A Phase 1/2 Open label Study of SL-401 in combination with Pomalidomide and Dexamethasone in Relapsed or Relapsed and Refractory Multiple Myeloma

Sponsor: Stemline Therapeutics, Inc.
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Study Product: SL-401

Protocol Number: STML-401-0414

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CONFIDENTIAL – PROPRIETARY INFORMATION

INVESTIGATOR PROTOCOL AGREEMENT

A Phase 1/2, Open Label Study of SL-401 in Combination with Pomalidomide (POM) and Dexamethasone (DEX) In Relapsed and Refractory Multiple Myeloma (RRMM)

I hereby agree to:

- Conduct the study as outlined in this protocol with reference to national/local regulations and current International Conference on 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: May 4, 2015

To be signed by Principal Investigator:

Print Name			
Signature		**Date**	
Institution			

To be signed by Stemline Therapeutics, Inc.:

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

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1 Protocol Synopsis

Name of Finished Product

SL-401

Name of Active Ingredient

DT388IL3

Study Number

STML-401-0414

Title

A Phase 1/2, Open label study of SL-401 in combination with Pomalidomide (POM) and Dexamethasone (DEX) in Relapsed or Relapsed and Refractory Multiple Myeloma (RRMM)

Investigator/Study Location(s)

This study will be conducted at multiple sites within the USA.

The Principal Investigator is Paul Richardson, MD, Dana Farber Cancer Institute.

Study Objectives

Primary Objective

- To evaluate the safety of single agent SL-401 in an initial run-in cycle in patients with multiple myeloma (MM).
- To determine the maximum tolerated dose (MTD) or maximum tested dose level of SL-401 given in combination with POM/DEX for the treatment of relapsed or RRMM.
- To characterize the safety and tolerability profiles of SL-401 in combination with POM/DEX at the MTD.

Secondary Objectives

- To evaluate immunogenicity of SL-401 in combination with POM/DEX.
- To evaluate the pharmacokinetics (PK) of SL-401 when administered as single agent and in combination.
- To evaluate the activity of the combination of SL-401/POM/DEX regimen in terms of:
    - Overall response rate (complete response [CR] + very good partial response [VGPR]+ partial response [PR]) and clinical benefit rate (CR + VGPR + PR + minimal response [MR]) based on International Myeloma Working Group (IMWG) defined response criteria and the duration of response (DOR) in RRMM patients.
    - Progression-free survival (PFS) and PFS at 6 months (PFS-6).
    - Overall survival (OS).

Exploratory Objectives

- To characterize the expression of interleukin-3 receptor (IL-3R)/CD123 (and other potentially relevant markers) on MM cells, plasmacytoid dendritic cells (pDCs), and associated cell populations in peripheral blood (PB) and bone marrow (BM) prior to and during/following therapy.
- To evaluate the treatment effects on IL-3R/CD123-expressing pDCs in the bone marrow microenvironment prior to, during, and following therapy. Specifically, we will assess (i) the

relative abundance of tumor cells to pDCs; (ii) immunohistochemistry (IHC) on BM biopsy specimens and flow cytometry analysis using antibodies specific against pDCs, to evaluate potential reduction in the pDC population in MM BM; and (iii) MM cell growth-promoting activity of pDCs will be determined by assessment of their ability to stimulate MM cell proliferation *ex-vivo*.

- To evaluate therapy-related effects on the levels of circulating cytokines/factors (i.e., IL-3 and others) associated with pDCs and MM cell growth, survival, and immune dysfunction using serum and plasma samples prior to, during, and following therapy.
- To identify surrogate markers of therapy-related anti-osteolytic activity. Specifically, we will assess the levels of bone turnover markers (potentially to include N and C teleopeptide, osteocalcin and bone alkaline phosphatase) prior to, during, and following therapy.

Eligibility Criteria

Inclusion Criteria

Eligible patients will be considered for inclusion if they meet all of the following criteria. (All necessary baseline studies for determining eligibility must be obtained within 21 days prior to enrollment or as indicated in the Schedule of Events [Table 13] prior to enrollment).

1. Male or female patient who is at least 18 years of age.
2. Patient has given voluntary written informed consent before performance of any study-related procedures not part of standard (non-investigational) medical care.
3. Patient has been previously diagnosed with MM based on standard criteria.
4. Patient has received:
   a) At least 2 prior therapies including a proteasome inhibitor (≥ 2 cycles) and lenalidomide (≥ 2 cycles), and
   b) Has achieved at least stable disease (SD) for ≥ 1 cycle of treatment on ≥ 1 prior treatment, and
   c) Has demonstrated disease progression subsequent to treatment, during or within 60 days following completion of the most recent therapy.
5. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2.
6. Patient has measurable disease defined as at least 1 of the following:
   a. Serum M protein ≥ 0.5 /dL (≥5 g/L)
   b. Urine M protein ≥ 200 mg/24 hours
   c. Serum free light chain (FLC) assay: Involved FLC assay ≥10 mg/dL (≥100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65)
7. Clinical Laboratory Inclusion Criteria: The following laboratory results must be met within 14 days (or as stipulated) prior to study drug (treatment) administration:
   a. Absolute neutrophil count (ANC) ≥ 1000 cells/µl (growth factor cannot be used within the previous 7 days).
   b. Aspartate aminotransferase (AST) and alanine aminotransferase (ALT) ≤ 2.5 × upper limit of normal (ULN).
   c. Platelet count ≥ 50,000/µl (without platelet transfusion in the previous 7 days).
   d. Total bilirubin ≤ 1.5 mg/dL.
   e. Serum creatinine ≤ 2.0 mL/dL and creatinine clearance ≥ 40 mL/min (calculated by the Cockcroft-Gault Equation or per 24 hour urine collection).

f. Serum albumin ≥ 3.2 g/dL.

g. Serum creatine phosphokinase (CPK) ≤ 2.5 × the ULN.

h. Serum calcium (corrected for albumin) level at or below the ULN range (treatment of hypercalcemia is allowed and subject may enroll if hypercalcemia returns to normal range with standard treatment).

8. Left ventricular ejection fraction (LVEF) ≥ institutional lower limit of normal as measured by multigated acquisition scan (MUGA) scan or 2-dimensional echocardiography (ECHO) within 28 days prior to start of therapy and no clinically significant abnormalities on a 12-lead electrocardiogram (ECG).

9. Females of childbearing potential (FCBP)* must have a negative serum or urine pregnancy test prior to initiation of the SL-401 Run in Cycle (if required) and repeated with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting POM and must either commit to continued abstinence from heterosexual intercourse or begin 2 acceptable methods of birth control, 1 highly effective method and 1 additional effective method at the same time, at least 28 days before she starts taking POM through 30 days after the last dose of POM and 60 days after the last dose of SL-401. FCBP must also agree to ongoing pregnancy testing during the entire duration of treatment. Men must agree to use a latex or synthetic condom during sexual contact with a FCBP even if they have had a vasectomy from the time of signing the informed consent form through 60 days after the last dose of POM or SL-401. These same patients must not donate sperm. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. All patients enrolled into this study, must agree to be registered in and must comply with all requirements of the POM REMS™ program.

   ** An FCBP is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).*

Exclusion Criteria:

Patients will be ineligible for this study if they meet any 1 of the following criteria:

1. The patient has an active malignancy and/or cancer history that may confound the assessment of the study endpoints. Patients with a past cancer history (within 2 years of entry) with substantial potential for recurrence and/or ongoing active malignancy must be discussed with the Sponsor before study entry. Patients with the following neoplastic diagnoses are eligible: non-melanoma skin cancer, carcinoma *in situ* (including superficial bladder cancer), cervical intraepithelial neoplasia, organ-confined prostate cancer with no evidence of progressive disease.
2. Prior therapy with SL-401 or received any investigational drug within the prior 30 days or 5 half-lives of the investigational drug, whichever is longer.
3. Prior anti-cancer therapy (chemotherapy, targeted agents, radiotherapy, and immunotherapy) within the prior 21 days except for alkylating agents (e.g., melphalan) within the prior 28 days.
4. Prior treatment with POM.
5. Primary refractory MM defined as disease that is non-responsive in patients that have never achieved at least stable disease or better with any therapy.
6. Any > grade 1 (according to the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events [CTCAE], v.4.03) adverse reaction unresolved from previous treatments or not readily managed and controlled with supportive care. The presence of alopecia of any grade and peripheral neuropathy ≤ grade 2 without pain is allowed.
7. Previous allogeneic stem cell transplantation with active graft-versus-host-disease, or treatment with immunosuppressive therapy in the 2 months prior to study entry.

8. Daily requirement for corticosteroids >10 mg prednisone daily (or equivalent); inhaled corticosteroids are permitted.
9. Patient is known to be human immunodeficiency virus positive, or have chronic or active hepatitis B (core- or surface antigen-positive) or active hepatitis C infection.
10. Clinically significant cardiovascular disease (e.g., uncontrolled or any New York Heart Association [NYHA] Class 3 or 4, congestive heart failure, uncontrolled or unstable angina, history of myocardial infarction or stroke within 6 months prior to study entry, uncontrolled hypertension or clinically significant arrhythmias not controlled by medication)
11. 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.
12. 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.
13. History of erythema multiforme or severe hypersensitivity to prior Immunomodulatory Drugs (IMiDs) such as thalidomide and lenalidomide.
14. The patient is receiving medications that are strong inhibitors of CYP1A2. Patients should have discontinued strong CYP1A2 inhibitors (e.g., ciprofloxacin and fluvoxamine; see Section 15.5) at least 5 half-lives before beginning study drug.
15. The patient continues to smoke cigarettes, which can induce CYP1A2.
16. Inability to tolerate thromboprophylaxis (see Section 7.2.1).
17. Pregnant or breast feeding.

Total Expected Number of Patients

The dose escalation stage (phase 1) will require approximately 12 to 18 patients to evaluate 3 dose levels of SL-401/POM/DEX. In phase 2, 14 additional patients will be treated (20 total patients) at the MTD or maximum tested dose of the combination therapy.

Study Treatment: Investigational Product, Dose, and Mode of Administration

SL-401

SL-401 injection 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 cancer stem cells and bulk of several hematopoietic malignancies relative to normal hematopoietic stem cells and other hematopoietic cells. It is also expressed on MM cells and on pDCs, which are abundant in the bone marrow of patients with MM and are believed to support MM cell growth.

SL-401 is provided as an intravenous (IV) injectable and administered as a 15-minute IV infusion via syringe pump "piggybacked" into an established IV line of 0.9% normal saline daily for the first 5 consecutive days of a 28-day cycle. POM is administered orally (PO) (4 mg/day daily on Days 1 – 21) as is DEX 40 mg on Days 1, 8, 15, and 22. The first cycle of SL-401 must be administered in the inpatient setting, with hospitalization beginning the day of the first infusion of SL-401 (or a prior day) and ending approximately 24 hours after the last infusion of SL-401. Subsequent cycles of SL-401 can be administered in the inpatient setting or in a suitable outpatient ambulatory care setting that is equipped for intensive monitoring of patients with hematopoietic malignancies undergoing treatment, per the discretion of the Investigator and institutional guidelines and capabilities. Patients will be monitored for at least 4 hours following the administration of each infusion of SL-401.

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

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

During the dosing period for each cycle, individual SL-401 infusions may be delayed to allow for toxicity resolution, but all 5 infusions should be completed within 10 days. During the first cycle, patients will receive a starting dose according to their assigned dosing cohort in phase 1, or the dose carried into phase 2, for 5 consecutive days (or 5 doses over a period not to exceed 10 days in the setting of specific adverse events [AEs]). Potential dose modifications for subsequent cycles relative to the prior cycle dose will be based on the severity and resolution of toxicities. Once the dose level of SL-401 has been reduced a subsequent increase is not permitted. Patients requiring more than 1 dose reduction should be discontinued from SL-401 treatment, unless there is evidence of MM response or stabilization according to their physician Investigator, beyond the initial treatment cycle.

For each scheduled administration of SL-401, SL-401 should be held for the following events.

- Heart rate $\geq$ 130 or $\leq$ 40 bpm.
- Systolic blood pressure (BP) $\geq$ 160 or $\leq$ 80 mmHg.
- Serum creatinine > 2.0 mg/dL.
- Serum albumin < 3.0 g/dL (SL-401 will be withheld for the remainder of the study cycle).
- AST > 5 × the ULN or ALT > 5 × the ULN (SL-401 will be withheld for the remainder of the study cycle).
- Body temperature $\geq$ 38°C.
- Increase in body weight by $\geq$ 1.5 kg over weight (pre-treatment) on the prior treatment day.

In settings in which albumin is reduced to <3.0g/dL or in which albumin is reduced by more than 1.0 g/dL below the level at the start of the cycle (i.e. from 4.3g/dL to 3.2g/dL), no subsequent SL-401 will be administered for the duration of the cycle.

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

Appropriate supportive measures are to be implemented (detailed in the protocol) and SL-401 may be administered pending resolution of the above conditions (this may be on the same day or subsequent days, depending on the nature/severity of the abnormality).

In the setting of delays secondary to findings consistent with capillary leak syndrome (i.e., in the setting of resolved hypotension, tachycardia, increased weight, or albumin reductions of a magnitude lower than those warranting withholding of SL-401 for the duration of a given cycle), subsequent SL-401 infusions are to be administered pending determination by the Investigator that there is no/minimal evidence of ongoing capillary leak syndrome and pending discussion with the study Medical Monitor. Any subsequent SL-401 infusions are to be administered on days *subsequent* to the identification of the abnormality (i.e., not the same day the abnormality was identified).

POMALIDOMIDE

POM, an analog of thalidomide, is an immunomodulatory agent with antineoplastic activity. In *in vitro* cellular assays, POM inhibits proliferation and induces apoptosis of hematopoietic tumor cells. Additionally, POM has been demonstrated to inhibit the proliferation of lenalidomide-resistant MM cell lines and synergizes with DEX in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. POM has also been shown to enhance T cell- and natural killer cell-mediated immunity and inhibit production of pro-inflammatory cytokines (e.g., tumor necrosis factor-α and IL-6) by monocytes. POM is indicated for patients with MM who have received at least 2 prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.

POM may be taken PO with water. Capsules should not be broken, chewed or opened. POM should be taken without food (at least 2 hours before or 2 hours after a meal).

POM will be commercially available.

DEXAMETHASONE

DEX, a high-potency corticosteroid, has known activity against MM and other (predominantly lymphoid) hematologic malignancies.

DEX will be commercially available. Tablets will be taken PO.

Study Design

This study is a phase 1/2 multi center, open label study of SL-401 in combination with standard doses of POM and DEX. The study will be conducted as a modified Fibonacci 3 + 3 dose escalation design to determine the MTD of SL-401 in combination with standard doses of POM and DEX. The study will be conducted in 2 Phases. Each evaluated SL-401 dose level will also incorporate an initial "Run-in Cycle" of single agent SL-401 in at least 3 patients; following the Run-in Cycle, patients who have not experienced a DLT will receive combination SL-401/POM/DEX. All patients in phase 2 will initiate therapy with the combination of SL-401/POM/DEX at the MTD or maximum tested dose established in phase 1.

Phase 1

Run-In Cycle: SL-401 will be administered as single agent during a Run-in Cycle. Upon completion of the Run-in Cycle patients will be evaluated for safety and response.

- Patients who do not experience a DLT during the Run-in Cycle will have POM/DEX added to their regimen at the assigned cohort dose.
- Patients who experience a DLT during the Run-in Cycle will be discontinued from study.

Table 1: Dose Levels to be Tested

	DLT EVALUTION PERIOD = RUN-IN CYCLE AND CYCLE 1			
	Run-In Cycle	Combination therapy Cycle 1 - 6		
Dose Level	SL-401 (IV) Daily on Days 1 – 5	SL-401 (IV) Daily on Days 1 – 5	POM (oral) Daily on Days 1 – 21	DEX (oral) on Days 1, 8, 15 and 22
-1	5 µg/kg	5 µg/kg	4 mg	40 mg
1	7 µg/kg	7 µg/kg	4 mg	40 mg
2	9 µg/kg	9 µg/kg	4 mg	40 mg
3	12 µg/kg	12 µg/kg	4 mg	40 mg

Cohorts of 3-6 patients will be treated at each dose level. All patients within a cohort must complete the Run-in Cycle and the first cycle of combination therapy (Cycle 1) before patients can be enrolled into the subsequent cohort of SL-401 (single agent) at the next higher dose. No intra-patient dose escalation is allowed. The first cohort of patients will receive SL-401 single agent at a dose of 7 µg/kg/day followed by SL-401 with POM/DEX. After all patients in this cohort complete the Run-in Cycle and Cycle 1 of combination therapy, the dose for the second cohort of patients will increase to 9 µg/kg/day, conditional on the dose-limiting toxicity (DLT) rules described below. Similarly, after all patients in the second cohort complete the Run-in Cycle and Cycle 1of therapy, the dose for the third cohort of patients will increase to 12 µg/kg/day, conditional on the dose-limiting toxicity (DLT) rules described below.

DLT Assessment:

Run-in Cycle:

In order to be evaluable for DLT assessment during the single agent Run-in Cycle, all patients must complete 5 doses of therapy (5 doses over a period not to exceed 10 days in the setting of specific AEs) and complete the 28 days of observation unless the patient experiences DLT (patients who discontinue prior to this juncture because of disease progression or for reasons unrelated to study therapy will be replaced).

Combination Therapy:

In order to be evaluable for DLT assessment of the combination therapy, a patient must receive at least 3 infusions of SL-401 and 16 (approximately 75%) doses of POM during Cycle 1, and complete the 28 days of observation unless the patient experiences DLT (patients who discontinue prior to this juncture because of disease progression or for reasons unrelated to study therapy will be replaced).

During phase 1, DLT is defined as any of the following AEs that are possibly, probably or definitely related to therapy:

- Any grade ≥ 4 neutropenia lasting greater than 7 days or grade ≥ 3 neutropenia associated with fever.
- Any grade ≥ 4 thrombocytopenia lasting greater than 7 days or grade ≥ 3 thrombocytopenia associated with bleeding.
- Any grade ≥ 3 non-hematologic toxicity except:
  - Grade 3 nausea, vomiting or diarrhea lasting no longer than 48 hours (with resolution to Grade ≤ 1 or baseline) with optimal supportive care.
  - Grade 3 arthralgia, myalgia, fever, in the absence of neutropenia, lasting no longer than 48 hours (with resolution to grade ≤ 1 or baseline).
  - Grade 3 fatigue lasting < 7 days.
  - Grade 3 laboratory abnormalities that are asymptomatic and not considered clinically significant by the Investigator, that respond to or do not require intervention and resolve to $\leq$ grade 1 or baseline ≤ 28 days after the last infusion of SL-401.
- Grade 4 transaminase or creatine phosphokinase (CPK) elevation (confirmed within 24 hours of initial identification) regardless of duration or relationship to SL-401.

The period of evaluation for DLT will include the Run-in Cycle and Cycle 1 (the first cycle of combination therapy.

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 1 of the initial 3 patients treated

(1/3) experiences a DLT, the cohort will be expanded to include an additional 3 patients treated at the same dose 7 µg/kg/day. If only 1 patient (1/6) from this expanded cohort experiences a DLT, then 3 new patients will be treated at the next higher dose of 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 dose level.

