML in Stage 2, as follows. Note that all sites of disease identified at baseline are to be followed thereafter for determination of disease response.

- **Bone marrow aspirates (± biopsy)** 21 (±7) days after the start of Cycles 1 and 2. Patients with evidence of bone marrow involvement prior to study treatment will also have bone marrow evaluations following Cycles 4 and 6 and then every 3 months from Months 6-12; every 6 months from 12 to 24 months; and every 12 months thereafter until there is evidence of relapsed or progressive disease. If the Cycle 1 (Day 21 [±7]) bone marrow examination is empty (i.e., hypocellular) or inadequate, a bone marrow examination should be repeated in 7 (±7) days to document response. If additional time is required to complete the repeat examination, consultation with the Medical Monitor is required. If CD123 flow cytometry or IHC stain assessment was performed on the bone marrow aspiration (± biopsy), the results should be recorded in the eCRF.
    - The Cycle 1-2 Day 21 (±7 days) bone marrow assessment should occur on Day 21 (±7 days) even in the setting of patients receiving SL-401 over 6-10 days (as opposed to 5 consecutive days) or in the setting of patients receiving less than 5 doses in a cycle.
- Collection of **peripheral blood samples** for determination of blasts 21 (±7) days after the start of Cycles 1 and 2. Patients with evidence of peripheral blasts at baseline will also have peripheral blood samples collected 21 (±7) days after the start of Cycles 1 and 2 and 21 (±7) days after the start of every 2nd cycle thereafter (Cycles 4, 6, etc.) until there is evidence of relapsed or progressive disease.

Assessment of the anti-tumor activity of SL-401 in patients with AML will be assessed by the Investigator on an exploratory basis using the criteria in Section 16.1, Appendix A.

8.12.3 Patients with BPDCN (Stages 2-4)

A global assessment paradigm is to be followed, with all potential disease sites assessed during screening, including the bone marrow (via aspirate and biopsy), blood (via clinical laboratory testing for blasts and hematologic parameters), skin (via visual examination and photography, with determination of skin disease burden using mSWAT), lymph nodes, liver, spleen, and other viscera (via CT), and lymph nodes, liver, spleen, and other viscera (via physical examination). Positive sites of disease identified during screening must be followed during the study in every response evaluation. (Disease in organs that were disease-positive at screening are to be assessed, documented, and recorded in the clinical database, even if the disease disappeared in subsequent response evaluations.) Sites with no evidence of disease during Screening must be documented as such and an assessment that baseline disease is not present are to be adequately documented in source and recorded in the clinical database; thereafter, these sites need not be followed, unless there is evidence of PD.

The following disease assessments will be performed at baseline within 14 days prior to the first administration of SL-401 and thereafter for determination of tumor response for patients in Stages 2-4, as follows. Note that all sites of disease identified at baseline are to be followed thereafter for determination of disease response.

- **Bone marrow aspirates (± biopsy)** samples 21 (±7) days after the start of Cycles 1 and 2. Patients with evidence of bone marrow involvement prior to study treatment will also have bone marrow evaluations following Cycles 4 and 6 and then every 3 months from Months 6-12; every 6 months from 12 to 24 months; and every 12 months thereafter until there is evidence of relapsed or progressive disease.

    - If the Cycle 1 (Day 21 [(±7]) bone marrow examination is empty (i.e., hypocellular) or inadequate, a bone marrow examination should be repeated in 7 (±7) days to document response. If additional time is required to complete the repeat examination, consultation with the Medical Monitor is required. If CD123 flow cytometry or IHC stain assessment was performed on the bone marrow aspiration (± biopsy), the results should be recorded in the eCRF.

    - The Cycle 1-2 Day 21 (±7 days) bone marrow assessment should occur on Day 21 (±7 days) even in the setting of patients receiving SL-401 over 6-10 days (as opposed to 5 consecutive days) or in the setting of patients receiving less than 5 doses in a cycle.

- **Skin assessments,** including photographs, for patients with skin involvement, and determination of skin disease burden using mSWAT (see Section 16.3, Appendix C) 21 (±7) days after the start of Cycles 1 and 2 and 21 (±7) days after the start of every 2nd cycle thereafter (Cycles 4, 6, etc.) until there is evidence of relapsed or progressive disease.

- **Photographs**: Body region(s) where skin lesions are present will be photographed. Digital images/photographs may be collected by the Sponsor or its representatives during routine monitoring visits. Care should be taken to ensure that patients cannot be identified from these images. Refer to the separate Photography Guidelines for detailed photography instructions.

- **Quantification of skin disease burden via the mSWAT**: Quantification of skin disease burden via the mSWAT (Section 16.3, Appendix C) is required at the time of each skin assessment. Refer to the separate mSWAT Manual for instructions regarding the quantitation of malignant lesions via the mSWAT and response assessment in skin.

- **Skin biopsies**: In situations in which there is substantial reduction of skin lesions (especially when accompanied by disappearance of BPDCN from bone marrow or other sites), a skin biopsy is required. The mSWAT guidance states: "A biopsy of normal appearing skin is unnecessary to assign a complete response. However a skin biopsy should be performed of a representative area of the skin if there is any question of residual disease (persistent erythema or pigmentary change) where otherwise a complete response would exist" (Olsen et al. 2011).

- **CT scans** of index lesions 21 (±7) days after the start of Cycles 2, 4 and 6 and 21 (±7) days after the start of every 4th cycle thereafter (for patients with baseline evidence of lymph node or visceral disease) until there is evidence of relapsed or progressive disease. For patients with no baseline evidence of lymph node or visceral BPDCN involvement, subsequent scans should be performed at the end of Cycle 2 (±7 days; or at time of disease progression (PD) if PD occurs prior to end of Cycle 2), 21 (±7) days after the start of Cycle 6, and at Investigator's discretion thereafter. Baseline CT scans should be full-body (chest/ abdomen/pelvis), whereas follow-up scans should document response of index lesions (Cheson et al. 2007).

  - During Stages 2-4, subsequent to the end of Cycle 2, imaging at intervals less frequent than those stipulated above may be permitted when required by local regulations; however, this must be reviewed with the Medical Monitor (or designee).

  - For patients in Stages 2-4, electronic copies of all baseline and subsequent CT scans will be submitted to a central archive (scans are to be submitted regardless of the presence/absence of BPDCN-related abnormalities).

- Collection of **peripheral blood samples** for determination of blasts 21 (±7) days after the start of Cycles 1 and 2. Patients with evidence of peripheral blasts at baseline will also have peripheral blood samples collected 21 (±7) days after the start of every 2nd cycle thereafter (Cycles 4, 6, etc.) until there is evidence of relapsed or progressive disease.

Tumor response will be assessed by the Investigators for all patients with BPDCN, with the Investigator's assessment to be used in the primary analysis. As a supportive assessment, tumor response was also evaluated by an IRC on a pre-specified subset of patients. Tumor response will be assessed using the Tumor Response Criteria for Patients with BPDCN presented in Section 16.2, Appendix B. All patients will also be followed for DOR and survival until study completion.

8.13 Pharmacokinetic Studies

An intensive schedule for collection of blood samples after specific infusions during Cycle 1 and 3 of SL-401 will be used to determine plasma concentrations of SL-401. During Stage 1 and early portions of Stage 2, PK assessment was conducted on samples for all patients.

The concentration of SL-401 in plasma samples will be determined by a sensitive and specific sandwich enzyme-linked immunosorbent assay 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 noncompartmental 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 ethylenediamine tetraacetic acid (EDTA) tubes (lavender top, at least 6mL 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 9 in Section 9.8). 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 pharmacokinetic sampling be recorded diligently.

The nominal blood sampling time schedule is summarized in Table 9 (in Section 9.8) for the following SL-401 treatment days:

- Cycle 1, infusion 1 (i.e., Study Day 1).
- Cycle 1, infusion 5 (i.e., usually Study Day 5).
- Cycle 3, infusion 1 (i.e., Day 1 of Cycle 3).
- Cycle 3, infusion 5 (i.e., usually Day 5 of Cycle 3).

8.14 Immunogenicity Studies

Peripheral blood samples (10 mL) will be collected (serum red top tube, no additive) for the detection and characterization of SL-401 reactive antibodies according to the following schedule:

- Cycle 1: Day 1 (pre-infusion), Day 15 (±3 days), and Day 21 (±3 days).
- Cycle 2, 3, 4, 5, or 6: Day 1 (pre-infusion) and Day 21 (±3 days). Note: A separate Day 1 (pre-infusion) sample does not need to be drawn if the Day 21 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 21 sample may be used both as the Day 21 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.
- A blood sample for immunogenicity studies will be collected between 16 weeks and 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.
- 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.

[redacted]

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 will 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 pharmacokinetic 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 Investigator.

9 Schedule of Events

The study schedule of events is summarized in Table 5, Table 6, Table 7, and Table 8 (in Section 9.8).

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 treatment.

All Patients, All Study Stages:

- Informed Consent
- Inclusion / Exclusion criteria
- Medical history, including prior therapy and concomitant medications
- ECOG performance status
- Physical examination
- 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 treatment)
- 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 treatment. If CD123 flow cytometry or IHC stain was performed on the bone marrow aspirations (± biopsy), the results should be recorded in the eCRF.

Patients with BPDCN Only

- Full-body CT scan (chest/abdomen/pelvis) within 14 days prior to start of first cycle of study treatment
- Skin assessment within 14 days prior to start of first cycle of study treatment (including quantification using mSWAT)

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

All Patients, All Study Stages:

- 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

All Patients, All Study Stages:

- Inpatient admission (Study Day 1)
- Vital signs and weight (pre-treatment weight should be recorded on each day for which an SL-401 infusion is planned)
- AE and SAE monitoring
- Clinical laboratory tests: hematology, serum electrolytes and chemistry (including albumin), coagulation parameters, and 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 each day of infusion (Infusions 1 and 5 of Cycles 1 and 3 will be triplicates at the specified timepoints)
- Diphenhydramine 50 mg IV 60 minutes prior to infusion
- Acetaminophen 650 mg PO (or equivalent dose of paracetamol) 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

All Patients, All Study Stages:

- 12-lead ECG (infusions 1 and 5) performed at 3 distinct time points (triplicates) 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

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

All Patients, All Study Stages:

- Concomitant medication assessment
- Physical examination
- Vital signs and weight
- 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

All Patients, All Study Stages:

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

9.3.5 Study Day 21 ±7 Days: End of Cycle

Note: The end-of-cycle evaluations (Day 21 or thereafter) may also serve as the pre-infusion evaluations for the subsequent cycles; with the exception of vital signs, these do not need to be duplicated on successive days unless there is an abnormality or other clinically relevant reason for repeat evaluation.

All Patients, All Study Stages:

- Concomitant medication assessment
- ECOG performance status
- Physical examination
- Vital signs and weight
- 12-lead ECG
- Clinical laboratory tests: hematology, serum electrolytes and chemistry (including albumin), coagulation parameters, and urinalysis
- Tumor response assessment: bone marrow aspiration (± biopsy) and peripheral blood sample (AML and BPDCN). If the Cycle 1 (Day 21 [±7]) bone marrow examination is empty (i.e., hypocellular) or inadequate, a bone marrow examination should be repeated in 7 (±7) days to document response. If additional time is required to complete the repeat examination, consult with the Medical Monitor. If CD123 flow cytometry or IHC stain was performed on the bone marrow aspirations (± biopsy), then the results should be recorded in the eCRF.

- Collection of peripheral blood (serum) for immunogenicity
- Monitoring for changes in visual acuity and color vision
- AE and SAE monitoring

Patients with BPDCN Only:

- Tumor response assessment: skin, including mSWAT

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

All Patients, All Study Stages:

- Concomitant medication assessment
- ECOG performance status
- Vital signs and weight
- 12-lead ECG
- Clinical laboratory tests: hematology, serum electrolytes and chemistry (including albumin), coagulation parameters, and urinalysis
- AE and SAE monitoring

9.4 Cycles 2 – 6

Note: The end-of-cycle evaluations (Day 21 or thereafter) may also serve as the pre-infusion evaluations for the subsequent cycles; with the exception of vital signs, these do not need to be duplicated on successive days unless there is an abnormality or other clinically relevant reason for repeat evaluation.

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

All Patients, All Study Stages:

- Inpatient admission (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
- 12-lead ECG each day of infusion (Infusions 1 and 5 of Cycles 1 and 3 will be triplicates at the specified timepoints)
- Collection of peripheral blood (plasma) for PK sampling (Cycle 3 only, infusions 1 and 5) immediately prior to the start of the infusion
- Diphenhydramine 50 mg IV 60 minutes prior to infusion
- Acetaminophen 650 mg (or equivalent dose of paracetamol) 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

All Patients, All Study Stages:

- 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 at 30 and 60 minutes post-infusion
- Collection of peripheral blood (plasma) for PK sampling (Cycle 3 only, 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

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

All Patients, All Study Stages:

- Concomitant medication assessment
- Physical examination
- Vital signs and weight
- 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

All Patients, All Study Stages:

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

9.4.5 Day 21 ±7 Days: End of Cycle

Note: The end-of-cycle evaluations (Day 21 or thereafter) may also serve as the pre-infusion evaluations for the subsequent cycles; with the exception of vital signs, these do not need to be duplicated on successive days unless there is an abnormality or other clinically relevant reason for repeat evaluation.

All Patients, All Study Stages:

- Concomitant medication assessment
- ECOG performance status
- 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)
- Monitoring for changes in visual acuity and color vision
- AE and SAE monitoring

Patients with BPDCN Only:

- Tumor response assessment: CT scan of index lesions as follows:
  - **Stage 1**: Cycles 2 and 4 and every 4th cycle thereafter.
  - **Stages 2-4** with baseline BPDCN involving lymph nodes or viscera: Cycles 2, 4, and 6 and following every 4th cycle thereafter. Without baseline BPDCN involving lymph nodes or viscera: Cycles 2, 6 and at Investigator's discretion thereafter.
- Tumor response assessment: skin (Cycles 2, 4, and 6, and every 2 cycles thereafter), including mSWAT

Stages 2-4

- Tumor response assessment: bone marrow aspiration (± biopsy). Bone marrow will be collected subsequent to Cycles 2, 4 and 6 and then every 3 months from Months 6-12; every 6 months from 12 to 24 months; and every 12 months thereafter until there is evidence of relapsed or progressive disease. If CD123 flow cytometry or IHC stain was performed on the bone marrow aspirations (± biopsy), the results should be recorded in the eCRF.
- Collection of peripheral blood samples for determination of blasts 21 (±7) days after the start of Cycle 2, and, for patients with evidence of peripheral blasts at baseline, 21 (±7) days after the start of Cycles 1 and 2 and 21 (±7) days after the start of every 2nd cycle thereafter (Cycles 4, 6, etc.) until there is evidence of relapsed or progressive disease.

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

All Patients, All Study Stages:

- Concomitant medication assessment
- ECOG performance status
- Vital signs and weight

- 12-lead ECG
- Clinical laboratory tests: hematology, serum electrolytes and chemistry (including albumin), coagulation parameters, and urinalysis
- AE and SAE monitoring

9.5 End of Treatment

All Patients, All Study Stages:

- ECOG performance status
- Physical examination
- Vital signs and weight
- Monitoring for changes in visual acuity and color vision

9.6 Safety Monitoring: Through 30 Days after Last Infusion

All Patients, All Study Stages:

- AE and SAE monitoring
- Survival status

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

Patients in PR/CR at End of Treatment:

- Survival status and response/disease progression status, 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 and delayed or failed engraftment as part of survival monitoring.