The highest dose intended for evaluation is 12 µg/kg/day in combination with POM/DEX. If this dose level is not declared the MTD after at least 6 patients are treated, it will be declared the maximum tested dose level and will be the dose recommended for phase 2 studies. Potential DLTs and laboratory abnormalities will be evaluated by the data safety review committee (DSRC; comprised of the Principal and Co-principal Investigators, Sponsor's Medical Monitor, and biostatistician) on an ongoing basis, who will evaluate the safety/tolerability of each dose level prior to investigation of a subsequent dose level. Although the dose escalation process is guided by the safety evaluation during the Run-in Cycle and the first combination cycle (Cycle 1) of treatment, cumulative toxicities observed in subsequent administrations should also be considered for the dose escalation decisions and recommended phase 2 dose.

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 of the combination therapy is defined as the dose preceding the dose level at which 2 patients experience a DLT during the Run-in Cycle and Cycle 1 of combination therapy. The MTD of the combination will be used in phase 2 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 if necessary to evaluate that cohort (e.g., if a patient is not evaluable for DLT but 2 others have experienced a DLT within the cohort, there will be no need to replace the patient as the MTD will have been exceeded).

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 5µg/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.

Phase 2

During phase 2, at least 14 additional patients (total, 20 patients) will be treated at the MTD or maximum tested dose at which multiple DLTs are not observed (identified in phase 1). During phase 2, the initial Run-in Cycle (SL-401 single agent) will no longer be administered. However, the first 6 patients treated at the MTD without the run in cycle will also be assessed for DLT during the first cycle of therapy. In the event that more than 1 DLT is identified in these initial 6 patients during phase 2, consideration will be given to the administration of a reduced SL-401 dose in the remainder of phase 2, or re-institution of the SL-401 single agent Run-in Cycle for the remainder of phase 2.

Dose Modification:

Patients will be evaluated for AEs at each visit with the NCI CTCAE, v.4.03, used as a guide for the grading of severity.

Doses of SL-401 may be held for criteria specified in Section 7.7.2, Table 11, concerning abnormalities in vital signs, serum creatinine, albumin, AST/ALT or increases in body weight; in the setting of these abnormalities, 5 doses may be given over 10 days; otherwise no dose modifications are permitted during the Run-in Cycle or Cycle 1 (initial cycle of combination therapy) unless the patient experiences a DLT. No dose escalations are permitted in any given patient once a dose level has been assigned. Patients experiencing DLT during the Run-in Cycle will be discontinued from study. Patients experiencing DLT

during Cycle 1 (initial cycle of combination therapy) may continue on therapy, if toxicity can be managed according to the dose modification guidelines outlined below and the patient has not experienced disease progression; the DLT event will nonetheless contribute to the assessment of MTD for that given cohort.

Dose modifications may be performed in all subsequent cycles of treatment. If toxicities cannot be managed by dose modification or the patient cannot tolerate the lowest dose of study drug, the patient is to be discontinued from study drug unless there is evidence of disease stabilization or response beyond the initial treatment cycle. However, patients that have achieved a plateau of response to study therapy will continue to adhere to the schedule of assessments followed during the treatment phase of the study even though study drug has been discontinued.

Dose Modification Guidelines are detailed in Section 7.7.

Safety Assessments:

Safety assessments include DLTs, AEs, serious adverse events (SAEs), physical examinations, vital sign measurements, clinical laboratory evaluations, and reasons for treatment discontinuation due to toxicity. The AE reporting period for a patient treated in the study begins with the initiation of SL-401 (or SL-401/POM/DEX in phase 2) and is continuous through 30 days after the last dose of SL-401 or SL-401/POM/DEX. 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/POM/DEX. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to SL-401/POM/DEX should also be reported as an AE.

Efficacy Assessments:

The study will preliminarily evaluate the activity of the SL-401/POM/DEX regimen. Secondary efficacy endpoints will include: PFS and PFS-6; overall response rate (CR + VGPR + PR) and clinical benefit rate (CR + VGPR + PR + MR) based on IMWG defined response criteria, as well as DOR (duration of response) and OS. Response will also be assessed following the Run-in cycle of single agent therapy.

Efficacy assessment parameters will include:

- M-protein determination using both of the following procedures:
  - Serum protein electrophoresis (SPEP) and serum protein immunofixation with quantitative immunoglobulins; and
  - Urine protein electrophoresis (UPEP) and urine protein immunofixation (all using the same 24-hour urine collection).
- Serum free light chains (FLC).
- Bone marrow to quantify percent MM cell involvement.
- Plasmacytoma evaluation: positron emission tomography/computed tomography (PET/CT) scan or magnetic resonance imaging (MRI) and or physical exam as clinically indicated.
- Skeletal survey.
- Serum β_2 microglobulin.
- Cytogenetic analysis/fluorescence *in situ* hybridization (FISH) on BM aspirate.

Biological/Target/Correlative Studies:

Correlative, translational studies will be performed to characterize the expression of IL-3R/CD123 (and other potentially relevant markers) on MM cells and associated cell populations in peripheral blood and bone marrow during treatment. Additionally, these studies will evaluate the effects of treatment on IL-3R/CD123 expressing pDCs in the bone marrow microenvironment during treatment.

Peripheral blood samples and bone marrow aspirates (if there is additional aspirate remaining after collection for tumor assessment) will be collected for translational assessments. All patient samples

will be collected at the respective treatment sites and immediately shipped to the designated laboratories for analysis.

Pharmacokinetic (PK) Studies:

Blood will be sampled to continue to characterize the PK of SL-401 on Day 1 and 5 of the Run-in Cycle and Cycle 1. Plasma sampling will be conducted for 6 hours on each day. In Cycle 2 (infusion 1 and 5), POM and DEX (Day 1 only) will be administered 6 hours after 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 the Time Points for PK Blood Draw Table (Table 14).

Immunogenicity Studies:

Blood samples (serum) will be collected for the detection of SL-401 reactive antibodies. The blood sampling time schedule is summarized in the Schedule of Events (Table 13).

Statistical Considerations

Sample size determination:

The primary objectives of phase 1 of the study are to evaluate the safety of Sl-401 as a single agent in an initial Run-in Cycle, to determine the MTD or the maximum tested dose where multiple DLTs are not observed and to further characterize the safety profile of SL-401/POM//DEX at the MTD. Based on such, a recommended dose for phase 2 studies will be defined. A maximum of 3 dose levels (7, 9 and 12 µg/kg/day) is anticipated and thus the total number of patients for this stage ranges from 6 to 18. The anticipated sample size is sufficient to evaluate these objectives. A secondary objective is to characterize the anti-tumor activity of SL-401/POM/DEX in terms of PFS-6. During phase 2, if approximately 14 patients are enrolled at the recommended phase 2 dose as defined in phase 1 over 12 months and follow-up continues for 12 months after the last enrolled patient, the total of 20 patients treated at this dose has approximately 75% power with a 1-sided type I error rate of 5% to reject the null hypothesis that the PFS-6 is <40% if the true rate is 60%.

Analysis population:

The all-treatment population is defined as all registered patients exposed to the study drug regardless of the amount of treatment administered. Safety and efficacy will be evaluated using the all-treated population. This population will include all patients who signed informed consent and who actually received at least 1 dose or a part of a dose of SL-401 or SL-401/POM/DEX.

General statistical approach:

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.

Treatment-emergent AEs through 30 days after last SL-401/POM/DEX dose will be summarized by Medical Dictionary for Regulatory Activities (MedDRA™), Version 13.1 (or higher), System Organ Class and preferred term. The incidences and percentages of patients experiencing each AE preferred term will be summarized with descriptive statistics. AEs will also be summarized by NCI CTCAE, v.4.03 (or higher), grade and by causality (relationship to study drug). Dose-limiting toxicities, grade 3-4 AEs, SAEs, and AEs resulting in dose modification or treatment discontinuation will also be summarized by preferred term. DLTs will be listed in the evaluable for DLT population. Laboratory results will be classified according to NCI CTCAE, v.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.

For subgroups of patients defined by disease and line of therapy, exact 1-sided 95% confidence intervals will be calculated for ORR and clinical benefit rates, and the distributions for duration of response, PFS, PFS-6, and OS will be estimated by Kaplan-Meier methodology.

Immune response, PK, and translational marker results will be descriptively summarized and tabulated.

Duration of Study Period (per patient) :

The study duration for an individual patient will include a screening period for inclusion of up to 21 days, the treatment period may continue for up to 6 cycles of combination therapy or until disease progression, unacceptable adverse reaction or other reason for discontinuation. The administration of additional cycles of SL-401 > 6 cycles (not including the Run-in Cycle if received) must be discussed with the Medical Monitor at which time the individual patient's potential risk/benefit of further treatment will be assessed. After study drug discontinuation an end of treatment (EOT) visit will be done at approximately 30 days to assess safety. Patients who discontinue treatment for reasons other than progression of disease will be followed monthly until progression or initiation of subsequent therapy. Following progression, either on or off therapy patients will be followed for overall survival every 3 months for a maximum of 1 year, whichever comes first.

Overall Study Duration:

The dose escalation stage (phase 1) will require approximately 6 to 18 patients to evaluate 3 dose levels of SL-401/POM/DEX. In phase 2, 14 additional patients will be treated (20 total patients) at the MTD or maximum tested dose. Total study duration is expected to be approximately 24 months. Patient enrollment is expected to occur over a 12-month period, with follow-up continuing until assessments of the primary and critical secondary objectives are completed for all treated patients.

2 Abbreviations and Definitions

Abbreviation	Definition
AE	Adverse Event
ALL	Acute Lymphoid Leukemia
ALT	Alanine Transaminase
AML	Acute Myeloid Leukemia
ANC	Absolute Neutrophil Count
AP	Alkaline Phosphatase
AST	Aspartate Transaminase
BM	Bone Marrow
BMSC	Bone Marrow Stromal Cell
BP	Blood Pressure
BPDCN	Blastic Plasmacytoid Dendritic Cell Neoplasm
BSA	Body Surface Area
BUN	Blood Urea Nitrogen
CBC	Complete Blood Count
CFR	Code of Federal Regulations
CML	Chronic Myeloid Leukemia
CPK	Creatine Phosphokinase
CR	Complete Response
CSC	Cancer Stem Cell
CTCAE	Common Terminology Criteria for Adverse Events
DEX	Dexamethasone
DLT	Dose-Limiting Toxicity
DOR	Duration of Response
DP	Drug Product
DSRC	Data Safety Review Committee
DT	Diphtheria Toxin
ECG	Electrocardiogram
ECHO	Echocardiogram
ECM	Extracellular matrix
ECM	Extracellular matrix

Abbreviation	Definition
ECOG	Eastern Cooperative Oncology Group
eCRF	Electronic Case Report Form
EDC	Electronic Data Capture
EDTA	Ethylenediaminetetraacetic Acid
ELISA	Enzyme-linked Immunosorbent Assay
EOS	End-of-Study
EOT	End-of-Treatment
FCBP	Females of Childbearing Potential
FDA	Food and Drug Administration
FISH	Fluorescence *in situ* Hybridization
FLC	Free light chain
GCP	Good Clinical Practice
GLP	Good Laboratory Practice
HIPAA	Human Insurance Portability Accountability Act
HR	Heart Rate
Hsp90	Heat shock protein 90
IC_{50}	Concentration that inhibits the growth of 50% of leukemia cells
ICF	Informed Consent Form
ICF	Informed Consent Form
ICH	International Conference of Harmonisation
IEC	Independent Ethics Committee
IGF-1	Insulin-like growth factor
IHC	Immunohistochemistry
IL-3	Interleukin-3
IL-3R	Interleukin-3 Receptor
IMiD	Immunomodulatory Drug
IMWG	International Myeloma Working Group
IND	Investigational New Drug (Application)
INR	International Normalized Ratio
IRB	Institutional Review Board
IV	Intravenous

Abbreviation	Definition
LDH	Lactate Dehydrogenase
LFT	Liver function test
LVEF	Left Ventricular Ejection Fraction
M	Monoclonal
MDS	Myelodysplastic Syndrome
MedDRA™	Medical Dictionary for Regulatory Activities
MM	Multiple Myeloma
MR	Minimal Response
MRI	Magnetic Resonance Imaging
MTD	Maximum Tolerated Dose
MUGA	Multigated Acquisition Scan
NCI	National Cancer Institute
NYHA	New York Heart Association
ORR	Overall Response Rate
OS	Overall Survival
PB	Peripheral Blood
PBMC	Peripheral Blood Mononuclear Cell
pDCs	Plasmacytoid Dendritic Cells
PET/CT	Positron Emission Tomography / Computed Tomography
PFS	Progression-free Survival
PFS6	Progression-free Survival at 6 Months
PK	Pharmacokinetics
PO	Oral(ly)
POM	Pomalidomide
PR	Partial Response
PT	Prothrombin Time
PTT	Partial Thromboplastin Time
RR	Respiratory Rate
RRMM	Relapsed/Refractory Multiple Myeloma
SAE	Serious Adverse Event
sCR	Stringent Complete Response

Abbreviation	Definition
SD	Stable Disease
SFLC	Serum Free Light Chain
SPEP	Serum Protein Electrophoresis
TEAE	Treatment-emergent Adverse Event
ULN	Upper Limit of Normal
UPEP	Urine Protein Electrophoresis
VEGF	Vascular Endothelial Growth Factor
VGPR	Very Good Partial Response

3 Introduction and Study Rationale

3.1 Multiple Myeloma

Multiple myeloma (MM) is a heterogeneous clonal B-cell malignancy characterized by the accumulation of abnormal antibody producing plasma cells in the bone marrow (BM). The disease is associated with a variety of clinical manifestations including lytic bone lesions, hypercalcemia, renal impairment and anemia. MM is the second most common hematologic malignancy and accounts for approximately 11,000 deaths per year in the United States and 19,000 in Europe (ACS 2013).

Current treatment strategies include the use of immunomodulatory drugs such as thalidomide and its derivatives, proteasome inhibitors such as bortezomib, synthetic corticosteroids, alkylating agents such as melphalan, anthracyclines, and autologous stem cell transplant. Despite recent therapeutic advances and the use of "novel agents", MM remains an incurable disease with a median survival of approximately 5 - 7 years (Kumar 2008).

The molecular mechanism by which MM cells evade drug–induced cytotoxicity and acquire drug resistant phenotypes include interaction of MM cells with the BM microenvironment which is composed of extracellular matrix (ECM) proteins such as fibronectin, collagen, and laminin, along with cellular elements such as hematopoietic stem cells, immune cells, BM endothelial cells, and bone marrow stromal cells (BMSCs). Adhesion of MM cells to ECM proteins and accessory cells leads to increased expression of factors such as IL-6, insulin-like growth factor (IGF-1), and vascular endothelial growth factor (VEGF), which in turn further stimulates growth and survival of the malignant clone (Chauhan 1996; Agarwal 2013).

In addition, early studies using both *in vitro* and *in vivo* MM models, have demonstrated increased numbers of pDCs in the BM microenviroment, which promotes MM cell growth and survival (Chauhan et al. 2009). These studies also showed increased interleukin-3 (IL-3) levels resulting from plasmacytoid dendritic cells (pDC) and MM cell interaction, which in turn, trigger MM cell growth and pDC survival.

3.2 Targeting Cancer Stem Cells

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

activity of cellular mechanisms that repair damaged deoxyribonucleic acid. 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 acute myeloid leukemia (AML) and brain cancer, respectively (van Rhenen et al. 2005; Zeppernick et al. 2008).

3.3 IL-3 Receptor (IL-3R) Over-Expression in AML and other Myeloid Malignancies

The alpha subunit of the human interleukin-3 receptor (IL-3 α receptor = IL-3Rα, also called multi-colony stimulating factor) is a type I transmembrane glycoprotein belonging to the cytokine receptor superfamily; all the members of this superfamily are characterized by a conserved region homologous to the fibronectin type III domain. The IL-3R is a heterodimer of α (CD123) and β chains; (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 BM including normal hematopoietic stem cells.

In addition to AML, IL-3R has also been shown to be differentially expressed on other hematological cancers, including blastic plasmacytoid dendritic cell neoplasm (BPDCN), myelodysplastic syndrome (MDS), chronic myeloid leukemia (CML), acute lymphoid leukemia (ALL), hairy cell leukemia, Hodgkin's disease, and certain aggressive non-Hodgkin's lymphomas (e.g., follicular cell, mantle cell, and Burkitt's lymphomas) (Tehranchi et al 2010; Aldinucci et al. 2005; Munoz et al. 2001; Aldinucci et al. 2002; Black et al. 2003; Frolova et al. 2010). Moreover, IL-3R is also over-expressed on CSCs of multiple hematologic malignancies, including CML, MDS, and T-cell ALL. (Jordan et al. 2006; Tehranchi et al. 2010; Florian et al. 2006; Lhermitte et al. 2006).

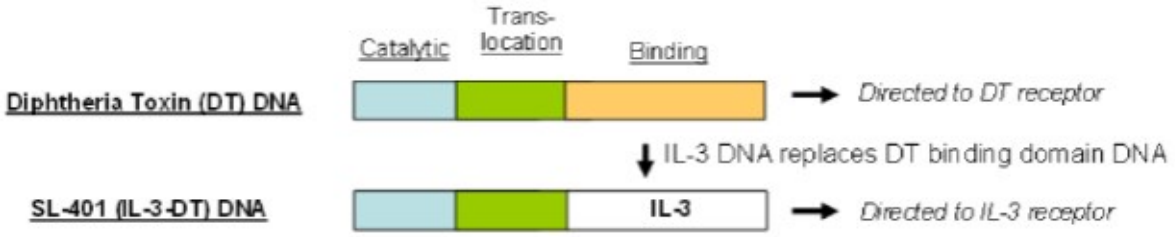
A higher percentage of IL-3R-expressing CSCs within a patient's tumor relates to poor outcome (Vergez et al. 2011). In particular, AML patients with IL-3R-expressing CSCs that comprise ≥ 3.5% of their entire leukemia have a worse prognosis than patients with IL-3R-expressing

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 BM of patients with MM 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.

Mechanism of Action of DT388IL3/SL-401

Diphtheria toxin (DT) IL-3 fusion protein (DT388IL3; designated SL-401 by Stemline Therapeutics), is a novel biologic targeted therapy directed to the IL-3R. SL-401 is comprised of recombinant human IL-3 genetically fused to a truncated DT, in which the binding domain of DT has been replaced with IL-3. As depicted in Figure 1, the IL-3 domain of SL-401 is able to target the agent to leukemia blasts and CSCs that over-express IL-3R, leading to receptor-mediated endocytosis and localization of SL-401 to early endosomes. The translocation domain of DT changes conformation in the acidic environment of the endosome, and the RXRR motif (residues 191-194) located between the catalytic and translocation domains of DT is cleaved by endosomal furin. The translocation domain of DT then inserts into the endosomal membrane. As the TAT-like domain of DT (residues 201-230) interacts with cytosolic heat shock protein 90 (Hsp90) and thioreduxin 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 elongation factor 2, leading to apoptosis (Yamaizumi et al. 1978; Deng et al. 2008; FitzGerald et al. 1989; Perentesis et al. 1992; Louie et al. 1997; Ratts et al. 2005; Thorburn et al. 2004).