9.8 Schedules of Events

The study schedule of events is summarized in Table 5, Table 6, Table 7, and Table 8.

Table 5: Study Events Schedule for Cycle 1 (Study Day -14 to Study Day 21): Stage 1 (All Pts) & Stage 2 (AML Pts)

		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[q] and 15±3**	**Study Day 21±7**	**Study Day 28±7, Then Every 7±3 days**
Tests and Observations	***Screening***	***Pre-treatment***	***Pre-Infusion***	***Infusion***		***End of Cycle***	***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	X	
Pregnancy test [a]	X						
Vital signs and weight[b]	X	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					X	
Tumor response assessment: CT scan[k]	X						
Tumor response assessment: Skin, including biopsies and/or photographs[l]	X					X	
Tumor response assessment: Peripheral blood						X	
Administration of premeds [m]			X				
SL-401 administration[n]				X			
Pharmacokinetic sampling[o]			X (Infusions 1, 5)	X (Infusions 1, 5)			
Immunogenicity sampling[p]			X (Infusion 1)		X (Day 15)	X	
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 21 (and Day 28 only if delayed end of cycle) of each cycle. During the days when patients are undergoing PK sampling (Cycle 1, infusions 1 and 5; Cycle 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 (p) and Table 9).
(d) MUGA or 2-D ECHO to quantify left ventricular ejection fraction (LVEF). Must be completed within 28 days prior to start of first cycle of study treatment.
(e) To be collected prior to SL-401 infusion if during dosing period. Hematology includes White blood cell (WBC) count, differential white cell count, red blood cell 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, blood urea nitrogen (BUN), and creatinine.
(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 during treatment days or in the immediate post-treatment period.
(h) To be collected prior to SL-401 infusion if during dosing period. Serum electrolytes and chemistry: Sodium, potassium, bicarbonate, chloride, blood urea nitrogen (BUN), creatinine, glucose, alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase, (AST), bilirubin (total, direct, and indirect), calcium, creatine phosphokinase (CPK), magnesium, lactate dehydrogenase (LDH), phosphate, total protein, 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 21 (±7) days after the start of Cycles 1 and 2, and at the Investigator's discretion thereafter until there is evidence of relapsed or progressive disease. If the Cycle 1 (Day 21 [±7]) bone marrow aspirate (±biopsy) is empty, hypocellular, or inadequate, a bone marrow examination should be repeated within 7 (±7) days to document response. During Stage 2, AML patients will also have bone marrow evaluations following Cycles 4 and 6, and at the Investigator's discretion prior to end of treatment and thereafter. If CD123 flow cytometry or IHC stain was performed on the bone marrow aspirations (± biopsy), the results should be recorded in the eCRF.
(k) BPDCN patients only. Baseline must be performed within 14 days prior to the first administration of SL-401. Subsequent CT scans will be performed 21 (±3) days after the start of Cycle 2 and 4 and 21 (±7) days after the start of every 4th cycle thereafter until there is evidence of relapsed or progressive disease. Baseline CT scans should be full-body, whereas follow-up scans should document response of index lesions.
(l) BPDCN patients only, with biopsies and/or photographs for patients with skin involvement. Baseline must be performed within 14 days prior to the first administration of Sl-401. Subsequent skin assessments will be performed 21 (±3) days after the start of Cycles 1 and 2 and 21 (±7) days after the start of every 2nd cycle thereafter (Cycles 4, 6, etc.) until there is evidence of relapsed or progressive disease.
(m) Refer to protocol Section 7.5.3.1 – Premedication
(n) Following treatment with premedication, SL-401 will be administered as a 15-minute infusion for the first 5 consecutive days of a 21-day cycle. Individual SL-401 infusions may be delayed to allow for toxicity resolution, all infusions should be completed within 10 days and fewer than 5 infusions are permitted in settings of incipient CLS or hepatotoxicity. Patients must be monitored for 4 hours post infusion.
(o) 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) (see (c) and Table 9).
(p) Blood samples (10 mL) will be collected for the detection of SL-401 reactive antibodies according on Day 1 (pre-infusion), Day 15, and Day 21 (if patient is to receive Cycle 2, can be Day 1, pre-infusion for Cycle 2). If infusions are held, please collect a sample within 3±3 days after the last SL-401 infusion(s) of the cycle.

Table 6: Study Events Schedule for Cycles 2-6 and Subsequent Cycles: Stage 1 (All Pts) & Stage 2 (AML Pts)

	Cycle 2+							
	Days 1-5 (Up to Day 10 if Infusion(s) Held) SL-401 Treatment		Day 8±3[q] and 15±3	Day 21±3	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***	***Delayed End of Cycle for Toxicity Resolution Only if Required***			
Medical history including prior therapy, concomitant medications								
Concomitant Medications			X	X	X			
ECOG performance status				X	X	X		
Physical examination			X	X		X		
Vital signs and weight[a]	X	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 [h]				
Tumor response assessment: CT scan[i]				X				
Tumor response assessment: skin, including biopsies and/or photographs[j]				X				
Tumor response assessment: peripheral blood				X[k]				
Administration of premeds [l]	X							
SL-401 administration[m]		X						
Pharmacokinetic sampling[n]	X (Cycle 3, Infusions 1, 5)	X (Cycle 3, Infusions 1, 5)						
Immunogenicity sampling[o]	X (Infusion 1)			X				
AE and SAE monitoring	X	X	X	X	X		X	
Long-term follow-up[p]							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 21 (and Day 28 only if delayed end of cycle) of each cycle. During the days when patients are undergoing PK sampling (Cycle 1, infusions 1 and 5; Cycle 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 (n) and Table 9).
(c) To be collected prior to SL-401 infusion if during dosing period. Hematology includes White blood cell (WBC) count, differential white cell count, red blood cell 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, blood urea nitrogen (BUN), and creatinine.
(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 during treatment days or in the immediate post-treatment period.
(f) To be collected prior to SL-401 infusion if during dosing period. Serum electrolytes and chemistry: Sodium, potassium, bicarbonate, chloride, blood urea nitrogen (BUN), creatinine, glucose, alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase, (AST), bilirubin (total, direct, and indirect), calcium, creatine phosphokinase (CPK), magnesium, lactate dehydrogenase (LDH), phosphate, total protein, 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. Bone marrow aspirates (± biopsy) will be performed 21 (±7) days after the start of Cycle 2, and, in Stage 1, at the Investigator's discretion prior to end of treatment and thereafter until there is evidence of relapsed or progressive disease. During Stage 2, AML patients will also have bone marrow evaluations following Cycles 4 and 6 and then every 3 months from Months 6-12; every 6 months from 12 to 24 months; and every 12 months thereafter until there is evidence of relapsed or progressive disease. If CD123 flow cytometry or IHC stain was performed on the bone marrow aspirations (± biopsy), the results should be recorded in the eCRF.
(i) BPDCN patients only. Baseline must be performed within 14 days prior to the first administration of SL-401. In Stage 1, subsequent CT scans will be performed 21 (±7) days after the start of Cycle 2 and 4 and 21 (±7) days after the start of every 4th cycle thereafter until there is evidence of relapsed or progressive disease. Baseline CT scans should be full-body, whereas follow-up scans should document response of index lesions.
(j) BPDCN patients only, with biopsies and/or photographs for patients with skin involvement. Baseline must be performed within 14 days prior to the first administration of SL-401. Subsequent skin assessments will be performed 21 (±7) days after the start of Cycles 1 and 2 and 21 (±7) days after the start of every 2nd cycle thereafter (Cycles 4, 6, etc.) until evidence of relapsed or progressive disease. Quantification of disease burden via the mSWAT is required at the time of each skin assessment.
(k) Patients with evidence of peripheral blasts at baseline will have peripheral blood samples collected 21 (±7) days after the start of Cycles 1 and 2 and 21 (±7) days after the start of every 2nd cycle thereafter (Cycles 4, 6, etc.) until there is evidence of relapsed or progressive disease.
(l) Refer to protocol Section 7.5.3.1 – Premedication
(m) Following treatment with premedication, SL-401 will be administered as a 15-minute infusion for the first 5 consecutive days of a 21-day cycle. Individual SL-401 infusions may be delayed to allow for toxicity resolution; all infusions should be completed within 10 days and fewer than 5 infusions are permitted in settings of incipient CLS or hepatotoxicity. Patients must be monitored for 4 hours post infusion.
(n) 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 Cycle 3 (see footnote (b) and Table 9).
(o) Blood samples (10 mL) will be collected for the detection of SL-401 reactive antibodies according on Day 1 (pre-infusion), Day 15, and Day 21 (if patient is to receive additional cycles, can be Day 1, pre-infusion for next cycle). If infusions are held, please collect a sample within 3±3 days the last SL-401 infusion(s) of the cycle.
(p) After the follow-up visit, patients will then be followed every 90 days for survival status. The survival follow-up may be by telephone contact. If the patient is in CR/PR at the time of discontinuation, disease assessments should continue to be performed as described in Section 8.11 on an every 6-week basis (±1 week) through 6 months post-C1D1 and then on an every 90-day basis or until, in the judgment of the Investigator, there is evidence of relapsed or progressive disease.

Table 7: Study Events Schedule for Cycles 1 & 2 (Study Day -14 to Study Day 21): BPDCN Patients in Stages 2-4

		Cycles 1 & 2					
	Study Day -14 to -4	**Study Day -1 to 0**	**Cycle Days 1-5 (Up to Study Day 10 if Infusion(s) Held) SL-401 Treatment**		**Study Day 8±3[q] and 15±3**	**Cycle Day 21±7**	**Cycle Day 28±7, Then Every 7±3 days**
Tests and Observations	***Screening***	***Pre-treatment***	***Pre-Infusion***	***Infusion***		***End of Cycle***	***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	X	
Pregnancy test [a]	X						
Vital signs and weight[b]	X	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					X	
Tumor response assessment: CT scan[k]	X					X (Cycle 2) [k]	
Tumor response assessment: Skin, including biopsies and/or photographs[l]	X					X	
Tumor response assessment: Peripheral blood						X	
Administration of premeds [m]			X				
SL-401 administration[n]				X			
Pharmacokinetic sampling[o]			X (Infusions 1, 5)	X (Infusions 1, 5)			
Immunogenicity sampling[p]			X (Infusion 1)		X (C1D15 only)	X	
Vision assessment	X					X	
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 21 (and Day 28 only if delayed end of cycle) of each cycle. During the days when patients are undergoing PK sampling (Cycle 1, infusions 1 and 5; Cycle 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 (p) and Table 9).
(d) MUGA or 2-D ECHO to quantify left ventricular ejection fraction (LVEF). Must be completed within 28 days prior to start of first cycle of study treatment.
(e) To be collected prior to SL-401 infusion if during dosing period. Hematology includes White blood cell (WBC) count, differential white cell count, red blood cell 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, blood urea nitrogen (BUN), and creatinine.
(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 during treatment days or in the immediate post-treatment period.
(h) To be collected prior to SL-401 infusion if during dosing period. Serum electrolytes and chemistry: Sodium, potassium, bicarbonate, chloride, blood urea nitrogen (BUN), creatinine, glucose, alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase, (AST), bilirubin (total, direct, and indirect), calcium, creatine phosphokinase (CPK), magnesium, lactate dehydrogenase (LDH), phosphate, total protein, uric acid
(i) To be collected prior to initial SL-401 infusion of the cycle. 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. For BPDCN patients in Stages 2-4, subsequent bone marrow aspirates (± biopsy) will be performed 21 (±7) days after the start of Cycles 1 and 2. If the Cycle 1 (Day 21 [±7]) bone marrow aspirate (± biopsy) is empty, hypocellular, or inadequate, a bone marrow examination should be repeated within 7 (±7) days to document response. If CD123 flow cytometry stain was performed on the bone marrow aspirations (± biopsy), the results should be recorded in the eCRF.
(k) Baseline CT must be performed within 14 days prior to the first administration of SL-401. For patients with baseline evidence of lymph node or visceral disease involvement, subsequent Stages 2-4 CT scans will be performed 21 (±7) days after the start of Cycles 2, 4 and 6, and 21 (±7) days after the start of every 4th cycle thereafter (approximately every 12 weeks) until there is evidence of relapsed or progressive disease. For patients with no baseline evidence of lymph node or visceral BPDCN involvement, subsequent scans should be performed at the end of Cycle 2 (±7 days; or at time of disease progression if PD occurs prior to end of Cycle 2), 21 (±7) days after the start of Cycle 6, and at Investigator's discretion thereafter. Baseline CT scans should be full-body, whereas follow-up scans should document response of index lesions.
(l) For patients with skin involvement. Baseline must be performed within 14 days prior to the first administration of Sl-401. Subsequent skin assessments will be performed 21 (±7) days after the start of Cycles 1 and 2 and 21 (±7) days after the start of every 2nd cycle thereafter (Cycles 4, 6, etc.) until there is evidence of relapsed or progressive disease. Quantification of skin disease burden via the mSWAT instrument is required at the time of each skin assessment.
(m) Refer to protocol Section 7.5.3.1 – Premedication and Administration
(n) Following treatment with premedication, SL-401 will be administered as a 15-minute infusion for the first 5 consecutive days of a 21-day cycle. Individual SL-401 infusions may be delayed to allow for toxicity resolution; all infusions should be completed within 10 days and fewer than 5 infusions are permitted in settings of incipient CLS or hepatotoxicity. Patient must be monitored for 4 hours post infusion.
(o) 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) of Cycles 1 & 3 (see Table 9).
(p) Blood samples (10 mL) will be collected for the detection of SL-401 reactive antibodies on Day 1 (pre-infusion), Day 15, and Day 21 (if patient is to receive Cycle 2, can be Day 1, pre-infusion for Cycle 2). If infusions are held, please collect a sample within 3±3 days after completion of the last SL-401 infusion of the cycle.

Table 8: Study Events Schedule for Cycles 3-6 and Subsequent Cycles: Stages 2-4 (BPDCN Patients)