Figure 1: Schematic of SL-401 Construction



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

reason why SL-401 may be an effective addition to the therapeutic armamentarium against hematologic malignancies.

3.4 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 BM progenitor cells were relatively insensitive. Anti-CSC activity was also exhibited. In particular, the SL-401 fusion toxin inhibited long-term AML colony formation, an assay for stem cell activity, compared with normal human BM. Additionally, engraftment and growth (i.e., tumorigenicity) of AML cells were reduced relative to normal human BM, when these cells were treated *ex vivo* and reimplanted into immunodeficient mice, which also indicates anti-tumor activity at the level of the CSC (Frankel et al. 2000). Treatment of severe combined immunodeficient mice also significantly reduced engraftment of AML (Feuring-Buske et al. 2002). AML engraftment was reduced by an average of 83% (range, 14–100) and 57% (range, 0–98) after 4 and 12 weeks, respectively (n = 6). Leukemia was not detected in 2 of 6 mice 12 weeks after SL-401 treatment. Repeating treatment every 4 weeks enhanced its effectiveness (Black et al. 2003; Frankel et al. 2000).

The cytotoxicity of SL-401 relates to the level of IL-3R expression on leukemia cells *in vitro* (Frankel et al. 2000). In studies performed to date, leukemia cells with high surface expression of IL-3R have been exquisitely sensitive to SL-401, with IC_{50} values ranging from 1-28 pM, whereas low cellular expression of IL-3R has been associated with higher IC_{50} values, i.e., ~1400 pM (Frankel et al. 2000). Even so, SL-401 plasma concentrations exceeding the entire range of IC_{50} values have been readily achievable in patients receiving SL-401 at doses below the maximum tolerated dose in a phase 1-2 study described in Section 3.5.

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).

3.4.1 Pre-clinical studies in Multiple Myeloma

The BMs of patients with MM have been demonstrated to contain high quantities of IL-3R-expressing pDCs. These pDCs have since been shown to augment the growth of MM and contribute to drug resistance, suggesting that killing pDCs may confer clinical benefit in patients with MM (Chauhan et al. 2009). DT388IL3 has been recently demonstrated to possess potent activity against MM cell lines and primary tumor samples, which appears to be related to both direct antitumor and anti-pDC effects of the drug in MM (Chauhan et al. 2013).

3.4.2 Repeat-dose Toxicity studies

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

Study Type and Duration	Dose Level(s)	Dose Regimen
Mice		
5-day efficacy study, survival data	2 µg (≈ 100 µg/kg)	Intraperitoneal 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)	Intraperitoneal 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 Therapeutics has conducted 2 non-Good Laboratory Practice (GLP) toxicity studies in cynomolgus monkeys and one GLP 5-day toxicity study in cynomolgus monkeys with a 3-week recovery period to confirm target organs of toxicity 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, Company-Sponsored IND

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

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

Three toxicity studies were conducted with SL-401 at doses ranging from 30µg/kg/day to 80µg/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 (IV) 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 IV slow bolus injection daily for 5 consecutive days.

Based on the collective data from 3 toxicology studies conducted with SL-401, the kidney, liver, and blood vessel manifestations observed were highly consistent with previous toxicity studies.

Inflammation and necrosis of epithelial cells lining the choroid plexus was consistent with previous toxicity studies using SL-401. However, severe brain hemorrhage was not observed with SL-401. The highest non-severely toxic dose from the combined toxicity studies in monkeys evaluating SL-401 ranged from 30µg/kg/day to 60µg/kg/day, which is equivalent to 9µg/kg/day to 20µg/kg/day in humans based on the body surface area (BSA) normalization method. A dose of 7.07µg/kg/day for 5 days was well-tolerated in the previous SL-401 clinical study, described in Section 3.5. Therefore, given the non-human primate toxicity results from SL-401 together with the full clinical safety database and the confirmatory target organ toxicity findings in 3 additional non-human primate studies with SL-401, the starting clinical dose will be 7 µg/kg/day. Furthermore, based on the previous clinical study, the maximum anticipated clinical dose is 12 µg/kg/day for a 5-day consecutive regimen.

3.5 SL-401 Clinical Studies

3.5.1 Study 50047 Synopsis

The safety and efficacy of SL-401 (Diphtheria Toxin Interleukin-3 Fusion Protein) drug product (DP) was evaluated in Study 50047, a multicenter, open-label, dose escalation phase 1/2 study, in which enrolled patients had relapsed or refractory adult AML, *de novo* AML unfit for chemotherapy, high-risk MDS, CML, or BPDCN. The study was conducted under investigator-sponsored IND #11314. 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 2 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 overall survival (OS) were also collected during the study.

3.5.2 Baseline Patient Characteristics, Treatment Administration, and DLTs

Ninety-two patients were enrolled and treated with SL-401 in the study. Table 4 summarizes the baseline characteristics of the enrolled patients.

Table 4: Patient and Disease Characteristics

Patient Characteristics	All Patients (N=92)	
Median Age, years (range)	**66**	**(7, 84)**
Gender, n (%)		
Male	58	(63.0)
Female	34	(37.0)
Disease, n (%)		
AML	70	(76.1)
Relapsed/refractory disease	59	(64.1)
De novo unfit for chemotherapy	11	(12.0)
MDS (high risk)	7	(7.6)
CML (accelerated/blast phase)	3	(3.3)
BPDCN	12	(13.0)
Therapy Line for Disease in Study, n (%)		
De novo AML unfit for chemotherapy	11	(12.0)
2nd Line for AML	24	(26.1)
3rd Line for AML	16	(17.4)
>3rd Line for AML	19	(20.7)
1st Line for BPDCN	4	(4.3)
2nd Line for BPDCN	4	(4.3)
3rd Line for BPDCN	2	(2.2)
>3rd Line for BPDCN	2	(2.2)
MDS; various prior lines of therapy	7	(7.6)
CML; various prior lines of therapy	3	(3.3)
AML Cytogenetic Risk, n (%)		
Intermediate	43	(61.4)
Poor	25	(35.7)
Unknown	2	(2.9)

Table 5 summarizes treatment administration (including the number of patients that received all planned infusions), incidences of DLTs, and responses by treatment regimen and dose during the first cycle of SL-401. The MTD for Regimen A (dosing every other day for up to 6 doses) was not achieved. The MTD for Regimen B (daily dosing for up to 5 doses) was 16.6 µg/kg/day with hypoalbuminemia and edema, manifestations of capillary leak, 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.

Table 5: Treatment Regimen, DLTs, and Response

Dose, µg/kg/day	Patients Treated (Received All Infusions)		Patients with DLT	Responses
Regimen A:				
4.00	7	(5)	0	1 PR
5.32	8	(6)	0	1 PR
7.07	13	(8)	0	2 PR, 1 CR
9.40	7	(3)	0	–
12.50	10	(3)	0	2 PR
Regimen B:				
7.07	5	(3)	0	1 PR
9.40	8	(8)	1[a]	–
12.50	24	(16)	1[b]	4 PR, 6 CR
16.60*	8	(7)	1[c]	–
22.12	2	(0)	2[c]	–

CR = complete response; PR = partial response.
a Gastrointestinal bleed.
b Transaminase and creatine kinase elevations.
c Capillary leak syndrome.
*Maximum tolerated dose for Regimen B.

3.5.3 Safety Summary

A summary of all ≥ grade 3 AEs attributed to SL-401 is presented in Table 6.

Table 6: Summary of ≥ Grade 3 Adverse Events Attributed to SL-401

Investigator Reported Term	All Patients (N=92) n (%)
Anaphylaxis	1 (1.1)
Anemia	1 (1.1)
Cardiopulmonary Arrest	1 (1.1)
Creatine kinase	2 (2.2)
Creatinine	1 (1.1)
Dyspnea/Wheezing	1 (1.1)
Edema	3 (3.3)
Fever	1 (1.1)
Hemorrhage/bleeding	1 (1.1)
Hyponatremia	1 (1.1)
Infection (excl sepsis, pneumonia, herpes)	1 (1.1)

Investigator Reported Term	All Patients (N=92) n (%)
INR	1 (1.1)
Leukopenia	1 (1.1)
Lymphopenia	1 (1.1)
Neutropenia	2 (2.2)
Pneumonia	1 (1.1)
Renal failure	1 (1.1)
Thrombocytopenia	8 (8.7)
Transaminase elevation	23 (25.0)
Tubular necrosis	1 (1.1)
Vascular leak syndrome	4 (4.3)

Attributed AEs includes events possibly, probably, or definitely related to DT388IL3.

Although transaminase elevation was one of the most common ≥ grade 3 AEs among patients treated with SL-401, almost all episodes were transient (i.e., lasting ≤ 2 weeks) since only 1 case met the criteria for a DLT. The time courses of liver function tests (LFTs) and albumin among the patients treated with Regimen B at the MTD (16.6 µg/kg/day) and the 2 doses below the MTD (12.5 and 9.4 µg/kg/day) indicate that LFT elevations tended to peak approximately 2 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.

3.5.4 Efficacy Summary

A single cycle of SL-401 was associated with single agent activity in patients with relapsed or refractory AML, including 2 durable complete responses (CRs) of 8 and > 25 months duration and 5 partial responses (PRs). Overall survival 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 2 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). Moreover, SL-401 treatment was associated with a greater than 3-fold greater median overall survival of AML patients who received at least 3 prior lines of treatment relative to historical results, when delivered at therapeutically relevant doses (including the MTD [16.6 µg/kg/day], and the 2 dose levels below the MTD [9.4 and 12.5 µg/kg/day]).

Multiple durable objective responses were also observed among the patients with BPDCN. Among 9 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%

(2 patients treated with 12.5 µg/kg/day and one patient treated with 9.4 µg/kg/day were not evaluable for response).

3.5.5 Pomalidomide

Pomalidomide (POM), an analog of thalidomide, is an Immunomodulatory Drug (IMiD) with antineoplastic activity. In *in vitro* cellular assays, POM inhibits proliferation and induces apoptosis of hematopoietic tumor cells. Additionally, POM has been demonstrated to inhibit the proliferation of lenalidomide-resistant MM cell lines and synergizes with dexamethasone (DEX) in both lenalidomide-sensitive and lenalidomide-resistant cell lines to induce tumor cell apoptosis. POM has also been shown to enhance T cell- and natural killer cell-mediated immunity and inhibit production of pro-inflammatory cytokines (e.g., tumor necrosis factor-α and IL-6) by monocytes.

POM is indicated for patients with MM who have received at least 2 prior therapies including lenalidomide and bortezomib and have demonstrated disease progression on or within 60 days of completion of the last therapy.

A phase 2 study randomized 221 patients to received either POM and DEX (n = 113) or POM alone (n = 108) (Richardson 2014). The efficacy of POM was enhanced by the addition of DEX; with a median follow-up of 14.2 months, median progression-free survival (PFS) was 4.2 and 2.7 months and the overall response rate (ORR) was 33% and 18% (P = 0.013) respectively. In a subsequent Phase 3 study of patients with advanced MM who had exhausted bortezomib and lenalidomide treatment the benefits of POM and low-dose DEX were further demonstrated in terms of PFS (4.0 months) and OS (12.7 months) versus high-dose DEX, the standard of supportive care (PFS 1.9 months and OS 8.1 months) (San Miguel 2013). POM and low-dose DEX are generally well tolerated, and provide an important new treatment option for relapsed/refractory multiple myeloma (RRMM) patients who have received multiple prior therapies. However, all patients ultimately progress with no further treatment options or die from their disease. Further studies are warranted to evaluate the use of POM in combination with other novel agents to improve upon these outcomes.

3.5.6 Discussion and Rationale for Current Study

In June, 2006, Stemline Therapeutics, Inc. ("Stemline") in-licensed development and commercialization rights for DT388IL3 and designated the product SL-401. The SL-401 DP to be utilized in the current study (conducted under a new IND) will be manufactured using a commercial-scale process.

IL-3R-rich pDCs have been demonstrated to be increased in the BM of patients with MM and contribute to disease aggressiveness and resistance to treatment (Chauhan 2009). pDC-MM cell interactions are associated with enhanced production of IL-3, which in turn, enhances MM cell growth and pDC survival. SL-401 has been shown to significantly decrease the viability of pDCs, even at low concentrations (IC_{50}, 14.6 pM). SL-401 also decreases the viability of MM

cells at clinically achievable concentrations without significantly affecting the viability of normal peripheral blood mononuclear cells (PBMCs). Co-culture of pDCs with MM cells triggers tumor growth, which, in turn, is blocked by low concentrations of SL-401. MM patient-derived pDCs also induces proliferation of MM cell lines and primary MM cells sampled from patients. Additionally, SL-401 has been shown to inhibit pDC-triggered MM cell growth, even in patients whose disease had progressed while receiving bortezomib, dexamethasone, and/or lenalidomide. SL-401 also blocked pDC-induced growth of dexamethasone-, doxorubicin- or melphalan-resistant MM cell lines. Additionally, combination of SL-401 with bortezomib, melphalan, or lenalidomide showed synergistic anti-MM activity. These preclinical results support the notion of directly targeting pDCs and inhibiting pDC-MM interactions, as well as targeting MM cells, in novel therapeutic strategies with SL-401 to enhance MM cytotoxicity, overcome drug-resistance, and improve overall patient outcome (Chauhan et al. 2013).

The prior clinical results with SL-401 indicate that the agent can be safely administered to patients with *de novo* AML, relapsed/refractory 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 and a safe starting dose for subsequent studies, the starting dose selected for this phase 1/2 study, 7 µg/kg/day (the lowest tested dose for this regimen (7.07 µg/kg/day in Study 50047), will allow for an initial (3 dose level) dose escalation/confirmation stage to an expected maximum tested dose (12 µg/kg/day) that is anticipated to have the most favorable risk/benefit profile.

The SL-401 drug product used in the current study will be manufactured using a commercial-scale process that will provide study material for all pivotal studies. The current study will generate clinical experience in which administration of multiple cycles of SL-401 can be evaluated in combination with POM/DEX in a patient population that may derive clinical benefit.

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. In this study, a 28-day schedule will be used in combination with POM and DEX to allow for additional time for recovery from potential toxicity. Capillary leak syndrome was the principal DLT in Study 50047, but was a relatively uncommon event at doses at or below the MTD. Similarly, capillary leak syndrome 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 capillary leak syndrome 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 capillary leak 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 7.3.2. Additional precautions, including a requirement that subjects 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).

4 Study Objectives

4.1 Primary Objectives

- To evaluate the safety of single agent SL-401 in an initial run-in cycle in patients with MM.
- To determine the MTD or the maximum tested dose of SL-401 given in combination with POM/DEX for the treatment of relapsed or RRMM.
- To characterize the safety and tolerability profiles of SL-401 in combination with POM/DEX at the MTD.

4.2 Secondary Objectives

- To evaluate immunogenicity of SL-401 in combination with POM/DEX.
- To evaluate the PK of SL-401 as single agent and when administered in combination.
- To evaluate the activity of the combination of SL-401/POM/DEX regimen in terms of:
  - Overall response rate (CR+ very good partial response [VGPR] + PR) and clinical benefit rate (CR + VGPR + PR + minimal response [MR]) based on International Myeloma Working Group (IMWG) defined response criteria and the duration of response (DOR) in RRMM patients.
  - PFS and PFS at 6 months (PFS-6).
  - OS.

4.3 Exploratory Objectives

- To characterize the expression of IL-3R/CD123 (and other potentially relevant markers) on MM cells, pDCs, and associated cell populations in peripheral blood (PB) and BM prior to and during/following therapy.
- To evaluate the treatment effects on IL-3R/CD123-expressing pDCs in the BM microenvironment prior to, during, and following therapy. Specifically, we will assess (i) the relative abundance of tumor cells to pDCs; (ii) immunohistochemistry (IHC) on BM biopsy specimens and flow cytometry analysis using antibodies specific against pDCs, to evaluate potential reduction in the pDC population in MM BM; and (iii) MM cell growth-promoting activity of pDCs will be determined by assessment of their ability to stimulate MM cell proliferation *ex-vivo*.
- To evaluate therapy-related effects on the levels of circulating cytokines/factors (i.e., IL-3 and others) associated with pDCs and MM cell growth, survival, and immune dysfunction using serum and plasma samples prior to, during, and following therapy.

- To identify surrogate markers of therapy-related anti-osteolytic activity. Specifically, we will assess the levels of bone turnover markers (potentially to include N and C teleopeptide, osteocalcin and bone alkaline phosphatase) prior to, during, and following therapy.

5 Patient Selection

5.1 Study Population

The dose escalation stage phase 1 will require approximately 6 to 18 patients to evaluate 3 dose levels of SL-401/POM/DEX. In phase 2, 14 additional patients will be treated (20 total patients) at the MTD or maximum tested dose. Approximately 32 adult patients with RRMM who have previously received at least 2 prior lines of therapy for their disease may be enrolled in phase 1 and phase 2 of this study.

5.2 Patient Inclusion Criteria

Eligible patients will be considered for inclusion if they meet all of the following criteria. (All necessary baseline studies for determining eligibility must be obtained within 21 days or as indicated in the Schedule of Events [Table 13] prior to enrolment).

1. Male or female patient who is at least 18 years of age.
2. Patient has given voluntary written informed consent before performance of any study-related procedures not part of standard (non-investigational) medical care.
3. Patient has been previously diagnosed with MM based on standard criteria.
4. Patient has received:
   a. at least 2 prior therapies including a proteasome inhibitor (≥ 2 cycles) and lenalidomide (≥ 2 cycles), and
   b. has achieved at least stable disease (SD) for ≥ 1 cycle of treatment on ≥ 1 prior treatment, and
   c. has demonstrated disease progression subsequent to treatment, during or within 60 days following completion of the most recent therapy
5. Patient has an Eastern Cooperative Oncology Group (ECOG) performance status score ≤ 2.
6. Patients has measurable disease defined as at least one of the following:
   a. Serum monoclonal (M) protein ≥ 0.5 /dL (≥5 g/L).
   b. Urine M protein ≥200 mg/24 hours.
   c. Serum free light chain (FLC) assay: involved FLC ≥10 mg/dL (≥100 mg/L) and an abnormal serum FLC ratio (<0.26 or >1.65).
7. Clinical Laboratory Inclusion Criteria: The following laboratory results must be met within 14 days prior to study drug (treatment) administration:
   a. Absolute neutrophil count (ANC) ≥ 1000 cells/µl (growth factor cannot be used within the previous 7 days)
   b. AST and ALT ≤ 2.5 × upper limit of normal (ULN)
   c. Platelet count ≥ 50,000/µl (without platelet transfusion in the previous 7 days)
   d. Total bilirubin ≤ 1.5 mg/dL

e. Serum creatinine ≤ 2.0 mL/dL and creatinine clearance ≥ 40 mL/min (calculated by the Cockcroft-Gault Equation or per 24 hour urine collection).
f. Serum albumin ≥ 3.2 g/dL.
g. Serum creatine phosphokinase (CPK) ≤ 2.5 × the ULN.
h. Serum calcium (corrected for albumin) level at or below the ULN range (treatment of hypercalcemia is allowed and subject may enroll if hypercalcemia returns to normal range with standard treatment).