	Cycle 3+							
	Days1-5 (Up to Day 10 if Infusion(s) Held) SL-401 Treatment		Day 8±3[q] and 15±3[q]	Day 21±7	Day 28±7, 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***	***Delayed End of Cycle for Toxicity Resolution Only if Required***			
Medical history including prior therapy, concomitant medications								
Concomitant Medications			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[i]				
Tumor response assessment: CT scan[i]				X				
Tumor response assessment: skin, including biopsies and/or photographs[j]				X				
Tumor response assessment: peripheral blood				X[k]				
Administration of premeds [l]	X							
SL-401 administration[m]		X						
Pharmacokinetic sampling[n]	X (Cycle 3, Infusions 1, 5)	X (Cycle 3, Infusions 1, 5)						
Immunogenicity sampling[o]	X (Infusion 1)			X				
Vision assessment					X	X		
AE and SAE monitoring	X	X	X	X	X		X	
Long-term follow-up[p]							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 21 (and Day 28 only if delayed end of cycle) of each cycle. During the days when patients are undergoing PK sampling (Cycle 1, infusions 1 and 5; Cycle 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 (m) and Table 9).
(c) To be collected prior to SL-401 infusion if during dosing period. Hematology includes White blood cell (WBC) count, differential white cell count, red blood cell 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, blood urea nitrogen (BUN), and creatinine.
(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 during treatment days or in the immediate post-treatment period.
(f) To be collected prior to SL-401 infusion if during dosing period. Serum electrolytes and chemistry: Sodium, potassium, bicarbonate, chloride, blood urea nitrogen (BUN), creatinine, glucose, alanine aminotransferase (ALT), albumin, alkaline phosphatase (ALP), aspartate aminotransferase, (AST), bilirubin (total, direct, and indirect), calcium, creatine phosphokinase (CPK), magnesium, lactate dehydrogenase (LDH), phosphate, total protein, uric acid
(g) To be collected prior to initial SL-401 infusion of the cycle. 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. In Stages 2-4, patients with evidence of bone marrow involvement prior to study will have bone marrow evaluations following Cycles 4 and 6 and then every 3 months from Months 6-12; every 6 months from 12 to 24 months; and every 12 months thereafter until there is evidence of relapsed or progressive disease. If CD123 flow cytometry stain was performed on the bone marrow aspirations (± biopsy), the results should be recorded in the eCRF.
(i) Baseline CT must be performed within 14 days prior to the first administration of SL-401. For patients with baseline evidence of lymph node or visceral disease involvement, subsequent Stages 2-4 CT scans will be performed 21 (±7) days after the start of Cycles 1, 2, 4 and 6, and 21 (±7) days after the start of every 4th cycle thereafter (approximately every 12 weeks) until there is evidence of relapsed or progressive disease. For patients with no baseline evidence of lymph node or visceral BPDCN involvement, subsequent scans should be performed at the end of Cycle 2 (±7 days; or at time of disease progression if PD occurs prior to end of Cycle 2), 21 (±7) days after the start of Cycle 6, and at Investigator's discretion thereafter. Baseline CT scans should be full-body, whereas follow-up scans should document response of index lesions.
(j) For patients with skin involvement. Baseline must be performed within 14 days prior to the first administration of Sl-401. Subsequent skin assessments will be performed 21 (±7) days after the start of Cycles 1 and 2 and 21 (±7) days after the start of every 2nd cycle thereafter (Cycles 4, 6, etc.) until there is evidence of relapsed or progressive disease. Quantification of skin disease burden via the mSWAT instrument is required at the time of each skin assessment.
(k) Peripheral blood samples will be collected 21 (±7) days after the start of Cycles 1 and 2 and, for patients with evidence of peripheral blasts at baseline, 21 (±7) days after the start of every 2nd cycle thereafter (Cycles 4, 6, etc.) until there is evidence of relapsed or progressive disease.
(l) Refer to protocol Section 7.5.3.1 – Premedication and Administration
(m) Following treatment with premedication, SL-401 will be administered as a 15-minute infusion for the first 5 consecutive days of a 21-day cycle. Individual SL-401 infusions may be delayed to allow for toxicity resolution; all infusions should be completed within 10 days and fewer than 5 infusions are permitted in settings of incipient CLS or hepatotoxicity. Patient must be monitored for 4 hours post infusion.
(n) 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 (see Table 9).
(o) Blood samples (10 mL) will be collected for the detection of SL-401 reactive antibodies on Day 1 (pre-infusion), Day 15, and Day 21 (if patient is to receive additional cycles, can be Day 1, pre-infusion for next cycle). If infusions are held, please collect a sample within 3±3 days after the last SL-401 infusion of the cycle.
(p) After the follow-up visit, patients will then be followed every 90 days for survival status. The survival follow-up may be by telephone contact. If the patient is in CR/PR at the time of discontinuation, disease assessments should continue to be performed as described in Section 8.12 on an every 6-week basis (±1 week) through 6 months post-C1D1 and then on an every 90-day basis or until, in the judgment of the Investigator, there is evidence of relapsed or progressive disease. Patients who undergo SCT will be followed for the occurrence of VOD and delayed or failed engraftment as part of survival monitoring.
(q) For Cycles 5 and beyond (Stages 2-4), the Day 8 and 15 concomitant medication and AE evaluations may be conducted via telephone and the laboratory evaluations may be performed at local laboratories for patients who live a considerable distance from the study center.

Table 9: Time Points for Pharmacokinetic Blood Draws and ECGs

	Cycle: Day/Dose							
	Cycle 1: Day 1/Infusion 1		Cycle 1: Day 5/Infusion 5		Cycle 3: Day 1/Infusion 1		Cycle 3: Day 5/Infusion 5	
Time Point	ECG	PK	ECG	PK	ECG	PK	ECG	PK
Pre-Infusion	X	X	X	X	X	X	X	X
Immediately After End of Infusion (time recorded)		X		X		X		X
15 Minutes Post-Infusion		X		X		X		X
30 Minutes Post-Infusion	X	X	X	X	X	X	X	X
45 Minutes Post-Infusion		X		X		X		X
60 Minutes Post-Infusion	X	X	X	X	X	X	X	X
90 Minutes Post-Infusion		X		X		X		X
120 Minutes Post-Infusion		X		X		X		X
180 Minutes Post-Infusion		X		X		X		X
240 Minutes Post-Infusion		X		X		X		X

ECGs will be performed at 3 distinct time points (triplicates) within 5 minutes prior to each PK sample collection at the time points indicated.

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 or designee, 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 serious adverse event (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 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 an 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, engraftment delay or failure 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.

Adverse events associated with inpatient 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 AEs 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 exam)
  - 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

Progression of the disease under study (including signs and symptoms of progression) should not be reported as SAEs 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 National Cancer Institute (NCI) Common Terminology Criteria for Adverse Events (CTCAE) Grade 5. PD 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) or upon death.

10.2 Period of Observation

Clinical signs and symptoms, and AEs (regardless of relationship to study treatment) 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 treatment 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 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 NCI 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 2 months 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 during Screening within 1 week prior to dosing. 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 treatment, 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 postpartum.

10.5 Documentation and Reporting of Adverse Events by Investigator

The Investigator is to report all directly observed AEs as well as those 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 non-leading 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 eCRFs.

All AEs that occur in study patients during the AE reporting period specified in the protocol must be reported to the Sponsor or designee, whether or not the event is considered study treatment-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 [redacted] Safety **within 24 hours** of the knowledge of the occurrence. To report the SAE, the SAE form is to be completed electronically in the electronic data capture (EDC) system for the study. When

the form is completed, [redacted] personnel will be notified electronically and will retrieve the form. If the event meets serious criteria and it is not possible to access the internet, an email to should be sent to [redacted] or a call made to the [redacted] within 24 hours of awareness. When the EDC system becomes available, the SAE information must be entered within 24 hours of the system becoming available.

[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., subject discharge summary or autopsy reports) to [redacted] via fax or e-mail. If it is not possible to access the EDC system, refer to the procedures outlined above for initial reporting of SAEs.

The Sponsor will report AEs, which are unexpected and reported as serious and associated with use of the study drug, to the US Food and Drug Administration (FDA) and all participating clinical sites. For events, which 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. Reports of delayed or failed engraftment post-SCT will be reported as 15-day safety reports.

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 subject may have.
- Concomitant medication: The other medications the subject is taking or the treatment the subject 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 AE. 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.x, pages 23 and 26]).

11 Excluded Prior and Concomitant Medications and Therapy

An enrolled patient may not receive investigational or approved anticancer or anti-leukemia agents, including cytotoxic chemotherapy agents, hypomethylating agents (5-azacytadine, decitabine or others), or anticancer tyrosine kinase inhibitors (including imatinib, ruxolitinib, sorafenib and others) or therapeutic monoclonal antibodies. Hydroxyurea may be administered (however its use should be discussed with the Medical Monitor).

12 Statistical Analysis

12.1 General Considerations

Study STML-401-0114 contains patients with both AML and first-line and R/R BPDCN. The current development strategy for SL-401 is to first pursue marketing authorization for an indication in first-line BPDCN patients, with potential additional indications in R/R BPDCN and/or AML, depending on the study results. Therefore, this statistical analysis section will focus primarily on the first-line BPDCN indication, with generally similar analytical approaches to be taken with the other potential indications upon achievement of sufficient data.

Analyses will be performed on all patients who 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. Study Day 1 for each individual patient is defined as the date the patient receives their first infusion of SL-401.