8. Left ventricular ejection fraction (LVEF) ≥ institutional lower limit of normal as measured by multigated acquisition scan (MUGA) scan or 2-dimensional echocardiography (ECHO) within 28 days prior to start of therapy and no clinically significant abnormalities on a 12-lead electrocardiogram (ECG).
9. Females of childbearing potential (FCBP)* must have a negative serum or urine pregnancy test prior to initiation of the SL-401 Run-in Cycle and repeated with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting POM and must either commit to continued abstinence from heterosexual intercourse or begin 2 acceptable methods of birth control, one highly effective method and 1 additional effective method at the same time, at least 28 days before she starts taking POM through 30 days after the last dose of POM and 60 days after the last dose of SL-401. FCBP must also agree to ongoing pregnancy testing during the entire duration of treatment. Men must agree to use a latex or synthetic condom during sexual contact with a FCBP even if they have had a vasectomy from the time of signing the informed consent form through 60 days after the last dose of POM or SL-401. These same patients must not donate sperm. All patients must be counseled at a minimum of every 28 days about pregnancy precautions and risks of fetal exposure. All patients enrolled into this study, must agree to be registered in and must comply with all requirements of the POM REMS™ program.

** An FCBP is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).*

5.3 Patient Exclusion Criteria

Patients will be ineligible for this study if they meet any one of the following criteria:

1. The patient has an active malignancy and/or cancer history that may confound the assessment of the study endpoints. Patients with a past cancer history (within 2 years of entry) with substantial potential for recurrence and/or ongoing active malignancy must be discussed with the Sponsor before study entry. Patients with the following neoplastic diagnoses are eligible: non-melanoma skin cancer, carcinoma *in situ* (including superficial bladder cancer), cervical intraepithelial neoplasia, organ-confined prostate cancer with no evidence of progressive disease.
2. Prior therapy with SL-401 or received any investigational drug within the prior 30 days or 5 half-lives of the investigational drug, whichever is longer.

3. Prior anti-cancer therapy (chemotherapy, targeted agents, radiotherapy, and immunotherapy) within the prior 21 days, except for alkylating agents (e.g., melphalan) within the prior 28 days.
4. Prior treatment with POM.
5. Primary refractory MM defined as disease that is non-responsive in patients that have never achieved at least stable disease or better with any therapy.
6. Any > grade 1 (according to the National Cancer Institute [NCI] Common Terminology Criteria for Adverse Events (CTCAE), v.4.03) adverse reaction unresolved from previous treatments or not readily managed and controlled with supportive care. The presence of alopecia of any and peripheral neuropathy ≤ grade 2 without pain is allowed.
7. Previous allogeneic stem cell transplantation with active graft-versus-host-disease or treatment with immunosuppressive therapy in the 2 months prior to study entry.
8. Daily requirement for corticosteroids >10 mg prednisone daily (or equivalent); inhaled corticosteroids are permitted.
9. Patient is known to be human immunodeficiency virus positive, or have chronic or active hepatitis B (core- or surface antigen-positive) or active hepatitis C infection.
10. Clinically significant cardiovascular disease (e.g., uncontrolled or any New York Heart Association [NYHA] Class 3 or 4, congestive heart failure, uncontrolled or uncontrolled angina, history of myocardial infarction or stroke within 6 months prior to study entry, uncontrolled hypertension or clinically significant arrhythmias not controlled by medication).
11. 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.
12. 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.
13. History of erythema multiforme or severe hypersensitivity to prior IMiDs such as thalidomide and lenalidomide.
14. The patient is receiving medications that are strong inhibitors of CYP1A2. Patients should have discontinued strong CYP1A2 inhibitors (e.g., ciprofloxacin and fluvoxamine [see Section 15.5]) at least 5 half-lives before beginning study drug.
15. The patient continues to smoke cigarettes, which can induce CYP1A2.
16. Inability to tolerate thromboprophylaxis (see section on concurrent medications).
17. Pregnant or breastfeeding females.

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. During phase 1, patients who discontinue the study prior to completing the DLT evaluation period because of disease progression or for reasons unrelated to study therapy will be replaced. All patients in phase 2

and those treated at the MTD or recommended phase 2 dose as established in phase 1, who are not evaluable for response will be replaced.

6 Investigational Plan

6.1 Dose and Schedule Rationale

Under an Investigator-sponsored IND (#11314), 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., capillary leak syndrome), 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 28 days with the allowance to delay the start of a subsequent cycle to allow toxicity resolution. Furthermore, a single cycle of SL-401 demonstrated single agent activity in patients with relapsed or refractory AML or BPDCN, with the majority of major responses occurring at the 12.5 µg/kg/day dose level. Therefore, the risk/benefit profile of SL-401 appeared to be most favorable at the 12.5 µg/kg/day dose level, and this is the expected dose that will be used in future studies of SL-401. This is the highest dose level planned in combination with POM/DEX.

In the interest of optimizing patient safety in combination therapy, the dose escalation in phase 1 of the study will begin 2 dose levels below, or at 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.

6.2 Overall Study Design

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

6.2.1 Phase 1: Dose Escalation

Run-In Cycle: SL-401 will be evaluated at doses of 7, 9, or 12 µg/kg/day, for 5 consecutive days (Days 1-5; with postponement as required by adverse events such that 5 doses over 10 days is permitted) as single agent during an initial Run-in Cycle. Upon completion of the Run-in Cycle patients will be evaluated for safety and response.

- Patients who do not experience a DLT during the Run-in Cycle will have POM/DEX added to their regimen at the assigned cohort dose.
- Patients who experience a DLT during the Run-in Cycle will be discontinued from study.

Table 7 details the SL-401/POM/DEX dose levels, beginning with dose level 1 to be evaluated.

Table 7: Dose Levels to be Evaluated

	DLT EVALUTION PERIOD = RUN IN CYCLE and CYCLE 1			
	Run-In Cycle	Combination therapy Cycles 1 - 6		
Dose Level	SL-401(IV) Daily on Days 1 – 5	SL-401(IV) Daily on Days 1 – 5	POM (oral) Daily on Days 1 – 21	DEX (oral) on Days 1, 8, 15 and 22
-1	5 µg/kg	5 µg/kg	4 mg	40 mg
1	7 µg/kg	7 µg/kg	4 mg	40 mg
2	9 µg/kg	9 µg/kg	4 mg	40 mg
3	12 µg/kg	12 µg/kg	4 mg	40 mg

Cohorts of 3-6 patients will be treated at each dose level. All patients within a cohort must complete the Run-in Cycle and the first cycle of combination therapy (Cycle 1) before patients can be enrolled into the subsequent cohort of SL-401 (single agent) at the next higher dose. No intra-patient dose escalation is allowed. The first cohort of patients will receive SL-401 single agent at a dose of 7 µg/kg/day followed by SL-401 with POM/DEX. After all patients in this cohort complete the Cycle 1 of therapy, the dose for the second cohort of patients will increase to 9 µg/kg/day, conditional on the DLT rules described below. Similarly, after all patients in the second cohort complete Cycle 1 of therapy, the dose for the third cohort of patients will increase to 12 µg/kg/day, conditional on the DLT rules described below.

Beginning with the dose level 7 µg/kg/day of SL-401 in combination with POM/DEX, a decision to allow treatment at the next higher dose level will depend on the number of patients who experience a DLT during the Run-in cycle and first cycle of combination therapy (Cycle 1). 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 1 of the initial 3 patients treated (1/3) experiences a DLT, the cohort will be expanded to include an additional 3 patients treated at the same dose 7 µg/kg/day. If only 1 patient (1/6) from this expanded cohort experiences a DLT, then 3 new patients will be treated at the next higher dose of 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 cohort.

The highest dose intended for evaluation is 12 µg/kg/day in combination with POM/DEX. If this dose level is not declared the MTD after at least 6 patients are treated, it will be declared the maximum tested dose level and will be the dose recommended for phase 2 studies. Potential DLTs and laboratory abnormalities will be evaluated by the DSRC (comprised of the Principal and Co-principal Investigators, Sponsor's Medical Monitor, and biostatistician) on an ongoing basis, who will evaluate the safety/tolerability of each dose level prior to investigation of a

subsequent dose level. Although the dose escalation process is guided by the safety evaluation during the Run-in Cycle and Cycle 1 of treatment, cumulative toxicities observed in subsequent administrations should also be considered for the dose escalation decisions.

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. The MTD will be used in phase 2 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 2 cycles of treatment for reasons other than the occurrence of DLT will be replaced by another patient who will receive the same dose regimen if necessary to evaluate that cohort (e.g., if a patient is not evaluable for DLT but 2 others have experienced a DLT within the cohort, there will be no need to replace the patient as the MTD will have been exceeded).

In the event that a DLT occurs in 2 patients treated at the 7 µg/kg/day dose level, 5µg/kg/day may 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 including a single agent Run-in Cycle prior to the first cycle of combination therapy. 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.

SL-401 related toxicities are AEs that are considered by the Investigator to be either possibly, probably or definitely related to investigational SL-401. (Refer to Section 10.6 for more thorough guidance as to the assessment of "relatedness" in the context of investigational anticancer therapy). It should be noted that although the cycle length is 28 days, cycle duration may extend beyond 28 days in the setting of AEs, which are detailed in Section 7.7.2.

6.2.2 Dose limiting Toxicity Definition

Run-In Cycle

In order to be evaluable for DLT assessment during the Run-in Cycle of single agent SL-401, a patient must receive all 5 doses within a 10 day time period (Days 1 – 10) and complete the 28 days of observation unless they experience DLT (patients who discontinue prior to this juncture because of disease progression or for reasons unrelated to study therapy will be replaced).

Combination Therapy Initial Cycle (Cycle 1)

In order to be evaluable for DLT assessment in Cycle 1 (initial cycle of combination therapy), a patient must receive at least 3 infusions of SL-401 and 16 (approximately 75%) doses of POM during Cycle 1, and complete the 28 days of observation unless they experience DLT. (Patients who discontinue prior to this juncture because of disease progression or for reasons unrelated to study therapy will be replaced).

The period of evaluation for DLT will include Run-in Cycle and Cycle 1 (the initial cycle of combination therapy).

DLT is defined as any of the following treatment-emergent adverse events (TEAEs) that are possibly, probably, or definitely related to therapy occurring in the first cycle:

- Any ≥ grade 4 neutropenia lasting greater than 7 days or ≥ grade 3 neutropenia associated with fever.
- Any grade ≥ 4 thrombocytopenia lasting greater than 7 days or ≥ grade 3 thrombocytopenia associated with bleeding.
- Any ≥ grade 3 non-hematologic toxicity except:
    - Grade 3 nausea, vomiting, or diarrhea lasting no longer than 48 hours (with resolution to ≤ grade 1 or baseline) with optimal supportive care.
    - Grade 3 arthralgia, myalgia, fever, in the absence of neutropenia, lasting no longer than 48 hours (with resolution to ≤ grade 1 or baseline).
    - Grade 3 fatigue lasting < 7 days.
    - Grade 3 laboratory abnormalities that are asymptomatic and not considered clinically significant by the Investigator, that respond to or do not require intervention and resolve to ≤ grade 1 or baseline ≤ 28 days after the last infusion of SL-401.
- Grade 4 transaminase or CPK elevation (confirmed within 24 hours of initial identification) regardless of duration or relationship to SL-401.

6.2.3 Maximum Tolerated Dose Definition

The MTD is defined as the dose preceding the dose level at which 2 patients experience a DLT during treatment in the Run-in Cycle and Cycle 1. A total of at least 6 patients must be evaluated in order to confirm the MTD. The MTD will be used in phase 2 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.

6.2.4 Phase 2: Expansion

During phase 2, at least 14 additional patients (total 20 patients) will be treated at the MTD or maximum tested dose at which multiple DLTs are not observed (identified in phase 1). During phase 2, the Run-in Cycle will no longer be administered. However, the first 6 patients treated at the MTD without the Run-in Cycle will also be assessed for DLT during the first cycle of therapy. In the event that more than one DLT is identified in these initial 6 patients during phase

2, consideration will be given to the administration of a reduced SL-401 dose in the remainder of phase 2, or re-institution of the SL-401 single agent Run-in Cycle for the remainder of phase 2.

6.3 Study Duration

The dose escalation stage (phase 1) will require approximately 6 to 18 patients to evaluate 3 dose levels of SL-401/POM/DEX. In phase 2, 14 additional patients will be treated (20 total patients) at the MTD or maximum tested dose. Total study duration is expected to be approximately 24 months. Patient enrollment is expected to occur over a 12-month period, with follow-up continuing until assessments of the primary and critical secondary objectives are completed for all treated patients. Refer to Section 7.9.2 regarding recommended procedures and follow-up after treatment discontinuation.

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

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

In the event that patients continue to receive investigational therapy without evidence of MM progression at the time of Study Completion, an Extension Phase may be implemented in which investigational SL-401 will be made available. During this Extension Phase, investigators are encouraged to continue evaluation of patients (including laboratory and imaging assessments) at a schedule appropriate for MM patients receiving investigational therapy and POM/DEX. Data collection by the Sponsor during this Extension Phase will be limited to information pertaining to SL-401 administration, reason for SL-401 discontinuation, AEs (including serious adverse events [SAEs]), and survival status. This information will comprise a Supplemental Database. The End-of-Study (EOS) occurs approximately 30 days after the last patient has discontinued SL-401. In the event that no patients are receiving ongoing investigational SL-401 at time of primary database lock (Study Completion), then Study Completion and EOS will occur at approximately the same time.

The study duration for an individual patient will include a screening period for inclusion of up to 21 days, the treatment period may continue for 6 cycles of combination therapy or until disease progression, unacceptable adverse reaction or other reason for discontinuation. The administration of additional cycles of SL-401 > 6 cycles (not including the Run-in Cycle if received) must be discussed with the Medical Monitor at which time the individual patient's potential risk/benefit of further treatment will be assessed. After study drug discontinuation an end-of-treatment (EOT) visit will be done at 30 days to assess safety. Patients who discontinue

therapy for reasons other than progression will be followed every month until progression of disease or initiation of subsequent therapy. Disease assessments should continue to be performed as described in the Schedule of Events (Table 13) until, in the judgment of the Investigator, there is evidence of relapsed or progressive disease. Following progression, either on or off therapy, patients will be followed for survival every 3 months for up to 1 year.

7 Study Treatment Identification, Administration, and Schedule

7.1 Product Manufacturing and Characterization

Refer to the Investigator Brochure for full details of product manufacturing and characterization for SL-401 and to the package insert for POM and DEX.

7.2 Concomitant Therapies

7.2.1 Required Concomitant Therapies

- Pomalidomide increases the risk of thromboembolism. Anti-coagulation prophylaxis is required after an assessment of each patient's underlying risk factors, unless there is an excess risk of bleeding.

- FCBP must either commit to continued abstinence from heterosexual intercourse or begin 2 acceptable methods of birth control, 1 highly effective method and 1 additional effective method at the same time, at least 28 days before she starts taking POM through 30 days after the last dose of POM and 60 days after the last dose of SL-401. Men must agree to use a latex or synthetic condom during sexual contact with a FCBP even if they have had a vasectomy from the time of signing the informed consent form through 30 days after the last dose of POM and 60 days after the last dose of SL-401.

- All patients enrolled into this study, must be registered in and must comply with all requirements of the POMALYST REMS™ program.

Refer to Section 7.3.2.2 for premedications required before each SL-401 infusion.

7.2.2 Recommended Concomitant Therapies

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

- Antibacterial: Avoid co-administration of strong CYP1A2 inhibitors (e.g., ciprofloxacin).

- Antifungal: fluconazole, voriconazole, or an equivalent antifungal.

- Antiviral: acyclovir, valacyclovir or an equivalent antiviral.

- Albumin 25 g IV daily should be administered if serum albumin is < 3 g/dL during treatment days or in the immediate post-treatment period. The Investigator has discretion with regard to frequency of administration per product and institutional guidelines.

7.2.3 Allowed Concomitant 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.

- Concomitant treatment with bisphosphonates will be permitted, as appropriate.
- Use of growth factors and platelet transfusions are not permitted during the Run-in Cycle and Cycle 1 unless the patient has experienced a DLT related to neutropenia or thrombocytopenia.

7.2.4 Prohibited Concomitant Therapies

The following procedures and treatments are prohibited during the study:

- Any antineoplastic treatment with activity against MM except for drugs in the treatment regimen specified in this study protocol.
- Radiation therapy (the requirement for local radiation therapy generally indicates disease progression) unless approved by the Medical Monitor.
- Platelet transfusions and growth factors to help patients meet eligibility criteria are not allowed within 7 days prior to the determination of eligibility or during the Run-in Cycle and Cycle 1 unless the patient experiences a DLT related to neutropenia or thrombocytopenia.
- CYP1A2 inhibitors: Avoid co-administration of strong CYP1A2 inhibitors (e.g., ciprofloxacin and fluvoxamine) with POM.

7.3 SL-401

7.3.1 Description of Active Substance and Drug Product

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

SL-401 injection will be provided frozen in a sterile, 2 mL glass vial containing a solution of 1 mL of SL-401 active pharmaceutical ingredient formulated at 1 mg/mL in a sterile solution of TRIS buffer. The solution has a pH of 7.5. SL-401 is prepared for administration by the pharmacy following the procedure listed in Section 7.3.2.

7.3.2 Storage, Premedication, Preparation and Administration

7.3.2.1 Storage

Intact vials should be stored at -20°C (± 5°C) and a document stating the product's expiry date will be provided with each shipment.

7.3.2.2 Premedication

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

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

7.3.2.3 Preparation

SL-401 is administered as a 15-minute IV infusion via syringe pump "piggybacked" into an established IV line of 0.9% normal saline. SL-401 is prepared for administration by the pharmacy by diluting with 0.9% normal saline to 100 µg/mL, loading the desired dose into a syringe with attached microbore tubing, and priming the infusion line. The total per-patient dose is calculated based on patient body weight in kilograms (kg) including one decimal place and the patient's dosing cohort, as described in Section 6.2 (µg/kg dose × patient weight in kg including one decimal place [example: 7 µg/kg x 70.3kg]). Additional dose preparation supplies and instructions are provided in detail within the Pharmacy Manual.

7.3.2.4 Administration

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

Prior to infusion, venous access should be established and maintained with 0.9% normal saline. The total infusion time (of the study agent) will be controlled using a syringe pump to deliver the entire dose over 15 minutes.

Attach the outlet of the primed infusion line (prepared by the pharmacy per Section 7.3.2.3) to the Y port in the patient's established IV line. Insert the diluted drug product syringe into the syringe pump, and set the pump parameters to deliver the total calculated dosage volume over 15 minutes. Stop the patient's running sterile saline line, and start the syringe pump. When the diluted DP syringe is empty, remove it from the pump and flush the system with sterile saline via the syringe pump to completely deliver the DP remaining in the administration set.

The first cycle of SL-401 must be administered in the inpatient setting (either as single agent or in combination), with hospitalization beginning the day of the first infusion of SL-401 (or a prior day) and ending approximately 24 hours after the last infusion of SL-401. Subsequent cycles of SL-401 can be administered in the inpatient setting or in a suitable outpatient ambulatory care setting that is equipped for intensive monitoring of patients with hematopoietic malignancies

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

Patients who do not have evidence of progressive disease or unacceptable toxicity may receive repeated cycles of SL-401 in combination with POM/DEX for up to 6 cycles. The administration of additional cycles of SL-401 > 6 cycles (not including the Run-in Cycle if received) must be discussed with the Medical Monitor at which time the individual patient's potential risk/benefit of further treatment will be assessed.

7.3.3 Dosing

During the dosing period for each cycle, individual SL-401 infusions may be delayed to allow for toxicity resolution, but all 5 infusions should be completed within 10 days. During the Run-in cycle of single agent SL-401 or the first cycle of combination therapy (Cycle 1), patients will receive a starting dose according to their dosing cohort assigned in Phase 1, or the dose carried into phase 2, for 5 consecutive days (or 5 doses over a period not to exceed 10 days if postponement is required for toxicity). The total per-patient dose is calculated based on patient body weight in kilograms (kg) and the patient's dosing cohort (µg/kg dose × patient weight in kg). This dose will be recalculated if there is a 10% or greater change in body weight from baseline. Dose changes should only occur once a cycle has been completed. Intra-cycle dose modifications are not permitted.

Potential dose modifications for subsequent cycles relative to the prior cycle dose will be based on the severity and resolution of toxicities. Once the dose has been reduced a subsequent increase is not permitted. Patients requiring > 1 dose reduction should be discontinued from SL-401 treatment unless there is evidence of disease response or stabilization and resolution of toxicity 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 disease control.

7.4 Pomalidomide

7.4.1 Handling and storage

Care should be exercised in handling of POM by caretakers. POM capsules should not be opened or crushed. If powder from POM contacts the skin, wash the skin immediately and thoroughly with soap and water. If POM contacts the mucous membranes, flush thoroughly with water. Female caregivers of childbearing potential should not handle or administer POM unless they are wearing gloves. POM should be stored at room temperature away from direct sunlight and protected from excessive heat and cold.

7.4.2 Prescribing Pomalidomide

POM will be provided in accordance with the Celgene Corporation's POMALYST REMS™ program. Per the standard POMALYST REMS™ program requirements, all physicians who

prescribe POM for research subjects enrolled into this study, and all research subjects enrolled into this study, must be registered in and must comply with all requirements of the POMALYST REMS™ program.

Only enough POM capsules for 1 cycle of therapy may be provided to the patient each cycle.

Commercial supplies of oral POM will be used in this study.

7.4.3 Pomalidomide Administration

POM should be taken with water and without food (2 hours before or 2 hours after a meal) and may be taken with DEX. (On the day of infusion 1 and 5 of Cycle 2, POM/DEX will be administered 4 - 6 hours after SL-401 to enable assessment of SL-401 PK without POM/DEX). If a dose of POM is missed, it should be taken as soon as possible on the same day. If it is missed for the entire day, it should not be made up, rather it should be taken at the next scheduled time point.

Patients who take more than the prescribed dose of POM should be instructed to seek emergency medical care if needed and contact study staff immediately.

7.5 Dexamethasone

Dexamethasone, a synthetic adrenocortical steroid, is a white to practically white, odorless, crystalline powder. It is stable in air. It is practically insoluble in water. The molecular formula is $C_{22}H_{29}FO_5$. The molecular weight is 392.47. It is designated chemically as 9-fluoro-11b,17,21-trihydroxy-16a-methylpregna-1,4-diene,3,20-dione.

Dexamethasone will be given once daily on Days 1, 8, 15 and 22. On the day of infusion 1 and 5 of Cycle 2, POM/DEX will be administered 4 - 6 hours after SL-401 to obtain SL-401 PK without POM/DEX).

Commercial supplies of oral DEX will be used in this study. Refer to the package insert for details on storage and administration.

7.6 Drug Accountability

7.6.1 SL-401

Refer to the Pharmacy manual for instructions on drug accountability for SL-401.

7.6.2 Pomalidomide and dexamethasone

A patient diary will be used to monitor patient compliance with POM and DEX PO administration.

7.7 Dose Modifications

Patients will be evaluated for AEs at each visit, with the NCI CTCAE, v.4.03, used as a guide for the grading of severity.

During the Run-in Cycle and Cycle 1 of combination therapy of phase 1, doses of SL-401 may be held per criteria detailed in Section 7.7.2.2, Section 7.7.2.3, and Table 11. In the setting of these criteria, 5 doses may be given over 10 days; otherwise no dose modifications are permitted during the Run-in Cycle and Cycle 1 of combination therapy unless the patient experiences a DLT. No dose escalations are permitted in any given patient once a dose level has been assigned. While patients experiencing DLT during Cycle 1 of combination therapy may continue on therapy, if toxicity can be managed according to the dose modification guidelines outlined below, the DLT event will contribute to the assessment of MTD for that given cohort.

Dose modifications may be performed in all subsequent cycles of treatment. If toxicities cannot be managed by dose modification or the patient cannot tolerate the lowest dose of study drug, the patient is to be discontinued from study drug unless there is evidence of clinical benefit beyond the initial treatment cycle. However, patients who have achieved disease control while receiving study therapy will continue to adhere to the schedule of assessments followed during the treatment phase of the study even though study drug has been discontinued.

7.7.1 Dose Reduction Steps for SL-401

The dose reduction steps for SL-401 are summarized in Table 8.

Table 8: Dose Reduction Steps for SL-401

Starting Dose	Daily on Days 1 – 5 every 28 days	
12 µg/kg	9 µg/kg	7 µg/kg *
9 µg/kg	7 µg/kg	5 µg/kg*
7 µg/kg	5 µg/kg	NA
5 µg/kg	NA	

*A second dose reduction may be permitted following consultation with the Medical Monitor.

7.7.1.1 Dose Reduction Steps for Pomalidomide

The dose reduction steps for POM are summarized in Table 9.

Table 9: Dose Reduction Steps for Pomalidomide

Starting Dose	Daily on Days 1 – 21 every 28 days		
4.0 mg	3.0 mg	2.0 mg	1.0 mg

7.7.1.2 Dose Reduction Steps for Dexamethasone

The dose reduction steps for DEX are summarized in Table 10.

Table 10: Dexamethasone Dose Reduction Steps

Starting Dose	Daily on Days 1, 8, 15 and 22 every 28 days		
40 mg	20 mg	12 mg	Discontinue DEX

7.7.2 Dose Modifications for Treatment Related Toxicity

As a general principal, patients with neutropenia or thrombocytopenia as a consequence of their disease may require dose reductions for myelosuppression. Dose-modifications in these patients should be considered on a case-by-case basis and discussed with the Medical Monitor. The following guidelines for hematologic toxicity should be used:

- The dose modification rules for treatment-related hematologic toxicity within each cycle are summarized below in Table 11, which are the approved prescribing recommendations for POM/DEX.
- If evidence of improving MM, hold the next cycle until ANC $\geq$ 1000/µL and platelets $\geq$ 50,000/µL, then resume SL-401/POM/DEX. In such patients who have had POM dose reductions in a cycle for hematologic toxicity in the face of improving MM, the POM dose level may be escalated back to the initial dose in a subsequent cycle.

Table 11: Dose Modification Guidelines for Toxicity Occurring during a Cycle of Therapy

CTCAE Category	Agents	Toxicity During a Cycle
Hematologic Toxicity during a cycle of therapy		
$\geq$ Grade 4 neutropenia (ANC <500 per mm^3) or febrile neutropenia (fever more than or equal 38.5°C and ANC <1,000 per mm^3)	Pomalidomide	Hold dose. Follow CBC weekly. If neutropenia resolved to < grade 4 (ANC $\geq$ 500 per mm^3 without fever) within the cycle, resume POM reduced by one dose level and continue through the scheduled end of the cycle. If not resolved to < grade 4 omit for remainder of cycle and reduce by one dose level at the start of the next cycle. Omitted doses are not made up.

CTCAE Category	Agents	Toxicity During a Cycle
Platelet count < 25,000/mm^3 or grade 3 thrombocytopenia with bleeding	Pomalidomide	Hold dose. Follow CBC weekly. If thrombocytopenia resolved to < grade 2 (50,000/mm^3) resume POM reduced by one dose level and continue through the scheduled end of the cycle. If not resolved to < grade 2 omit for remainder of cycle and reduce by one dose level at the start of the next cycle. Omitted doses are not made up.
For recurrent episodes of hematologic toxicity, POM may be further dose reduced at the Investigator's discretion to manage this toxicity.		
Non-Hematologic toxicity during a cycle of therapy		
Grade 1 or 2 non-hematologic A/E, regardless of drug attribution, do not require dose modifications, unless in the opinion of the Investigator, the event is intolerable and warrants dose modification in consultation with the Medical Monitor.		
SL-401 Adverse events that require holding SL-401 (all treatment cycles)		
Heart rate ≥ 130 or ≤ 40 bpm		Investigate and address potential etiologies of tachy/bradycardia.
Systolic BP ≥ 160 or ≤ 80 mmHg		Hypertension: administer antihypertensive therapy as appropriate. Hypotension: evaluate potential capillary leak syndrome; administer parenteral hydration/electrolyte support as appropriate (refer to Section 7.7.3.3).
Serum creatinine > 2.0 mg/dL		Evaluate potential etiologies of renal dysfunction; parenteral hydration/electrolyte support as appropriate.
Serum albumin < 3.0 g/dL		Evaluate potential capillary leak syndrome. Administer parenteral (IV) albumin as indicated in protocol Section 7.7.3.3. Withhold subsequent SL-401 for the duration of the cycle.
Reduction in serum albumin by more than 1.0g/dL below level at the start of the current cycle (i.e. from 4.3g/dL to 3.2g/dL)		Evaluate potential capillary leak syndrome. Administer parenteral (IV) albumin as indicated in protocol Section 7.7.3.3. Withhold subsequent SL-401 for the duration of the cycle.
AST > 5 × the ULN or ALT > 5 × the ULN		Ongoing observation of clinical, laboratory and other parameters of hepatic dysfunction. Withhold subsequent SL-401 for the duration of the cycle.
Body temperature ≥ 38°C		Evaluate potential etiologies of fever, including infectious complications. Administer anti-pyretic therapy (i.e., acetaminophen/paracetamol) as appropriate.

CTCAE Category	Agents	Toxicity During a Cycle
Increase in body weight by ≥ 1.5 kg over weight (pre-treatment) on the prior treatment day.		Evaluate potential capillary leak syndrome. Evaluate for fluid retention or other potential etiologies of weight gain. Diuresis as appropriate.
Capillary Leak Syndrome (including suspected capillary leak syndrome) as manifested by hypotension, tachycardia, reduced albumin, or increased weight.		In the setting of delays secondary to findings consistent with capillary leak syndrome (i.e., in the setting of resolved hypotension, tachycardia, increased weight, or albumin reductions of a magnitude lower than those warranting withholding of SL-401 for the duration of a given cycle), subsequent SL-401 infusions are to be administered pending determination by the Investigator that there is no/minimal evidence of ongoing capillary leak syndrome and pending discussion with the study Medical Monitor. Any subsequent SL-401 infusions are to be administered on days subsequent to the identification of the abnormality (i.e., not the same day the abnormality was identified). In settings in which albumin is reduced to <3.0g/dL or in which albumin is reduced by more than 1.0 g/dL below the level at the start of the cycle (i.e. from 4.3g/dL to 3.2g/dL), no subsequent SL-401 will be administered for the duration of the cycle.
Any other grade 3 SL-401 related non-hematologic toxicity.		In the case of arthralgia, myalgia, fever responding to treatment, or nausea, vomiting and diarrhea with suboptimal treatment or reversible lab abnormalities, implement supportive care and resume at same dose if resolved to ≤ grade 1 or baseline and complete the scheduled cycle (up to 5 doses over 10 days if feasible). If not resolved by Day 1 of subsequent cycle, monitor weekly or more frequently if appropriate. Resume at one level dose reduction when resolved to ≤ grade 1. If treatment is held for more than 14 days of planned start of subsequent cycle, discontinue study drug. Additional options may be pursued following discussion with the Medical Monitor for patients with evidence of MM stabilization/response.
Any grade 4 SL-401 related non-hematologic toxicity.		Consider permanent discontinuation of therapy. Additional options may be pursued following discussion with the Medical Monitor for patients with evidence of MM stabilization or response.
SL-401 Adverse events that require specific management		
Chills, Anaphylaxis and Hypersensitivity Reaction		Refer to Section 7.7.3.1
Symptomatic hypotension		Refer to Section 7.7.3.2
Capillary leak syndrome		Refer to Section 7.7.3.3
Pomalidomide		
Rash Grade 2 or 3		Hold POM. Follow weekly.

CTCAE Category	Agents	Toxicity During a Cycle
		If the toxicity resolves to ≤ grade 1, restart POM and continue through the scheduled end of the cycle. Otherwise, omit for remainder of cycle and reduce the dose of POM by one dose level at the start of the next cycle. Omitted doses are not made up.
Grade 4 Non-blistering rash		Discontinue POM.
Desquamating (blistering) rash-any grade or erythema multiforme ≥ grade 3		Discontinue POM
Venous Thrombosis/embolism ≥ grade 3		Hold therapy and start full anticoagulation as appropriate; restart at Investigator's discretion (maintain dose level).
Any grade 3 POM related non-hematologic toxicity		Hold POM. Follow at least weekly. If toxicity resolves to ≤ grade 2 or baseline, resume therapy with one level dose reduction.
Any grade 4 POM related non-hematologic toxicity		Consider permanent discontinuation of therapy. Exceptions may be made following discussion with the Medical Monitor for patients that are experiencing disease stabilization or response.

7.7.2.1 Dexamethasone Dose Modification Guidelines.

DEX dose modification guidelines are summarized in Table 12.

Table 12: Dexamethasone Dose Modification Guidelines

Dexamethasone dose modifications		
Gastrointestinal	Dyspepsia, gastric or duodenal ulcer, gastritis Grade 1-2 (requiring medical management)	Treat with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, decrease dexamethasone dose by 1 dose level
	> Grade 3 (requiring hospitalization or surgery)	Hold dexamethasone until symptoms adequately controlled. Restart and decrease one dose level and continue therapy with H2 blockers, sucralfate, or omeprazole. If symptoms persist despite above measures, discontinue dexamethasone and do not resume.
	Acute pancreatitis	Discontinue dexamethasone and do not resume.
Cardiovascular	Edema > Grade 3 (limiting function and unresponsive to therapy or anasarca)	Diuretics as needed, and decrease dexamethasone dose by 1 dose level; if edema persists despite above measures, decrease dose another dose level. Discontinue dexamethasone and do not resume if symptoms persist despite second reduction. Evaluate for additional evidence of Capillary Leak Syndrome and withhold/discontinue SL-401 as stipulated in protocol (Refer to Section 7.7.3.3).
Neurology	Confusion or Mood alteration	Hold dexamethasone until symptoms resolve. Restart with one dose level reduction. If symptoms persist despite

	> Grade 2 (interfering with function +/- interfering with activities of daily living)	above measures, discontinue dexamethasone and do not resume.
Musculoskeletal	Muscle weakness > Grade 2 (symptomatic and interfering with function +/- interfering with activities of daily living	Decrease dexamethasone by one dose level. If weakness persists despite above measures decrease dose by one level. Discontinue dexamethasone and do not resume if symptoms persist.
Metabolic	Hyperglycemia > Grade 3 or higher	Treatment with insulin or oral anti-diabetic agents as needed. If uncontrolled despite above measures, decrease dose by one dose level until levels are satisfactory.

7.7.2.2 Procedures Required During Dosing Period

During each cycle, the following testing and procedures are required:

Vital Signs: Blood pressure, heart rate, respiration rate, body temperature, and pulse oximetry during dosing period (usually Days 1, 2, 3, 4 and 5) and Days 8, 15, and 22. Heart rate (HR), temperature, respiratory rate (RR), blood pressure (BP) to be taken pre- SL-401 infusion, at end of SL-401 infusion, every 30 minutes for 4 hours following the end of infusion and as clinically indicated for all doses of the Run-in Cycle. For Cycle 1 and thereafter, vital signs are to be taken pre-infusion, at end of infusion and as clinically indicated. For temperature > 38ºC, obtain blood cultures (2 sets) and collect urine for urinalysis and culture.

Diagnostic Tests:

- During dosing period, prior to SL-401 infusion (usually Days 1, 2, 3, 4, 5) and Days 8, 15, and 22: complete blood count (CBC) with differential, platelets, sodium, potassium, chloride, bicarbonate, blood urea nitrogen (BUN), creatinine, glucose, total protein, albumin, calcium, phosphorus, uric acid, total bilirubin, ALT, AST, alkaline phosphatase, lactate dehydrogenase (LDH), CPK, prothrombin time (PT) / International Normalized Ratio (INR), and partial thromboplastin time (PTT).
- Days 1 (prior to SL-401 infusion): routine urinalysis
- For temperature ≥ 38°C, draw blood culture × 2, and collect urine for urinalysis and culture/
- Daily weight (during the period of the 5 infusions) and Days 8, 15 and 22.

The results of these evaluations may result in withholding of a scheduled SL-401 infusion, largely based on unresolved manifestations of fluid retention and/or other relevant acute toxicities during daily dosing, are described below and in Table 11.

7.7.2.3 Events Requiring Holding of SL-401

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

- Body temperature ≥ 38°C
- HR ≥ 130 or ≤ 40 bpm
- Systolic BP ≥ 160 or ≤ 80 mmHg
- Serum creatinine > 1.8 mg/dL
- Serum albumin < 3.0 g/dL (SL-401 will be withheld for the remainder of the study cycle).
- AST > 5 × the ULN or ALT > 5 × the ULN (SL-401 will be withheld for the remainder of the study cycle).
- Increase in body weight by ≥ 1.5 kg over weight (pre-treatment) on the prior treatment day.

In situations where SL-401 administration is postponed because of deviations in vital signs, weight or laboratory values outside of the above parameters, SL-401 may be re-administered subsequently, pending normalization of the abnormalities and pending evidence of stabilization of the underlying clinical conditions resulting in these abnormalities, as detailed below. As indicated in Section 7.3.3, postponed doses may be administered within a 10-day period following the initial day of treatment within a cycle.

In the setting of temperature ≥ 38°C, SL-401 may be administered pending resolution, provided that an appropriate evaluation for infectious etiologies has been undertaken, and provided that the Investigator determines that there is minimal likelihood of uncontrolled systemic infection including sepsis; this may occur on the same day as the temperature elevation, or on subsequent days.

In the setting of delays secondary to findings consistent with capillary leak syndrome (i.e., in the setting of resolved hypotension, tachycardia, increased weight, or albumin reductions of a magnitude lower than those warranting withholding of SL-401 for the duration of a given cycle), subsequent SL-401 infusions are to be administered pending determination by the Investigator that there is no/minimal evidence of ongoing capillary leak syndrome and pending discussion with the study Medical Monitor. Any subsequent SL-401 infusions are to be administered on days *subsequent* to the identification of the abnormality (i.e., not the same day the abnormality was identified).

In settings in which albumin is reduced to <3.0g/dL or in which albumin is reduced by more than 1.0 g/dL below the level at the start of the cycle (i.e. from 4.3g/dL to 3.2g/dL), no subsequent SL-401 will be administered for the duration of the cycle.