Unless otherwise stated, all analyses will be performed using SAS Version 9 and all hypothesis tests will be conducted at a two-sided significance level of 0.05 or at a one-sided significance level of 0.025. P-values will be presented with 3 decimals and p-values that are less than 0.001 will be presented as <0.001. Selected data summaries will be presented by disease (BPDCN and AML), with the primary data presentations provided for data from patients with BPDCN. For data from BPDCN patients, further categories for summarization will consist of line of therapy (first-line, R/R, and total) and dose (12 µg/kg/day and all doses). Efficacy endpoints will be summarized separately for Stage 3 patients, with an additional summary for all first-line and R/R BPDCN patients across all study stages. Stage 4 will be analyzed separately.

Continuous (non-survival related) data will be summarized using descriptive statistics: number of observations (n), mean, standard deviation (SD), median, minimum, and maximum. Time to event data will be summarized using frequency and percentage of events and censored observations. Kaplan-Meier analysis will be performed to estimate the 25th percentile, median, and 75th percentile for time to events with corresponding two-sided 95% confidence intervals.

Unless otherwise stated, confidence intervals, when presented, will be constructed at the 2-sided 95% level. For binomial variables, 95% confidence intervals will be constructed using the Clopper Exact method instead of normal approximation.

Data listings will present all data collected on eCRFs by study drug dose, center, Stage of study enrollment, and patient number.

12.2 Populations for Analysis

Safety analysis will be performed on the population of patients who have received any amount of study treatment. The primary population for the analysis of efficacy will be the modified intent-to-treat (mITT) population, consisting of those patients who are eligible based on screening criteria, and have received at least one dose of study drug. For BPDCN patients an additional criterion for mITT patients will be a confirmed diagnosis based on central pathology review. BPDCN patients in the mITT population will be said to be evaluable. Additional efficacy analyses will be performed on a per-protocol (PP) population, consisting of those patients who are in the mITT population, are compliant with all major aspects of the protocol, and have received a minimum of 2 cycles of study treatment.

12.3 Determination of Sample Size

The sample size was originally planned to be approximately 40-50 patients with BPDCN, including approximately 40 first-line patients planned to be treated with the optimal SL-401 dose as determined in the completed Stage 1 of this study (12 µg/kg/day). In addition, up to approximately 36 patients with R/R AML were planned to be enrolled in Stage 2 of the study.

In Stage 3, a sufficient number of patients were enrolled to ensure 10 evaluable patients were included, with evaluable patients being those with a diagnosis of BPDCN, as confirmed via

central pathology review who received at least 1 dose of SL-401. The sample size allocated for Stage 3 is intended to satisfy specific statistical criteria established by the Sponsor at the request of the US FDA. [redacted] The primary efficacy analysis for Stage 3 compares the lower bound of a two-sided 95% Clopper Exact confidence interval surrounding the observed CR rate to a clinically meaningless value of 10%. Statistical significance is determined if the lower bound of this confidence interval falls above the rate of 10%. Assuming a CR rate of at least 60%, a sample size of a minimum of 10 first-line BPDCN patients provides at least 90% power for this the primary efficacy assessment. [redacted] To avoid possible selection bias, all first-line BPDCN patients enrolled in this time period are included in the Stage 3 analysis. This sample size also ensures there are 10 patients in the PP analysis population.

After the maximum number of patients with first-line BPDCN in Stage 3 were enrolled, subsequent first-line BPDCN patients are enrolled in Stage 4. Furthermore, any patient with R/R BPDCN enrolled in this study on or after 26 October, 2016, will be allocated to Stage 4. Enrollment will continue in Stage 4 up until enrollment of up to approximately 145 patients or prior termination of the study.

12.4 Demographics and Baseline Characteristics

Demographic (e.g., gender, age, 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.

12.5 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. Safety data analysis will be performed primarily on the pool of first-line BPDCN patients treated with the 12 µg/kg/day dose level, with additional summaries across all BPDCN patients, patients with R/R disease and the pool of all BPDCN patients. Separate safety tabulations will be produced for patients with AML, patients who are treated with the lyophilized formulation of SL-401, and an overall pool of all enrolled patients.

Treatment-emergent AEs through 30 days after last SL-401 infusion will be summarized by 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 treatment). Dose-limiting toxicities, ≥Grade 3 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.

12.6 Analysis of Efficacy Data in First-Line BPDCN

Efficacy assessments include CR rate (i.e., CR + CRi + CRc), DOR, ORR, PFS, and OS. The following sections refer specifically to patients with first-line BPDCN, treated at the 12 µg/kg/day dose level. The following sub-sections refer specifically to patients with first-line BPDCN, treated at the 12 µg/kg/day dose level. The analysis of efficacy of SL-401 in these patients will be performed to address several objectives, based on data from the different stages of the study.

Analyses by stage are intended as follows. Stage 3 will provide the pivotal results for a potential registrational submission in first-line BPDCN patients as assessed by rate of CR+CRc. Stage 1 and 2 results will be presented, similar to the interim analysis as noted in Section 12.10. Stage 4 results will be presented separately and may be used to assess consistency across drug formulations.

12.6.1 Order of Statistical Analyses of Efficacy

The primary evidence of efficacy will be derived from an analysis of the rate of CR+CRc, as assessed by the Investigator, in patients in Stage 3, accompanied by an evaluation of the durability of these CRs as a key secondary endpoint. A formal statistical analysis will first be performed for the primary efficacy endpoint to test the hypothesis that the rate of CR in first-line patients in Stage 3 exceeds the lower benchmark value of 10%. The primary analysis will be performed when all patients in Stage 3 have been followed for a minimum of 3 cycles or discontinued treatment, whichever occurs first. In addition, the durability of CR will be evaluated; refer to Section 12.6.3 for analysis methods for duration.

A number of additional secondary analyses will then be performed, to further evaluate the rate of CR in other stages of the study and to assess additional efficacy parameters in support of the primary analysis results. The analyses of all secondary endpoints will be descriptive, with

summaries of secondary endpoints to be evaluated and presented in the following order of importance (as noted above, these analyses will be performed on data from first-line BPDCN patients treated at the 12 µg/kg/day dose level):

1. Bone-marrow CR (BMCR) and DOR for Stage 3
2. CR rate and DOR for Stages 1 and 2
3. CR rate and DOR for pooled data from Stages 1, 2, 3, and 4
4. ORR and DOR for Stages 1 and 2
5. ORR and DOR for pooled data from Stages 1, 2, 3, and 4
6. Proportion of patients who receive SCT based on pooled data from Stages 1, 2, 3 and 4
7. PFS for Stages 1, 2, 3, and 4
8. OS for Stages 1, 2, 3, and 4

Response will be assessed using International Working Group (IWG) criteria for AML (for patients with AML) (Cheson et al. 2003) and a modified version of the Revised Response Criteria for Malignant Lymphoma (for patients with BPDCN) (Cheson et al. 2007). Disease response in skin will be assessed using the weighted BSA/modified Severity Weighted Assessment tool (mSWAT) score (for patients with BPDCN) (Olsen et al. 2011). For the patients with BPDCN, assessment of response and disease progression will include evaluation of all sites of disease involvement at baseline, which may include skin, lymph nodes, spleen, liver, peripheral blood, and bone marrow. Up to 6 of the largest dominant nodes or nodal masses should be identified as index lesions for radiographic response assessments. Response criteria for AML and BPDCN are summarized in Sections 16.1 and 16.2, respectively, and the mSWAT template is presented in Section 16.3.

12.6.2 Response Rate

For rates of response, including CR and ORR, as appropriate, two-sided 95% Clopper Exact confidence intervals around the response rate will be presented. For CR+CRc in first-line patients in Stage 3, statistical significance at the one-sided 0.025 will be declared if the lower bound of this confidence interval exceeds the lower clinical benchmark level of 10%. An analysis of the rate of bone-marrow CR (BMCR) will also be performed, by pooling data from patients who had either CR or PR with complete bone-marrow response (reduction to <5% blast cells), as a proportion of all patients with marrow disease (≥ 5% blast cells) at baseline.