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

7.7.3 Management of Specific Toxicities

7.7.3.1 Chills, Anaphylaxis, and Hypersensitivity Reactions

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

In the setting of grade 1-2 hypersensitivity reactions, subsequent administration of SL-401 may be attempted, provided that any systemic symptoms of the prior grade 1-2 hypersensitivity reaction resolve within 24 hours with appropriate supportive measures. Premedication for patients with prior grade 1-2 hypersensitivity reactions should include the agents specified in Section 7.3.2.2; additional premedication may be provided at the Investigator's discretion and should be discussed with the study Medical Monitor or designee. Refer to Section 10.7 concerning recommended optimal reporting of SL-401 related hypersensitivity reactions.

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

7.7.3.2 Symptomatic Hypotension

Symptomatic hypotension will be treated with a bolus of 500 cc normal saline and a hold (postponement) on further drug infusion until resolution. During the dosing period, if the BP fails to improve with two 500 cc bolus saline infusions, further standard measures to correct the BP will be undertaken, regardless of the rapidity or delay in resolution, and SL-401 will be withheld on that day. If low BP persists such that further treatment is not feasible during the day of the intended dose and the following day, no further SL-401 will be administered to that patient for that cycle.

7.7.3.3 Capillary Leak Syndrome

Capillary leak syndrome is associated with vascular endothelial injury related to fusion protein administration and may occur 3 – 8 days after initiation of treatment. Patients may exhibit symptoms of hypotension, weight gain, edema, nausea, and anorexia, shortness of breath and, at

times, confusion and muscle injury. Findings may include hypoalbuminemia, reductions in blood oxygen saturation, and evidence of pulmonary edema on chest x-ray. Patients with hypotension will receive 500 cc normal saline boluses and observation as detailed in Section 7.7.3.2. Patients will have serum albumin measurements daily until completion of SL-401 administration and will receive 25 g albumin IV each day the serum albumin is < 3 g/dL. Patients with > 10% weight gain and no hypotension may be treated with fluid restriction and/or diuretics such as furosemide as clinically indicated per Investigator discretion.

As indicated above in the setting of delays secondary to findings consistent with capillary leak syndrome (i.e., in the setting of resolved hypotension, tachycardia, increased weight, or albumin reductions of a magnitude lower than those warranting withholding of SL-401 for the duration of a given cycle), subsequent SL-401 infusions are to be administered on days subsequent to the identification of the abnormality (not the same day), pending determination by the Investigator that there is no/minimal evidence of ongoing capillary leak syndrome and pending discussion with the study Medical Monitor.

In settings in which albumin is reduced to <3.0g/dL or in which albumin is reduced by more than 1.0 g/dL below the level at the start of the cycle (i.e. from 4.3g/dL to 3.2g/dL), no subsequent SL-401 will be administered for the duration of the cycle.

7.8 Guidelines for Initiation of a New Cycle of Therapy

For a new cycle of treatment to begin, the patient must meet the following criteria:

- ANC must be ≥ 1,000/mm^3.
- Platelet count must be ≥ 50,000/mm^3.
- All other non-hematologic SL-401 related toxicity must have resolved to ≤ grade 1 or to the patient's baseline condition.
- The patient does not have any adverse events that require holding SL-401 (Table 11) or has not had prior anaphylaxis or ≥ grade 3 hypersensitivity reaction.
- All other non-hematologic POM/DEX related toxicity must have resolved to ≤ grade 2 or to the patient's baseline condition.

If the patient fails to meet the above-cited criteria for initiation of the next cycle of treatment, dosing should be delayed for 1 week. At the end of that time, the patient should be re-evaluated to determine whether the criteria have been met. If the patient continues to fail to meet the above-cited criteria, within 14 days from a scheduled day one of therapy, then discontinue treatment. In patients in whom there may be evidence of MM response or stability as determined by the treating physician, treatment may be resumed at a reduced SL-401/POM/DEX dose level after discussion with the Medical Monitor.

7.9 Treatment Discontinuation

7.9.1 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
- Disease recurrence/progression.
- Intercurrent illness that prevents further administration of SL-401.
- Patient non-compliance.
- Occurrence of pregnancy.
- Completion of 6 cycles of treatment.
- Investigator's decision.

The reason for SL-401 discontinuation and the date of discontinuation should be recorded in the electronic case report form (eCRF).

7.9.2 Procedures and Follow-up after Treatment Discontinuation

The evaluation during which the Investigator determines that SL-401 or SL-401/POM/DEX will be discontinued should be considered the EOT Evaluation; all tests and procedures for the EOT Evaluation are listed in Table 13. In addition, patients should be followed for a minimum of 30 days after the last dose of SL-401 or SL-401/POM/DEX for assessment of AEs (including potential new AEs and potential change/resolution of existing AEs).

Patients who discontinue therapy for reasons other than progression will be followed every month until progression of disease or initiation of subsequent therapy. Disease assessments should continue to be performed as described in Table 13, until there is evidence of relapsed or progressive disease in the judgment of the Investigator. Following progression, either on or off therapy, patients will be followed for survival every 3 months for up to 1 year.

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.

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 RRMM who have previously received at least 2 lines of therapy for their disease 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 informed consent form (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 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 [redacted] 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 MM diagnosis, prior MM treatment, response to prior treatment, and date of relapse, if applicable. Information concerning any prior malignant diagnoses with particular focus on cytotoxic therapies received for prior malignancies (i.e., dates/duration of anthracycline for prior breast cancer) is to be collected whenever feasible.

8.3 Prior and Concomitant Medication

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

8.4 ECOG Performance Status

See Section 15.1 for a scoring guide.

8.5 Physical Examination

Physical examination includes evaluation by body system, weight, and height (at screening only), evaluation for extramedullary plasmacytomas and neurologic assessment.

8.6 Vital Signs

Vital signs include temperature, HR, RR, pulse oximetry, and BP. Collection should occur after the patient has been sitting for 3-5 minutes. See Section 7.7.2.2 for collection schedule.

8.7 Electrocardiograms

All patients will have a 12-lead ECG performed at the screening visit, Day 1 of each cycle and at the EOT visit.

8.8 Clinical Laboratory Tests

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

- Hematology: Minimally, scheduled hematology collections should include white blood cell count, differential white cell count (lymphocytes, monocytes, basophils, eosinophils, neutrophils), red blood cell count, hematocrit, hemoglobin and platelet count.
- Serum albumin: May be a component of the serum chemistry panel. See Section 7.2.2 for administration of albumin if serum albumin decreases to < 3 g/dL during treatment days or in the immediate post-treatment period.
- Serum electrolytes and chemistry: Chemistry includes: glucose (fasting at baseline), albumin, total protein, AST, ALT, bilirubin (total and direct), alkaline phosphatase (AP), LDH, CPK, sodium, potassium, chloride, bicarbonate/carbon dioxide, calcium, magnesium, phosphate, uric acid, blood urea nitrogen (BUN), serum creatinine and estimated creatinine clearance (Cockroft-Gault formula; see Appendix 15.7). Albumin, transaminases (AST/ALT) and creatinine must be evaluated prior to each SL-401 dose.
- Coagulation parameters: PT and/or INR, aPTT.
- Urinalysis: Appearance, color, pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilinogen, and occult blood.

8.9 Urine or Serum Pregnancy Test

Urine or serum pregnancy tests must be completed prior to the Run-in Cycle of Sl-401 and urine or serum pregnancy tests of at least 50 mIU/mL must be performed for females of child bearing potential within 7 to10 days and again within 24 hours of initiation of POM therapy. Repeat pregnancy test every week for the first 4 weeks and then every 28 days while on therapy and during interruptions in therapy and 28 days following discontinuation of POM Women with irregular menstruation must have pregnancy testing every 14 days while on therapy and during interruptions and 14 and 28 days after discontinuation of POM. All patients enrolled into this study must be registered in and must comply with all requirements of the POMALYST REMS™ program.

8.10 Tumor Assessments

Secondary efficacy endpoints will include: PFS; PFS-6; ORR (CR + VGPR + PR) and clinical benefit rate (CR + VGPR + PR + MR) based on IMWG defined response criteria, as well as the DOR; and OR. Tumor assessments are to be done prior to the start each cycle and may be performed within the 7 days prior to Day 1 of a new cycle.

Efficacy assessment parameters will include:

- M-protein determination using both of the following procedures:
  - Serum protein electrophoresis (SPEP) and serum protein immunofixation with quantitative immunoglobulins; and
  - Urine protein electrophoresis (UPEP) and urine protein immunofixation (all using the same 24-hour urine collection)
- Serum FLC
- Bone marrow aspirate to quantify percent MM cell involvement
- Plasmacytoma evaluation: positron emission tomography/computed tomography (PET/CT) scan or magnetic resonance imaging (MRI) and or physical examination, as clinically indicated
- Skeletal survey
- Serum β_2 microglobulin (at baseline only)
- Cytogenetics/fluorescence *in situ* hybridization (FISH) on BM aspirate (at baseline only)

8.11 Translational/Correlative Research Assessments

Additional BM and blood samples (beyond what is required for assessment of response/progression) will be obtained for correlative research to identify mechanism(s) of response/resistance to SL-401 therapy as follows:

- Bone marrow aspirate and biopsy will be obtained prior to, during and following therapy in order to characterize the expression of IL-3R/CD123 (and other potentially relevant markers) on MM cells and associated cell populations using IHC and flow cytometry.
- Peripheral blood (whole blood) for MM and other relevant mononuclear cells will be obtained at baseline, Day 1 of Cycles 2, 4 and 6 and at EOT in order to characterize the expression of IL-3R/CD123 (and other potentially relevant markers) on MM cells and associated cell populations using IHC and flow cytometry.

- Peripheral blood (serum and plasma) will be obtained at baseline, Day 1 of Cycles 2, 4 and 6 and at EOT to evaluate levels of circulating cytokines (i.e., IL-3 and others) relevant to MM cell interactions with accessory (non-neoplastic) cells.

Specimen Collection and Handling Instructions:

- BM aspirate (10-15 mL in heparinized syringe; smaller amounts if 10 cc not available)

- Peripheral blood: 4 tubes total

(3 × 10 mL green top tubes, 2 for whole blood; 1 for plasma)

(1 × 10 mL red top/serum-separating tube for serum)

Labeling and shipping for all samples

Bone marrow and peripheral blood samples will be immediately sent to: Dr. Dharminder Chauhan's laboratory, as follows:

450 Brookline Avenue
Mayer Building, 5th Floor, Room M553
Boston, MA 02215.

Label all specimens with the following:

i. Subject initials

ii. Subject study number (will include protocol number)

iii. Visit at which sample was drawn (i.e., C1D4)

iv. Date sample drawn (i.e., mm/dd/yyyy)

v. Time sample drawn (24 hour clock)

vi. Sample type (e.g., plasma, serum, BM cells, tumor cells)

8.12 Pharmacokinetic Studies

During the phase 1 component of the study, blood samples after specific infusions during Run-in Cycle and Cycle 2 of SL-401 will be used to determine plasma concentrations of SL-401. The concentration of SL-401 in plasma samples will be determined by a sensitive and specific sandwich enzyme-linked immunosorbent assay (ELISA) method at a contract laboratory according to industry GLP bioanalytical practices. Plasma concentration data over time will be used to characterize the PK disposition of SL-401, to assess any change in the PK properties of SL-401 during the 5-day course of treatment or between cycles of treatment, and relate the PK characteristics of SL-401 to immunogenicity, toxicity, and disease activity.

Collectively, the SL-401 plasma concentration-time data will be analysed by conventional non-compartmental PK methods to define the fundamental PK properties of SL-401. Furthermore, if supported by the adequacy of the data, a population PK model will be developed, in which the effects of various potentially relevant co-variants (i.e., gender, age, IL-3R expression, immunogenicity) on relevant PK parameters, will be evaluated. Sample collection requires that the actual date and time (24-hour clock) that the SL-401 treatment begins (start of infusion) and ends (end of infusion) 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. PK sample aliquots will be shipped either to MRL or directly to the EMD Millipore Corporation/Eurofins Pharma Bioanalytical Services US Inc. and evaluated.

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

Samples will be collected immediately prior to the start of the infusion of SL-401, immediately after end of infusion (time recorded), then 15, 30, 45, 60, 90, 120, 180, and 240 minutes after the completion of the infusion (see Table 14). 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 14 for the following SL-401 treatment days:

- Cycles Run-in Cycle and Cycle 2, infusion 1 (i.e., Day 1).
- Cycles Run-in Cycle and Cycle 2, infusion 5 (i.e., usually Day 5).

8.13 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:

- Run-in Cycle: Day 1 (pre-infusion) and Day 5 (pre-infusion), Day 1 of each subsequent cycle (pre-infusion) and at the EOT visit.

- 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.
- If there are clinical manifestations suggesting either an infusion related reaction or drug hypersensitivity, an immunogenicity sample should be obtained, as indicated in Section 7.7.3.1.

Samples for immunogenicity assessment will be shipped to MRL, and will subsequently be evaluated by the EMD Millipore Corporation/Eurofins Pharma Bioanalytical Services US Inc. 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 pharmacokinetic analysis.

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

9 Schedule of Events

The study schedule of events is summarized in Table 13.

9.1 Day -21 to -1: Screening

The following evaluations will be performed on Day -21 to -1 to determine the patient's eligibility for the study and in anticipation of study drug:

- Informed Consent and registration in POMALYST REMS system.
- Inclusion / Exclusion criteria review.
- Medical and MM history, including prior therapy and concomitant medications.
- Physical examination.
- ECOG performance status.
- Vital signs, height and weight.
- 12-lead ECG.
- ECHO or MUGA scan.
- Urine or serum pregnancy (see Section 8.9 and Table 13).
- Clinical laboratory tests: hematology, serum chemistry.
- PT / INR, aPTT.
- Urinalysis.
- Plasmacytoma evaluation.
- Skeletal survey.
- Bone marrow aspiration and biopsy (biopsy required for correlative samples).
- Peripheral blood (whole blood, serum, plasma) for correlative studies.
- MM-specific laboratory tests.
- AE and SAE monitoring (baseline signs and symptoms).
- Prior and ongoing medications.

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 Run-in Cycle

9.2.1 Days 1 – 5 (Up to Day 10 if infusion[s] held): Pre-infusion

- Inpatient admission (Day 1).
- ECOG performance status (Day 1 only).
- Physical examination (complete physical examination on Day 1; symptom-directed on other days, as warranted).
- Vital signs and weight.
- Clinical laboratory tests: hematology, serum chemistry.
- Urinalysis (Day 1 only).
- Collection of peripheral blood for immunogenicity (serum) Pre-infusion (on Days 1 and 5 only).
- MM-specific laboratory tests (Day 1 only).
- PK sampling (infusions 1 and 5) prior to and following infusion.
- Diphenhydramine 50 mg IV 60 minutes prior to infusion.
- Acetaminophen 650 mg PO 60 minutes prior to infusion.
- Methylprednisolone 50 mg IV (or an equivalent dose of another corticosteroid) 60 minutes prior to infusion.
- Ranitidine 50 mg IV (or an equivalent doses of another H_2-histamine antagonist) 60 minutes prior to infusion.

9.2.2 Days 1 – 5 (Up to Day 10 if infusion(s) held): During/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.

- 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.

9.2.3 Day 8 ±3 Days, or 3 ±3 Days after completion of infusions if infusion(s) held

- Vital signs and weight.
- Clinical laboratory tests: hematology and serum chemistry.
- AE and SAE monitoring.
- Concomitant medication assessment.

9.2.4 Day 15 ±3 Days

- Vital signs and weight.
- Clinical laboratory tests: hematology and serum chemistry.
- AE and SAE monitoring.
- Concomitant medication assessment.

9.2.5 Day 22 ±3 Days

- Vital signs and weight.
- Pregnancy test for FCBP within 7 – 10 days prior to initiation of POM in Cycle 1 (see Section 8.9 and Table 13).
- Clinical laboratory tests: hematology and serum chemistry.
- AE and SAE monitoring.
- Concomitant medication assessment.

9.2.6 Cycle Delay

- If Cycle 1 is delayed end of cycle evaluation for toxicity resolution if required Day 28 ±3 days, then every 7 ±3 days.
- Concomitant medication assessment.
- ECOG performance status.
- Vital signs and weight.
- Clinical laboratory tests: hematology, serum chemistry (including albumin)

- AE and SAE monitoring

9.3 Cycles 1 through 6 combination therapy (Phase 1 and 2)

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

- Inpatient admission or treatment at a suitable outpatient facility.
- Physical examination (complete physical examination on Day 1; symptom-directed on other days, as warranted).
- ECOG performance status (Day 1 only).
- Vital signs and weight.
- 12-lead ECG – (Day 1 only of each cycle).
- Pregnancy test for FCBP within 24 hours prior to initiation of POM.
- Clinical laboratory tests: hematology and serum chemistry (Day 1 of each cycle).
- PT or INR/aPTT.
- Urinalysis (Day 1 only of each cycle).
- Extramedullary disease evaluation according to IMWG criteria (if needed to confirm response).
- BM aspiration (if needed to confirm response).
- Collection of blood (whole blood, serum, plasma) for correlative studies; Phase 1: Day 1 of Cycles 1, 3 and 5. Phase 2: Day 1 of Cycles 2, 4, and 6.
- Collection of peripheral blood for immunogenicity (serum) - 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.
- MM-specific laboratory tests (Day 1 only – a -7 day window is permitted for scheduling).
- PK sampling; **phase 1 only** (Cycle 2 only, infusions 1 and 5) prior to and following infusion.
- Diphenhydramine 50 mg IV 60 minutes prior to infusion.
- Acetaminophen 650 mg PO 60 minutes prior to infusion.

- Methylprednisolone 50 mg IV (or an equivalent dose of another corticosteroid) 60 minutes prior to infusion.
- Ranitidine 50 mg IV (or an equivalent doses of another H_2-histamine antagonist) 60 minutes prior to infusion.Days 1 – 5 (up to Day 10 if infusion(s) held): infusion 15-minute IV infusion of SL-401 at required dose.
- POM administration (Days 1 – 21) (POM to be administered 4 – 6 hours post infusion on the day of infusion 1 and 5 of Cycle 2).
- DEX administration (Days 1, 8, 15 and 22) (DEX to be administered 4 – 6 hours post infusion on the day of infusion 1of Cycle 2).
- 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.Concomitant medication assessment.

9.3.2 Day 8 ±3 Days

- Vital signs and weight.
- Pregnancy test for FCBP required for Cycle 1 only).
- Clinical laboratory tests: hematology, serum chemistry.
- POM administration (Days 1 -21).
- DEX administration (Days 1, 8, 15 and 22).
- AE and SAE monitoring.Concomitant medication assessment.

9.3.3 Day 15 ±3 Days

- Vital signs and weight.
- Pregnancy test for FCPB (required for Cycle 1) then if applicable for subsequent cycles.
- Clinical laboratory tests: hematology, serum chemistry (including albumin).
- POM administration (Days 1 -21).
- DEX (Days 1, 8, 15 and 22).
- AE and SAE monitoring.Concomitant medication assessment.