12.6.3 Duration of Response

DOR is defined as the time from when measurement criteria are first met for CR/CRi/CRc (whichever is recorded first) until the date that the criteria for relapse after CR/CRi/CRc is met.

For patients who receive bone marrow transplant after CR/CRi/CRc is observed, duration of response will include time to disease relapse post-transplant. Patients who are lost to follow-up or who do not relapse after CR/CRi/CRc as of the cut-off for analysis will be censored at the date of last radiologic assessment while on study. The same definition will be used for ORR, with the obvious modification that data from patients with either CR or PR will be included.

Analysis of duration of response will be performed by Kaplan-Meier time to event analysis to estimate the 25th percentile, median, and 75th percentile of times to event, number, and percentage of events, censored observations, and appropriate confidence intervals. Additional descriptive analysis will be performed separately for patients who do and do not receive bone marrow transplant.

12.6.4 Bridge to SCT

The proportion of patients who become eligible and receive SCT will be analyzed, using the data from Stage 1-4. Patients may receive SCT subsequent to CR or PR; therefore, this analysis will be performed by response category as well as overall.

12.6.5 Progression-free Survival

Progression-free survival is defined as the time from the date of first infusion of SL-401 to the date of progressive disease (PD) or death from any cause, whichever occurred first. The distribution for progression free survival will be estimated by Kaplan-Meier methodology.

12.6.6 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.

12.6.7 Exploratory and Subgroup Analyses

Exploratory and subgroup analyses may be performed to assess the influence of demographic and baseline characteristics on the rate of CR. In general, the exploratory and subgroup analyses will use the pooled data from first-line BPDCN patients from Stages 1, 2, 3, and 4.

12.7 Additional Efficacy Analyses

Analysis of efficacy data from patients with R/R disease at study entry will be performed for all such patients, pooled Stage 1 and 2, using descriptive methods similar to those intended for the analysis of first-line BPDCN patients. Data from patients enrolled into Stage 4 will be presented separately; response data from the pool of Stages 3 and 4 may also be presented to augment the results from the pivotal Stage 3. A pooled, descriptive analysis of R/R patients across Stages 1, 2, and 4 will be performed.

Additional efficacy analysis, including assessments of CR, DOR, and ORR, may be performed on patients treated with the lyophilized formulation of the SL-401 product. Analysis will be performed separately for R/R and first-line BPDCN patients. Efficacy for patients with AML will be analysed separately upon achievement of sufficient data.

Efficacy data from first-line BPDCN patients treated with an initial dose other than 12 µg/kg/day dose level will be summarized.

12.8 Pharmacokinetic and Immunogenicity Analyses

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

12.9 Blinding

This is an open-label study.

12.10 Interim Analyses

In Stages 2-4 of the study, the DSRC will conduct a safety data review on an every 1-2-month basis.

An informal interim analysis was performed on efficacy data from Stages 1 and 2 [redacted] (see Section 3.7.2). This analysis was performed on the 32 patients enrolled in the study through 29 August, 2016; note that no further enrollment of first-line BPDCN patients occurred until October, 2016. [redacted]

12.11 Final Analysis

The final safety and efficacy analyses will be performed upon study completion. Study completion is the date in which every patient who is alive had at least 12 months of follow up data.

12.12 Study Oversight Committees

Study conduct will be monitored by the following oversight committees: a DSRC and an IRC. The roles of these committees are outlined briefly as follows, and will also be delineated in detail in designated committee charters.

- The DSRC includes Sponsor representatives and study Investigators. The DSRC will review cumulative safety data and make decisions regarding DLT determination, dose escalation, and cohort progression during Stage 1. The DSRC may also make other recommendations pertinent to patient safety, both in Stage 1 and Stages 2-4, and will periodically review data during Stages 2-4 on an every 1-2-month basis.
- Tumor response will be assessed by the Investigators for all patients with BPDCN, with the Investigator's assessment to be used in the primary analysis. A central pathologist will confirm histopathological BPDCN diagnosis. As a supportive assessment, tumor response was also evaluated by an IRC on a pre-specified subset of patients in Stages 2-4. The IRC will be comprised of clinicians with expertise in hematologic and/or dermatologic malignancies who are not involved in the clinical study, and will review

data as reported by the Investigators for the assessment of response. It is anticipated that the IRC will meet several times per year.

13 Emergency Procedures

13.1 Emergency Contact

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

13.2 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.

13.3 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.

14 Ethical and Regulatory Considerations

14.1 Good Clinical Practice

As the Sponsor of this clinical study, Stemline Therapeutics Inc. 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, ICH Guideline E6, Declaration of Helsinki, and Good Clinical Practice (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 ensuring IRB approvals are obtained, 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.

14.2 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 treatments, 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.

14.3 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 Informed Consent Form (ICF) that includes information about the study 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 about the study 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.

After reading the informed consent document, 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. An original copy of the signed consent document 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 regulatory authorities.

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.

14.4 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.

14.5 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.

14.6 IRB/IEC Approval and Reporting

The Investigator must obtain appropriate IRB/IEC 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 Institution affiliations, gender makeup, and occupations) or supply a statement from the IRB specifying that the membership complies with applicable regulations.

The study protocol, ICF, 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.

14.7 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.

14.8 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. Patient records must be retained even 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.

14.9 Liability and Insurance

Liability and insurance provisions for this study are provided in the Investigator's contract with Stemline.

14.10 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.

14.11 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 by the Investigator.

14.11.1 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; 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, 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.

14.11.2 Study Documentation

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

- Completed and signed 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 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 in the Form 1572.
- A financial disclosure form for the Principal Investigator and any other persons listed in the 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 FWA/DHHS 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. A list of normal laboratory values

and units of measure for all laboratory tests required by the protocol is to be provided.

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

14.11.3 Site Audits

For the purpose of compliance with Good Clinical Practices (GCP) and regulatory agency guidelines, it may be necessary for Sponsor authorized Quality Assurance personnel and/or authorized personnel from a 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.

14.12 Documentation and Use of Study Findings

14.12.1 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 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, photographs (de-identified), 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 replace the information with the patient's study identification number.

14.12.2 Use of Study Findings

All information concerning the product, as well as any matter concerning the operations 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 in the study. 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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16 Appendices

16.1 Appendix A. Tumor Response Criteria for Patients with AML

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

Source: Cheson BD, Bennett JM, Kopecky KJ, et al. Revised recommendations of the international working group for diagnosis, standardization of response criteria, treatment outcomes, and reporting standards for therapeutic trials in acute myeloid leukemia. J Clin Oncol 2003;21:4642-4649.