9.3.4 Day 22 ±3 Days

- Vital signs and weight.
- Pregnancy test for FCBP (required for Cycle 1 only).
- Clinical laboratory tests: hematology serum chemistry.
- DEX administration (Days 1, 8, 15 and 22).
- AE and SAE monitoring.
- Concomitant medication assessment.

9.3.5 Cycle Delay

- If a cycle is delayed, end of cycle evaluation for toxicity resolution if required Day 28 ± 3 days, then Every 7 ± 3 days.
- Concomitant medication assessment.
- ECOG performance status.
- Vital signs and weight.
- Clinical laboratory tests: hematology, serum chemistry (including albumin).
- AE and SAE monitoring.

9.4 Additional Cycles

- In the event that patients are permitted to continue therapy beyond 6 cycles, the same study procedures as during Cycles 1 – 6 will be followed.

9.5 End of Treatment

- Physical examination.
- ECOG performance status.
- Vital signs and weight.
- 12-lead ECG.
- Pregnancy test.
- Clinical laboratory tests: hematology, serum electrolytes, and chemistry (including albumin).

- PT or INR/aPTT.
- Urinalysis.
- Extramedullary disease evaluation,
- BM aspiration.
- Collection of peripheral blood (whole blood, serum, plasma) for correlative studies.
- MM-specific laboratory tests.
- Collection of peripheral blood for PK sampling.
- Collection of peripheral blood (serum) for immunogenicity.
- AE and SAE monitoring.
- Concomitant medication assessment.

9.6 Safety Monitoring: Through 30 days after Last Infusion

- AE and SAE monitoring.
- Survival status.
- Concomitant medications.
- Myeloma-specific laboratory tests.
- Skeletal survey.
- Extramedullary disease evaluation.

9.7 Follow-Up

Patients who discontinue therapy for reasons other than MM progression will be followed for disease response every month until progression of disease or initiation of subsequent therapy. Patients who have discontinued study therapy and have had MM progression should be contacted approximately every 3 months (telephone contact is permitted) to assess survival status for up to one year; patients who discontinue therapy for reasons other than disease progression and are no longer willing to follow-up for evaluation of disease progression should also be contacted for survival status whenever feasible.

Table 13: Schedule of Events

Evaluation	Screening/ Baseline	Run in Cycle Cycle is 28 days								Cycles 1 - 6 [u] Each Cycle is 28 days								EOT[v]	F/U[w]
	D-21 to -1	D 1	D 2	D 3	D 4	D 5	D 8	D 15	D 22	D 1	D 2	D 3	D 4	D 5	D 8	D 15	D 22		
Informed Consent & Pomalyst REMS[a]	X																		
Entry Criteria Review	X																		
Medical and Myeloma History[b]	X																		
Physical Examination[c]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Performance Status (ECOG)	X	X								X								X	
Height (Baseline only) / Weight	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
Vital Signs (HR, Temperature, RR, BP)[d]	X	X	X	X	X	X	X	X		X	X	X	X	X	X	X		X	
ECG	X									X								X	
ECHO/MUGA	X																		
Pregnancy testing [FCBP) and counseling [e]	X								X[e]	X					X[e]	X[e]	X[e]	X	
Hematology[f]	X	X	X	X	X	X	X	X	X	X[f]	X	X	X	X	X	X	X	X	
Serum Chemistry[g]	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	X	
PT / INR aPTT	X									X								X	
Urinalysis [h]	X	X								X								X	
Plasmacytoma Evaluation [i]	X									X[i]								X	As needed
Skeletal Survey [j]	X																		As needed
Bone Marrow Aspiration and biopsy[k]	X									X[k]								X	
Peripheral blood for correlative studies[l]	X									X[l]								X	

Evaluation	Screening/ Baseline	Run in Cycle Cycle is 28 days								Cycles 1 - 6 [n] Each Cycle is 28 days								EOT[v]	F/U[w]
	D-21 to -1	D 1	D 2	D 3	D 4	D 5	D 8	D 15	D 22	D 1	D 2	D 3	D 4	D 5	D 8	D 15	D 22		
Myeloma-specific Laboratory Tests[m]	X	X								X								X	As needed
PK (SL-401)[n]		X				X				X C2				X C2				X	
Immunogenicity (SL-401)[o]		X				X				X								X	
SL-401 Pre-medication[p]		X	X	X	X	X				X	X	X	X	X					
SL-401 Administration[q]		X	X	X	X	X				X	X	X	X	X					
Pomalidomide[r]										Days 1 - 21									
Dexamethasone										X					X	X	X		
Adverse Event monitoring[s]	X	← X →																	X
Prior/Concomitant Medication[t]	X	← X →																	X

a. **Informed consent** All patients must sign an IRB approved informed consent prior to screening and agree to enroll in the Pomalyst REMS program prior to starting POM.

b. **Medical History:** Includes relevant history of previous/associated pathologies other than the tumor. **Myeloma History:** Includes date of initial diagnosis, stage, and extent of the disease both at diagnosis and at study entry, previous anti-tumor therapy (including surgical, radiation and systemic therapy; for systemic therapy, includes approximate dates of administration, best response and approximate dates of disease progression).

c. **Physical Examination:** Consists of examination of major body systems including neurologic, digestive, respiratory, any evaluable sites of extramedullary disease. Physical examination is required at screening/baseline and Day 1 of each treatment cycle. Symptom directed physical examination may also be performed on other treatment days or mid-cycle evaluations if there are symptoms or vital sign abnormalities warranting examination.

d. **Vitals signs:** HR, temperature, RR, BP, and pulse oximetry to be taken pre- SL-401 infusion, end of SL-401 infusion, every 30 minutes for 4 hours post end of infusion and as clinically indicated for all doses of the Run-in Cycle. Cycle 1 +, vital signs are to be taken pre-infusion, at end of infusion and as clinically indicated. For temperature $\geq$ 38°C, draw blood cultures ×2 and collect urine for urinalysis and culture.

e. **Pregnancy tests** for FCBP at screening, test must be repeated within 10 – 14 days prior to initiation of POM therapy (before Cycle 1) and again within 24 hours prior to initiation of POM therapy (before Cycle 1). While on POM, repeat pregnancy test every week for the first 4 weeks and then every 28 days while on therapy and during interruptions in therapy and 28 days following discontinuation of POM. Women with irregular menstruation must have pregnancy testing every 14 days while on therapy and during interruptions and 14 and 28 days after discontinuation of POM. All patients enrolled into this study, must be registered in and must comply with all requirements of the POMALYST REMS™ program. A FCBP is a female of childbearing potential is a sexually mature woman who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months.

f. **Hematology:** CBC to be performed and reviewed by clinician prior to SL-401 dosing on Days 1 – 5 and Days 8, 15 and 22 or as clinically indicated. The Run in and Cycle 1, Day 1, results must remain within the entry criteria values to initiate therapy.

g. **Serum Chemistry:** to be performed and reviewed by clinician prior to SL-401 dosing on Days 1 – 5 and Days 8, 15, and 22 or as clinically indicated. The Run in and Cycle 1 Day 1 results must remain within the entry criteria values to initiate therapy. Chemistry includes: glucose (fasting at baseline), albumin, total protein, AST, ALT, bilirubin

(total and direct), alkaline phosphatase, LDH, CPK, sodium, potassium, chloride, bicarbonate/carbon dioxide, calcium, magnesium, phosphate, uric acid, BUN, serum creatinine and estimated creatinine clearance (Cockroft-Gault formula Appendix 15.7). Albumin, transaminases (AST/ALT) and creatinine must be evaluated prior to each SL-401 dose.

h. **Urinalysis:** Appearance, color, pH, specific gravity, ketones, leukocytes, protein, glucose, bilirubin, urobilinogen, and occult blood. To be performed at baseline, during the treatment period as clinically indicated and EOT.

i. **Plasmacytoma Assessment Disease:** For patient with known or suspected plasmacytomas, assess by physical exam and/or radiologic evaluation at baseline and as clinically indicated. Disease that can be assessed by physical exam should be evaluated on Day 1 of each cycle. Disease that can be assessed by radiologic evaluation should be assessed according the IMWG criteria for evaluation of response. This may include computerized tomography (CT) scan, ultrasound, PET/CT or MRI. The same method of assessment should be used at each evaluation for any individual patient. Assess the need to evaluate for suspected new, worsening, or improved plasmacytomas to confirm response or progression every cycle. Evaluations may be performed on Day 1 of a cycle or during the 7 days prior to Day 1 of the Cycle as needed for scheduling.

j. **Skeletal Survey:** Plain film X-rays to including skull, vertebrae, all long bones, pelvis and chest are required. PET/CT MRI may be done to supplement X-rays of any disease site at Investigators discretion. Also required at any time when clinically indicated, for suspected progression per IMWG response criteria.

k. **Bone Marrow Aspiration:** Bone marrow aspiration for cytogenetic analysis both by FISH and standard karyotyping, and morphologic evaluation including assessment of plasma cell percentage is required at screening/baseline (within 21 days prior to study drug administration. Bone marrow aspirate should be repeated if CR or stringent complete response (sCR) is suspected to confirm achievement of response according to IMWG criteria, and at End of therapy. Additional BM aspirate material (10-15cc if feasible) and biopsy for correlative studies are to be collected at baseline and any time a specimen is obtained to confirm response.

l. **Peripheral blood for correlative studies** should be obtained at baseline, for **phase 1** Day 1 of Cycles 1, 3, and 5 and for **phase 2** on Day 1 of Cycles 2, 4, and 6 and at EOT for all patients. Four 10 mL tubes in total (3 green top, 1 red top/serum separator tube). Whole blood will be evaluated for circulating MM/plasma cells (and other mononuclear cells of interest); serum and plasma will be for evaluated for potentially relevant circulating cytokines, and surrogate markers of osteolytic activity.

m. **Myeloma-specific laboratory tests:** β2 Microglobulin (at baseline only), serum and 24-hour urine immunoelectrophoresis, serum immunoglobulin assay, serum/urine immunofixation and serum FLC with kappa/lambda ratio to be performed at baseline, every cycle prior to study drug administration thereafter and at end of treatment (if last tests were > 4 weeks) and for patients who discontinue therapy for reasons other than disease progression. Myeloma laboratory tests will be repeated every month until disease progression or initiation of subsequent therapy. Response assessment will be done at the beginning of every cycle. Following pre-treatment evaluations on Day 1 of the first cycle evaluations may be performed on Day 1 of a subsequent cycle or during the 7 days prior to Day 1 of the Cycle as needed for scheduling. (Note that an evaluation performed during the final week of Cycle 1 should nonetheless be recorded as the evaluation for the beginning of Cycle 2, with similar assignments for subsequent cycles).

n. **Pharmacokinetic Assessment: phase 1 only**. PK samples (plasma) are to be obtained at the following time points: pre-infusion, immediately after infusion then 15, 30, 45, 60, 90, 120, 180, and 240 minutes post-infusion.in Phase on Day 1 and 5 of the Run-in Cycle and Cycle 2. See table 13. Pomalidomide will be administered approximately 4-6 hours post SL-401 end of infusion for the purpose of obtaining PK samples on the day of infusion 1 and 5 of Cycle 2.

o. **Immunogenicity:** Serum for immunogenicity evaluation will be collected prior to the infusion during the run-in Cycle 1 on Days 1 and 5 and on Day 1 pre-infusion at the beginning of all subsequent cycles, and at End-of-therapy. 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.

p. **Pre-medication:** Approximately 60 minutes prior to each dose of SL-401, patients shall receive pre-medication with acetaminophen, diphenhydramine, methylprednisolone and ranitidine according to Section 7.3.2.2.

q. **SL-401 administration:** SL-401 will be given by iv infusion over 15 minutes on Days 1 – 5 of each 28 day cycle (Run-in Cycle and Cycles 1 – 6) with delays permitted as delineated in relevant protocol sections such that administration on days 6-10 of any cycle is also permitted (5 doses may be administered over 10 days, if necessary). Dose modifications are permitted following the Run-in Cycle and Cycle 1; 5 doses of SL-401 may be administered over the initial 10 day period of each cycle. See Section 7.3.2.4 for drug administration instructions and Section 7.7 for dose modification guidelines

r. **Pomalidomide:** Pomalidomide will be administered approximately 4-6 hours post SL-401 end of infusion for the purpose of obtaining SL-401 PK samples on the days of infusion 1 and 5 of Cycle 2. Pomalidomide should be taken on an empty stomach 2 hours before or after a meal. Capsules should not be opened, broken or chewed.

s. **AE monitoring:** Patients to be observed for AEs at least 4 hours post each infusion. All AEs, including AEs of new onset as well as worsening of baseline signs and symptoms are to be reported from the signing of the informed consent to 30 days following the last administration of any study drug. After the 30 day follow-up all ongoing and new related AEs, and all the SAEs regardless of causal relationship are to be followed up to resolution or stabilization.

t. **Prior/concomitant medication** should be recorded including medications taken during the 28 days prior to initial study therapy, at any/all times during study therapy/participation, and through approximately 30 days following the last dose of investigational therapy.

u. Patients with evidence of MM stabilization or response and without unacceptable toxicity will receive the Run-in Cycle and 6 cycles of SL-401/POM/DEX. If, following completion of these cycles, there is ongoing evidence of MM stabilization or response, patients may receive additional therapy on-study if the Investigator believes the potential risk/benefit of additional therapy is justifiable. During Cycle 7 and beyond, SL-401 will be administered on Day 1-5 of **every other cycle (every 56 days)**, POM administered on Days 1-21, and DEX administered on Days 1, 8, 15 and 22 of each cycle.

v. **EOT:** Evaluations should be completed at the time a decision is made to discontinue study therapy, and approximately 30 ±7 days following the last dose of study therapy regardless for the reason of discontinuation, unless patient withdraws consent and refuses further evaluation.

w. **Follow-up**: Patients who discontinue therapy for reasons other than MM progression will be followed for response every month until progression of disease or initiation of subsequent therapy. Patients who have discontinued study therapy and have had MM progression should be contacted approximately every 3 months (telephone contact is permitted) to assess overall survival status for 1 year; patients who discontinue therapy for reasons other than disease progression and are no longer willing to follow-up for evaluation of disease progression should also be contacted for survival status whenever feasible.

Table 14: Time Points for Pharmacokinetic Blood Draws

PK Blood Sample times		
	Phase 1 – Run in Cycle and Cycle 2 [b]	
Time Point	**Day 1/Infusion 1**	**Day 5 [a]/Infusion 5**
Pre-Infusion	X	X
Immediately After End of Infusion (time recorded)	X	X
15 Minutes Post-Infusion	X	X
30 Minutes Post-Infusion	X	X
45 Minutes Post-Infusion	X	X
60 Minutes Post-Infusion	X	X
90 Minutes Post-Infusion	X	X
120 Minutes Post-Infusion	X	X
180 Minutes Post-Infusion	X	X
240 Minutes Post-Infusion	X	X

a Day 5 may shift based on treatments held for toxicity. PK should be done on the day of the 5th infusion.

b POM and DEX to be administered 4 – 6 hours post infusion on the day of infusions 1 and 5 of Cycle 2 (POM only on Day 5). PK assessments will be performed in phase 1 only.

10 Adverse Events and Safety Evaluation

The AE reporting period for a patient treated in the study begins with the initiation of SL-401/POM/DEX and is continuous through 30 days after the last SL-401/POM/DEX dose. 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/POM/DEX. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to SL-401/POM/DEX 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 Investigator, who is a physician, or medical staff responsible for study conduct and safety evaluations, should be available during the administration SL-401 and follow-up to assess, treat, or report as necessary any AE or SAE that may occur.

10.1 Definitions

All observed or volunteered AEs regardless of suspected causal relationship to SL-401/POM/DEX will be reported as described in the following subsections.

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 BM aspirate 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.

10.1.2 Serious Adverse Event (SAE)

An AE that meets 1 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.
- Confirmed or suspected pregnancy

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 1 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 in-patient hospitalization, or prolongation of an existing hospitalization, are considered serious. Any initial admission, even if the duration is less than 24 hours is considered serious. In addition, any transfer within the hospital to an acute/intensive

care unit is considered serious. However, the following hospitalizations should not be considered serious:

- Hospitalization or prolonged hospitalization in the absence of precipitating clinical 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 examination).
  - Protocol-specified admission during the study (e.g., admission for SL-401 treatment).
  - Preplanned treatments or surgical procedures.
  - Admission exclusively for the administration of blood products.

Progress of the disease under study (including signs and symptoms of progression) should not be reported as 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 CTCAE grade 5. Disease progression is NOT an SAE; however some sequelae of disease progression (i.e., pain, thrombocytopenia) may be reported as AEs or SAEs (generally not related to investigational therapy).

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

10.2 Period of Observation

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

Conditions that the patient experienced prior to SL-401/POM/DEX treatment should be recorded in the patient medical history section of the eCRF. All the AEs should be followed-up at the discretion of the Investigator until the symptoms dissipate or become stable even if AEs continue beyond the period of observation. AEs unresolved at the end of the observation period will be considered "ongoing" with an undetermined outcome; however, if after the period of observation completes but prior to the completion of the study, additional outcome information becomes available, it will be reported. The severity of the signs, symptoms, or AEs should be determined using the NCI CTCAE, v.4.03. A complete CTCAE list can be downloaded at http://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf.

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 1 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

A FCBP is a sexually mature female who: 1) has not undergone a hysterectomy or bilateral oophorectomy; or 2) has not been naturally postmenopausal for at least 24 consecutive months (i.e., has had menses at any time in the preceding 24 consecutive months).

FCBP must have a negative serum or urine pregnancy test prior to the first dose of SL-401 in the Run-in Cycle and FCBP must have a negative serum or urine pregnancy test prior with a sensitivity of at least 50 mIU/mL within 10 – 14 days prior to and again within 24 hours of starting SL-401/POM/DEX and must either commit to continued abstinence from heterosexual intercourse or begin 2 acceptable methods of birth control, 1 highly effective method and 1 additional effective method at the same time, at least 28 days before she starts taking SL-401/POM/DEX through 30 days after the last dose of POM and 60 days after the last dose of SL-401. FCBP must also agree to ongoing pregnancy testing during the entire duration of treatment. Men must agree to use a latex or synthetic condom during sexual contact with a FCBP even if they have had a vasectomy from the time of signing the ICF through 30 days after the last dose of POM and 60 days after the last dose of SL-401. These same patients must not donate sperm. All patients enrolled into this study, must be registered in and must comply with all requirements of the POMALYST REMS™ program.

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

If following initiation of study drug, it is subsequently discovered that a patient is pregnant or may have been pregnant at the time of exposure to study therapy, including during at least 2 months after SL-401, study therapy will be permanently discontinued in an appropriate manner.

If a female partner of a male subject taking SL-401or POM becomes pregnant, the male subject should notify the Investigator immediately, and the pregnant female partner should be advised to call their healthcare provider immediately.

Pregnancies and suspected pregnancies (including a positive pregnancy test regardless of age or disease state) of a female subject occurring while the subject is on SL-401 or POM, or within 60 days of the subject's last dose of therapy), are considered immediately reportable events. SL-401and POM are to be discontinued immediately. A pregnancy, suspected pregnancy, or positive pregnancy test must be reported.

The female subject should be referred to an obstetrician-gynecologist, preferably one experienced in reproductive toxicity for further evaluation and counseling.

The Investigator will follow the female subject until completion of the pregnancy, and must notify the Sponsor about the outcome of the pregnancy (either normal or abnormal outcome). If the outcome of the pregnancy was abnormal (e.g., spontaneous or therapeutic abortion), the Investigator should report the abnormal outcome as an AE. If the abnormal outcome meets any of the serious criteria, it must be reported as an SAE.

All neonatal deaths that occur within 28 days of birth should be reported, without regard to causality, as SAEs. In addition, any infant death after 28 days that the Investigator suspects is related to the *in utero* exposure to SL-401 and POM should also be reported.

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.

10.5 Documentation and Reporting of Adverse Events by Investigator

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

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

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

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

For any event that meets 1 of the SAE criteria, the Investigator must notify Medpace Clinical Safety **within 24 hours** of the knowledge of the occurrence. To report the SAE, complete the SAE form electronically in the electronic data capture (EDC) system for the study. When the form is completed, Medpace Safety 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, send an email to Medpace Safety at medpace-safetynotification@medpace.com or call the Medpace SAE hotline (phone number listed below), and fax the completed paper SAE form to Medpace (fax number listed below) 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.

Safety Contact Information:

Medpace Clinical Safety

Medpace SAE hotline – USA:

Telephone: +1-800-730-5779, ext. 2999 **or** +1-513-579-9911, ext. 2999

Facsimile: +1-866-336-5320 **or** +1-513-579-0444

E-mail: medpace-safetynotification@medpace.com

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 Medpace Clinical Safety 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 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.

10.6 Assessment of Causal Relationship

In this study, the investigational medicinal product is SL-401/POM/DEX. 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/POM/DEX. 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/POM/DEX.

- 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/POM/DEX. It should be emphasized that ineffective study drug treatment should not be considered as causally related in the context of adverse event reporting (in other words, disease progression is not considered an adverse event; however some sequellae 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 pharmacokinetics 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 adverse events on the eCRFs, the Investigator will use the severity grading as described in NCI CTCAE, v.4.03.

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

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

Note the distinction between the severity and the seriousness of an AE. A severe event is not necessarily a serious event. For example, a headache may be severe (interferes significantly with patient's usual function) but would not be classified as serious unless it met 1 of the criteria for serious events.

It is requested that when reporting AEs for which potentially redundant CTCAE terms exist, the Investigator utilizes 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 the Investigator reports both the specific symptoms associated with the reaction (e.g., "urticaria," "chills," "dyspnea,") and also reports 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 Statistical Analysis

11.1 General Considerations

Analyses will be performed on all patients that received any quantity of SL-401/POM/DEX (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/POM/DEX. Day 1 for each individual patient is defined as the date the patient receives their first infusion of SL-401.

11.2 Populations for Analysis

11.2.1 Phase 1 (Evaluable for Toxicity)

Patients will be considered evaluable for toxicity if they receive any study drug. Patients will be considered evaluable for dose limiting toxicity if they receive any study drug and are followed for the full 2 cycles or experience a DLT prior to completion of 2 cycles. All patients who are not evaluable for DLT will be replaced.

11.2.2 Phase 2 (Evaluable for Toxicity)

Patients will be considered evaluable for toxicity if they receive any study drug. Patients in phase 2 will not be replaced based on toxicity.

11.2.3 Phase 1 and 2 (Evaluable for Response)

Patients will be considered evaluable for response if they have baseline disease assessments, received at least 1 cycle of therapy and have had their disease re-evaluated. These patients will have their response classified according to the IMWG response criteria. All patients in phase 2 and those treated at the recommended phase 2 dose in phase 1 who are not evaluable for response will be replaced.

11.3 Determination of Sample Size

The primary objectives of phase 1 of the study are to evaluate the safety of Sl-401 as a single agent in an initial Run-in Cycle, to determine the MTD or the maximum tested dose where multiple DLTs are not observed and to further characterize the safety profile of SL-401/POM//DEX at the MTD. Based on such a recommended dose for phase 2 studies will be defined. A maximum of 3 dose levels (7, 9, and 12 µg/kg/day) is anticipated and thus the total number of patient for this stage ranges from 6 to 18. The anticipated same size is sufficient to evaluate these objectives. A secondary objective is to characterize the anti-tumor activity of SL-401/POM/DEX in terms of ORR, CBR, PFS and PFS-6. During phase 2, if approximately 14 patients are enrolled at the recommended phase 2 dose as defined in phase 1 over 12 months and follow-up continues for 12 months after the last enrolled patient, the total of 20 patients treated at this dose has approximately 75% power with a 1-sided type I error rate of 5% to reject the null hypothesis that the PFS-6 is <40% if the true rate is 60%.

11.4 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.

11.5 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. The AE reporting period for a patient treated in the study begins with the initiation of SL-401 or SL-401/POM/DEX and is continuous through 30 days after the last dose of SL-401 or SL-401/POM/DEX. 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/POM/DEX. Any known untoward event that occurs beyond the AE reporting period that the Investigator assesses as related to SL-401/POM/DEX should also be reported as an AE.

Treatment-emergent adverse events through 30 days after last dose of SL-401/POM/DEX 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 NCI CTCAE, v.4.03 (or higher), grade and by causality (relationship to study drug). Dose-limiting toxicities, grade 3-4 AEs, SAEs, and AEs resulting in dose modification or treatment discontinuation will also be summarized by preferred term.

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

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

11.6 Analyses of Efficacy Data

The study will preliminary evaluate the activity of the SL-410/POM/DEX regimen. Secondary efficacy endpoints will include: PFS and PFS-6; ORR (CR + VGPR + PR) and clinical benefit rate (CR + VGPR + PR + MR) based on IMWG defined response criteria, as well as DOR; and OS. Response rates and depth of response will be calculated as the percent of evaluable patients that have confirmed sCR/CR/VGPR or PR, and exact 95% confidence intervals will be calculated for these estimates. Time to response, duration of response, and survival will be estimated using the product-limit method of Kaplan and Meier. For subgroups of patients defined by disease and line of therapy, exact 1-sided 95% confidence intervals will be calculated

for ORR and clinical benefit rates, and the distributions for duration of response, PFS, PFS6, and OS will be estimated by Kaplan-Meier methodology.

Efficacy assessment parameters will include:

- M-protein determination using both of the following procedures:
  - SPEP and serum protein immunofixation with quantitative immunoglobulins; and
  - UPEP and urine protein immunofixation (all using the same 24-hour urine collection)
- Serum FLC
- BM to quantify percent MM cell involvement
- Plasmacytoma evaluation: PET/CT scan or MRI and or physical exam as clinically indicated
- Skeletal survey
- Serum β2 microglobulin
- Cytogenetic analysis/FISH from BM aspirate

11.7 Translational, Pharmacokinetic, and Immunogenicity Analyses

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

11.8 Blinding

This is an open-label study.

12 Emergency Procedures

12.1 Emergency Contact

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

12.2 Emergency Treatment

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

13 Ethical and Regulatory Considerations

13.1 Good Clinical Practice

As the Sponsor of this clinical study, Stemline 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, International Conference of Harmonisation (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 obtaining IRB approvals, providing Investigators with information required to conduct the study, ensuring proper investigative site monitoring, verifying that appropriate patient informed consent is obtained, submitting an IND to FDA, and ensuring that the IRB and regulatory agencies are promptly informed of significant new information regarding the study.

13.2 Delegation of Investigator Responsibilities

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

13.3 Patient Information and Informed Consent

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

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

patient or the patient's legally authorized representative. The signed ICF must be available for verification by the Sponsor's designated monitors or FDA inspectors.

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

13.4 Confidentiality

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

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

13.5 Protocol Amendments

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

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

13.6 IRB/IEC Approval and Reporting

The Investigator must obtain appropriate IRB approval prior to study initiation. A copy of the written approval from the IRB and a copy of the approved ICF should be sent to the Sponsor or its delegate. It is also necessary to submit a list of the IRB members (including their Institution

affiliations, gender makeup, and occupations) or supply a statement from the IRB specifying that the membership complies with applicable regulations.

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

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

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

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

13.7 Closure of the Study

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

13.8 Record Retention

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

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

inform the Investigator when storage of these documents is no longer required. The Investigator should contact the Sponsor if the site's archiving arrangements change at any time.

13.9 Liability and Insurance

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

13.10 Financial Disclosure

Prior to study initiation the Investigator will be asked to sign a Clinical Trial Agreement. The Investigator will be required to sign a Financial Disclosure Form in accordance with 21 Code of Federal Regulations (CFR) Part 54; Financial Disclosure by Clinical Investigators.

13.11 Study Monitoring and Auditing

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

13.11.1 Study Monitoring and Source Data Verification

The Investigator is responsible for the validity of all data collected at the site and must accept the various monitoring procedures employed by the Sponsor. The purpose of monitoring is to verify the rights and well-being of human patients are protected; that study data is 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, participation in initial study sessions, review of eCRFs, source documents and results, and ensuring clear communication between Investigators and the Sponsor.

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

13.11.2 Study Documentation

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

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

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

13.11.3 Site Audits

For the purpose of compliance with GCP and regulatory agency guidelines, it may be necessary for Sponsor authorized Quality Assurance personnel and/or authorized personnel from an

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

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

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

13.12 Documentation and Use of Study Findings

13.12.1 Documentation of Study Findings

Source documentation will be maintained to document the treatment and study course of a patient and to substantiate the integrity of the study data submitted for review to regulatory agencies. Source documentation for Stemline Therapeutics, Inc., 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, BM biopsy reports, BM aspirate reports, ECHO readings, and MUGA readings may be collected by the study monitor during the course of the study. Every effort should be made by the site to de-identify personal patient information from these reports and replaces with the patients study identification number.

13.12.2 Use of Study Findings

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

All publications and presentations of the results of the Study are governed by the applicable provisions of the Clinical Trial Agreement between the Sponsor and the institution. By signing the study protocol, the Investigator agrees that the results of the study may be used for the purposes of national and international registration, publication, and information for medical and pharmaceutical professionals by the Sponsor. If necessary, the authorities will be notified of the

Investigator's name, address, qualifications, and extent of involvement. The Investigator may not publish or present any information on this study without the express written approval of the Sponsor. Additionally, the Sponsor may, for any reason, withhold approval for publication or presentation. If the Investigator is to be an author of a publication manuscript prepared by the Sponsor, the Sponsor will allow the Investigator 30 days for full review of the manuscript before publication. Such manuscript or materials should be provided for Sponsor review only after the final database is available.

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15 Appendices

15.1 ECOG Performance Status

Grade	Description
0	Able to carry out all normal activities without restriction.
1	Restricted in physically strenuous activity but ambulatory and able to carry out work of a light or sedentary nature.
2	Ambulatory and capable of all self-care but unable to carry out any work activities: up and about more than 50% of waking hours.
3	Capable of limited self-care; confined to bed or chair more than 50% of waking hours.
4	Completely disabled; cannot carry on self-care; totally confined to bed or chair.

15.2 International Myeloma Working Group Response Criteria

Response	IMWG criteria
sCR	CR as defined below plus: • normal FLC ratio and • absence of clonal cells in bone marrow by immunohistochemistry or 2 – 4 color flow cytometry
CR	• Negative immunofixation on the serum and urine and • disappearance of any soft tissue plasmacytomas and • < 5% plasma cells in bone marrow. • In patients with only FLC disease, a normal FLC ratio of 0.26–1.65 is required.
VGPR	• Serum and urine M-protein detectable by immunofixation but not on electrophoresis or • 90% reduction in serum M-protein plus urine M-protein level < 100 mg/24 h. • In patients with only FLC disease, >90% decrease in the difference between involved and uninvolved FLC levels is required.
PR	• 50% reduction of serum M-protein and reduction in 24 hours urinary M-protein by ≥90% or to < 200 mg/24 h • If the serum and urine M-protein are unmeasurable,[3] a ≥ 50% decrease in the difference between involved and uninvolved FLC levels is required in place of the M-protein criteria • If serum and urine M-protein are not measurable, and serum free light assay is also not measureable, ≥ 50% reduction in plasma cells is required in place of M-protein, provided baseline bone marrow plasma cell percentage was ≥ 30% • In addition to the above listed criteria, if present at baseline, a ≥ 50% reduction in the size of soft tissue plasmacytomas is also required
Minimal response in patients with RRMM adapted from the EMBT criteria	≥ 25% but < 49% reduction of serum M protein *and* reduction in 24 hour urine M protein by 50 – 89%, which still exceeds 200 mg/24hrs. In addition to above; if present at baseline, 25-49% reduction in the size of soft tissue plasmacytomas is also required • No increase in size or number of lytic bone lesions (development of compression fractures does not exclude response)
Stable Disease	• Not meeting criteria for CR, VGPR, PR or progressive disease

Response	IMWG criteria
Progressive disease	Increase of ≥ 25% from lowest response value in any 1 of the following: • Serum M-component (the absolute increase must be ≥ 0.5 g/dL)[4] and/or • Urine M-component (the absolute increase must be ≥ 200 mg/24 h) and/or • Only in patients without measurable serum and urine M-protein, the difference between involved and uninvolved FLC levels. The absolute increase must be > 10 mg/dL • Only in patients without measurable serum and urine M-protein and without measurable disease by FLC levels, bone marrow plasma cell percentage (absolute % must be ≥ 10%) • Definite development of new bone lesions or soft tissue plasmacytomas or definite increase in the size of existing bone lesions or soft tissue plasmacytomas • Development of hypercalcemia (corrected serum calcium > 11.5 mg/dL) that can be attributed solely to the plasma cell proliferative disorder

All relapse categories (CR, sCR, VGPR, and progressive disease) require 2 consecutive assessments made at any time before the institution of any new therapy; complete response and PR and SD categories also require no known evidence of progressive or new bone lesions if radiographic studies were performed. VGPR and CR categories require serum and urine studies regardless of whether disease at baseline was measurable in serum, urine both or either. Radiographic studies are not required to satisfy these response requirements. Bone marrow assessments need not be confirmed. For progressive disease, serum M-component increases of ≥ I gm/dl are sufficient to define response if starting M-component is ≥ 5 g/dl.

IMWG clarification for coding progressive disease: Clarified that Bone marrow criteria for progressive disease are to be used only in patients without measurable disease by M protein and by FLC levels. Clarified that 25% increase refers to M protein, FLC, and bone marrow results and does not refer to bone lesions, soft tissue plasmacytomas or hypercalcemia. Note the lowest response value does not need to be a confirmed value.

FreeLite™ Disease Response Criteria

Complete Response: For those patients being followed by serum free light chain (and NO measurable serum or urine M-spike), which were immunofixation negative at enrollment, normalization of serum free light chain ratio.

Normalization is defined as the serum free light chain ratio being within the normal range. If the serum free light chain ratio is not within the normal range, but the individual kappa and lambda light chain values are within normal range, this may be considered CR.

Partial Response: If only measurable parameter is serum immunoglobulins FLC, EITHER of the following changes quality as partial response:

- A 50% decrease in the difference between involved and uninvolved FLC levels; OR
- A 50% decrease in the level of involved FLC AND a 50% decrease (or normalization) in the ratio of involved/uninvolved FLC

Progressive Disease: If only measurable parameter is serum immunoglobulins free light (FLC), either of the following qualify as progression:

- 50% increase in the difference between involved and uninvolved FLC levels from the lowest response level, which must also be an absolute increase of at least 10 mg/dL; OR
- 50% increase in the level of involved FLC AND a 50% increase in the ratio of involved/uninvolved FLC from the lowest response level.

15.3 Definition of Lines of Therapy

A line of therapy is defined as 1 or more cycles of a planned treatment program. This may consist of 1 or more planned cycles of single-agent therapy or combination therapy, as well as a sequence of treatments administered in a planned manner. For example, a planned treatment approach of induction therapy followed by autologous stem cell transplantation, followed by maintenance is considered 1 line of therapy. A new line of therapy starts when a planned course of therapy is modified to include other treatment agents (alone or in combination) as a result of disease progression, relapse, or toxicity. A new line of therapy also starts when a planned period of observation off therapy is interrupted by a need for additional treatment for the disease.

15.4 Definition of Relapsed and Refractory Myeloma

Refractory Myeloma:

Refractory myeloma is defined as disease that is non-responsive (failure to achieve minimal response or develops progressive disease while on therapy) while on primary or salvage therapy, or progresses within 60 days of last therapy. There are 2 categories of refractory myeloma.

- Relapsed and refractory myeloma: Relapsed and refractory myeloma is defined as disease that is non-responsive while on salvage therapy or progresses within 60 days of last therapy in patients who have achieved minimal response or better at some point previously to then progressing in their disease course.
- Primary refractory myeloma: refractory myeloma is defined as disease that is non-responsive in patients who have *never* achieved minimal response or better with any therapy. It includes patients who never achieve MR or better in whom there is no significant change in M protein and no evidence of clinical progression; as well as primary refractory, progressive disease where patients meet criteria for true progressive disease.

Relapsed myeloma

Relapsed myeloma is defined as previously treated myeloma which progresses and requires the initiation of salvage therapy but does not meet the criteria for either primary refractory myeloma or relapsed and refractory myeloma.

15.5 CYP Enzymes Inhibitors

Strong Inhibitors (≥ 5-fold increase in AUC or > 80% decrease in CL)

Ciprofloxacin, enoxacin, fluvoxamine

Moderate inhibitors (≥ 2 but < 5-fold increase in AUC or 50-80% decrease in CL)

Methoxsalen, mexiletine, oral contraceptives, phenylpropanolamine, thiabendazole, zileuton

Weak inhibitors (≥ 1.25 but < 2-fold increase in AUC or 20-50% decrease in CL)

Acyclovir, allopurinol, caffeine, cimetidine, daidzein, disulfiram, echinacea, famotidine, norfloxacin, propafenone, propranolol, terbinafine, ticlopidine, verapamil

Classification of *In Vivo* Inhibitors of CYP Enzymes:

http://www.fda.gov/Drugs/DevelopmentApprovalProcess/DevelopmentResources/DrugInteractionsLabeling/ucm093664.htm#classInhibit

15.6 The New York Heart Association Classification of Cardiac Disease

The following table presents the NYHA classification of cardiac disease:

Class	Functional Capacity	Objective Assessment
I	Patients with cardiac disease but without resulting limitations of physical activity. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea, or anginal pain.	No objective evidence of cardiovascular disease.
II	Patients with cardiac disease resulting in slight limitation of physical activity. They are comfortable at rest. Ordinary physical activity results in fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of minimal cardiovascular disease.
III	Patients with cardiac disease resulting in marked limitation of physical activity. They are comfortable at rest. Less than ordinary activity causes fatigue, palpitation, dyspnea, or anginal pain.	Objective evidence of moderately severe cardiovascular disease.
IV	Patients with cardiac disease resulting in inability to carry on any physical activity without discomfort. Symptoms of heart failure or the anginal syndrome may be present even at rest. If any physical activity is undertaken, discomfort is increased.	Objective evidence of severe cardiovascular disease.

15.7 Estimated Creatinine Clearance rate (eCCr) using Cockcroft-Gault Formula

$$eC_{Cr} = \frac{(140 - \text{Age}) \times \text{Mass (in kilograms)} \times [0.85 \; if \; Female]}{72 \times \text{Serum Creatinine (in mg/dL)}}$$