16.2 Appendix B. Tumor Response Criteria for Patients with BPDCN

Response	Location	Criteria
Complete Response (CR)	Marrow[b]	• Normalization of blast percentage (≤5%) [b]
	Peripheral Blood	• Normalization of neutrophil count (≥1,000/μL) and platelet count (≥100,000/μL) • Absence of leukemic blasts
	Skin[a]	• 100% clearance of all skin lesions from baseline; no new lesions in patients without lesions at baseline[a]
	Nodal Masses	• Regression to normal size on CT
	Spleen, Liver	• Not palpable, nodules disappeared
CR with incomplete blood count recovery (CRi)	Marrow[b]	• Normalization of blast percentage (≤5%) [b]
	Peripheral Blood	• Incomplete recovery of neutrophil and/or platelet count • Absence of leukemic blasts
	Skin[a]	• 100% clearance of all skin lesions from baseline; no new lesions in patients without lesions at baseline[a]
	Nodal Masses	• Regression to normal size on CT
	Spleen, Liver	• Not palpable, nodules disappeared
CR [clinical] with minimal residual skin abnormality (CRc)	Marrow[b]	• Normalization of blast percentage (≤5%) [b]
	Peripheral Blood	• Normalization of neutrophil count (≥1,000/μL) and platelet count (≥100,000/μL) • Absence of leukemic blasts
	Skin[a]	• Marked clearance of all skin lesions from baseline; residual hyperpigmentation or abnormality with BPDCN identified on biopsy (or no biopsy performed) [a]
	Nodal Masses	• Regression to normal size on CT
	Spleen, Liver	• Not palpable, nodules disappeared
Partial Response (PR)	Marrow[b]	• Decrease by ≥50% in blast percentage to 5 − 25% [b]
	Peripheral Blood	• Normalization of neutrophil count (≥1,000/μL) and platelet count (≥100,000/μL)
	Skin[a]	• 50% − <100% clearance of all skin lesions from baseline; no new lesions in patients without lesions at baseline[a]
	Nodal Masses	• ≥50% decrease in SPD of up to 6 largest dominant masses; no increase in size of other nodes
	Spleen, Liver	• ≥50% decrease in SPD of nodules (for single nodule in greatest transverse diameter); no increase in size of liver or spleen
Stable Disease (SD)		• Failure to achieve at least a PR, but no evidence of progression for at least 8 weeks
Relapse after CR/CRi/CRc	Marrow[b]	• Blast percentage >5% (if no peripheral blasts, then confirmation aspirate required ≥1 week later) [b]
	Peripheral Blood	• Presence of leukemic blasts
	Skin[a]	• Increase in skin score greater than the sum of nadir plus 50% baseline score[a]
	Nodal Masses	• Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase from nadir in SPD of more than one node, or ≥50% increase from nadir in longest diameter of a previously identified node >1 cm in short axis
	Spleen, Liver	• >50% increase from nadir in the SPD of any previous lesions

Relapse after PR[c]	Marrow[b]	• Blast percentage ≥25% (if no peripheral blasts, then confirmation aspirate required ≥1 week later) [b]
	Skin[a]	• Increase in skin score greater than the sum of nadir plus 50% baseline score[a]
	Nodal Masses	• Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase from nadir in SPD of more than one node, or ≥50% increase from nadir in longest diameter of a previously identified node >1 cm in short axis
	Spleen, Liver	• >50% increase from nadir in the SPD of any previous lesions
Progressive Disease (PD) [c]	Marrow[b]	• ≥50% increase in blasts from baseline (and blast percentage >5%)[b]
	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
	Skin[a]	One or more of the following: • ≥25% increase in skin disease from baseline[a] • Any new tumors in patients without tumors at baseline
	Nodal Masses	• Appearance of a new lesion(s) >1.5 cm in any axis, ≥50% increase from nadir in SPD of more than one node, or ≥50% increase from nadir in longest diameter of a previously identified node >1 cm in short axis
	Spleen, Liver	• >50% increase from nadir in the SPD of any previous lesions

Source: Cheson BD, Pfistner B, Juweid ME, et al. The International Harmonization Project on Lymphoma. Revised response criteria for malignant lymphoma. J Clin Oncol 2007;25:579-586.
Abbreviations: CT, computed tomography; SPD, sum of the product of the diameters.
All parameters detailed above (including bone marrow, blood, skin [including mSWAT quantification], lymph nodes and viscera) are to be assessed both at baseline and stipulated subsequent timepoints. Responses are determined via comparison to baseline values (or post-treatment nadir values as stipulated in the above table).

[a] The percentage of clearance or increase in skin disease is calculated using the Modified Severity Weighted Assessment Tool (mSWAT), which is provided in Section 16.3/Appendix C. Detailed guidance and examples regarding the calculation of an mSWAT assessment based on the size and nature of a patient's skin lesions are provided in a separate document.

[b] In settings in which there is a change in the blast population on bone marrow evaluation by means of flow cytometry or other molecular methodology without a similar degree of change in the morphologic blast percentage, the morphologic percentage should be utilized to determine response/progression; however the findings from flow cytometry (or other molecular methodology) should be recorded as part of the study record.

[c] In settings in which there is preliminary but not conclusive evidence of disease progression (i.e., new skin lesions of indeterminate etiology, new lymph nodes ≤1.5cm, modest increase in bone marrow blast percentage subsequent to an initial marked reduction, appearance of new blast population on bone marrow evaluation by means of flow cytometry or other molecular methodology without increase in blast percentage consistent with PD), additional SL-401 cycles may be administered, provided that the Investigator documents that the evidence of potential disease progression is inconclusive and that the overall risk/benefit assessment favors additional investigational therapy. Additional SL-401 may also be administered in situations of mixed response BPDCN in which response/progression is not consistent between a given patient's disease sites, provided that the Investigator documents that the overall risk/benefit assessment favors additional investigational therapy. In such situations, it is essential that relevant findings and assessments are documented, and that areas of potential disease progression are followed closely on subsequent assessments.

16.3 Appendix C. Modified Severity Weighted Assessment Tool

Body Region	%BSA in Body Region	Assessment of Involvement in Patient's Skin		
		Patch[a]	Plaque[b]	Tumor[c]
Head	7			
Neck	2			
Anterior trunk	13			
Arms	8			
Forearms	6			
Hands	5			
Posterior trunk	13			
Buttocks	5			
Thighs	19			
Legs	14			
Feet	7			
Groin	1			
Subtotal of weighted BSA				
Weighting factor		× 1	× 2	× 4
Weighted subtotal				

Note: mSWAT score equals summation of weighted subtotals.
Abbreviations: BSA, body surface area; mSWAT, modified Severity Weighted Assessment Tool. Detailed guidance and examples regarding the calculation of an mSWAT assessment based on the size and nature of a patient's skin lesions are provided in a separate document.
[a]Any size lesion without induration or significant elevation above the surrounding uninvolved skin; poikiloderma may be present.
[b]Any size lesion that is elevated or indurated; crusting, ulceration, or poikiloderma may be present.
[c]Any solid or nodular lesion ≥1 cm in diameter with evidence of deep infiltration in the skin and/or vertical growth.

16.4 Appendix D. 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.

16.5 Appendix E. CLS Management Guidance

Time of Presentation	**CLS Sign/Symptom**	**Recommended Action**	**ELZONRIS Dosing Management**
Prior to first dose of ELZONRIS in cycle 1	Serum albumin < 3.2 g/dL	Administer ELZONRIS when serum albumin ≥ 3.2 g/dL.	
During ELZONRIS dosing	Serum albumin < 3.5 g/dL	Administer 25g intravenous albumin (q12h or more frequently as practical) until serum albumin is ≥ 3.5 g/dL AND not more than 0.5 g/dL lower than the value measured prior to dosing initiation of the current cycle.	Interrupt ELZONRIS dosing until the relevant CLS sign/symptom has resolved[1].
	Serum albumin reduced by ≥ 0.5 g/dL from the albumin value measured prior to ELZONRIS dosing initiation of the current cycle		
	A predose body weight that is increased by ≥ 1.5 kg over the previous day's predose weight	Administer 25g intravenous albumin (q12h or more frequently as practical), and manage fluid status as indicated clinically (e.g., generally with intravenous fluids and vasopressors if hypotensive and with diuretics if normotensive or hypertensive), until body weight increase has resolved (i.e. the increase is no longer ≥ 1.5 kg greater than the previous day's predose weight).	
	Edema, fluid overload and/or hypotension	Administer 25g intravenous albumin (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 sign/symptom or as indicated clinically. Aggressive management of fluid status and hypotension if present, which could include intravenous fluids and/or diuretics or other blood pressure management, until resolution of CLS sign/symptom or as clinically indicated.	

[1] ELZONRIS administration may resume in the same cycle if all CLS signs/symptoms have resolved and the patient did not require measures to treat hemodynamic instability. ELZONRIS administration should be held for the remainder of the cycle if CLS signs/symptoms have not resolved or the patient required measures to treat hemodynamic instability (e.g. required administration of intravenous fluids and/or vasopressors to treat hypotension) (even if resolved), and ELZONRIS administration may only resume in the next cycle if all CLS signs/symptoms have resolved, and the patient is hemodynamically stable.